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Development and Application of Synthetic Methods for the Production of Small Molecule Libraries

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Abstract

The synthesis of chemical libraries is a fundamental tool used to identify molecules with desirable biological activity. Recent developments in combinatorial synthesis techniques have allowed for the rapid generation of very large and diverse chemical libraries that can be used in conjunction with high-throughput screening (HTS) technology to identify lead molecules that can be potentially developed into pharmaceuticals. Libraries based around an oxindole scaffold (previously identified as inhibitors of cRAf1 kinase) were recently shown to display inhibitory effects against aminoglycoside phosphotransferases (APH) enzymes found in bacteria responsible for antibiotic resistance to aminoglycosides. Additionally, substituted quinazolines (similar in structure to the known drug Lapatinib) were identified as a potent inhibitor of both APH(2")Id and ANT(2"). The present thesis involves the development of synthetic protocols suitable for the generation and subsequent biotesting of chemical libraries based around these hits in order to determine the pharmacophore in each case.

Acknowledgements

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Abbreviations

3D	Three-dimensional
AAC	Aminoglycoside acetyltransferase
ANT	Aminoglycoside nucleotidyltransferase
APH	Aminoglycoside phosphotransferase
EtOH	Ethanol
Ar	Aryl
Bn	Benzyl
Bu	Butyl
cAMP	Cyclic adenosine monophosphate
CDK	Cyclin-dependant kinase
CIC_{95}	Cell culture inhibitory concentration of 95%
CONV	Conventional heating
COX	Cyclooxygenase
CVS	Cardiovascular system
dba	Dibenzylideneacetone
DCM	Dichloromethane
de	Diastereomeric excess
DIPEA	Diisopropylethylamine
DME	Dimethylether
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide

DNA	deoxyribonucleic acid
DOS	Diversity-oriented synthesis
DTS	Diverted total synthesis
E1cB	Elimination unimolecular conjugate base
EC_{50}	Half maximal effective concentration
Et	Ethyl
EtOAc	Ethyl acetate
MW	Microwave
Fmoc	Fluorenylmethyloxycarbonyl
GSK	GlaxoSmithCline
H_2O	Water
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HOAc	Acetic acid
HTS	High Throughput Screening
iPrOH	Isopropanol
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
LOX	Lysyl oxidase
MDR	Multidrug-resistant
Me	Methyl
MeCN	Acetonitrile
OAc	Acetyl

OMe	Methoxy
BIOS	Biology-oriented synthesis
OTf	Triflate
PA	Phosphaadamantane
Ph	Phenyl
PKIS	Published kinase inhibitor set
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
SAR	Structure activity relationship
IC_{50}	Half maximal inhibitory concentration
SCONP	Structural classification of natural products
TBAF	Tetrabutylammonium fluoride
^{t}Bu	*tert*-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tRNA	Transfer ribonucleic acid

Chapter 1: Introduction

1.1 Chemical Library Synthesis

1.1.1 History

Historically, therapeutic agents and medicines have been discovered in biological organisms such as plants and fungi. Isolation and characterization of these biologically active molecules allowed insight into what structurally constituted a biologically-active molecule. Oftentimes, however, natural products are scarce and isolation of required quantities of the product can be difficult and tedious. Taking our inspiration from nature and developing synthetic analogues circumvents these issues and allows for the discovery of potent small molecules that can mimic the activity of natural products.

One of the earliest examples of small-molecule drug discovery was Paul Ehrlich's development of Salvarsan 606.[1] Realising that the synthetic dye aniline was capable of selectively staining certain microorganisms over others, Ehrlich combined the selective properties of aniline with the toxic properties of arsenic acid to generate atoxyl; an arsenic-based drug aimed at treating syphilis (figure 1.1).

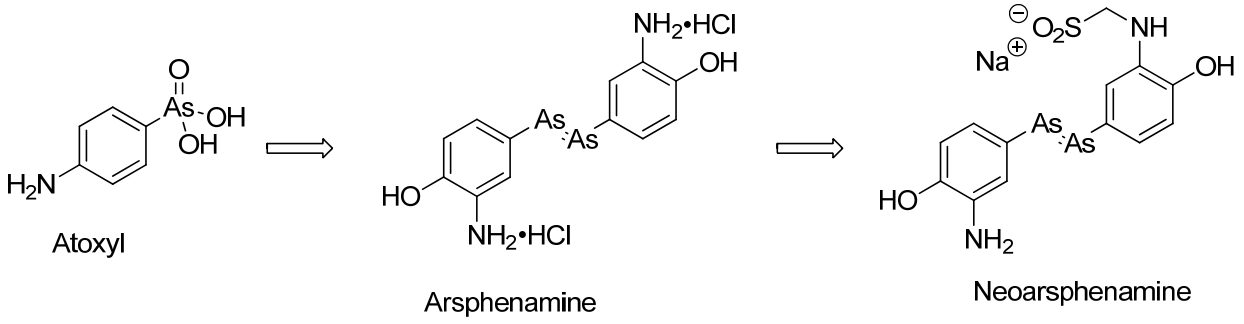


Figure 1.1. Evolution of arsenic-based drugs used in the treatment of syphilis.

[1] Li, J.J.; Corey, E.J. History of Drug Discovery. In *Drug Discovery: Practices, Processes, and Perspectives*; Li, J.J.; Corey, E.J., Ed.; John Wiley & Sons, Inc., Hoboken, NJ, 2004; p 1-46.

The toxicity of atoxyl, however, was too high for human consumption. In conjunction with Alfred Bertheim, Ehrlich synthesized one of the first chemical libraries of arsenobenzene compounds, leading to the discovery of arsphenamine (also known as Salvarsan 606, figure 1.1) which displayed a much more acceptable safety profile.[2] Bertheim took Salvarsan 606 further and through the use of chemical libraries, discovered neoarsphenamine (figure 1.1) which was much less toxic and more water soluble.

Inspired by Ehrlich's discovery of arsphenamine, Gerhard Domagk discovered that the structurally-similar 2`-4`-diaminoazobenzene-4-sulfonamide (Prontosil, Figure 1.2) was effective as a treatment for *Streptococcus pyrogenes* infections and did not show detrimental toxic side effects.[3] Prontosil is another example of a drug being generated from a 'lead' compound, or a compound that has previously demonstrated desirable biological effects from which a pharmaceutical can be developed

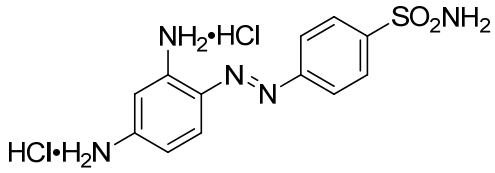


Figure 1.2. 2`-4`-diaminoazobenzene-4-sulfonamide (Prontosil). Note the structural similarity to arsphenamine.

1.1.2 Leads Generation

Modern chemical libraries are utilized in much the same way as Ehrlich and Bertheim did in their discovery of Salvarsan 606 and Neoarsephenamine, respectively. Once a lead molecule is identified, a library of structurally-similar molecules is synthesized and tested, and the compounds with the most desirable properties (most potent, least harmful, etc.) are selected for

[2] Riethmiller, S. *Chemotherapy* **2005**, *51*, 234-242.
[3] Bankston, J. *Gerhard Domagk and the Discovery of Sulfa*, Mitchell Lane Publishers, Bear, DE, 2003.

further structural modification. These compound collections are often described as "focussed libraries" as they are generally based a single scaffold augmented with a number of structurally unique fragments.

One of the most challenging aspects of the drug discovery process, however, is the discovery of the initial "hit" compound. Initially, natural products were the first class of molecules employed for drug design. As use of natural products plateaued, attention shifted towards more modern methods of finding "hit" compounds.

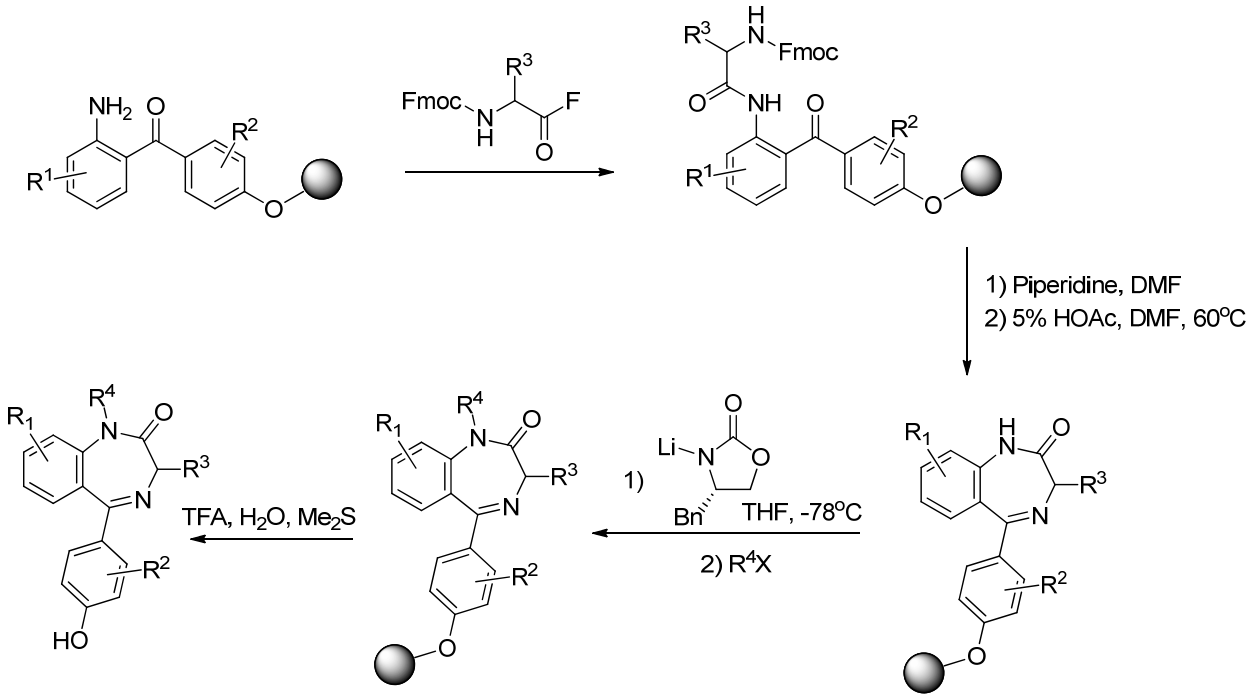
Recent developments in robotics has led to the successful application of combinatorial chemistry and high-throughput screening (HTS) in the drug discovery process. HTS involves the use of robotic systems to fully automate the bioassay process. These systems are capable of screening thousands to millions of different molecules against a selected biological assay. In this way "hits" provide the needed starting point for the drug discovery process. In short, HTS is effectively a 'shotgun' approach to identifying lead compounds. This approach has proven to be very successful with many drugs currently on the market originating from HTS "hits" including Gefitinib, Erlotinib, Tipranavir, Sitagliptin, Maraviroc, Lapatinib, Tolvaptan, and Eltombopag.[4]

The other vital compliment to HTS is the chemical library to be screened. For this application, "diverse libraries" are used wherein large numbers of structurally different molecules are synthesized in order to maximize the diversity of chemical space occupancy. These chemical libraries are often synthesized using combinatorial techniques that aim to maximize the diversity of molecules produced in the shortest amount of time. A number of strategies for diversity have been developed and include the diversity-oriented synthesis (DOS)[5]

[4] Macarron, R.; Banks, M.N.; Bojanic, D.; Burns, D.J.; Cirovic, D.A.; Garyantes, T.; Green, D.V.S.; Hertzberg, R.P.; Janzen, W.P.; Paslay, J.W.; Schopfer, U.; Sittampalam, G.S. *Nat. Rev. Drug Discov.* **2011**, *10*, 188-195.
[5] Schreiber, S.L. *Science* **2000**, *287*, 1964-1969.

approach developed by Schreiber, the diverted total synthesis (DTS) approach described by Danishefsky, and biology-oriented synthesis (BIOS).

The goal of DOS is to generate massive collections of structurally and stereochemically complex and diverse compounds from simple starting materials which can be quickly screened for biological activity through HTS.[6] One of the first examples of combinatorial synthesis of small molecules was employed for the generation of a library of benzodiazepine by Ellman *et al.*[7]



Scheme 1.1. Stepwise combinatorial solid phase synthesis performed by Ellman *et al.* towards the generation of substituted benzodiazepines.

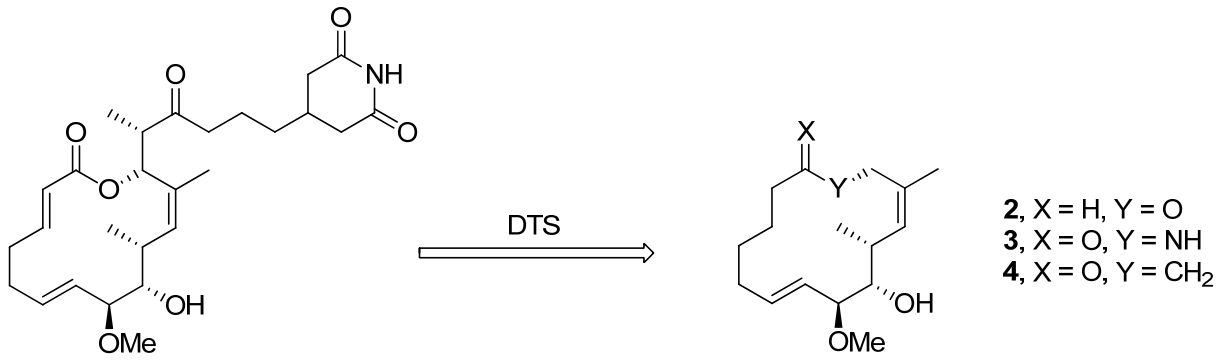
Upon the addition of a substituted 2-aminobenzophenone to solid support, an activated fmoc-protected amino acid is then added which adds a stereocenter to the substrate (scheme 1.1). Basic deprotection followed by mild acidification of the resin results in cyclization. A fourth

[6] Kaiser, M.; Wetzel, K.; Kumar, K. Waldmann, H. *Cell. Mol. Life. Sci.* **2008**, *65*, 1186-1201
[7] Bunin, B.A.; Ellman, J.A. *J. Am. Chem. Soc.* **1992**, *114*, 10997-10998.

alkylation is then performed followed by treatment with lithiated 5-(phenylmethyl)-2-oxazolidinone which selectively deprotonates the anilide. The final product is then cleaved from the resin with TFA. This synthetic protocol takes advantage of cheap and commercially available amino acids and alkylating agents in order to rapidly generate very large libraries of structurally-similar compounds which can be quickly screened for biological activity through HTS.

While combinatorial synthesis is an excellent way to generate large libraries of molecules, the practice depends on the availability of substituted components.[8] The Ellman chemistry described above, for example, suffers from the scarcity of commercially available substituted 2-aminobenzophenones. However, this issue was addressed in a later article where additional solid-supported alkylation steps were implemented.[9]

Another method used to generate diversity for chemical libraries takes advantage of natural product total synthesis and is known as diverted total synthesis (DTS). The approach modifies steps in a total synthesis of a natural product by adding or reducing complexity to synthetic intermediates allowing for the generation of multiple analogues.[10]



Scheme 1.2. DTS employed by Danishefsky *et al.* in the generation of migrastatin analogues.

[8] Gordon, E.M.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gallop, M.A. *J. Med. Chem.* **1994**, *31*, 1386-1401.
[9] Ellman, J.A. Pharmaceutical Manufacturers Association, Drug Discovery Management Subsection, September 19-21, 1993, Philadelphia, PA.
[10] Cragg, G.M.; Grothaus, P.G.; Newman, D.J.; *Chem. Rev.* **2009**, *109*, 3012-2043.

Danishefsky *et al.* employed the principles of DTS to generate analogues of migrastatin (scheme 1.2) which serve as inhibitors of tumor metastasis.[11] Particularly, it was noted that deletion of the glutarimide chain as well as reducing the α,β-unsaturated lactone resulted in a 10^3 increased potency.

A third method of chemical library generation is biology-oriented synthesis (BIOS).[6] This approach focuses on chemical scaffolds that are seen in natural products and in other small molecules with prevalidated biological activity. For example, Waldmann *et al.* compiled a list of chemical scaffolds derived from natural products to which they coined the term "Structural Classification of Natural Products," or SCONP.[12] This process was made possible through the principles of BIOS.

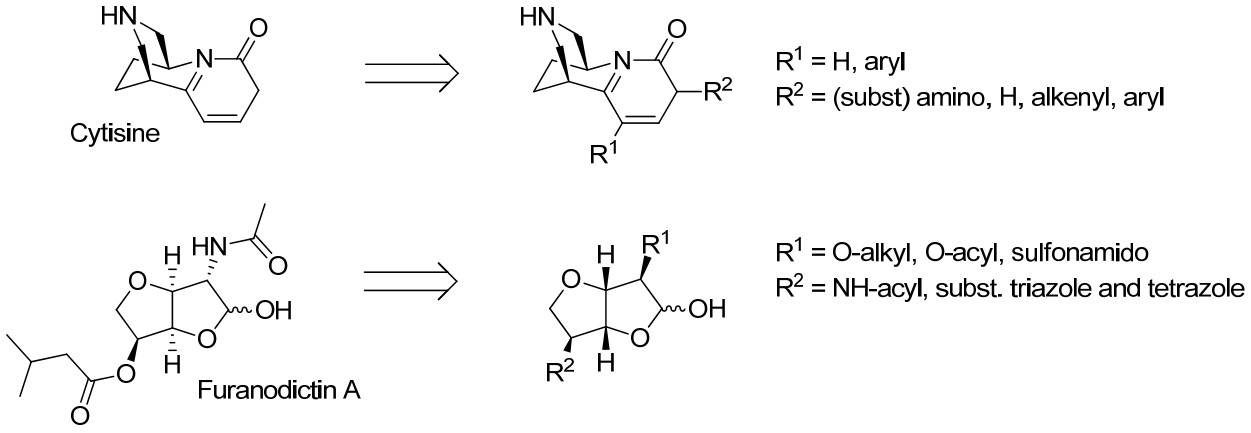


Figure 1.3. Scaffold reduction used in the functionalization of protein tyrosine phosphatase inhibitors discovered by Waldmann *et al.*

The process of reducing a natural product to its scaffold involves substituting the functional groups from the (usually) heterocyclic core with an R group and conducting structural activity relationship (SAR) studies to determine which R groups are relevant for biological

[11] Oskarsson, T.; Nagorny, P.; Krauss, I.J.; Perez, L.; Mandal, M.; Yang, G.; Ouerfelli, O.; Xiao, D.; Moore, M.A.S.; Massague, J.; Danishefsky, S.J. *J. Am. Chem. Soc.* **2010**, *132*, 3224-3228.
[12] Noren-Muller, A.; Reis-Correa Jr., I.; Prinz, H.; Rosenbaum, C.; Saxena, L; Schwalbe, H.J.; Vestweber, D.; Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. *Proc. Natl. Acad. Sci.* **2006**, *103*, 10606-10611.

activity (figure 3). Beginning the leads discovery phase with a basic idea of which chemical scaffold to use enables a significantly more targeted approach in comparison with the DOS method.

While many methods exist to generate an enormous degree of chemical diversity for HTS, the "hits" in HTS screening are often poor drug candidates or false positives. HTS screens require multiple counter-screens in order to validate the process and ensure that the "hits" are biologically meaningful. Once a lead molecule is identified, the molecule must then be optimized to make the potential drug candidate more drug-like.

1.1.3 Leads Optimization and Drug Development

Lead molecules identified by HTS are then screened through biological assays that determine the half maximal inhibitory concentration (IC_{50}) or the half maximal effective concentration (EC_{50}). An IC_{50} measurement is the concentration of a particular substance which inhibits a target protein by half, where an EC_{50} measurement is the concentration which produces a response halfway between the baseline response and the maximal response.[13] Once a lead compound is identified, this substance transitions to the leads optimization phase, where the goal is to make the lead compound more drug-like, more potent, more selective and appropriately bioavailable while minimizing any toxicity.

One of the first points to consider is the solubility of the lead. Assays are typically conducted in stock solutions of DMSO which does not adequately represent solubility *in vivo*. Therefore, an ideal drug should be soluble in both lipophilic and lipophobic environments. Typically this solubility is measured through a calculation known as the partition coefficient, or

[13] Cockbain, J. Chemistry, Molecular Sciences, and Chemical Engineering: Comprehensive Medicinal Chemistry II, April 2007, Frank B Dehn & Co., Oxford, UK, p779-815.

logP, which is the log of the concentration of solute in un-ionized octanol divided by the concentration of solute in un-ionized water.[14] Issues from poor solubility can result in misrepresented assay results, artificially low potency, and poor bioavailability. Structural modifications (while taking stereochemical and electronic effects into consideration) can be made in order to improve solubility and bioavailability. One of the most common practices includes introducing a basic nitrogen.[15]

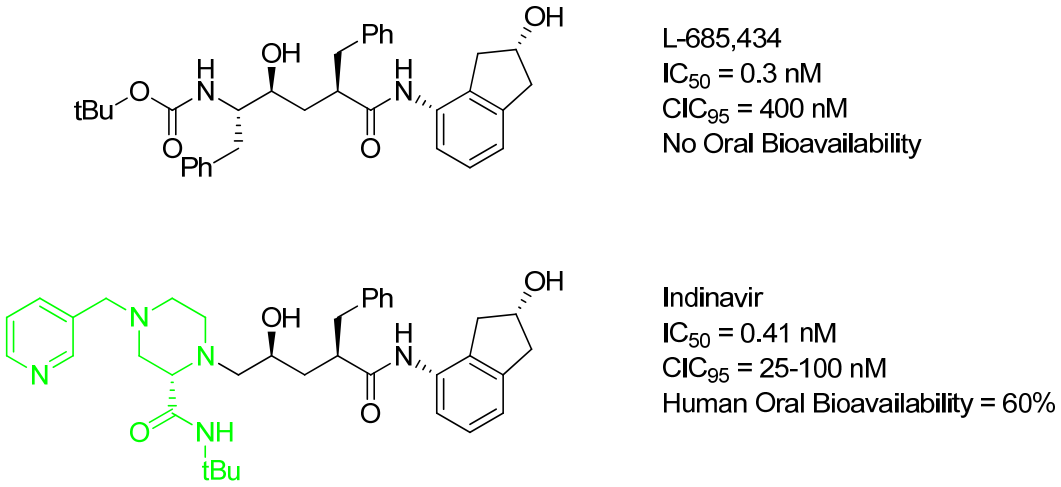


Figure 1.4. Solubility improvements to a lead compound identified for an HIV protease inhibitor conducted by Eldred *et al.* CIC_{95} is the 95% inhibition in cell culture.

Figure 1.4 illustrates one such improvement. Eldred *et al.* modified an existing lead identified by Vacca *et al.*[16] mainly by the introduction of the 3-pyridyl methyl substitution at N4.[17] This new substituent is ionisable and thus improves solubility in aqueous media and overall bioavailability. Such modifications are necessary to ensure lead compounds can be successfully utilized in living systems.

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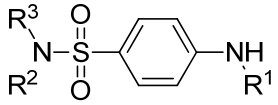
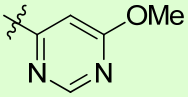
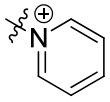
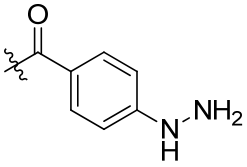
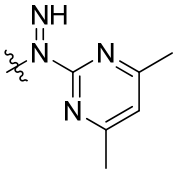
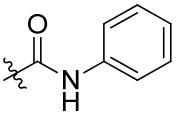
[14] Leo, A.; Corwin, H.; Elkins, D. *Chem. Rev.* **1971**, *71* (6), 525-616.
[15] Borchardt, R.; Kerns, E.; Hageman, M.; Thakker, D.; Stevens, J. Optimizing the "Drug-Like" Properties of Leads in Drug Discovery. Dec. 31, 2007, Springer Science & Business Media.
[16] Vacca, J.P.; Guare, J.P.; deSolms, S.J.; Sanders, W.M.; Guiliani, E.A.; Young, S.D.; Darke, P.L.; Zugay, J.; Sigal, I.S.; Schleif, W.A.; Quintero, J.C.; Emini, E.A.; Anderson, P.S.; Huff, J.R. *J. Med. Chem.* **1991**, *34*, 1225-1228.
[17] Eldred, C.D.; Evans, B.; Hindley, S.; Judkins, B.D.; Kelly, H.A.; Kitchen, J.; Lumley, P.; Porter, B.; Ross, B.C.; Smith, K.J.; Taylor, N.R.; Wheatcroft, J.R. *J. Med. Chem.* **1994**, *37*, 3882-3885.

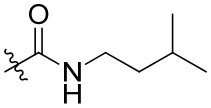
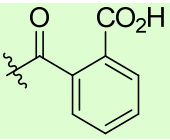
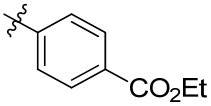
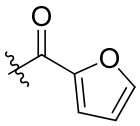
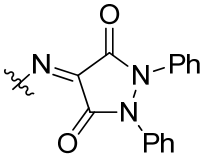
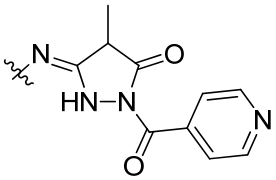
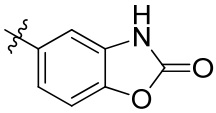
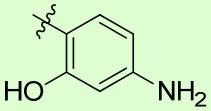
Most of the further optimization steps include conducting structure-activity relationship studies (SAR) in order to determine which structural features are needed for biological activity ultimately allowing for a determination of the pharmacophore of the molecule. SAR studies the 3D relationship between the lead compound and the target, incorporating steric and electronic interactions, and the corresponding biological activity.[18] The functional aspects of the lead compound are determined by synthesizing variations of each substituent and varying steric, polar, and electronic properties then conducting the biological assays to determine which groups optimize activity. The SAR informs additional synthetic efforts that allow for a maximization of the potency (minimize the EC_{50}/IC_{50}) of the compound as well as the selectivity towards the specific target.

Table 1.1. Initial SAR study conducted by Johnson *et al.* in order to determine important components of sulfanilamides on dihydropteroate synthetase inhibition.



Entry	Substituent at position:			IC_{50} (μM)
	R_1	R_2	R_3	
1	-H		-OMe	34
2	-H		-H	498.5
3	-H		-H	-
4			-H	515.7

[18] McKinney, J.D.; Richard, A.; Waller, C.; Newman, M.C.; Gerberick, F. *Toxicol. Sci.* **2000**, *56* (1), 8-17.

5			-H	783.6
6			-H	108.97
7			-H	238
8			-H	1309
9			-H	454.4
10			-H	2105
11			-H	601.6
12			-H	53.9

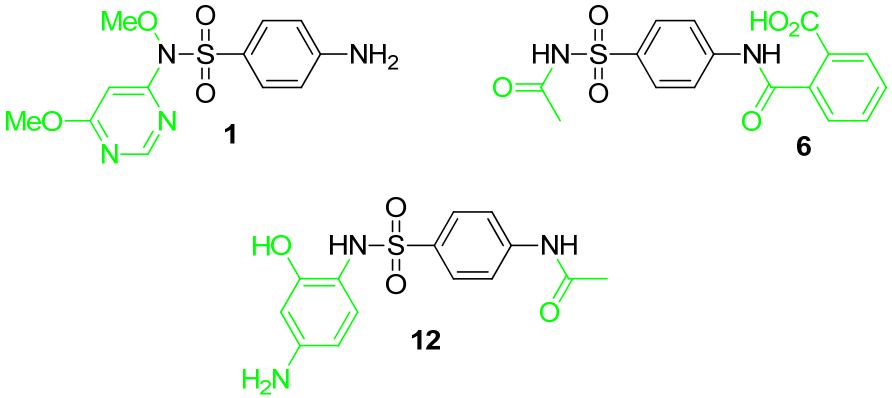


Figure 1.5. Summary of the most biologically-active results of the SAR study presented in table 1.1.

For example, while it was known that sulfone and sulfanilamide drugs inhibit dihydropteroate synthetase in *Pneumocystis carinii*, little was known about exactly which

structural features contained within sulfa drugs were responsible for inhibition. Johnson *et al.* began their studies on sulfa drugs by first analyzing the sulfone core and determining which components are necessary (table 1.1).[19] This initial SAR study revealed one key factor for activity in sulfa drugs: the substituent at the amide position (R_2 and/or R_3) must be ionisable, reflected by entries 1 and 12, and to a lesser degree, entry 6. With this piece of information, a second generation library was generated focusing exclusively on which ionisable substituents result in the lowest IC_{50}'s.

The ultimate goal of these SAR studies is to identify the pharmacophore, or the parts of the molecule required for binding to the target protein.[20] Once these aspects of the molecule are understood, an even more targeted approach towards optimizing the lead molecules can be taken. For example, in the sulfa drugs presented in table 1.1, the researchers could further explore ionisable moieties at the R_2 and R_3 positions and find an even more potent and more drug-like molecule.

1.2 Techniques and Chemistry Used

The focus of this thesis involves the development and application of synthetic methods for the production of compound libraries capable of optimizing lead molecules identified through HTS. Many of the protocols developed take advantage of microwave chemistry and organopalladium cross-coupling chemistry and a discussion of these appears below.

1.2.1 Microwave-Assisted Chemistry

[19] Johnson, T.; Khan, I.A.; Avery, M.A.; Grant, J.; Meshnick, S.R.; *Antimicrob. Agents. Chemother.* **1998**, *42* (6), 1454-1458.
[20] Wermuth, C.G.; Ganellin, C.R.; Lindberg, P.; Mitscher, L.A. *Pure Appl. Chem.* **1998**, *70* (5), 1129-1143.

1.2.1.1 Theory

Microwave-assisted chemistry has been an emerging field of study over the past thirty years.[21] The use of microwave irradiation enables a number of reactions that are either inaccessible or perform poorly using conventional heating. The exact mechanism behind this so-called "microwave effect" is widely debated. Microwave effects can be divided into two categories: thermal (specific) and non-thermal (non-specific) effects.[22]

Thermal effects are the generally-accepted mechanism underlying the greater majority of microwave-assisted reactions and refer to heating effects that are unique to the microwave environment including: superheating of solvents at atmospheric pressure, selective heating of strongly microwave-absorbing catalysts/reagents, selective molecular heating in homogenous solutions creating "hot spots," and the elimination of wall effects.[23,24] Non-thermal effects refer to phenomena that are independent of heating and focus on the effects caused directly by the microwave field. For example polarization of the reaction mixture results in the alignment of molecule dipoles thus increasing the pre-exponential factor *A* in the Arrhenius equation.[25] However, these non-thermal microwave effects are still debated in the literature.

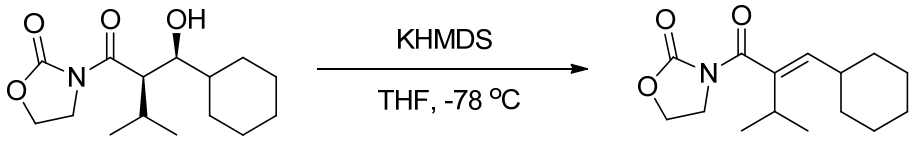
Regardless, microwave chemistry is a very effective tool for accessing products that are difficult to reach using conventional heating. The use of microwave chemistry in chemical library synthesis is a core technique in this thesis.

1.2.1.2 Use of Microwave Irradiation in Aldol Reactions

[21] Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tet. Lett*. **1986**, *27*, 279.
[22] Perroux, L.; Loupy, A. *Tetrahedron*, **2001**, *57*, 9199.
[23] Kappe, C.O. *Angew. Chem. Int. Ed.* **2004**, *116*, 6408.
[24] Kappe, C.O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.
[25] De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.

The aldol condensation provides a means for forming C-C bonds in organic synthesis between carbonyl species though enols/enolates (one of the carbonyl species must possess an α-hydrogen) and has been described as early as 1881 by Rainer Ludwig Claisen and J. G. Schmidt, independently.[26,27] One of the great advantages of using aldol chemistry is the ability to control the stereocenter of the β-hydroxyl species with a predictive model described late in the 1950s by Zimmerman and Traxler.[28]

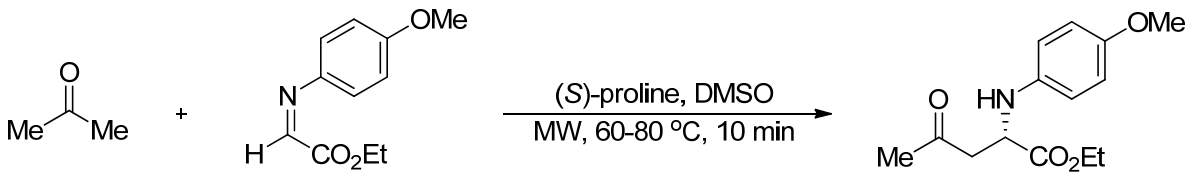
Additionally, the aldol condensation product can be dehydrated to form an α-β unsaturated carbonyl though an E1cB elimination.[29] Non-nucleophilic basic conditions are typically employed to facilitate the E1cB elimination. One particular example by Feuillet *et al.* describes the elimination of β-hydroxy ketones forming the *E* product in greater than 90% de.[30]



Scheme 1.3. Stereoselective elimination discovered by Feuillet *et al.*

An aldol condensation/elimination reaction has been recently reported between aryl aldehydes and oxindoles using a catalytic amount of piperidine.[31] However, this particular method required long reaction times in reflux and demonstrated difficulty accessing electron-poor aldehydes.

[26] Claisen, L.; Claparede, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14* (1), 2460-2468.
[27] Schmidt, J.G. *Ber. Dtsch. Chem. Ges.* **1881**, *14* (1), 1459-1461.
[28] Zimmerman, H.E.; Traxler, M.D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.
[29] Zhang, Y.; Wang, M.G.; Liang, J.; Shang, Z.C. *Lett. Org. Chem.* **2010**, *7* (1), 27-31.
[30] Feuillet, F.J.P.; Cheeseman, M.; Mahon, M.F.; Bull, S.D. *Org. Biomol. Chem.* **2005**, *3*, 2976-2989.
[31] Ribeiro, C.J.A.; Amaral, J.D.; Rodrigues, C.M.P.; Moreira, R.; Santos, M.M.M. *Bioorg. Med. Chem.* **2014**, *22* (1), 577-584.



Scheme 1.4. Organocatalytic experiments using microwave irradiation to substantially reduce reaction times conducted by Kappe *et al.*

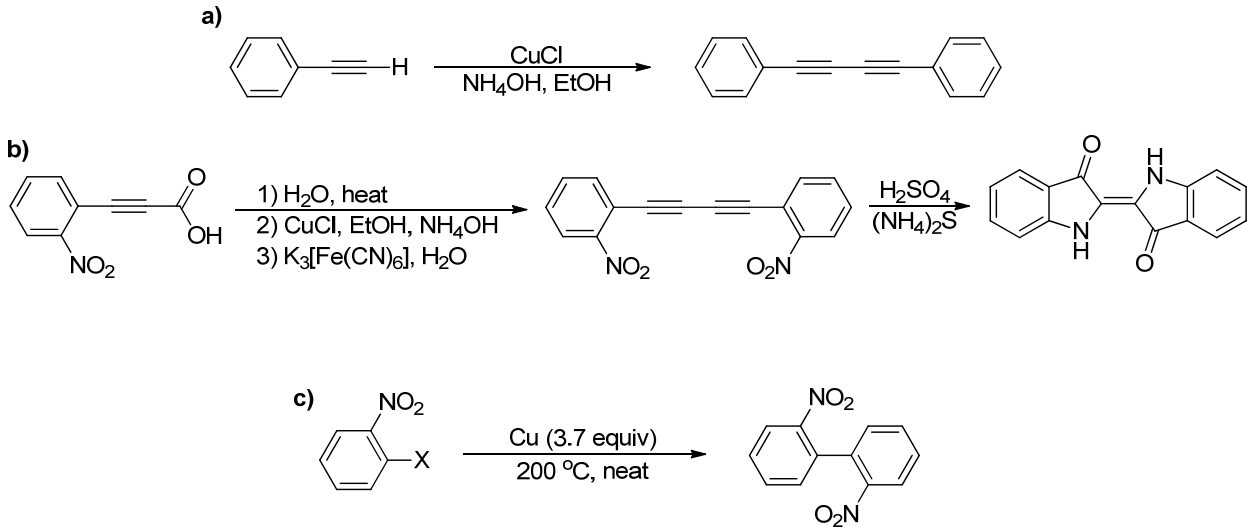
Microwave-assisted aldol condensations have already been shown to be superior to those performed with conventional heating. An example by Kappe *et al.* substantially reduced the reaction time from two hours to ten minutes of a previously reported (*S*)-proline catalyzed aldol condensation.[32,33] However, microwave-assisted aldol condensation and dehydration reactions have not received much attention in the scientific community, and are thus explored in detail in this thesis.

1.2.2 Palladium Catalyzed Cross-Coupling Reactions

1.2.2.1 Introduction and History

Another theme that appears throughout the present thesis involves the use of organopalladium cross-coupling chemistry. Cross-coupling reactions are defined by a bond formation between two different substrates involving metal catalysis.[34] The earliest examples of coupling reactions were homocouplings, or metal-catalyzed coupling between the same substrate, such as the Glaser coupling,[35] Baeyer's synthesis of indigo,[36] and the Ullmann reaction[37] (scheme 7 a, b, and c, respectively).

[32] Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, O.C. *J. Org. Chem.* **2007**, *72*, 1417-1424.
[33] Cordova, A.; Notz, W.; Zhong, G. F.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842.
[34] Johansson Seechurn, C.C.C.; Kitching, M.O.; Colacot, T.J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.
[35] Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422-424.
[36] Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 50-56.
[37] Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174-2185.



Scheme 1.5. Homocoupling schematics of the Glaser coupling (a), Baeyer indigo synthesis (b), and Ullman coupling (c).

Following the pioneering work of homocoupling reactions, many variations of cross-coupling reactions using palladium have emerged including the Nobel prize winning work of Heck, Negishi, and Suzuki. These palladium-catalyzed cross-coupling reactions typically involve an aryl halide, an activated nucleophile, and a catalyst (often requiring a base). For instance, the Heck reaction (figure 1.6d), first described in 1972 following the work of Mizoroki, involves the coupling between vinylic halides and alkenes using $Pd(OAc)_2$ and Bu_3N.[38]

[38] Heck, R.F.; Nolley, J.P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

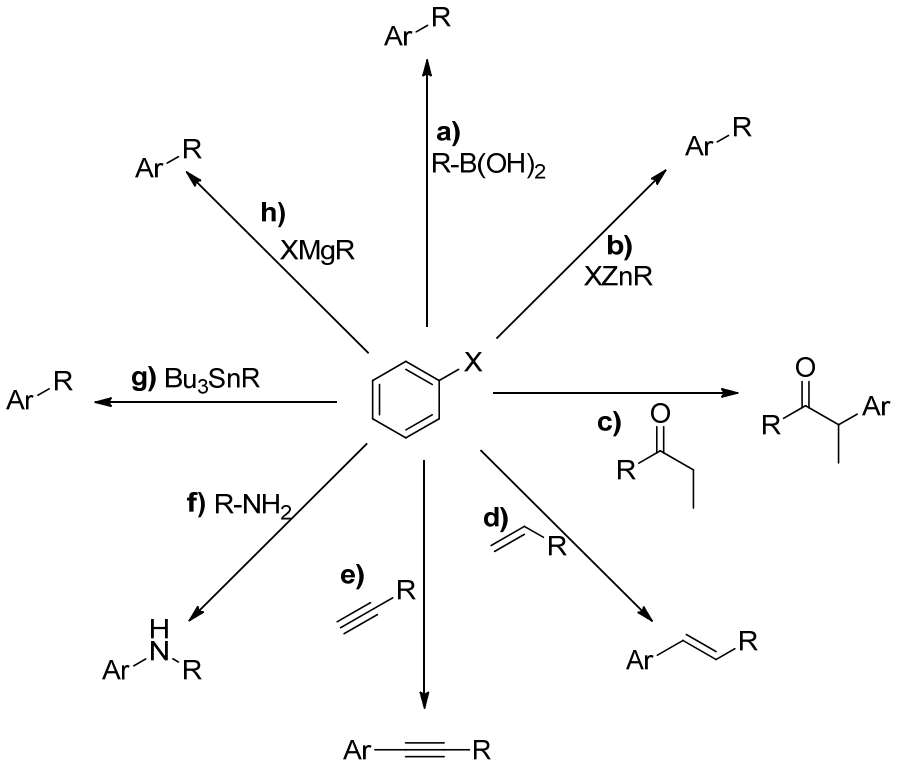


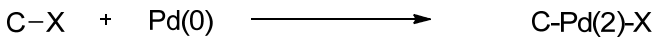
Figure 1.6. Overview of common palladium-catalyzed cross-coupling reactions. a) Suzuki, b) Negishi, c) α-arylation, d) Heck, e) Sonogashira, f) Buchwald amination, g) Stille, h) Kumada.

Other prominent examples of cross-coupling reactions with aryl or vinylic halides (or pseudo-halides) include the Suzuki-Miyaura coupling (using boronic acids),[39] Sonogashira (using terminal alkynes),[40] Stille (using tin-derivatives of carbon nucleophiles),[41] α-arylation of enolates (using asymmetrical ketones),[42] Buchwald amination (involving primary or secondary amines),[43] Negishi (using zinc-derivatives of carbon nucleophiles),[44] and Kumada reactions (using magnesium-derivatives of carbon nucleophiles).[45]

[39] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95* (7), 2457-2483.
[40] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tet. Lett.* **1975**, *16* (50), 4467-4470.
[41] Stille, J.K. *Angew. Chem. Int. Ed.* **1986**, *25* (6), 508-524.
[42] Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57* (1), 242-246.
[43] Surry, D.S.; Buchwald, S.L. *Chem. Sci.* **2011**, *2*, 27-50.
[44] Negishi, E. *Acc. Chem. Res.* **1982**, *15* (11), 340-348.
[45] Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94* (12), 4374-4376.

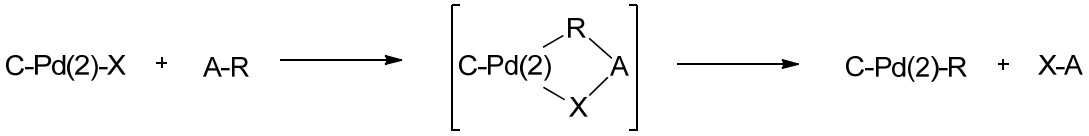
1.2.2.2 Mechanistic Overview and Phosphine ligands

Palladium-catalyzed cross-coupling reactions are made possible by the ability of palladium to interconvert between the +2 and 0 oxidation states. While different cross-coupling reactions employ their own unique mechanisms, in general palladium-catalyzed cross-coupling reactions typically employ the same common three steps: 1) oxidative addition, 2) transmetallation, and 3) reductive elimination.[46] During the oxidative addition step, the palladium source facilitates homeolytic cleavage of the C-X bond (where X typically = I, OTf, Br, Cl) with concomitant oxidation of the palladium source from 0 to +2. The rate of oxidative addition typically follows the trend of faster rates with decreasing bond energy, that is C-I > C-OTf > C-Br >> C-Cl >>> C-F.[47]



Scheme 1.6. General oxidative addition step in palladium-catalyzed cross-coupling reactions.

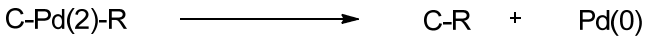
Following the oxidative addition step, the transmetallation step occurs where the C-Pd(2)-X complex exchanges the X group for the activated nucleophile of the coupling species (ie boronic acid, hydride, and main group metals).



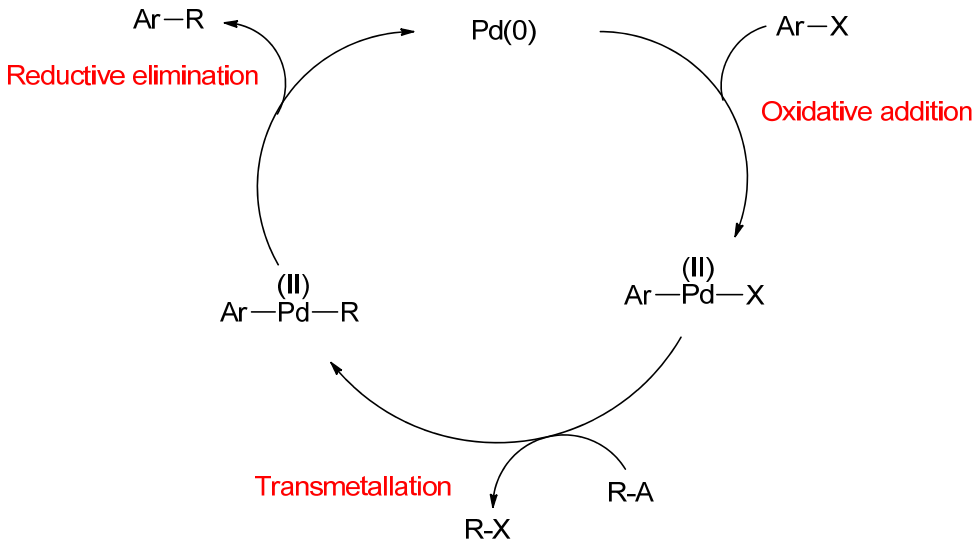
Scheme 1.7. General transmetallation step, where A = activated nucleophile.

Finally, reductive elimination occurs where the C-Pd(2)-R complex effectively decomposes forming a new C-R bond and regenerates Pd(0) which can return to the catalytic cycle for a new substrate.

[46] Chen, X.; Engle, K.M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**. *48* (28), 5094-5115.
[47] Kirchhoff, J.H.; Dai, C.; Fu, G.C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945-1947.



Scheme 1.8. General reductive elimination step producing the desired product and regenerating Pd(0)



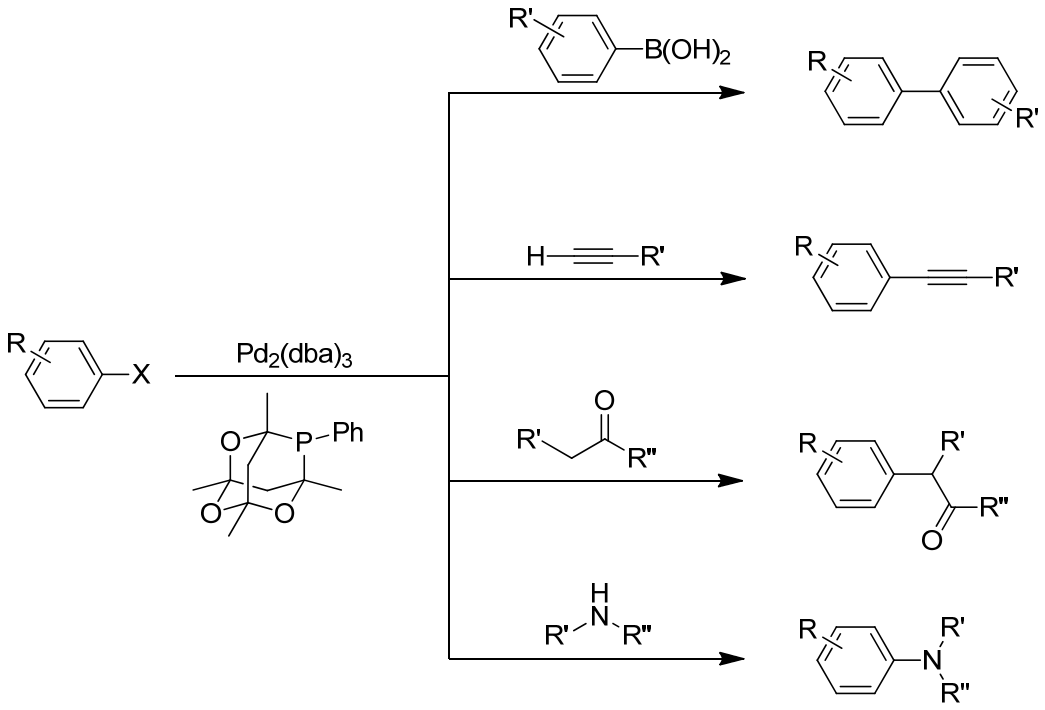
Scheme 1.9. General catalytic cycle schematic of palladium-catalyzed cross-coupling reactions.

The choice of ligand for the Pd(0) complex is instrumental to the success of cross-coupling reactions. Phosphine ligands have received a wealth of attention due to their ability to act as σ donors/π acceptors, which adds an appreciable degree of stability to the metal-phosphine complex, in addition to many other factors which make phosphines ideal ligands for organometallic catalysis. Phosphine ligands useful for Pd catalyzed cross-coupling chemistry typically have two things in common: they are electron-rich and sterically bulky which enhances the rate of oxidative addition and reductive elimination, respectively.[48]

The Capretta group has been interested in palladium-phosphine catalysis for many years and has developed a series of 1,3,5,7-tetramethyl-2,4,8-trioxo-6-phosphaadamantane (PA) ligands. When derivatized and used with a palladium source, the resultant catalytic system is

[48] Martin, R.; Buchwald, S.L. *Acc. Chem. Res.* **2008**, *41* (11), 1461-1473.

capable of enabling a number of cross-coupling reactions including Suzuki,[49] Sonogashira and σ-arylation of ketones,[50] and aminations.[51]



Scheme 1.10. Summary of cross-coupling reactions completed by the Capretta group using the PA-Ph ligand.

Following the discovery of the use of the PA-Ph ligand with $Pd_2(dba)_3$ for aryl-aryl cross-coupling reactions, the Capretta group attempted to employ this same system in the cross-coupling of alkyl halides and alkyl boranes without success due to limited reactivity and/or β-hydride elimination reactions being favoured over the coupling product. In an attempt to uncover the "one-size-fits-all" ligand, the Capretta group then synthesized a library of PA-Ph ligands in order to determine which properties facilitate alkyl couplings.[52]

[49] Adjabeng, G.; Brenstrum, T.; Wilson, J.; Frampton, C.S.; Robertson, A.J.; Hillhouse, J.; McNulty, J.; Capretta, A. *Org. Lett.* **2003**, *5* (6), 953-955.
[50] Adjabeng, G.; Brenstrum, T.; Frampton, C.S.; Robertson, A.J.; Hillhouse, J.; McNulty, K.; Capretta, A. *J. Org. Chem.* **2004**, *69* (15), 5082-5086.
[51] Gerristma, D.; Brenstrum, T.; McNulty, J.; Capretta, A. *Tet. Lett.* **2004**, *45* (45), 8319-8321.
[52] Brenstrum, T.; Gerristma, D.A.; Adjabeng, G.M.; Frampton, C.S.; Britten, J. Robertson, A.J.; McNulty, J.; Capretta, A.; *J. Org. Chem.* **2004**, *69*, 7635-7639.

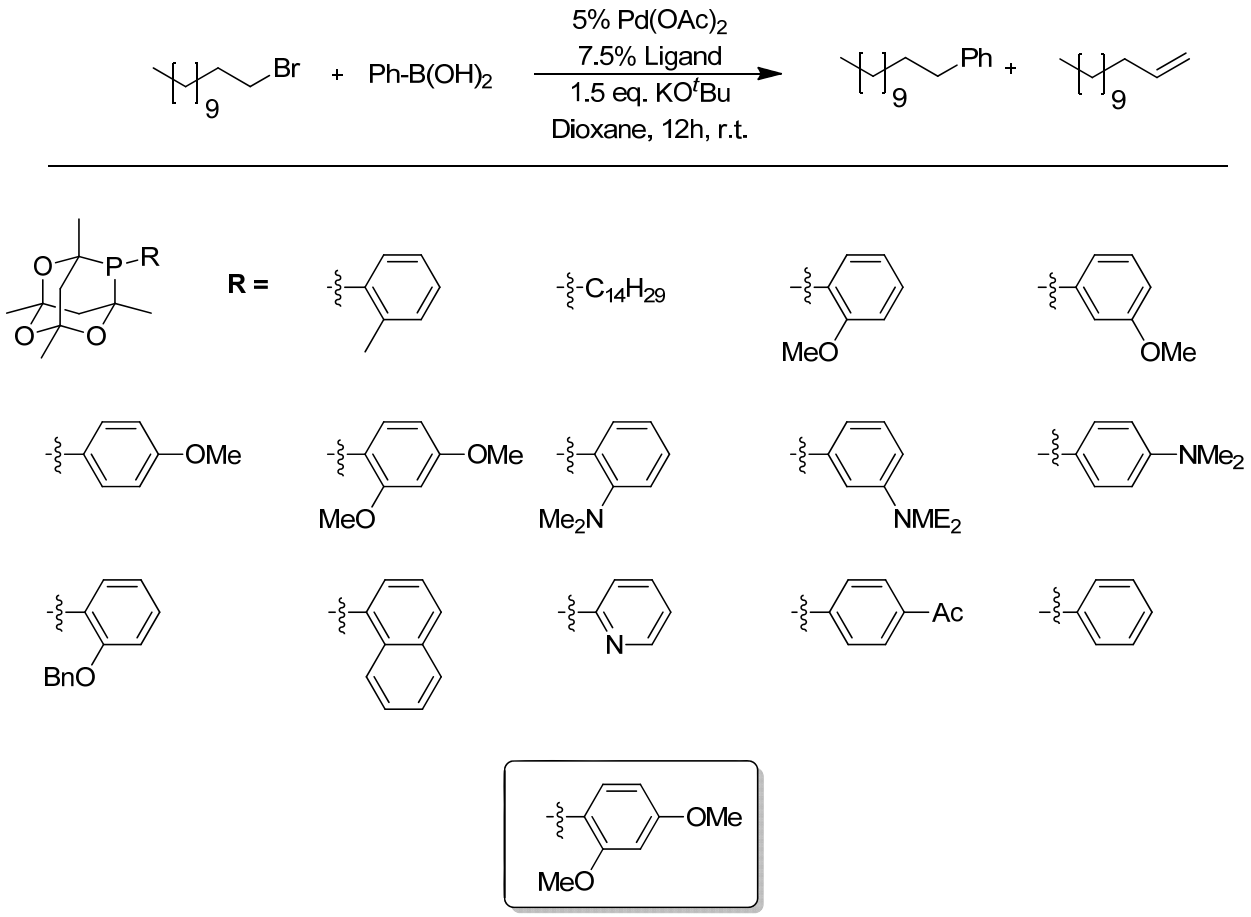


Figure 1.7. Library screen of PA-Ph ligands in efforts to find the "one-size-fits-all" ligand completed by the Capretta group.

The 2,4-dimethoxyphenyl ligand appeared to be the best ligand as it resulted in significantly higher conversion to the coupled product (96%) than any of the other ligands while at the same time minimizing the degree of β-hydride elimination (4%). While the aforementioned catalyst system has proven potential between simple phenyl and alkyl systems, little work has been done in the realm of heterocyclic cross-coupling.

1.3 Antibiotic Resistance

Combined, the use of microwave-assisted chemistry and organopalladium cross-coupling chemistry form the bulk of the chemical techniques used to generate targeted chemical libraries

in this thesis. The lead molecules identified play a role in curbing antibiotic resistance. This topic is explored below.

1.3.1 History and Discovery of Antibiotics

A serendipitous discovery by Alexander Fleming in 1928 pioneered the era of antibiotics.[53] Fleming noticed a contaminating *Penicillium* fungus had significantly reduced the size of staphylococcal colonies on his petri plates. Following this observation, Fleming discovered that *Penicillium* fungus was producing the antimicrobial penicillin which was responsible for the bactericidal activity. While Fleming was credited with the discovery of penicillin, it was Howard Florey and Ernest Chain who later developed methods to mass produce penicillin for clinical use.[54]

Another important contributor to the era of antibiotic discovery was Selman Waksman who was credited with the discovery of streptomycin, the first aminoglycoside antibiotic, along with at least fifteen other antibiotics found in organisms that live in soil.[55] Selman employed methods inspired by Fleming where he tested microbial isolates from soil for bactericidal activity on petri dishes.

While the years between 1945 and 1970 would see the discovery of more than twenty classes of antibiotics,[56] the discovery of new antibiotics plateaued shortly thereafter. The majority of the previously discovered antibiotics were complex natural products isolated from various organisms and as a result, synthetic chemistry techniques were very limited in the

[53] Fleming, A. *Br. J. Exp. Pathol.* **1929**, *10*, 226-236.
[54] Ligon, B.L. *Semin. Pediatr. Infect. Dis.* **2004**, *15*, 109-114.
[55] Lewis, K. *Nat. Rev. Drug. Discov.* **2013**, *12*, 371-387.
[56] Coates, A.R.; Halls, G.; Hu, Y. *Br. J. Pharmacol.* **2011**, *163*, 184-194.

modifications that could be performed on existing scaffolds. The need for new antibiotics, however, began to grow significantly with the rise of antibiotic resistant organisms.

1.3.2 Antibiotic Resistance and Treatment Strategies

Surprisingly, Fleming noticed the ability of bacteria to survive penicillin treatment and develop resistance early on. In fact, he even cited that it was easy to produce penicillin-resistant bacteria when treating the culture with an insufficiently lethal concentration of penicillin.[57] However, this cautionary statement did not resonate with the scientific community. Antibiotics were widely and, some would argue, carelessly used in the clinic and agriculture. For example, livestock, feed, and soil, are often systematically loaded non-specifically with broad-spectrum antibiotics.[58] In the clinic, antibiotics were largely prescribed for viral infections. A particularly alarming recent study illustrates the gross misuse of antibiotics in China, where approximately 75% of patients with seasonal influenza were prescribed antibiotics, 80% for inpatients, and around 97% of surgical patients.[59] The discovery of new antibiotics is also slowed by tighter regulations surrounding clinical trials, higher competition when acquiring funding, and increased financial risk.[60] Such widespread misuse of antibiotics coupled with the hindered discovery process of new treatments has led to the development of large populations of multidrug-resistant (MDR) bacteria. Approximately 25,000 people die each year in Europe as a result of MDR bacteria with an annual bill of €1.5 billion.[61] In the United States, approximately 2 million people

[57] Fleming, A. *Nobel Lecture.* December 11, **1945.**
[58] Misato, T.; Ko, K.; Yamaguchi, I. *Adv. Appl. Microbiol.* **1977**, *21*, 53-83.
[59] Li, Y. *BMJ.* **2014,** *348*, 1083.
[60] Harbarth, S.; Theuretzbacher, U.; Hackett, J. *Antimicrob. Chemother.* **2015**, *70*, 1604-1607.
[61] Walker, D.; Fowler, T. *Annual Report of the Chief Medical Officer: Volume Two*, 2011: Infections and the Rise of Antimicrobial Resistance (Department of Health, 2011).

each year are infected with MDR bacteria with approximately 23,000 deaths.[62] Needless to say, MDR bacteria pose a substantial hurdle to modern medicine.

Antibiotic resistance can be intrinsic and/or acquired, with widely varying mechanisms of action. Intrinsic resistance is defined by mechanisms the wildtype bacteria already have in place to defend against toxins, such as selectively permeable membranes and efflux pumps, that are independent of selective pressure due to the presence of an antibiotic.[63] On the other hand, acquired resistance is a direct result of selective pressure which involves mechanisms such as horizontal gene transfer and *de novo* chromosomal mutations.[64] One of the more common mechanisms of resistance in MDR bacteria is mutations resulting in upregulation of low-specificity efflux transport proteins such as the resistance nodulation division efflux pumps.[65]

Bacteria can also acquire resistance through mutations that result in conformational change at the binding site of the antibiotic target (figure 1.8), thus reducing the antibiotic's efficacy. Point mutations in the gene encoding the antibiotic target can be sufficient to cause a significant conformational change.[66]

[62] Hampton, T. *JAMA*, **2013**, *310*, 1661–1663.
[63] Blair, J.M.A.; Webber, M.A.; Baylay, A.J.; Ogbolu, D.O.; Piddock, L.J.V. *Nat. Rev.* **2015**, *13*, 42-51.
[64] Drake, J.W.; Charlesworth, B.; Charlesworth, D.; Crow, J.F. *Genetics*, **1998**, *148*, 1667-1686.
[65] Piddock, L.J.V. *Nat. Rev. Microbiol.* **2006**, *4*, 629-636.
[66] Billal, D.S.; Feng, J.; Leprohon, P.; Legare, D; Ouellette, M. *BMC Genomics,* **2011**, *12*, 512-521.

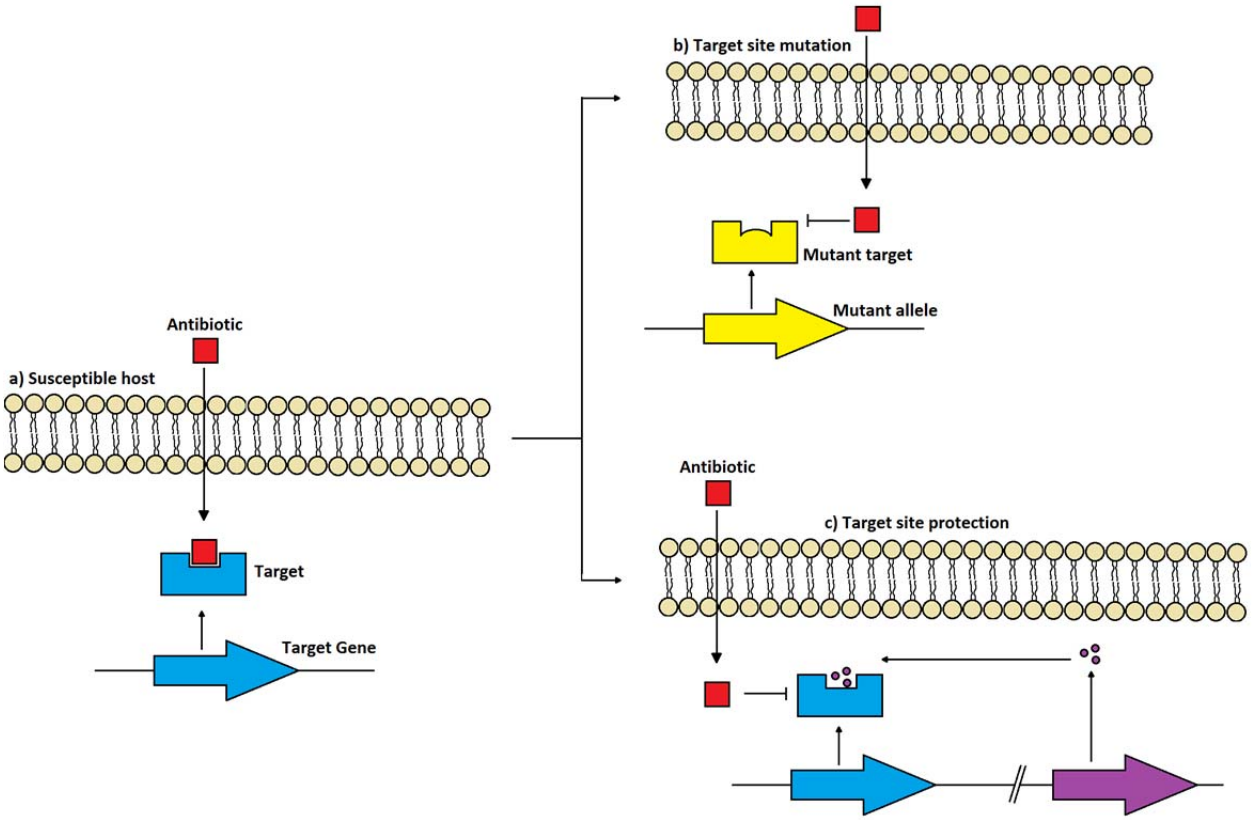


Figure 1.8. Effects of target site changes. a) Susceptible host takes up antibiotic which binds tightly to target providing the inhibitory effect. b) Conformation change occurs at the target site due to mutation in the target gene resulting in poor inhibition. c) Wildtype target is chemically modified preventing antibiotic binding. (Blair *et al.*)

The wildtype target site can also be modified by means other than conformational change. For instance, it was recently discovered that the erythromycin ribosome methylase family of genes can methylate 16S rRNA and alter the antibiotic target site preventing entire classes of antibiotics from binding including macrolides, lincosamines, and streptogrammins.[67]

Another major method underlying bacterial resistance is chemical inactivation of the antibiotic by hydrolysis or addition of chemical groups (figure 1.9). Shortly after the discovery of penicillin and the discovery of penicillin resistance, Chain and Abraham discovered

[67] Kumar, N.; Radhakrishnan, A.; Wright, C.C; Chou, T.-H.; Lei, H.-T.; Bolla, J.R.; Tringides, M.L.; Rajashankar, K.R.; Su, C.-C.; Purdy, G.E.; Yu, E.W. *Protein Sci.* **2014**, *23*, 423-432.

penicillinase, an enzyme of the β-lactamase family capable of hydrolyzing β-lactam antibiotics.[68] In this case, the susceptible bacteria have acquired a gene to encode a new enzyme with the purpose of inactivating antibiotics. The complexity of β-lactamases has also greatly evolved over the years of antibiotic misuse resulting in the development of extended-spectrum β-lactamases which are capable of hydrolyzing newer classes of synthetic antibiotics.[69]

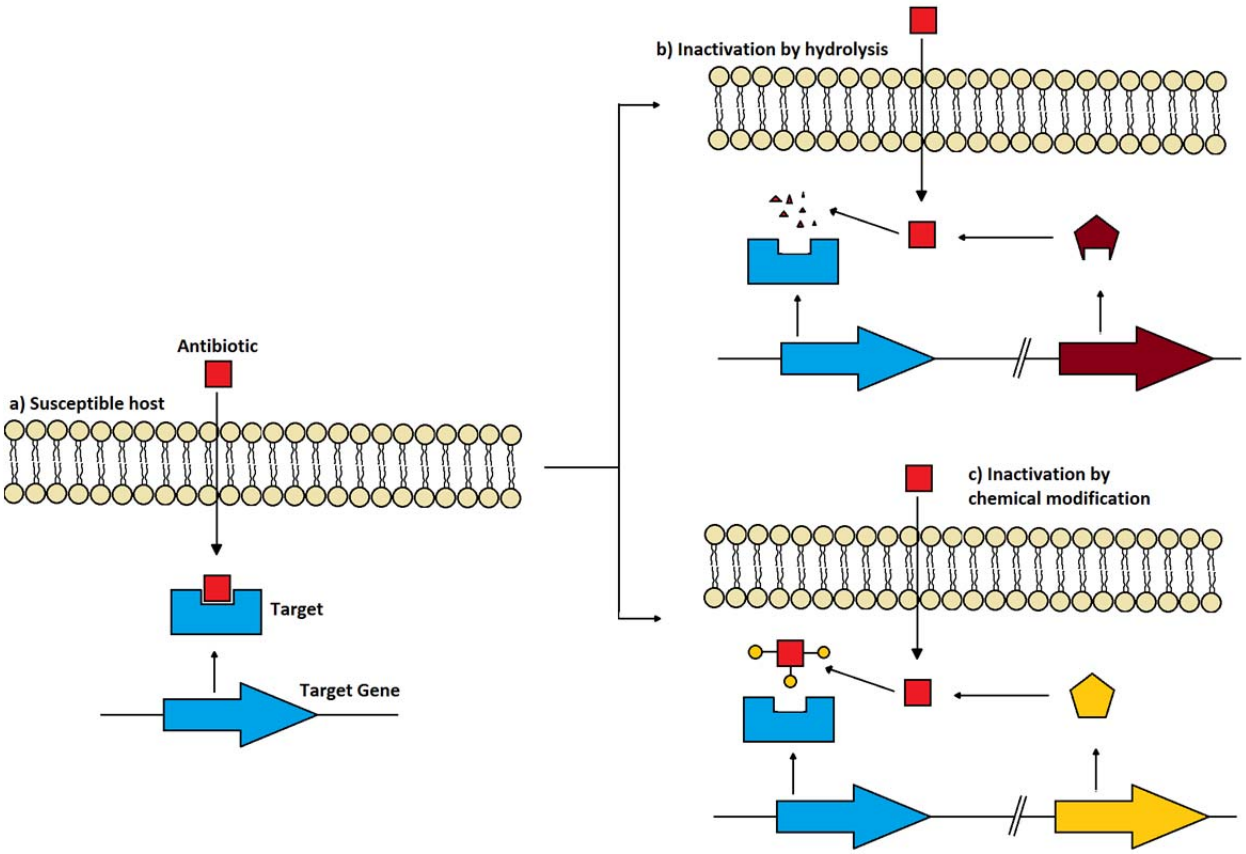


Figure 1.9. Effects of antibiotic modifications. a) Susceptible host takes up antibiotic which binds tightly to target providing the inhibitory effect. b) Gene for a new hydrolase enzyme is acquired and expressed which destroys the incoming antibiotic. c) Gene for an enzyme that modifies the existing antibiotic structure is acquired which inactivates the incoming antibiotic by steric hindrance. (Blair *et al.*)

Chemical modification and inactivation are also commonly seen. The addition of chemical groups such as acyl, phosphate, nucleotidyl, and ribitoyl groups significantly affect the

[68] Abraham, E.P.; Chain, E. *Rev. Infect. Dis.* **1940**, *10*, 677-678.
[69] Johnson, A.P.; Woodford, N. *J. Med. Microbiol.***2013**, *62*, 499–513.

ability of the antibiotic to bind to its target site through steric hindrance.[70] Rifamycins and aminoglycosides are particularly susceptible to this form of inactivation due to the presence of many nucleophilic moieties. Needless to say, resistance due to enzymatic chemical inactivation presents a significant problem with respect to resistance to aminoglycoside antibiotics.

Currently, the best line of defense against most antibiotic-resistant bacteria is selecting an antibiotic to which the particular bacteria are sensitive. However, the diminishing antibiotic pipeline is significantly limiting options.[71] Antibiotic adjuvants have been proven to substantially increase the potency of antibiotics towards antibiotic-resistant bacteria. One of the most prominent examples of antibiotic adjuvants is clavulanic acid which inhibits a wide range of β-lactamases and restores potency to amoxicillin.[72] Similar inhibitors of β-lactamases have been identified and widely studied following the discovery of clavulanic acid, in addition to a number of efflux pump inhibitors, outer membrane permeabilizers, inhibitors of biofilm production, quorum-sensing inhibitors, and antivirulence drugs.[73]

1.3.3 Aminoglycoside Antibiotics and Resistance

Aminoglycoside antibiotics are a particularly interesting class of antibiotics as they are oligosaccharide-based. Some of the most important aminoglycoside antibiotics include kanamycin A, gentamicin, paromomycin, and streptomycin.

[70] Wright, G. D. *Adv. Drug Delivery Rev.* **2005**, *57*, 1451–1470.
[71] Spellberg, B.; Guidos, R.; Gilbert, D.; Bradley, J.; Boucher, H.W.; Scheld, W.M.; Bartlett, J.G.; Edwards Jr., J. *Clin. Infect. Dis.* **2008**, *46*, 155-164.
[72] Reading, C.; Cole, M. *Antimicrob. Agents Chemother.* **1977**, *11* (5), 852-857.
[73] Gill, E.E.; Franco, O.L.; Hancock, R.E.W. *Chem. Biol. Drug Des.* **2015**, *85* (1), 56-78.

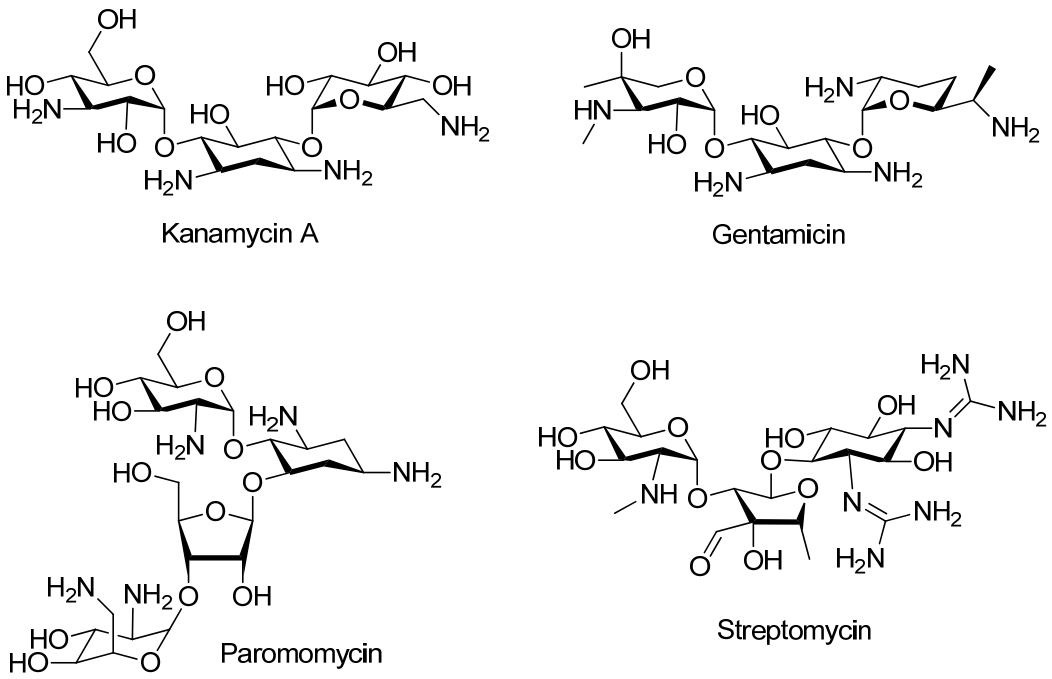


Figure 1.10. Common aminoglycoside antibiotics.

Many aminoglycoside antibiotics are currently on the World Health Organization's List of Essential Medicines.[74] Aminoglycoside antibiotics are typically used in treatment of aerobic, Gram-negative bacilli,[75] but have demonstrated use in a variety of other infections due to their wide spectrum of activity.[76] The bactericidal mechanism of action of aminoglycosides typically involves interfering with protein synthesis, primarily by binding to the A-site on the 16S rRNA portion of the ribosome allowing non-cognate aminoacyl-tRNAs to bind.[77] Resistance towards aminoglycosides is typically a result of enzymatic inactivation by acetyltransferases (AAC), nucleotidylltransferases (ANT) and phosphotransferases (APH).[78]

[74] WHO Model List of Essential Medicines. *World Health Organization*, **2013**.
[75] Jagielski, T.; Ignatowska, H.; Bakuła, Z.; Dziewit, Ł.; Napiórkowska, A.; Augustynowicz-Kopeć, E.; Zwolska, Z.; Bielecki, J. *PLoS One*. **2014**, *9*, e100078.
[76] Ramirez, M.S.; Tolmasky, M.E. *Drug. Res. Update,* **2010**, *13*, 151-171.
[77] Demeshkina, N.; Jenner, L.; Westhof, E.; Yusupov, M.; Yusupova, G. *Nature*, **2012**, *484*, 256-259.
[78] Shaw, K.J.; Rather, P.N.; Hare, R.S.; Miller, G.H. *Microbiol. Rev.* **1993**, *57* (1), 138-163.

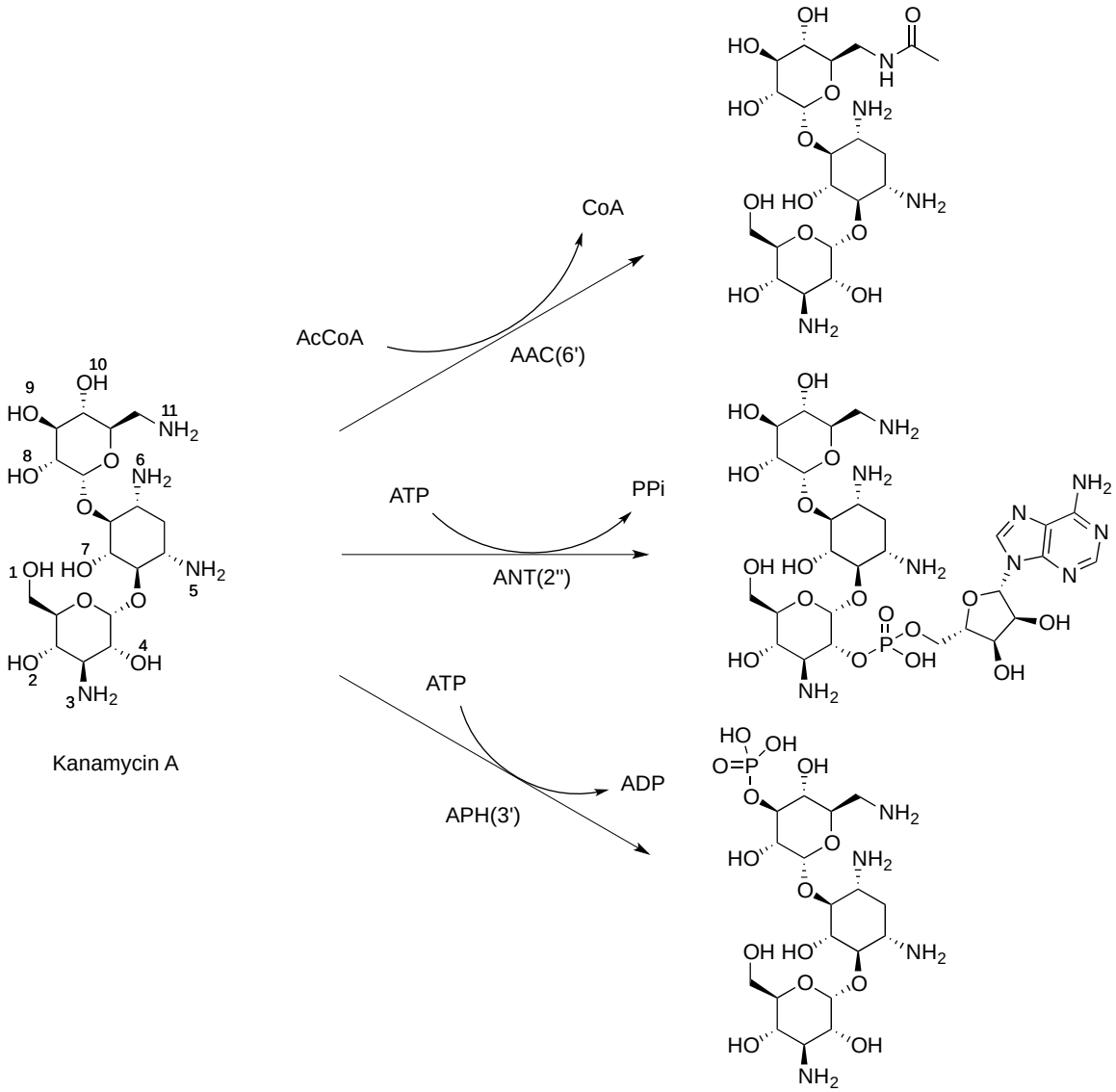


Figure 1.11. Enzymatic inactivation of Kanamycin A by addition of an acetyl group, an AMP moiety, and a phosphate group (Shaw *et al.*).

A limited number of antibiotic/adjuvant approaches have been taken with success to combat the aforementioned resistance enzymes. One lab was able to successfully kill off resistant colonies of *A. baumannii*, *E. cloacae*, and *K. pneumoniae* using a combination of Zn^{2+} ions with amikacin. However, the concentrations of Zn^{2+} required do not translate effectively to physiological proportions, and the mechanism of inactivating the resistance enzymes could not

be determined.[79] Another lab has made a series of aminoglycosides modified with sulfone- and sulfoxide-CoA motif which demonstrated inhibitory action against AAC(6')-Ii.[80]

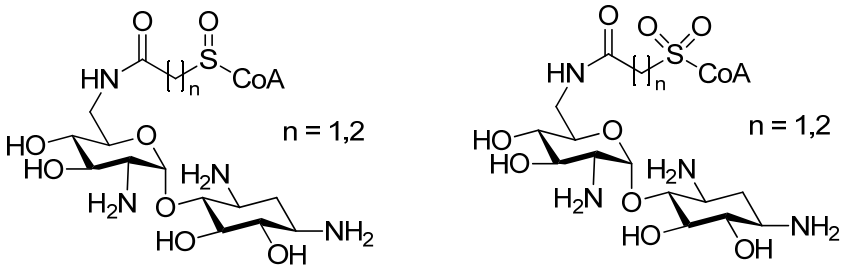


Figure 1.12. Sulfone- and sulfoxide-CoA analogues of aminoglycosides that exhibit inhibitory action against AAC(6')-Ii by Gao *et al.*

However, these substances are quite difficult and expensive to synthesize rendering them unfavourable for progress into clinical use. Thankfully, studies are now focusing towards small molecule inhibitors of aminoglycoside resistance enzymes. A recent study by Stogios *et al.* discovered that three scaffolds (anthrapyrazolone, 4-anilinoquinazoline, and pyrazolopyrimidine) from known eukaryotic protein kinase inhibitor libraries demonstrated the ability to reverse aminoglycoside resistance in a resistant *E. coli* strain by attenuating APH(3')-Ia.[81] This finding was not only important in that it was one of the earlier studies that showed the capability of easy-to-access small molecules to inhibit aminoglycoside resistance enzymes, but it also provided a direction into which chemical libraries could be used for future HTS experiments, namely protein kinase inhibitor libraries.

[79] Li, Y.; Green, K.D.; Johnson, B.R.; Garneau-Tsodikova, S. *Antimicrob. Agents Chemother.* **2015**, *59* (7), 4148-4156.
[80] Gao, F.; Yan, X.; Zahr, O.; Larsen, A.; Vong, K.; Auclair, K. *Bioorg. Med. Chem. Lett.* **2008**, *18* (20), 5518-5522.
[81] Stogios, P.J.; Spanogiannopoulos, P.; Evdokimova, E.; Egorova, O.; Shakya, T.; Todorovic, N.; Capretta, A.; Wright, G.D.; Savchenko, A. *Biochem. J.* **2013**, *454*, 191-200.

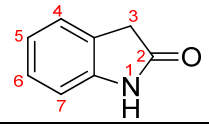
In fact, a major class of biologically-active small molecules known as oxindoles were identified as a common scaffold in the HTS screen that identified the lead molecules which provided the premise for this thesis.

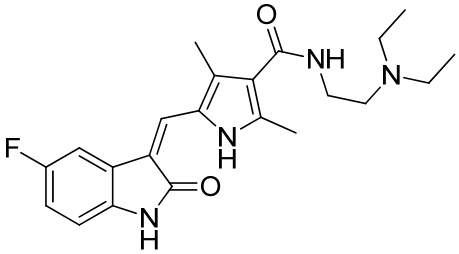
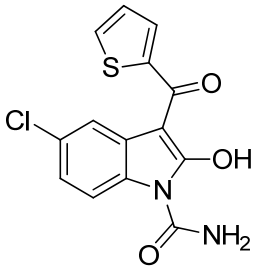
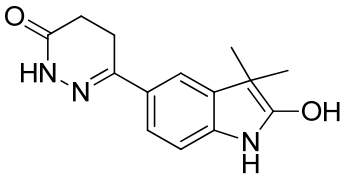
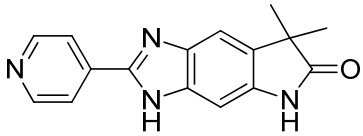
1.4. Oxindoles: Preceding Research and Importance

Oxindoles are an important class of molecules that have been extensively studied, with a review article being published as early as 1945.[82] Importantly, oxindole derivatives constitute many biologically active compounds including many pharmaceuticals currently on the market. Current uses for oxindole derivatives include anti-HIV agents, anti-cancer agents, anti-inflammatory agents, CVS agents, protein tyrosine kinase and serine/threonine inhibitors, sleep inducers, and anti-bacterial agents.[83]

[82] Sumpter, W. C. *Chem. Rev.* **1945**, *37* (3), 443-479.
[83] Rudrangi, S.R.S.; Bontha, V.K.; Manda, V.R.; Bethi, S. *Asian J. Research Chem.* **2010**, *4* (3), 335-338.

Table 1.2. Summary of current examples of biologically-active oxindole derivatives.



	Sunitinib Renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor.[84]
	Tenidap COX/5-LOX inhibitor and cytokine-modulating anti-inflammatory drug candidate rejected due to liver and kidney toxicity.[85]
	Indolidan Type IV cAMP Phosphodiesterase inhibitor drug candidate for congestive heart failure.[86]
	Adibendan Phosphodiesterase III inhibitor.[87]

Oxindoles bearing unsaturated substitutions at the 3-position are also well known CDK2 and GSK inhibitors.[88,89]

1.5 Quinazoline: Preceding Research and Importance

[84] Motzer, R.J.; Hutson, T.E.; Tomczak, P.; Michaelson, D.; Bukowski, R.M.; Rixie, O.; Oudard, S.; Negrier, S.; Szczylik, C.; Kim, S.T.; Chen, I.; Bycott, P.W.; Baum, C.M.; Figlin, R.A. *N. Engl. J. Med.* **2007**, *356*, 115-124.
[85] Kirchner, T.; Argentieri, D.C.; Barbone, A.G.; Singer, M.; Steber, M.; Ansell, J.; Beers, S.A.; Wachter, M.P.; Wu, W.; Malloy, E.; Stewart, A.; Ritchie, D.M. *J. Pharmacol. Exp. Ther.* **1997**, *282* (2), 1094-1101.
[86] Kauffman, R.F.; Robertson, D.W.; Franklin, R.B.; Sandusky Jr, G.E.; Dies, F.; McNay, J.L.; Hayes, Scott. *Cardiovasc. Drug Rev.* **1990**, *8* (4), 303-322.
[87] Dorszewski, A.; Muller-Beckmann, B.; Kling, L.; Sponer, G.; *Br. J. Pharmacol.* **1990**, *101* (3), 686-690.
[88] Bramson, H.N.; Corona, J.; Davis, S.T.; Dickerson, S.H.; Edelstein, M.; Frye, S.V.; Gampe Jr, R.T.; Harris, P.A.; Hassell, A.; Holmes, W.D.; Hunter, R.N.; Lackey, K.E.; Lovejoy, B.; Luzzio, M.J.; Montana, V.; Rocque, W.J.; Rusnak, D.; Shewchuk, L.; Veal, J.M.; Walker, D.H.; Kuyper, L.F. *J. Med. Chem.* **2001**, *44* (25), 4339-4358.
[89] Dranchak, P.; MacArthur, R.; Guha, R.; Zuercher, W.J.; Drewry, D.H.; Auld, D.S.; Inglese, J. *PLoS One*, **2013**, *8* (3), e57888.

Quinazolines are most prominently known in the recent literature as tyrosine kinase inhibitors used for the treatment of numerous cancers, particularly the 4-anilinoquinazoline due to its ability to inhibit epidermal growth factor receptors (EGFR) which has been filed in over 100 patents between 2007 and 2010. Note the presence of the 4-anilinoquinazoline scaffold present in the cancer drugs represented in table 1.3 – this particular feature is noted for binding to the ATP-binding pocket of EGFR with very high affinity.[90] The quinazoline scaffold is very robust and has been identified in earlier literature as purinic and folic acid metabolic pathway inhibitors[91] as well as antiparasite and antimicrobials[92] and antivirals.[93]

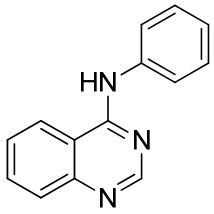
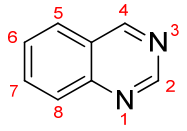


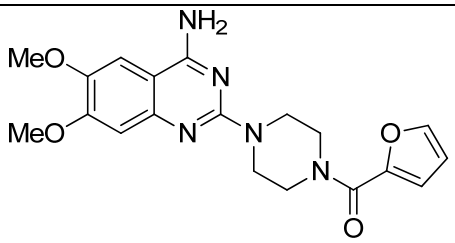
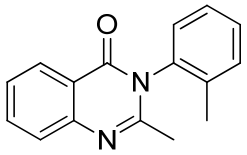
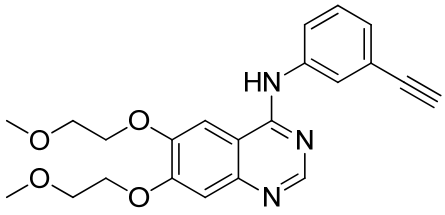
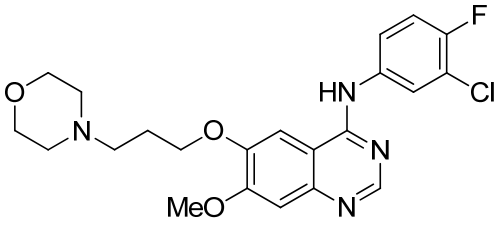
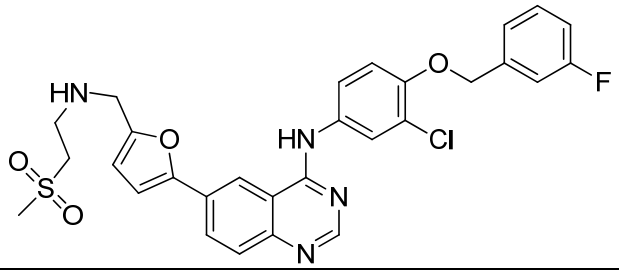
Figure 1.13. Structure of the 4-anilinoquinazoline common in recent cancer drugs.

Many pharmaceuticals based off the quinazoline scaffold are currently on the market including Prazosin, Metaqualone, Metolazone, Erlotinib, Gefitinib, Vandetanib, and Lapatinib.

[90] Marzaro, G.; Guiotto, A.; Chilin, A. *Expert Opin. Ther. Pat.* **2012**, *22* (3), 223-252.
[91] Skelton, L.A.; Ormerod, M.G.; Titley, J.; Kimbell, R.; Brunton, L.A.; Jackman, A.L. *Br. J. Cancer.* **1999**, *79* (11-12), 1692-1701.
[92] Cavalli, A.; Lizzi, F.; Bongarzone, S.; Belluti, F.; Piazzi, L.; Bolognesi, M.L. *Med. Microbiol. Immun.* **2010**, *58*, 51-60.
[93] Desai, N.C.; Undavia, N.K.; Trivedi, P.B.; Dave, D.; Vyas, G.D. *Indian J. Exp. Biol.* **1998**, *36*, 1280-1283.

Table 1.3. Current examples of pharmaceuticals based off the quinazoline scaffold.



	Prazosin High blood pressure, anxiety, and posttraumatic stress disorder.[94]
	Metaqualone Sedative, muscle relaxant, and treatment for insomnia.[95]
	Erlotinib Non-small cell lung cancer and pancreatic cancer treatment (EGFR inhibitor).[96]
	Gefitinib Breast and lung cancer treatment (EGFR inhibitor).[97]
	Lapatinib Breast cancer and solid tumour treatment (tyrosine kinase and EGFR inhibitor).[98]

[94] Bylund, D.B.; Blaxall, H.S.; Iversen, L.J.; Caron, M.G.; Lefkowitz, R.J.; Lomasney, J.W. *Mol. Pharmacol.* **1992**, *42*, 1-5.
[95] Kales, A.; Kales, J.D.; Scharf, M.B.; Tan, T.-L. *Arch. Gen. Psychiatry*. **1970**, *23* (3), 219-225.
[96] Raymond, E.; Faivre, S.; Armand, J.P. *Drugs*. **2012**, *60*, 15-23.
[97] Pao, W.; Miller, V.; Zakowski, M.; Doherty, J.; Politi, K.; Sarkaria, I.; Singh, B.; Heelan, R.; Rusch, V.; Fulton, L.; Mardis, E.; Kupfer, D.; Wilson, R.; Kris, M.; Varmus, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* (36), 13306-13311.
[98] Higa, G.M.; Abraham, J. *Expert Rev. Anticancer Ther.* **2014**, *7* (9), 1183-1192.

1.6 Objectives

Known GlaxoSmithKline libraries based off the oxindole scaffold (GSK-1) previously identified as inhibitors of cRAf1 kinase[99] were recently screened by Wright *et al.*[100] revealing inhibitory action against aminoglycoside acetyltransferase (AAC), nucleotidyltransferase (ANT), and phosphotransferase (APH) (figure 1.14); enzymes found in bacteria responsible for antibiotic resistance to aminoglycosides.

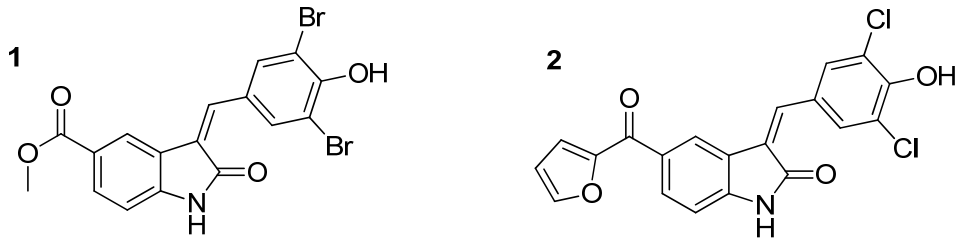


Figure 1.14. Lead molecules identified for inhibition against AAC, ANT, and APH. **1** was identified as an inhibitor of AAC(3)-Ia and **2** was identified as an inhibitor of APH(2")-IVa and ANT(2").

A similar GSK PKI library was also recently screened by Wright *et al.* (2015, unpublished results) which identified a substituted isoquinazoline based off the known drug Lapatinib, a treatment for breast cancer,[101] as a potent inhibitor of both APH(2")Id and ANT(2") (figure 1.15).

[99] Lackey, K.; Cory, M.; Davis, R.; Frye, S. V.; Harris, P. A.; Hunter, R. N.; Jung, D. K.; McDonald, O. B.; McNutt, R. W.; Peel, M. R.; Rutkowske, R. D.; Veal, J. M.; Wood, E. R. *Bioorg. Med. Chem. Lett*. **2000**, *10* (3), 223-226.
[100] Azad, M.A. (2015). *Reversing Antibiotic Resistance With Inhibitors of Bacterial Acetyltransferases*. McMaster University, Hamilton, Canada.
[101] Petrov, K. G.; Zhang, Y.-M.; Carter, M.; Cockerill, G. S.; Dickerson, S.; Gauthier, C. A.; Guo, Y.; Mook Jr, R. A.; Rusnak, D. W.; Walker, A. L.; Wood, E. R.; Lackey, K. E. *Bioorg. Med. Chem. Lett.* **2006**, *16* (17), 4686-4691.

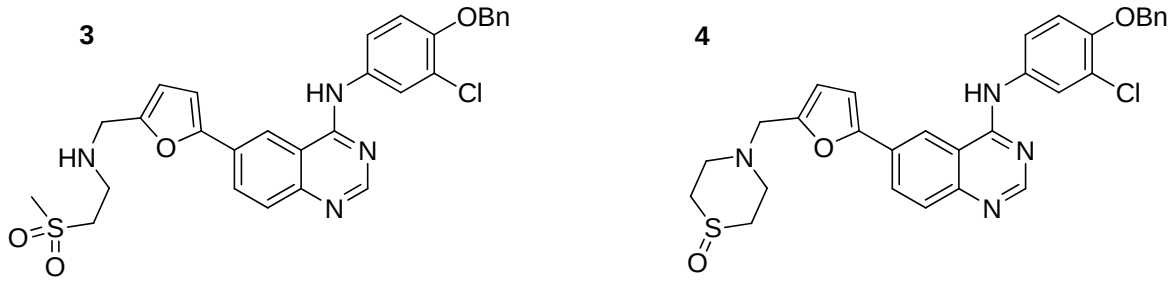


Figure 1.15. Inhibitors identified by Wright *et al.* for APH(2")Id and ANT(2") based on the GSK PKIS library.

Aminoglycoside-resistant bacteria express one or more of the aforementioned enzymes which are responsible for inactivating aminoglycoside drugs resulting in resistance. Inhibiting these enzymes can render the bacteria susceptible to treatment with aminoglycoside antibiotics when co-administered. Thus, a library based off the leads present in figures 1.14 and 1.15 will be synthesized in order to determine the pharmacophore in each case and gain insight into potential drug candidates. Additionally, efforts were made to expand the functionalization at the 5-position of the oxindole system through the use of Pd-catalyzed cross-coupling chemistry.

Chapter 2: Inhibitors of AAC(3)-Ia: Substitution at the 3- and 5-Position of the Oxindole

2.1 Inhibitors of AAC(3)-Ia as Antibiotic Adjuvants.

As discussed in the Introduction, enzymatic inactivation is one of the most predominant resistance mechanism used by bacteria against aminoglycosides. Among the aminoglycoside modifying enzymes (AMEs) are the aminoglycoside nucleotidyltransferases (ANTs), phosphotransferases (APHs), and acetyltransferases (AACs) with new AMEs continuously being reported. Inhibitors of AMEs could potentially find use as antibiotic adjuvants. Administration of the adjuvant would block the action of the AME thereby allowing the antibiotic to carry out its function.

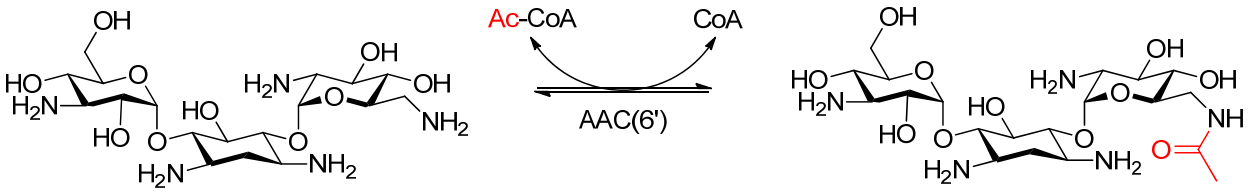


Figure 2.1. Enzymatic inactivation of Kanamycin B through the transfer of an acetyl group to the 6' amine.[102]

The AACs inactivate aminoglycosides by transferring an acetyl group from acetyl-coenzyme A (as is the case with AAC(6'), figure 2.1) to a free amine of the aminoglycoside. As part of a recent screening campaign aimed at finding inhibitors of aminoglycoside resistance enzymes, Marisa Azad in the Wright Lab[103] identified two oxindoles (compounds **1** and **2**, figure 2.2) capable of inhibiting AAC(3)-Ia with IC_{50} values of approximately 50 μM. With these initial hits in hand, the present chapter describes the development of synthetic methods aimed at

[102] Benveniste, R.; Davies, J. Biochemistry, 1971, 10 (10), 1787-1796.
[103] Azad, M.A. (2015). *Reversing Antibiotic Resistance With Inhibitors of Bacterial Acetyltransferases*. McMaster University, Hamilton, Canada.

generating libraries of functionalized oxindoles with an emphasis on diversity at positions 3 and 5.

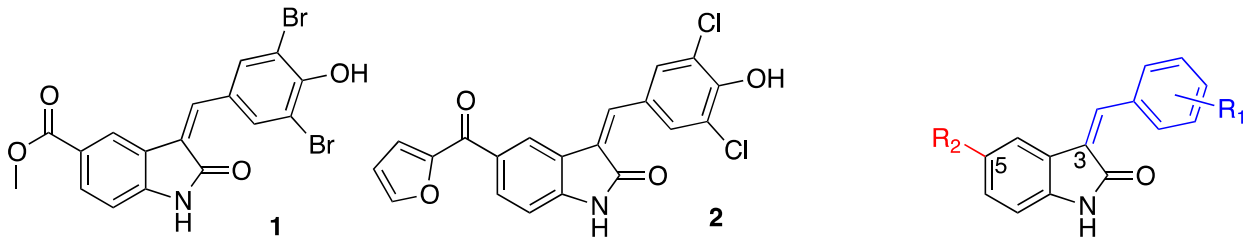


Figure 2.2. Lead compounds identified by Marisa Azad from the Wright Lab.

2.2 Novel Microwave Chemistry to Generate AAC(3)-Ia Inhibitors

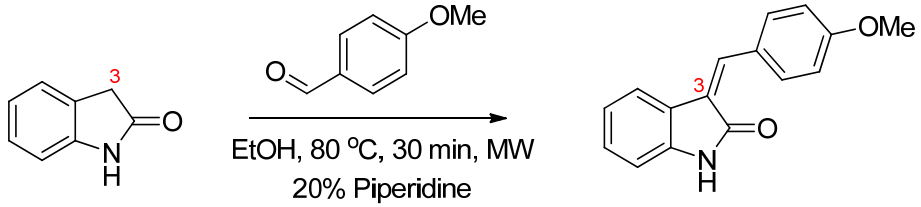
Lead molecules **1** and **2** possess a styrenyl moiety at the 3-position that is likely installed *via* an aldol condensation/dehydration reaction. A review of the literature revealed that strategies for generating unsaturated aldol condensation products with oxindoles have employed reflux conditions with long reaction times,[104] NaOH-catalyzed at 0 °C with long reaction times,[105] ionic liquids,[106] and microwave irradiation with potassium fluoride on alumina which experienced difficulties with hindered aryl aldehydes.[107] These conditions are less than ideal for the purposes of synthesizing an oxindole library and, therefore, a novel approach using microwave irradiation was developed.

Currently, the most facile and promising method known for generating oxindole aldol condensation products was that of Ribeiro *et al.* who employed 20% piperidine in ethanol (see table 2.1). Given the advantages of microwave irradiation on reaction kinetics, a pilot reaction was conducted using the same conditions; however microwave irradiation was used in place of

[104] Ribeiro, C.J.A.; Amaral, J.D.; Rodrigues, C.M.P.; Moreira, R.; Santos, M.M.M. *Bioorg. Med. Chem.* **2014**, *22* (1), 577-584.
[105] Suthar, S.K.; Bansal, S.; Alam, M.M.; Jaiswal, V.; Tiwari, A.; Chaudhary, A.; Alex, A.T.; Joseph, A. *Bioorg. Med. Chem. Lett.* **2015**, *25* (22), 5281-5285.
[106] Hu, Y.; Kang, H.; Zeng, B.-W.; Huang, H.; Wei, P. *Heterocycl. Comm.* **2011**, *14* (4), 263-268.
[107] Villemin, D.; Martin, B. *Synth. Comm.* **1998**, *28* (17), 3201-3208.

standard heating. When irradiated at 80 °C for 2 hours, a complete reaction was observed, providing the Z isomer as the major product, with a small amount of the *E* isomer present. Time optimization studies were undertaken and determined that 30 minutes was the ideal reaction time to reach completion with the majority of aldehydes.

Table 2.1. Base screen for the aldol condensation of oxindoles.



Entry	Base	Yield (%)[a]
1	Diisopropylethylamine	N/R
2	Triethylamine	N/R
3	Diethylamine	N/R
4	Pyrrolidine	INC
5	Diisopropylamine	N/R
6	Piperidine	82%[b]

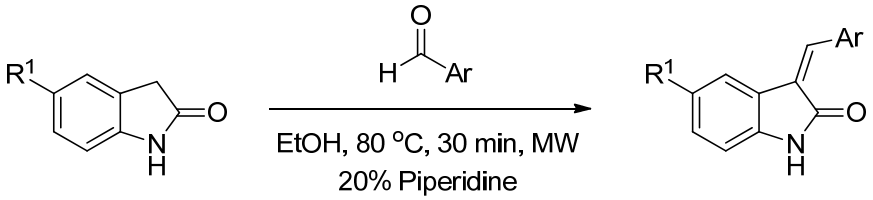
N/R = no reaction. INC = Incomplete. [a] Yields were not isolated and judged my TLC. [b]Isolated yield.

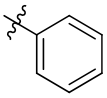
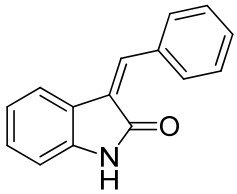
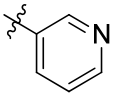
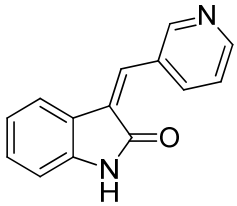
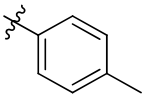
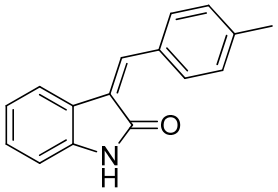
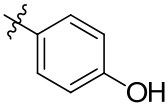
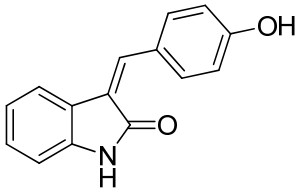
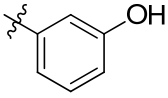
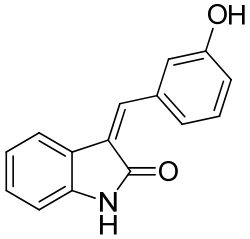
A base screen was then conducted (table 2.1) to observe its impact on the reaction. While pyrrolidine showed similar, though lesser, reactivity to piperidine, other bases such as diisopropylethylamine, trimethylamine, diethylamine, and diisopropylamine showed little to no reactivity after 30 minutes. In addition, we found that either ethanol or in some cases methanol were the ideal solvents in that they allowed for dissolution of the majority of the reagents and allowed for precipitation of the final product. We determined, therefore, that optimal reaction conditions require the use of piperidine in ethanol and 30 minutes of microwave irradiation.

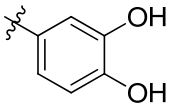
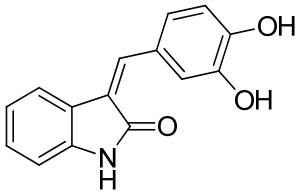
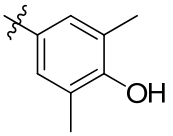
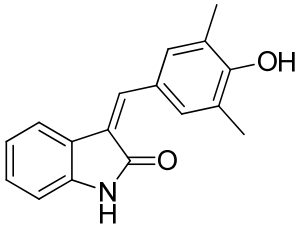
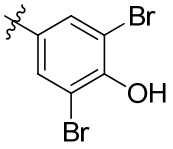
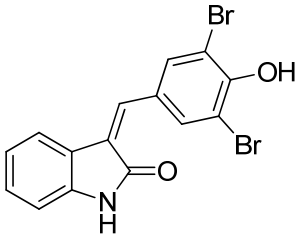
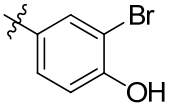
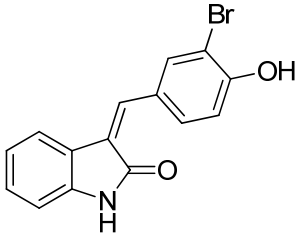
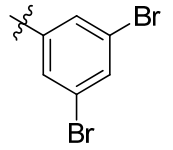
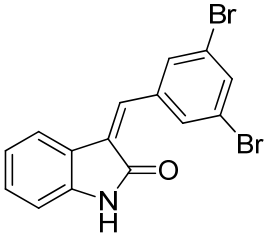
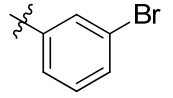
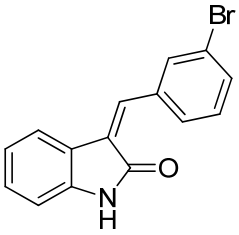
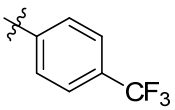
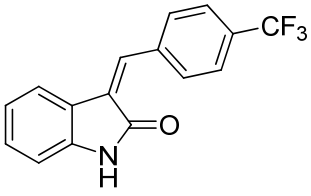
Using these conditions, the first library of oxindoles dervived at the 3-position was synthesized (table 2.2). Based on the leads presented in figure 2.2, oxindoles containing either an –H, -CO_2Me or –Br at the 5-position were utilized as substrates. The library generated would

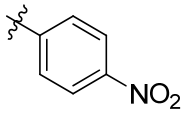
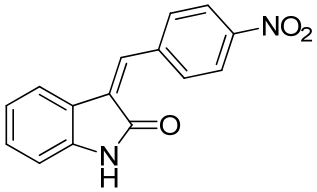
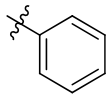
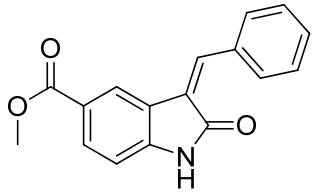
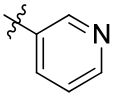
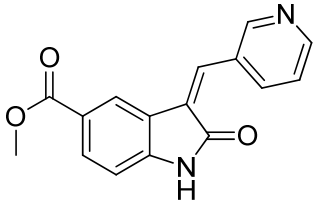
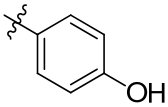
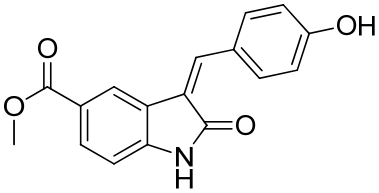
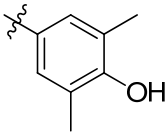
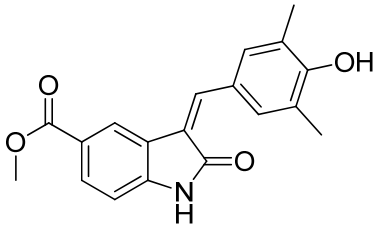
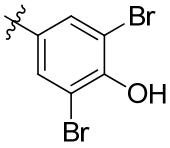
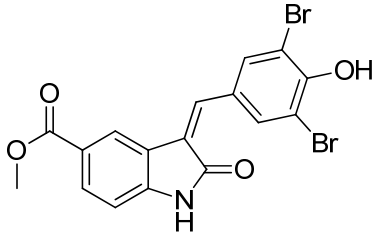
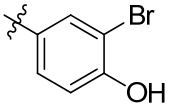
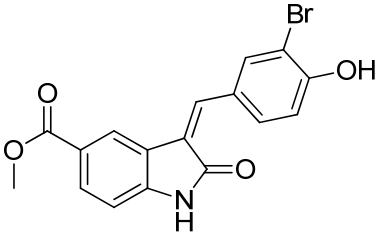
allow us to determine whether any substitution is required at the 5-position or the aryl moiety (table 2.2 entry 1), whether the 5-position requires substitution (table 2.2 entry 8), and which parts of the aryl group are required for activity (table 2.2 entries 16-21).

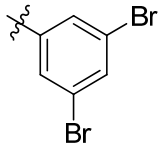
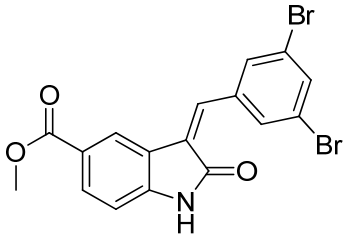
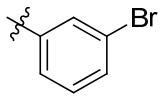
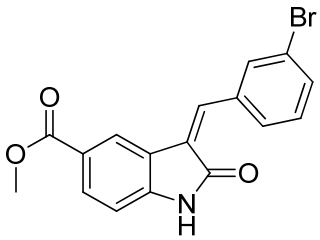
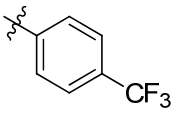
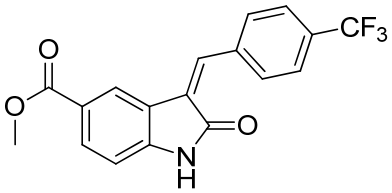
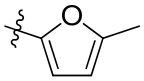
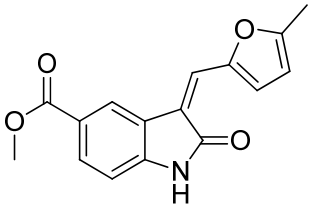
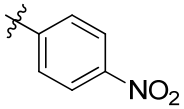
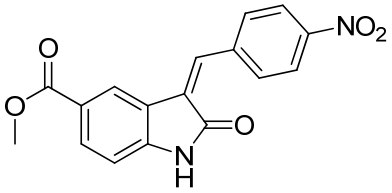
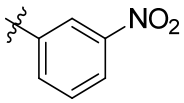
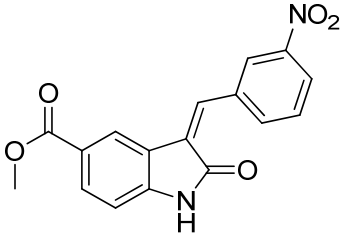
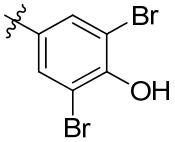
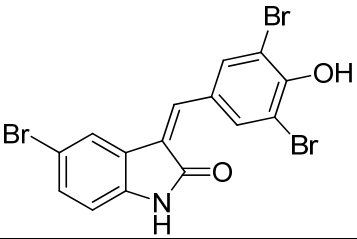
Table 2.2. First generation library of AAC(3)-Ia oxindole inhibitors.



Entry	R^1 =	Ar =	Product	Yield (%)	Z:E
1[a]	-H			68	>20:1
2[a]	-H			53	1:1
3	-H			76	>20:1
4	-H			75	>20:1
5	-H			85	>20:1

6	-H			85	5:2
7	-H			75	>20:1
8[d]	-H			56	3:2
9[a]	-H			63	>20:1
10[a]	-H			59	5:4
11[a]	-H			49	5:4
12[a]	-H			61	>20:1

13	-H			62	3:2
14	-COOMe			71	7:3
15	-COOMe			94	1:1
16[b]	-COOMe			88	>20:1
17	-COOMe			95	3:1
18[c]	-COOMe			61	2:1
19	-COOMe			77	>20:1

20	-COOMe			82	4:3
21	-COOMe			93	3:2
22[a]	-COOMe			77	3:2
23	-COOMe			77	>20:1
24	-COOMe			90	10:9
25	-COOMe			91	3:2
26[c]	-Br			65	4:1

[a]Reaction time = 1h. [b]Reaction time = 20 min. [c]Reaction time = 6 h. [d]Conditions: 72 hour reflux.
Note: Substrates with R^1 = -COOMe used methanol as a solvent.

A number of the compounds generated are worth taking note of, specifically: entries 8, 18 and 26 possesses the same aryl moiety as lead compound **1**; and aldehydes were chosen as they represent a variety of structural and functional group types.

During the synthesis of the library, it became apparent that electron-rich aldehydes tended to provide better yields and faster reactions; whereas electron-poor aldehydes tended to be slower and provided lower yields. This was a striking observation, as electron-poor aldehydes are more 'activated' and should result in faster reaction rates. Given that the initial condensation reaction likely proceeds via an imine route (see scheme 2.1 below), aldehydes bearing electron withdrawing substituents should be more electrophilic and therefore better substrates for initial imine formation. In the same way, electron withdrawing groups should help increase the electrophilicity of the imine carbon. However, as an example, if one compares the yields obtained in entry 1 (unsubstituted giving a yield of 68%) with entry 4 (electron donating –OH giving a yield of 75%) and entry 12 (electron withdrawing $–CF_3$ group giving a yield of 61%), the effect is counterintuitive. Furthermore, the entry 4 was complete in half the time as entry 12. These electronic effects need to be carefully considered as the ability of ethanol to solubilize specific substrates was different in specific entries and may be having an effect on yields and rates.

Substitution at the 5-position with an electron withdrawing group also had an effect on the reaction allowing for increased yields and faster reaction times. For example, compare the yields obtained between entry 4 (with an –H at position 5 giving a yield of 75%) with entry 16 (with an $–CO_2Me$ at position 5 giving a yield of 88%). Reaction rates were also affected with entry 16 complete in 20 minutes while entry 4 required 30 minutes. Contrast entries 12 and 22 for an additional example.

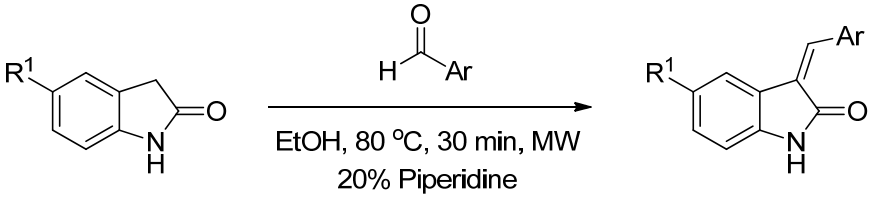
The compounds generated in this library were fully characterized (see experimental section) and are currently undergoing biological assessment in the Wright lab. Note that the *E* and *Z* isomers were identified using a NOESY experiment and their ratio determined via integration of appropriate signals in the ^{1}H-NMR.

A few additional points regarding this collection are worth noting. Entries 8, 18 and 26 were prepared as they possess the same aryl moiety as lead compound **1**. We were disappointed, however, as these compounds could not be prepared using the methodology developed and required harsher conditions and longer reactions time with accompanying lower yields. These issues are addressed in section 2.4. In addition, we were curious as to the effect of an electron donating group at position 5 and wanted to include additional heterocyclic fragments at the 3-postion (as these provide interesting steric and electronic features as well as providing additional H-bonding in biological systems). As a result, we generated another library presented in table 2.3.

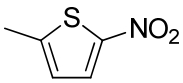
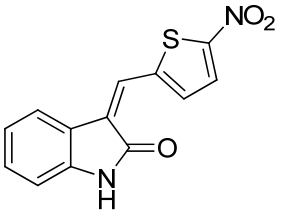
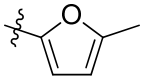
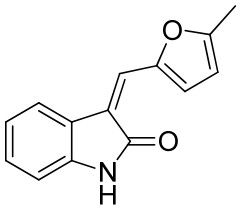
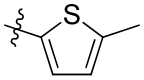
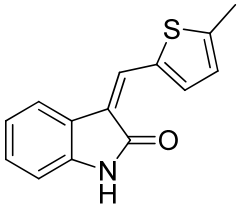
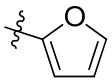
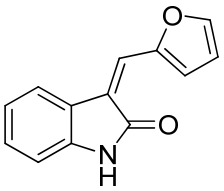
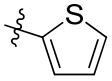
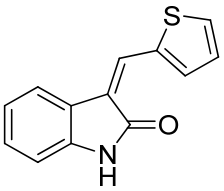
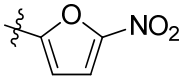
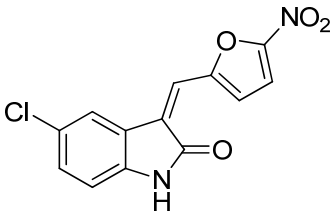
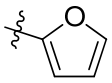
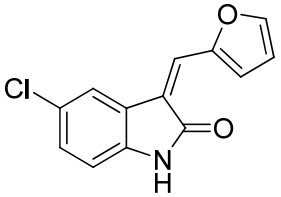
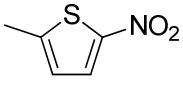
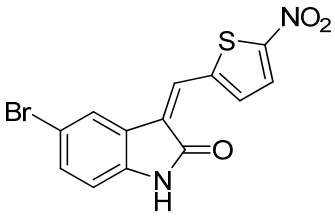
2.3 Additional Aldehyde Screen

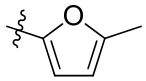
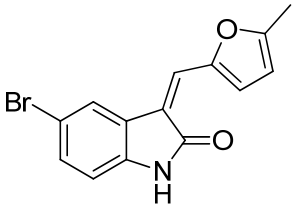
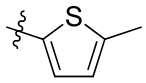
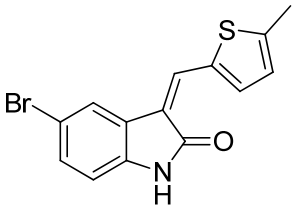
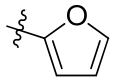
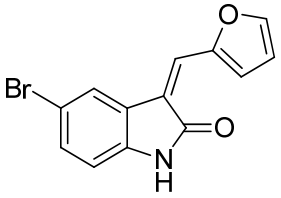
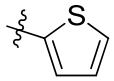
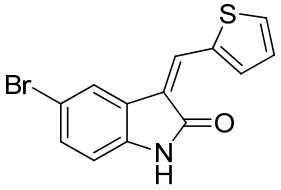
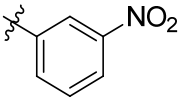
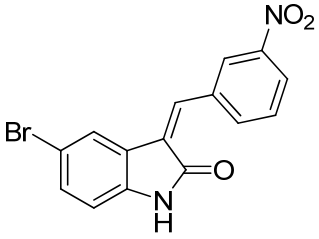
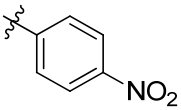
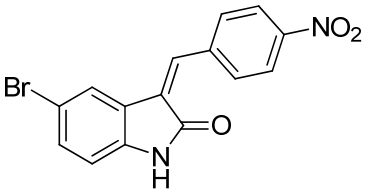
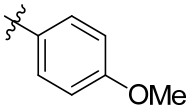
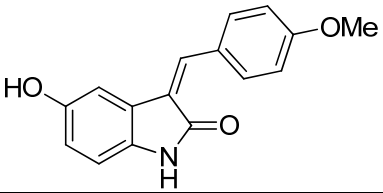
Given the apparent electronic trends described in the section above, an additional library of aldehydes for further extrapolation was utilized to generate the library presented in table 2.3.

Table 2.3. Additional aldehyde screen testing electronic trends



Entry	R^1 =	Ar =	Product	Yield (%)	Z:E

1	-H			79 [b]	>20:1
2	-H			69	>20:1
3	-H			93	>20:1
4	-H			84	>20:1
5	-H			68	4:3
6	-Cl			61 [b]	>20:1
7[a]	-Cl			85 [b]	>20:1
8	-Br			85 [b]	>20:1

9[a]	-Br			76 [b]	5:1
10[a]	-Br			80 [b]	>20:1
11[a]	-Br			89 [b]	>20:1
12[a]	-Br			92 [b]	10:3
13	-Br			91 [b]	2:1
14	-Br			84 [b]	1:1
15	-OH			NR	-

[a]Reaction time = 20 min. [b]Yields based on filtration purification rather than column chromatography. NR = no reaction

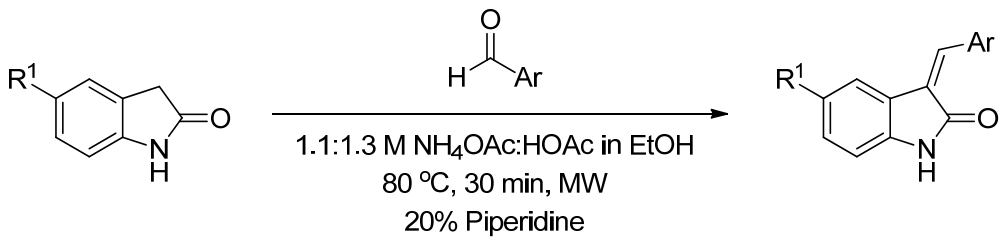
Heterocyclic systems, given their electron-rich nature, unsurprisingly provided excellent yields and were easy to operate synthetically. Note that halogens at the 5-position were

employed as the resultant molecules will be used as substrates for organopalladium cross-coupling reactions. An OH at the 5 position (entry 15) is in keeping with the effect seen in the previous table in that, unlike electron withdrawing groups at the 5-position aiding in the reaction, electron donating groups at the 5 positions hamper the reaction significantly where no observable product was seen.

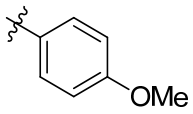
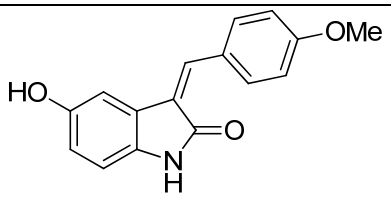
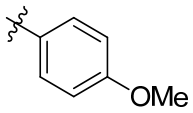
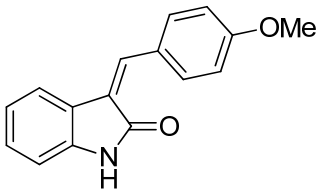
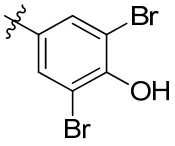
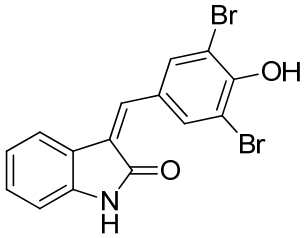
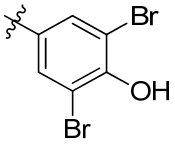
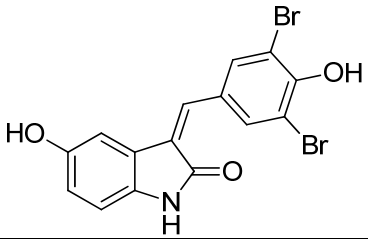
2.4 Theory Behind the Knoevenagel Condensation on Oxindoles and Alcoholic NH_4OAc Solutions

At this point, two electronic effects were clear: 1) electron-poor aldehydes lead to lower yields and longer reaction times and 2) electron-withdrawing groups at the 5-position also lead to higher yields and faster reaction times. Upon considering the mechanism of the reaction and the role of piperidine, it was likely that the aldehyde was forming an iminium intermediate prior to the aldol condensation, similar to a Knoevenagel-type aldol condensation. If this was the case, previous studies have shown that a pH of approximately 4.5 is optimal for iminium formation.[108] We attempted the reaction listed in table 1 in a NH_4OAc solution in water buffered at pH 4.5, but no reaction was observed, likely due to poor water solubility of the reactants. Our next idea was to prepare an NH_4OAc/HOAc solution in ethanol to address the solubility issue. To our surprise, we found staggering results with a 1.1:1.3 M NH_4OAc:HOAc solution in ethanol.

Table 2.4. Successful reactions using the NH_4OAc/HOAc solution in ethanol.



[108] Erkkila, A.; Majander, I.; Pihko, P.M.; *Chem. Rev.* **2007**, *107* (12), 5416-5470.

Entry	R^1 =	Ar =	Product	Yield (%)
1[a]	-OH			95
2[b,c]	-H			91
3	-H			87
4	-OH			92

[a]Reaction time = 10 minutes. [b]No piperidine was added. [c]Reaction time = 1 minute.

We were first surprised to see that our initial pilot reaction (table 2.4, entry 2), a reaction that previously did not work in ethanol, had reduced the reaction time to only 1 minute. Realizing the power of these new conditions, we then decided to reduce the piperidine loading incrementally. 20% piperidine seemed to be an optimal amount for 5-hydroxyoxindoles, but we were surprised to observe that piperidine was not required for oxindoles bearing no substitution on the 5-position. Table 2.4 entry 2 was a surprising result, as the reaction time still only took 1 minute to go to completion without any piperidine added. It is likely that the aldehyde formed an intermediary imine with the ammonia in solution, as alcoholic ammonia solutions have been previously reported to activate ketones to ketimines.[109] Table 2.4 entry 3 was another interesting

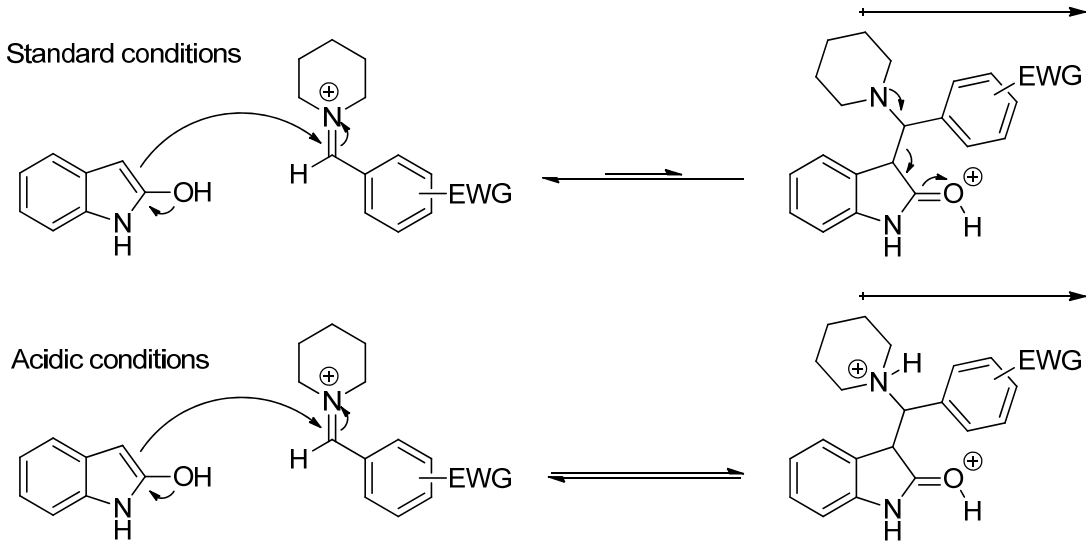
[109] Song, A.; Wang, X.; Lam, K.S. *Tet. Lett.* **2003**, *44* (9), 1755-1758.

result as this new method brought the reaction time down from 72 hours to only 30 minutes. The previously inaccessible product of table 2.4 entry 4 was also able to be synthesized in only 30 minutes.

NH_4OAc has been previously used to catalyze the Knoevenagel condensation reactions on solid-supported basic alumina under solvent-free microwave irradiation.[110] Another procedure focused on the use of ultrasound-promoted Henry and Knoevenagel condensations using NH_4OAc solutions.[111] However, these procedures still required long reaction times and tended to avoid the use of electron-poor aldehydes. While they also observe higher yields with electron-rich aldehydes, they do not address why this is, as one would expect an electron-poor aldehyde to be more reactive.

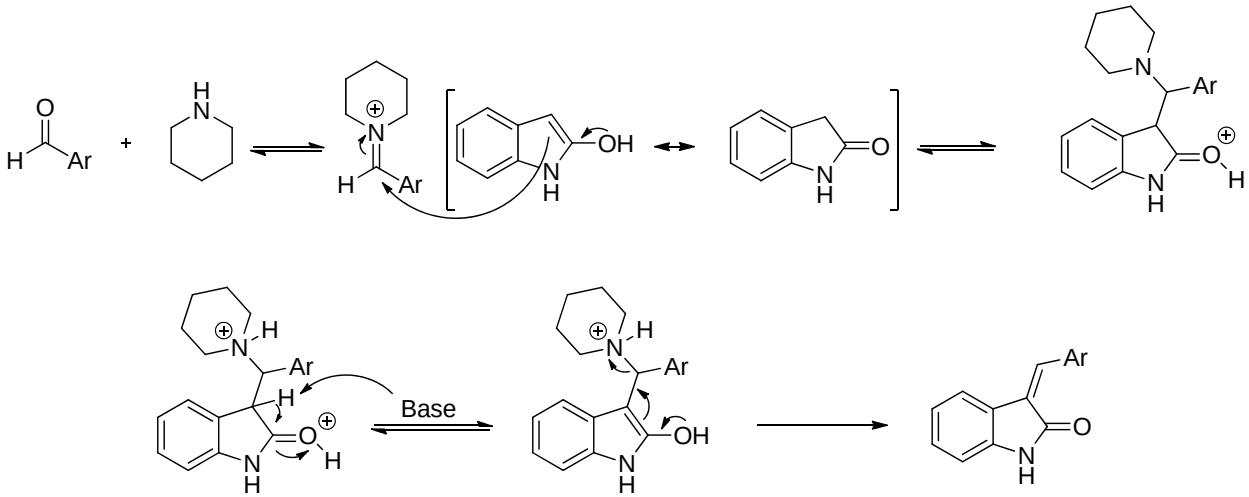
Our evidence suggests that the aldol condensation between aldehydes and oxindoles proceeds through a Knoevenagel-type mechanism. Since the pK_a of the alpha hydrogen to the amide on the oxindole is too high to be deprotonated by piperidine, the oxindole must first tautomerize to the enol form. Given the profound electronic effects observed at the 5-position, we hypothesize that this must be contributing to the ability of the oxindole to tautomerize. However, the exact mechanism behind this observation is still not clear.

[110] Balalaie, S.; Nemati, N. *Synth. Commun.* **2000**, *30* (5), 869-875.
[111] McNulty, J.; Steere, J.A.; Wolf, S. *Tet. Lett.* **1998**, *39* (44), 8013-8016.



Scheme 2.1. Electronic hypothesis favouring the reverse reaction.

The electron-withdrawing groups present on the electron-poor aryl aldehydes could be responsible for providing a driving force for the reverse reaction in the standard ethanol conditions (scheme 2.1). However, in the acidic NH_4OAc/HOAc alcoholic conditions, the piperidine intermediate formed following the initial enol attack would likely be quickly protonated which would 1) occupy the electrons responsible for the reverse reaction and 2) activate piperidine as a better leaving group.



Scheme 2.2. Proposed mechanism for the Knoevenagel-type aldol condensation of oxindoles.

Thus, the combination of an electron-donating group at the 5-position and an electron-poor aldehyde leads to very unfavourable reaction conditions which were previously inaccessible. We are proud to report a new system of ethanolic NH_4OAc/HOAc solutions capable of overcoming and addressing the electronic limitations present in oxindole chemistry. It is our hope that this new process can facilitate the streamlining of combinatorial synthesis of oxindoles for screening projects, without straying away from highly inactivated aldehydes.

2.5 AAC(3)-Ia oxindole inhibitors: Derivatization of the 5-position

Having successfully developed chemistry for the installation of a styrenyl moiety at the 3-position of oxindole, attention was then turned to the derivitization of the 5-position. Lead compounds **1** and **2** possess either an ester or a ketone functionality, repectively, at this position. Initially it was believed that a ketone functionality could be installed *via* a Friedel-Crafts reaction given the plethora of patent literature surrounding this procedure.[112,113] However, this reaction proved to be exceedingly difficult and no product of a Friedel-Crafts acylation could be obtained.

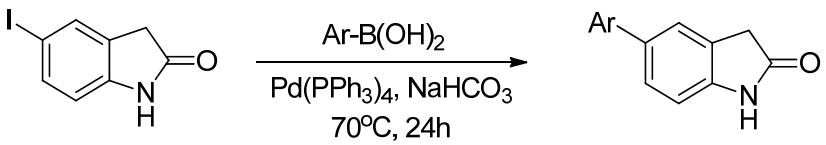
We then invisioned the installation of an ester at the 5-position of the oxindole *via* a palladium-catalyzed carbonylation reaction. The Capretta group has utilized this reaction in the past;[114,115] however, we chose to carry out a series of more straightforward cross-coupling reactions in order to introduce diversity and became interested in Suzuki cross-coupling chemistry.

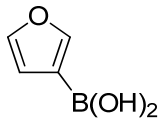
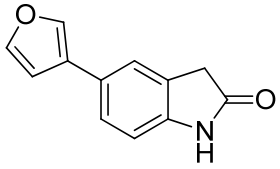
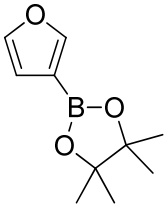
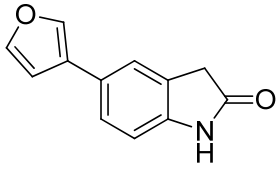
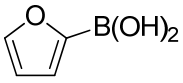
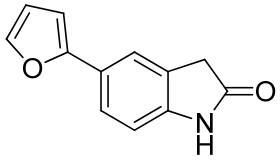
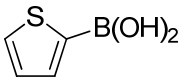
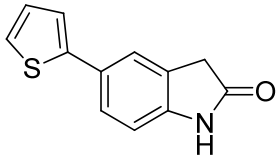
Determining ideal conditions to conduct Suzuki cross-coupling reactions on the oxindole proved to be difficult at first. The first method attempted was that described in Chapter 4 using

[112] Kassehin, U.C.; Gbaguidi, F.A.; Carato, P.; McCurdy, C.R.; Poupaert, J.H. *Organic Chem. Curr. Res.* **2015**, *4* (1), 1-4.
[113] Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077-1104.
[114] McNulty, J.; Nair, J.J.; Capretta, A. *Tet. Lett.* **2009**, *50* (28), 4087-4091.
[115] Awuah, E.; Capretta, A. *Org. Lett.* **2009**, *11* (15), 3210-3213.

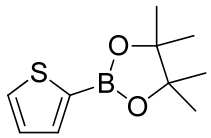
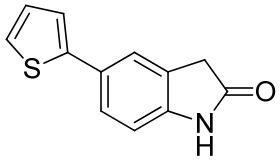
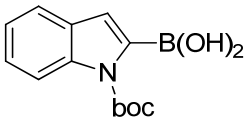
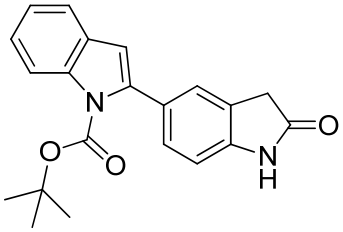
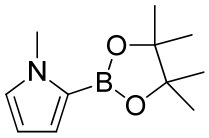
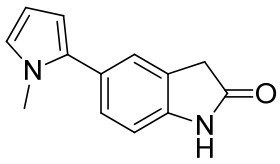
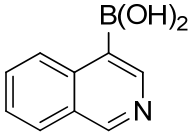
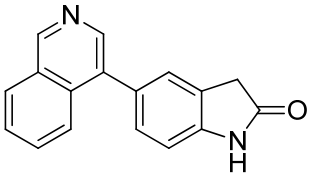
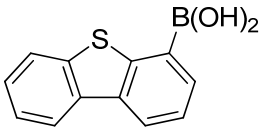
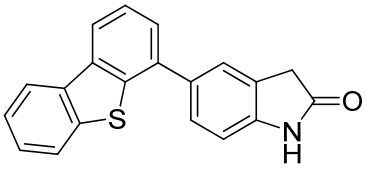
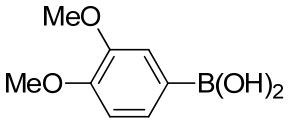
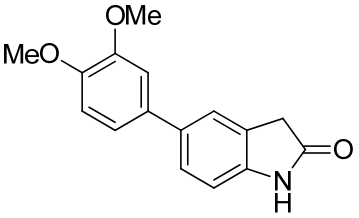
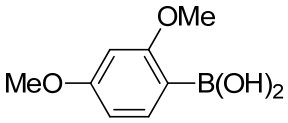
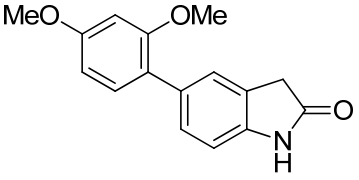
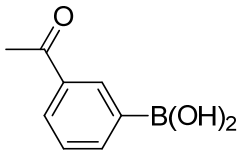
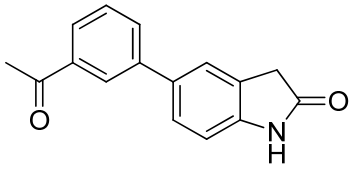
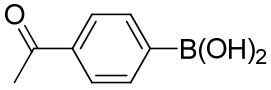
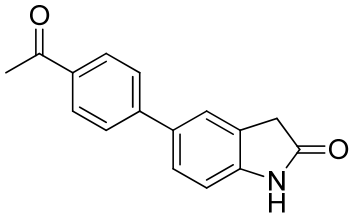
the phosphaadamantane ligands with $Pd(OAc)_2$ or $Pd_2(dba)_3$ where, unfortunately, no reaction was observed. Knowing that there was a good chance that the heteroatoms on the oxindole were poisoning the formation of the active catalyst *in situ*, the next attempt was to use the preassociated catalyst described in Chapter 4.2 $(PA\text{-}Ph(OMe)_2)_2PdO_2$. However, while some conversion was observed, reactions did not go to completion, which was a little perplexing considering how powerful this catalyst is on other heterocycles. Finally, a working set of conditions was determined based off a previously published procedure which was used for the Suzuki cross-coupling between aryl boronic acids and isatins using $Pd(PPh_3)_4$ as a catalyst.[116]

Table 2.5. List of products from the Suzuki cross-coupling reaction on oxindoles.



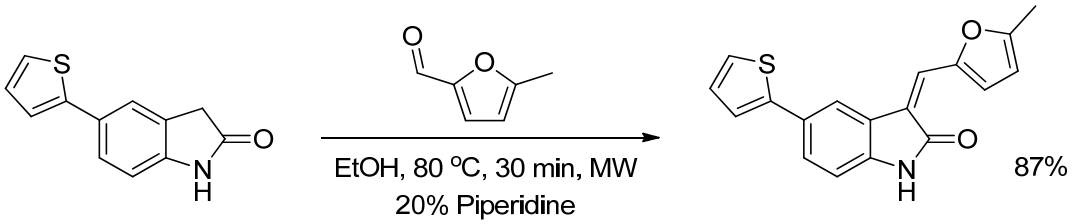
Entry	Boronic Species	Product	Yield (%)
1			42
2			30
3			99
5			56

[116] Gerard, A.-4L.; Lisowski, V.; Rault, S. *Tetrahedron* **2005**, *61*, 6082-6087.

6			99
7			69
8			35
9			46
10			43
11			29
12			53
13			19
14			25

Unsurprisingly, electron-poor boronic acids/pinacol esters tended to provide lower yields as these substrates are weaker nucleophiles than their electron-rich counterparts.

Finally, to ensure the microwave aldol chemistry was compatible with the Suzuki products, a pilot reaction (scheme 2.3) was conducted and the results were consistent with those presented earlier in this section.



Scheme 2.3. Pilot reaction of aldol condensation with a Suzuki product from table 2.5.

While the compounds generated in this chapter are still awaiting biological assessment, the chemistry developed should allow for the rapid synthesis of subsequent libraries aimed at optimizing biological activity.

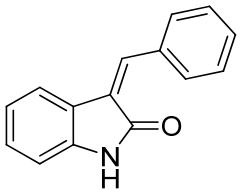
2.6 Experimental

Microwave reactions were performed in 2.0 – 5.0 mL microwave vials, sealed under ambient atmosphere, and loaded to a CEM Discover SP-D 80 Microwave Reactor (100 W, < 100 psi). Heated non-microwave reactions were performed in a temperature-controlled oil bath. TLC was performed on F-254 (0.25 mm) precoated silica gel (Merck) and visualized under UV, aqueous $KMnO_4$, or aqueous ninhydrin stain. Flash column chromatography purifications were performed using a normal phase Teledyne Isco CombiFlash® Rf 200 with standard RediSep RF 12 g silica columns.

Compounds were characterized by ^{1}H NMR, ^{13}C NMR, DEPT Q, NOESY, ESI-MS, and HRMS. NMR spectra were obtained from a Bruker AvanceIII 700 (700 MHz). Chemical shifts

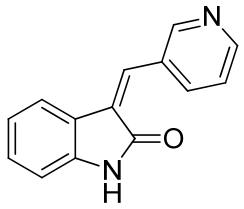
are reported as ppm, coupling constants in Hz, and peaks were calibrated to the solvent residual peak ($CDCl_3$ = 7.27 (^1H), 77.16 (^{13}C), DMSO = 2.50 (^1H), 39.51 (^{13}C)). Mass spectrometry was conducted with a Bruker Maxis 4G/TOF in either positive or negative ion mode with direct infusion.

General procedure A (microwave-assisted aldol condensation): To a clean microwave vial charged with a stir bar was added the oxindole (1.0 equiv.), aldehyde (1.2 equiv.), piperidine (0.2 equiv.), and absolute EtOH (0.25 M) as the solvent. The vial was then sealed with a microwave cap and irradiated for thirty minutes at 79 °C. After cooling to room temperature, the contents of the vial were purified by flash column chromatography or filtration to yield the corresponding title compound.



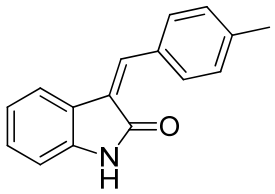
(Z)-3-benzylideneindolin-2-one: Oxindole (0.100 g, 0.751 mmol) and benzaldehyde (0.0920 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for one hour. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% Et_2O/hexanes) to provide the title compound as a yellow amorphous solid with a trace amount of the *E* isomer. (112.5 mg, 68% yield). ^1H NMR (700 MHz; DMSO): δ 10.60 (s, 1H), 7.71 (m, 2H), 7.63 (s, 1H), 7.53 (m, 3H), 7.47 (m, 1H), 7.23 (t, J = 6.0 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.58 (C), 142.94 (C), 135.76

(CH), 134.44 (C), 130.18 (CH), 129.67 (CH), 129.24 (CH), 128.75 (CH), 127.65 (C), 122.32 (CH), 121.11 (CH), 120.85 (C), 110.13 (CH). HRMS (ESI): Exact mass calcd for $C_{15}H_{11}NO$ $[M]^+$: 221.0841. Found: $[M+H]^+$: 222.0905.

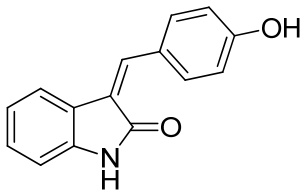


(Z)-3-(pyridin-3-ylmethylene)indolin-2-one: Oxindole (0.144 g, 0.751 mmol) and nicotinaldehyde (84.6 μL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the solution was concentrated under reduced pressure and purified by column chromatography (hexanes/EtOAc) to provide the title compound as a yellow-orange amorphous solid in a mixture with the E isomer. (75.6 mg, 53% yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ *10.68 (bs, 1H), 10.66 (bs, 1H), *9.19 (s, 1H), 8.88 (m, 1H), 8.64 (d, *J* = 4.3 Hz, 1H), *8.58 (d, *J* = 4.3 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), *7.82 (s, 1H), *7.71 (d, *J* = 7.3 Hz, 1H), 7.62 (s, 1H), 7.54 (dd, *J* = 7.6, 4.8 Hz, 1H), *7.48 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.24 (m, 1H), *7.00 (t, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.84 (m, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.17 (C), *167.04(C), *152.37 (CH), *150.24 (CH), 150.09 (CH), 149.75 (CH), 143.20 (C), *141.13 (C), *137.85 (CH), 136.38 (CH), *132.71 (CH), 132.05 (CH), 130.63 (CH), *129.92 (C), *129.57 (CH), 129.39 (C), *128.79 (C), 124.37 (C), 123.69 (CH), *123.16 (CH), 122.25 (CH), 121.28 (CH), 120.62 (C), *120.20 (CH), 110.33 (CH),

*109.54 (CH). HRMS (ESI): Exact mass calcd for $C_{14}H_{10}N_2O$ $[M]^+$: 222.0793. Found: $[M+H]^+$ 223.0866.

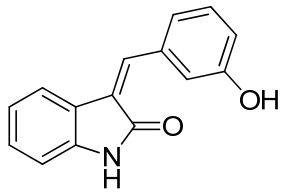


(Z)-3-(4-methylbenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 4-methylbenzaldehyde (0.107 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% Et_2O/hexanes) and the title compound was obtained as an amorphous yellow solid with trace amounts of the *E* isomer. (140.8 mg, 80% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.58 (s, 1H), 7.59 (m, 4H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.6Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (176 MHz; DMSO) δ 168.74 (C), 142.84 (C), 139.68 (C), 135.97 (CH), 131.54 (C), 129.96 (CH), 129.40 (CH), 129.33 (CH), 126.93 (C), 122.26 (CH), 121.07 (CH), 121.01 (C), 110.09 (CH), 21.09 (CH_3), HRMS (ESI): Exact mass calcd for $C_{16}H_{13}NO$ $[M]^+$: 235.0997. Found $[M+Na]^+$: 258.0879.



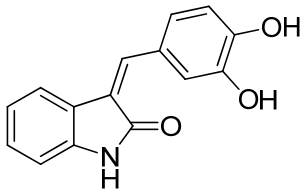
(Z)-3-(4-hydroxybenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 4-hydroxybenzaldehyde (0.110 mg, 0.901 mmol) were added to ethanol (3 mL) in a microwave

tube charged with a stir bar as per general procedure A. Piperidine (14.8 μL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water and DCM to provide the title compound as a sandy yellow amorphous solid with trace amounts of the E isomer. (134.2 mg, 75 % yield). ^{1}H NMR (700 MHz; DMSO): δ 10.51 (s, 1H), 10.13 (bs, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.54 (s, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 6.87 (m, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.06 (C), 159.31 (C), 142.49 (C), 136.60 (CH), 131.83 (CH), 129.41 (CH), 125.00 (C), 124.65 (C), 122.04 (CH), 121.31 (C), 121.02 (CH), 115.64 (CH), 109.94 (CH). HRMS (ESI): Exact mass calcd for C15H11NO2 $[M]^{+}$: 237.0790 Found: $[M+H]^{+}$ 238.0861.

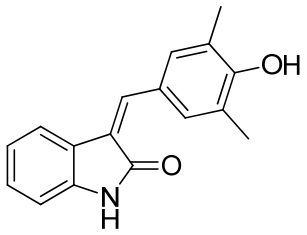


(Z)-3-(3-hydroxybenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 3-hydroxybenzaldehyde (0.110 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% EtOAc/hexanes) to provide the title compound as a yellow amorphous solid with a trace amount of the *E* isomer. (150.9 mg, 85% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.59 (bs, 1H), 9.73 (bs, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.86 (m, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.66 (C), 157.49 (C), 142.91 (C), 135.99 (CH), 135.59 (C),

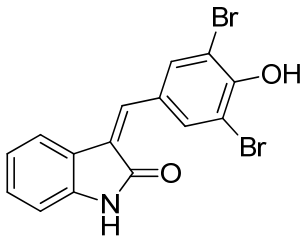
130.08 (CH), 129.90 (CH), 127.40 (C), 122.64 (CH), 121.09 (CH), 120.87 (C), 120.15 (CH), 116.84 (CH), 115.53 (CH), 110.08 (CH). HRMS (ESI): Exact mass calcd for $C_{15}H_{11}NO_2$ $[M]^+$: 237.0790. Found: $[M+H]^+$: 238.0854.



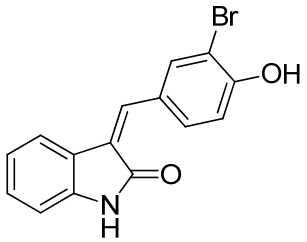
(Z)-3-(3,4-dihydroxybenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 3,4-dihydroxybenzaldehyde (0.124 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% EtOAc/hexanes) and the title compound was obtained as a mixture of *E*/*Z* isomers as an amorphous yellow solid. (161.5 mg, 85% yield). ^{1}H NMR (700 MHz; DMSO): *denotes the minor *E* isomer. δ 10.51 (bs, 1H), 9.50 (bs, 2H), *8.23 (m, 1H), 7.79 (m, 1H), *7.73 (m, 1H), *7.63 (m, 1H), *7.60 (m, 1H), 7.48 (m, 1H), 7.22 (m, 2H), *7.14 (m, 1H), 7.08 (m, 1H), 6.94 (m, 1H), 6.87 (m, 3H), *6.81 (m, 2H). ^{13}C NMR (176 MHz; DMSO) δ 169.20 (C), *167.44 (C), *148.97 (C), 147.93 (C), 145.32 (C), *144.69 (C), 142.47 (C), *140.00 (C), *138.01 (CH), 137.07 (CH), 129.35 (CH), *127.79 (CH), *126.55 (CH), *126.14 (C), *125.68 (C), 125.49 (C), 124.35 (C), 122.90 (CH), *122.71 (C), 122.34 (CH), 121.38 (C), 121.00 (CH), *120.78 (CH), *119.49 (CH), *118.97 (CH), 116.68 (CH), 115.87 (CH), *115.20 (CH), 109.33 (CH), *109.07 (CH), HRMS (ESI): Exact mass calcd for $C_{15}H_{11}NO_3$ $[M]^+$: 253.0739. Found $[M+Na]^+$: 274.0461.



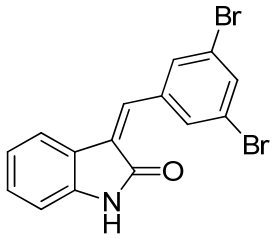
(Z)-3-(4-hydroxy-3,5-dimethylbenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 3,5-dimethyl-4-hydroxybenzaldehyde (0.135 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% EtOAc/hexanes) to provide the title compound as a yellow amorphous solid with a trace amount of the *E* isomer. (149.9 mg, 75% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 10.50 (s, 1H), *10.48 (s, 1H), 8.97 (bs, 1H), *8.17 (s, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), *7.61 (m, 2H), 7.49 (s, 1H), 7.35 (s, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), *7.14 (t, *J* = 7.5 Hz, 1H), *6.95 (m, 1H), 6.87 (m, 2H), *6.80 (d, *J* = 7.5 Hz, 1H), 2.22 (s, 6H), *2.21 (s, 6H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.06 (C), *167.36 (C), 156.36 (C), 155.38 (C), 142.46 (C), *140.00 (C), *137.67 (CH), 136.91 (CH), 133.48 (CH), 130.28 (CH), *129.31 (CH), *127.74 (CH), *125.66 (C), *125.58 (C), 125.07 (C), *124.57 (C), 124.49 (C), 123.70 (C), 122.76 (C), 121.89 (CH), 121.44 (C), 120.99 (CH), *120.75 (CH), *118.85 (CH), 109.92 (CH), *109.04 (CH), *16.68 (CH_3), 16.54 (CH_3). HRMS (ESI): Exact mass calcd for $C_{17}H_{15}NO_2$ $[M]^+$: 265.1103. Found: $[M+H]^+$: 266.1175.



(Z)-3-(3,5-dibromo-4-hydroxybenzylidene)indolin-2-one: Oxindole (0.066 g, 0.500 mmol) and 3,5-dibromo-4-hydroxybenzaldehyde (0.168 g, 0.600 mmol) were added to ethanol (3 mL) in a carousel tube charged with a stir bar. Piperidine (9.88 μL, 0.100 mmol) was then added and the tube was sealed and heated with reflux at 90 °C for 3 days. After cooling to room temperature, the solution was concentrated under reduced pressure and purified by column chromatography (hexanes/Et2O) to provide the title compound as a yellow-orange amorphous solid in a mixture with the E isomer. (110.0 mg, 56 % yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ *10.65 (bs, 1H), 10.60 (bs, 1H), 8.79 (s, 1H), 7.9 (s, 1H), *7.69 (s, 1H), *7.63 (d, *J* = 7.3 Hz, 1H), 7.48 (m, 1H), 7.22 (m, 1H), 6.90 (m, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ *168.44 (C), 167.28 (C), *152.60 (C), 151.95 (C), *143.07 (C), 140.61 (C), 136.07 (CH), *133.94 (CH), 133.19 (CH), *133.09 (CH), *130.29 (CH), 128.89 (CH), *128.64 (C), 128.57 (C), 127.56 (C), *127.42 (CH), 125.97 (C), 124.88 (C), *124.36 (CH), 121.95 (CH), 121.12 (CH), *120.73 (C), 119.61 (CH), *111.79 (C), 111.10 (C), *110.32 (CH), 109.44 (CH), *109.09 (CH). HRMS (ESI): Exact mass calcd for $C_{15}H_9Br_2NO_2$ $[M]^+$: 392.9000 Found: $[M+H]^+$ 393.9039.

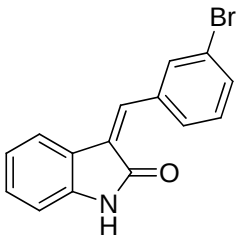


(Z)-3-(3-bromo-4-hydroxybenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 3-bromo-4-hydroxybenzaldehyde (0.181 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for one hour. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a yellow amorphous solid with a trace amount of the *E* isomer. (149.1 mg, 63% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.95 (bs, 1H), 10.55 (s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.62 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.50 (s, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.88 (m, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.73 (C), 155.63 (C), 142.76 (C), 134.83 (CH), 134.39 (CH), 130.37 (CH), 129.83 (CH), 126.72 (C), 126.03 (C), 122.01 (CH), 121.09 (CH), 121.00 (C), 116.34 (CH), 110.10 (CH), 109.47 (C). HRMS (ESI): Exact mass calcd for $C_{15}H_{10}BrNO_2$ $[M]^+$: 314.9895. Found: $[M+H]^+$: 315.9961.



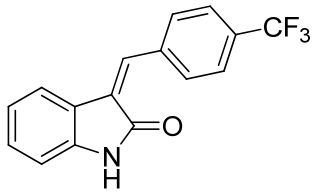
(Z)-3-(3,5-dibromobenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 3,5-dibromobenzaldehyde (0.238 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 60 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water to provide the title compound as a yellow-orange crystalline solid in a mixture with the E isomer. (166.80

mg, 59% yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ *11.71 (bs, 1H), 11.66 (bs, 1H), *8.63 (d, *J* = 1.6 Hz, 2H), 7.93 (s, 1H), 7.88 (m, 2H), *7.75 (s, 1H), *7.67 (d, *J* = 7.5 Hz, 1H), 7.53 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), *7.01 (t, *J* = 7.6 Hz, 1H), 6.86 (m, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.06 (C), *166.88 (C), 143.40 (C), *141.28 (C), 138.74 (C), *137.70 (C), *134.31 (CH), 133.92(CH), 132.96 (CH), *132.95 (CH), *132.21 (CH), 130.84 (CH), 130.63 (CH), *129.87 (CH), *129.76 (C), 129.36 (C), 124.26 (C), 122.73 (C), 122.30 (CH), 122.07 (C), *121.31 (CH), 121.28 (CH), *120.35(CH), 120.30 (CH), 110.43 (CH), *109.63 (CH). HRMS (ESI): Exact mass calcd for $C_{15}H_9Br_2NO$ $[M]^+$: 376.9051. Found: $[M+H]^+$ 377.9091.



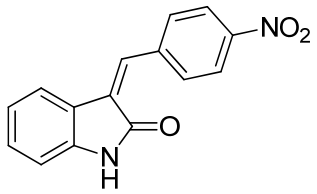
(Z)-3-(3-bromobenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 3-bromobenzaldehyde (105.1 μL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (14.8 μL, 0.150 mmol) was then added and the tube was sealed and microwaved for 60 minutes. After cooling to room temperature, the solution was concentrated under reduced pressure and purified by column chromatography (hexanes/Et2O) to provide the title compound as a yellow amorphous solid in a mixture with the E isomer. (110.8 mg, 49 % yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ 10.67 (s, 1H), *10.64 (s, 1H), 8.75 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), *7.87 (s, 1H), 7.78 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), *7.67 (d, *J* = 7.0 Hz, 1H), 7.63 (dd, *J* = 7.9, 0.9 Hz, 1H), *7.58 (s, 1H), *7.48 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H),

7.00 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 166.97 (C), 141.04 (C), *136.97(C), 136.18 (C), 134.71 (CH), *133.86(CH), 133.70 (CH), 132.69 (CH), *132.17(CH), *131.63(CH), 130.87 (CH), *130.55 (CH), 130.25 (CH), 129.46 (CH), *128.80 (C), 128.12 (C), *127.99 (CH), 124.53 (C), *122.33 (CH), *121.94 (C), 121.41 (C), 121.19 (CH), 120.10 (CH), *110.29 (CH), 109.49 (CH). HRMS (ESI): Exact mass calcd for $C_{15}H_{10}BrNO$ $[M]^+$: 298.9946 Found: $[M+H]^+$ 300.0015.

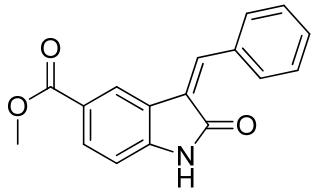


(Z)-3-(4-(trifluoromethyl)benzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 4-(trifluoromethyl)benzaldehyde (0.123 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for one hour. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% EtOAc/hexanes) to provide the title compound as a yellow crystalline solid with a trace amount of the *E* isomer. (131.5 mg, 61% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ *10.69 (s, 1H), 10.67 (s, 1H), *8.46 (d, *J* = 8.1 Hz, 2H), *7.90 (m, 1H), 7.89 (m, 4H), *7.81 (d, *J* = 8.1 Hz, 2H), *7.73 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), *7.25 (m, 1H), *7.01 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.85 (t, *J* = 7.5 Hz, 1H), *6.85 (m, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.27 (C), *166.85 (C), 143.30 (C), *141.29 (C), 138.79 (C), *137.74 (C), *134.39 (CH), 133.67 (CH), *131.99 (CH), 130.74 (CH), 129.91 (CH), *129.77 (CH), 129.37 (C), 129.23 (C), 125.63 (CH), *124.88 (CH), 124.34 (C), 122.62 (CH), 121.32 (CH), *121.26 (CH), 120.42 (C), *120.39 (CH),

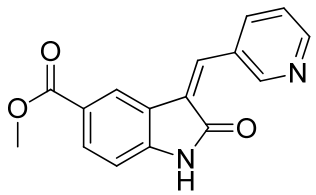
110.30 (CH), *109.55 (CH). HRMS (ESI): Exact mass calcd for $C_{16}H_{10}F_3NO$ $[M]^+$: 289.0714. Found: $[M+H]^+$: 290.0782.



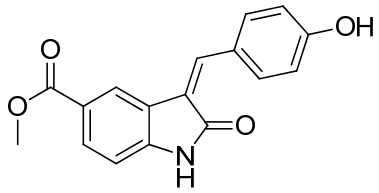
(Z)-3-(4-nitrobenzylidene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 4-nitrobenzaldehyde (0.135 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (10-100% Et_2O/hexanes) and the title compound was obtained as a mixture of *E*/*Z* isomers as an amorphous yellow solid. (143.4 mg, 62% yield). ^{1}H NMR (700 MHz; DMSO): *denotes the minor *E* isomer. δ *10.72 (s, 1H), 10.69 (s, 1H), *8.48 (d, *J* = 8.8 Hz, 2H), 8.33 (d, *J* = 8.7 Hz, 2H), *8.26 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 2H), *7.89 (s, 1H), *7.73 (d, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 7.6, 1H), 6.84 (m, 1H). ^{13}C NMR (176 MHz; DMSO) δ 168.18 (C), *166.78 (C), 147.45 (C), *147.39 (C), 143.51 (C), *141.56 (C), 141.46 (C), *140.25 (C), *133.45 (CH), 132.91 (CH), *132.47 (CH), 131.03 (CH), 130.45 (CH), *130.18 (CH), *130.15 (C), 130.08 (C), *124.22 (C), 129.91 (CH), *123.13 (CH), 122.88 (CH), 121.40 (CH), *121.38 (CH), *120.67 (CH), 120.28 (C), 110.40 (CH), *109.68 (CH), HRMS (ESI): Exact mass calcd for $C_{15}H_{10}N_2O_3$ $[M]^+$: 266.0691. Found $[M+Na]^+$: 289.0574.



(Z)-methyl 3-(3,5-dibromo-4-hydroxybenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and benzaldehyde (0.0920 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with a 30:70 mixture of *E*/*Z* isomers as a yellow amorphous solid. (148.4 mg, 71% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 11.04 (bs, 1H), *11.04 (bs, 1H), *8.43 (m, 2H), *8.33 (s, 1H), 8.17 (s, 1H), *8.04 (s, 1H), 7.87 (m, 1H), *7.87 (m, 1H), 7.73 (m, 3H), 7.54 (m, 2H), *7.54 (m, 2H), 7.48 (m, 1H), *7.48 (m, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), *6.93 (d, *J* = 8.1 Hz, 1H), *3.85 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 169.26 (C), *167.77 (C), *166.72 (C), 166.34 (C), 147.45 (C), *145.18 (C), *139.23 (CH), 137.95 (CH), 134.55 (C), *134.29 (C), 132.67 (CH), 132.32 (CH), *131.26 (CH), *130.60 (CH), 129.84 (CH), 129.26 (CH), *128.68 (CH), 127.14 (C), *125.91 (C), *125.53 (C), 123.64 (CH), *123.00 (C), 122.80 (C), 121.41 (C), *121.31 (CH), 110.44 (CH), *109.68 (CH), 52.39 (CH_3), *52.35 (CH_3). HRMS (EI): Exact mass calcd for $C_{17}H_{13}NO_3$ $[M]^+$: 279.0895. Found $[M+H]^+$: 280.0962.

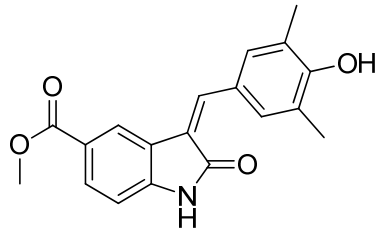


(Z)-methyl 2-oxo-3-(pyridin-3-ylmethylene)indoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3-pyridinecarboxaldehyde (0.0846 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with a 50:50 mixture of *E*/*Z* isomers as a yellow amorphous solid. (198.2 mg, 94% yield). ^{1}H NMR (700 MHz; DMSO): δ 11.08 (bs, 2H), 9.24 (s, 1H), 8.92 (d, *J* = 7.9 Hz, 1H), 8.90 (s, 1H), 8.69 (d, *J* = 4.5 Hz, 1H), 8.59 (d, *J* = 4.3 Hz, 1H), 8.31 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.87 (t, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.57 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.49 (dd, *J* = 7.9, 4.9 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 168.82 (C), 167.73 (C), 166.61 (C), 166.22 (C), 153.22 (CH), 151.07 (CH), 150.93 (CH), 150.21 (CH), 147.66 (C), 145.50 (C), 138.53 (CH), 137.03 (CH), 135.24 (CH), 134.25 (CH), 132.67 (CH), 131.74 (CH), 130.75 (C), 130.23 (C), 128.81 (C), 127.92 (C), 125.01 (C), 124.11 (CH), 123.65 (CH), 123.46 (CH), 123.14 (C), 122.92 (C), 121.65 (CH), 121.20 (C), 110.60 (CH), 109.86 (CH), 52.42 (CH_3), 52.37 (CH_3). HRMS (EI): Exact mass calcd for $C_{16}H_{12}N_2O_3$ $[M]^+$: 280.0848. Found $[M+H]^+$: 281.0927.



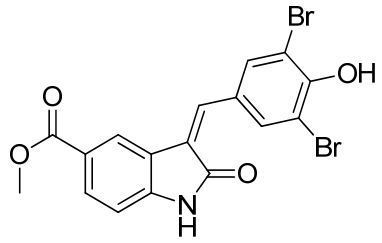
(Z)-methyl 3-(4-hydroxybenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 4-hydroxybenzaldehyde (0.110 g, 0.901 mmol) were

added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 20 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a yellow amorphous solid with traces of the *E* isomer. (194.5 mg, 88% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.95 (s, 1H), 10.25 (bs, 1H), 8.34 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 6.4 Hz, 2H), 7.62 (s, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 169.21 (C), 166.05 (C), 159.76 (C), 146.50 (C), 138.29 (CH), 132.03 (CH), 131.13 (CH), 124.62 (C), 123.54 (C), 122.71 (CH), 122.17 (C), 121.40 (C), 115.67 (CH), 109.73 (CH), 51.91 (CH_3). HRMS (EI): Exact mass calcd for $C_{17}H_{13}NO_4$ $[M]^+$: 295.0845. Found $[M+H]^+$: 296.0911.



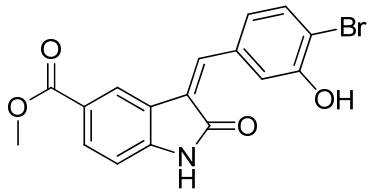
(Z)-methyl 3-(4-hydroxy-3,5-dimethylbenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3,5-dimethyl-4-hydroxybenzaldehyde (0.135 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a yellow amorphous solid with a 66:33 mixture of *Z*/*E* isomers. (231.5 mg, 95% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 10.93 (s, 1H), *10.90 (s, 1H), 9.10 (bs, 1H), *9.10

(bs, 1H), 8.47 (s, 1H), *8.25 (s, 1H), 8.24 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), *7.83 (s, 1H), *7.82 (d, *J* = 8.1 Hz, 1H), *7.58 (s, 2H), 7.41 (s, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), *6.91 (d, *J* = 8.1 Hz, 1H), *3.84 (s, 3H), 3.78 (s, 3H), 2.24 (s, 6H), *2.21 (s, 6H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.26 (C), *167.56 (C), *166.39 (C), 166.01 (C), *156.91 (C), 155.83 (C), 146.42 (C), *143.87 (C), *139.65 (CH), 138.49 (CH), 133.98 (CH), *130.98 (CH), 130.70 (CH), *129.55 (CH), *125.84 (C), *125.47 (C), 124.60 (C), 123.75 (C), 123.38 (C), 122.90 (CH), *122.20 (C), 122.08 (C), 121.43 (C), *121.22 (C), *119.84 (CH), 109.70 (CH), *108.86 (CH), 51.86 (CH_3), *51.80 (CH_3), *16.69 (CH_3), 16.38 (CH_3). HRMS (ESI): Exact mass calcd for $C_{19}H_{17}NO_4$ $[M]^+$: 323.1158. Found: $[M+Na]^+$: 346.1052.



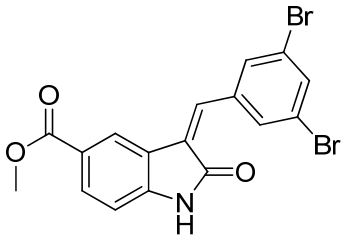
(Z)-methyl 3-(3,5-dibromo-4-hydroxybenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3,5-dibromo-4-hydroxybenzaldehyde (0.252 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 6 hours. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with a 45:65 mixture of *E*/*Z* isomers as a yellow amorphous solid. (206.3 mg, 61% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 11.06 (s, 1H), *11.02 (s, 1H), 10.71 (bs, 1H), *10.71 (bs, 1H), 8.85 (s, 2H), 8.28 (s, 1H), *8.25 (s, 1H), *7.97 (s, 2H), 7.92 (s, 1H), *7.87 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), *7.58 (s, 1H), *6.97 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J*

= 8.1 Hz, 1H), 3.85 (s, 3H), *3.78 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ *168.67 (C), 167.50 (C), 166.21 (C), *165.75 (C), 152.95 (C), *152.30 (C), *146.98 (C), 144.48 (C), 136.47 (CH), *135.86 (CH), *134.71 (CH), 133.56 (CH), *131.84 (CH), 130.59 (CH), 128.44 (C), *128.14 (C), *126.36 (C), 125.06 (C), 124.58 (C), 122.55 (C), *122.32 (C), *120.76 (C), *111.84 (C), 111.06 (C), *110.07 (CH), 109.25 (CH), *51.90 (CH_3), 51.88 (CH_3). HRMS (EI): Exact mass calcd for $C_{17}H_{11}Br_2NO_4$ [M]+: 450.9055. Found $[M+Na]^+$: 473.8953.



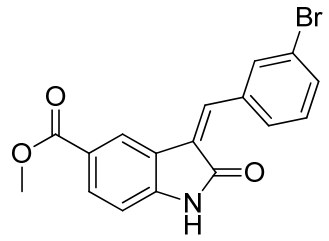
(Z)-methyl 3-(4-bromo-3-hydroxybenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3-bromo-4-hydroxybenzaldehyde (0.181 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for one hour. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a yellow amorphous solid with trace amount of the *E* isomer. (202.0 mg, 77% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 11.14 (bs, 1H), 11.01 (s, 1H), *10.99 (s, 1H), 8.98 (s, 1H), 8.32 (d, *J* = 8.5, 1H), *8.29 (d, *J* = 8.4 Hz, 1H), *8.28 (s, 1H), *7.96 (s, 1H), 7.92 (s, 1H), *7.87 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), *7.62 (m, 1H), *7.60 (s, 1H), *7.09 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), *6.97 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 3.84 (s, 3H), *3.78 (s, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ *168.99 (C), 167.62 (C), 166.34 (C), *165.94 (C), 156.80 (C), *156.08 (C), *146.75 (C), 144.20 (C), 137.70 (CH), 137.32 (CH), *136.54 (CH), *134.46 (CH), 134.26 (CH), *131.50 (CH), *130.95 (CH), 130.16 (CH), 126.99

(C), *126.31 (C), 125.42 (C), *124.90 (C), 122.91 (C), *122.87 (CH), 122.43 (C), *122.28 (C), *121.09 (C), 120.36 (CH), *116.35 (CH), 115.88 (CH), *109.93 (CH), *109.63 (C), 109.22 (C), 109.11 (CH), *51.93 (CH_3), 51.88 (CH_3). HRMS (ESI): Exact mass calcd for $C_{17}H_{12}BrNO_4$ $[M]^+$: 372.9950. Found: $[M\text{-}H]^+$: 371.9887.

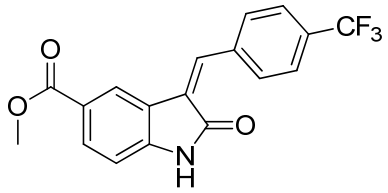


(*Z*)-methyl 3-(3,5-dibromobenzylidene)-2-oxoindoline-5-carboxylate: Methyl-2-oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3,5-dibromobenzaldehyde (0.238 g, 0.901 mmol) were added to methanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 60 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water, DCM, and MeOH to provide the title compound as a yellow amorphous solid in a mixture with the *E* isomer. (271.3 mg, 82% yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ 11.10 (bs, 1H), *11.10 (bs, 1H), *9.92 (s, 1H), 8.67 (s, 2H), 8.30 (s, 1H), *8.18 (s, 1H), *8.07 (s, 2H), 7.98 (m, 2H), 7.95 (m, 2H), 7.90 (m, 3H), 7.63 (s, 1H), 6.99 (m, 1H), *6.94 (m, 1H), 3.85 (s, 3H), *3.77 (s, 3H).^{13}C NMR (176.06 MHz; DMSO): δ 190.92 (C), 168.40 (C), 167.19 (C), 166.15 (C), 165.70 (C), 147.37 (C), 145.19 (C), 138.79 (CH), 138.19 (C), 137.54 (C), 134.95 (CH), 134.77 (CH), 134.38 (CH), 133.92 (CH), 133.21 (CH), 132.46 (CH), 131.61 (CH), 131.10 (CH), 130.97 (CH), 128.76 (C), 128.10 (C), 124.51 (C), 123.44 (CH), 123.41 (C), 122.85 (C), 122.83 (C), 122.51 (C), 122.18 (C), 121.43 (CH),

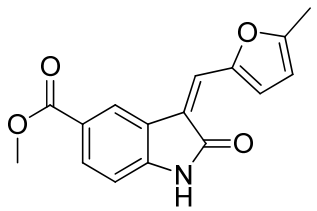
120.46 (C), 110.33 (CH), 109.59 (CH), 52.00 (CH_3), 51.99 (CH_3). HRMS (ESI): Exact mass calcd for $C_{17}H_{11}Br_2NO_3$ $[M]^+$: 437.0821. Found: $[M\text{-}H]^-$ 435.9015.



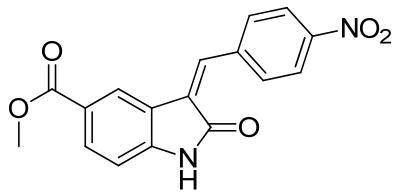
(Z)-methyl 3-(3-bromobenzylidene)-2-oxoindoline-5-carboxylate: Methyl-2-oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3-bromobenzaldehyde (105.1 μL, 0.901 mmol) were added to methanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 60 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water to provide the title compound as a yellow amorphous solid in a mixture with the E isomer. (250.30 mg, 93% yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ 11.04 (bs, 1H), *8.78 (s, 1H), 8.31 (s, 1H), 8.10 (s, 1H), *8.01 (s, 1H), 7.93 (s, 1H), 7.88 (t, *J* = 6.9 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.68 (s, 1H), *7.65 (d, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), *7.44 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), *6.93 (d, *J* = 8.1 Hz, 1H), *3.85 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.52 (C), *167.19 (C), *166.14 (C), 165.72 (C), 147.15 (C), *144.93 (C), *136.69 (CH), 136.47 (C), *136.00 (C), 135.49 (CH), 134.04 (CH), *133.09 (CH), *132.57 (CH), 132.12 (CH), 131.68 (CH), *131.17 (CH), *131.13 (CH), 130.83 (CH), *130.27 (CH), 128.31 (CH), 127.76 (C), *126.80 (C), *124.72 (C), 123.26 (CH), *122.64 (C), 122.38 (C), 122.00 (C), *121.42 (C), *121.13 (CH), 120.63 (C), 110.10 (CH), *109.34 (CH), 51.88 (CH3). HRMS (ESI): Exact mass calcd for $C_{17}H_{12}BrNO_3$ $[M]^+$: 357.0001. Found: $[M+Na]^+$ 379.9881.



(Z)-methyl 2-oxo-3-(4-(trifluoromethyl)benzylidene)indoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 4-(trifluoromethyl)benzaldehyde (0.123 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for one hour. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as yellow needles with a 60:40 mixture of *Z*/*E* isomers. (202.0 mg, 77% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 11.10 (s, 1H), *11.10 (s, 1H), *8.51 (d, *J* = 8.1 Hz, 2H), *8.36 (s, 1H), *8.14 (s, 1H), 7.94 (s, 1H), 7.91 (m, 4H), *7.91 (m, 1H), 7.88 (dd, *J* = 8.2, 1.4 Hz, 1H), *7.83 (d, *J* = 8.2 Hz, 2H), 7.78 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), *6.94 (d, *J* = 8.1 Hz, 1H), *3.86 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.41 (C), *167.06 (C), *166.13 (C), 165.72 (C), 147.27 (C), *145.19 (C), 138.52 (C), *137.53 (C), *136.42 (CH), 135.42 (CH), 132.26 (CH), *131.48 (CH), 129.94 (CH), *129.76 (C), *129.57 (C), 128.49 (C), 127.80 (C), 125.63 (CH), *124.91 (CH), *124.52 (C), 123.37 (CH), 122.72 (C), 122.43 (C), *121.43 (CH), *120.57 (C), 110.15 (CH), *109.43 (CH), 51.93 (CH_3), *51.91 (CH_3). HRMS (ESI): Exact mass calcd for $C_{18}H_{12}F_3NO_3$ $[M]^+$: 347.0769. Found: $[M+H]^+$: 348.0833.

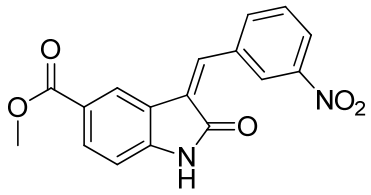


(Z)-methyl 3-((5-methylfuran-2-yl)methylene)-2-oxoindoline-5-carboxylate: Methyl-2-oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 5-methylfurancarboxaldehyde (89.64 µL, 0.901 mmol) were added to methanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (14.8 µL, 0.150 mmol) was then added and the tube was sealed and microwaved for 20 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water, DCM, and MeOH to provide the title compound as a yellow amorphous solid with trace amounts of the *E* isomer. (163.7 mg, 77 % yield). ^{1}H NMR (700 MHz; DMSO): δ 10.89 (br s, 1H), 9.06 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.30 (s, 1H), 7.21 (d, *J* = 3.0 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 3.84 (s, 3H), 3.34 (s, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.67 (C), 166.26 (C), 157.48 (C), 149.20 (C), 146.15 (C), 130.75 (CH), 125.69 (CH), 123.46 (CH), 122.38 (C), 121.42 (C), 120.42 (CH), 119.57 (C), 110.60 (CH), 109.29 (CH), 51.79 (CH_3), 13.75 (CH_3). HRMS (ESI): Exact mass calcd for $C_{16}H_{13}NO_4$ $[M]^+$: 283.0845 Found: $[M+H]^+$ 284.0915.



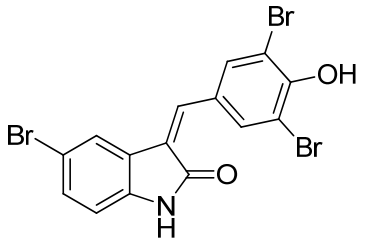
(Z)-methyl 3-(4-nitrobenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 4-nitrobenzaldehyde (0.136 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with a 50:50 mixture

of *E*/*Z* isomers as a yellow amorphous solid. (218.9 mg, 90% yield). ^{1}H NMR (700 MHz; DMSO): δ 11.12 (bs, 2H), 8.53 (d, *J* = 8.7 Hz, 2H), 8.36 (d, *J* = 8.4 Hz, 2H), 8.34 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 2H), 8.14 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 2H), 7.96 (s, 1H), 7.89 (dd, *J* = 12.9, 8.2 Hz, 2H), 7.76 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 168.32 (C), 166.98 (C), 166.07 (C), 165.72 (C), 147.70 (C), 147.60 (C), 147.46 (C), 145.40 (C), 141.05 (C), 139.97 (C), 135.40 (CH), 134.56 (CH), 132.72 (CH), 132.51 (CH), 131.80 (CH), 130.59 (CH), 129.03 (C), 128.81 (C), 124.38 (C), 123.85 (CH), 123.51 (CH), 123.13 (CH), 122.80 (C), 122.52 (C), 121.68 (CH), 120.39 (C), 110.24 (CH), 109.53 (CH), 51.98 (CH_3), 51.93 (CH_3). HRMS (EI): Exact mass calcd for $C_{17}H_{12}N_2O_5$ [M]+: 324.0746. Found $[M+Na]^+$: 347.0622.



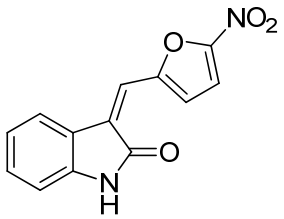
(Z)-methyl 3-(3-nitrobenzylidene)-2-oxoindoline-5-carboxylate: Methyl oxindole-5-carboxylate (0.144 g, 0.751 mmol) and 3-nitrobenzaldehyde (0.136 mg, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with a 40:60 mixture of *E*/*Z* isomers as a yellow amorphous solid. (220.8 mg, 91% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 11.10 (bs, 1H), *11.10 (bs, 1H), 9.40 (s, 1H), 8.70 (d, *J* = 7.6 Hz, 1H), *8.55 (s, 1H), 8.33 (m, 1H), *8.33 (m, 1H), 8.26 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.16 (m, 1H), *8.16 (m, 1H), *7.99 (s, 1H), 7.88 (m, 1H), *7.88 (m, 1H), *7.83 (t, *J* = 8.0 Hz, 1H), *7.78

(s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), *6.97 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 3.84 (s, 3H), *3.72 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 168.86 (C), 167.64 (C), 166.57 (C), 166.13 (C), 148.38 (C), 148.11 (C), 147.82 (C), 145.62 (C), 138.52 (CH), 136.26 (C), 136.19 (CH), 136.17 (CH), 135.64 (C), 135.04 (CH), 132.84 (CH), 131.93 (CH), 130.89 (CH), 130.12 (CH), 129.03 (C), 128.29 (C), 126.61 (CH), 125.18 (CH), 124.96 (CH), 124.82 (CH), 124.30 (CH), 123.69 (CH), 123.22 (C), 122.92 (C), 121.87 (CH), 120.88 (C), 110.68 (CH), 109.94 (CH), 52.37 (CH_3). HRMS (EI): Exact mass calcd for $C_{17}H_{12}N_2O_5$ [M]+: 324.0746. Found $[M+Na]^+$: 347.0618.



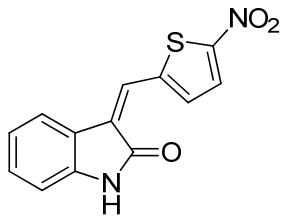
(Z)-5-bromo-3-(3,5-dibromo-4-hydroxybenzylidene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 3,5-dibromo-4-hydroxybenzaldehyde (0.252 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound in a mixture of *E*/*Z* isomers, and traces of a tautomer, as a yellow amorphous solid. (231.6 mg, 65% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer, ** denotes trace tautomer. δ 10.78 (s, 1H), *10.74 (s, 1H), 8.78 (s, 2H), **8.01 (s, 1H), *7.92 (s, 2H), 7.87 (s, 1H), 7.81 (s, 1H), *7.60 (s, 1H), *7.55 (s, 1H), *7.41 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.2 Hz, 1H), *6.84 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), **6.75 (d, *J* = 8.2 Hz, 1H), 3.31 (bs, 1H). ^{13}C NMR (176 MHz; DMSO): δ **175.88 (C), *168.00 (C), 166.91 (C), 153.20 (C), 152.33 (C), *142.09 (C), 139.55

(C), 136.41 (CH), 135.91 (CH), *134.95 (CH), 133.37 (CH), *132.38 (CH), 130.91 (CH), *130.05 (CH), 128.18 (C), *128.07 (C), 127.27 (C), *127.20 (CH), *126.51 (C), *124.51 (C), *124.48 (CH), *122.90 (C), 122.34 (CH), 113.09 (C), *112.59 (C), *112.08 (CH), 111.85 (C), 111.28 (CH), 111.17 (C), *110.86 (CH). HRMS (EI): Exact mass calcd for $C_{15}H_8Br_3NO_2$ [M]+: 470.8105. Found $[M+Na]^+$: 493.8003.

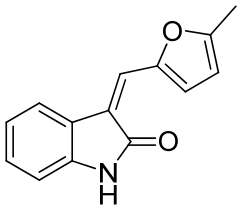


(*Z*)-3-(5-nitrofuran-2-yl)methylene)indolin-2-one: oxindole (0.100 g, 0.751 mmol) and 5-nitrofurfural (0.127 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a sandy yellow amorphous solid with a trace amount of the *E* isomer. (192.0 mg, 85% yield). ^{1}H NMR (700 MHz; DMSO): * denotes minor isomer. δ *10.78 (s, 1H), 10.72 (s, 1H), 8.54 (d, *J* = 7.8 Hz, 1H), *8.33 (d, *J* = 4.0 Hz, 1H), 7.86 (d, *J* = 4.0 Hz, 1H), *7.84 (d, *J* = 7.5 Hz, 1H), *7.80 (d, *J* = 4.0 Hz, 1H), *7.75 (s, 1H), 7.49 (d, *J* = 3.9 Hz, 1H), 7.37 (s, 1H), 7.34 (td, *J* = 7.6 Hz, 0.7 Hz, 1H), *7.27 (t, *J* = 7.0 Hz, 1H), 7.05 (7.7 Hz, 0.8 Hz, 1H), *6.99 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), *6.84 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.43 (C), *166.65 (C), 152.63 (C), 152.38 (C), *151.43 (C), 143.96 (C), *141.72 (C), 131.71 (CH), *130.80 (CH), *130.20 (C), 128.00 (C), 125.49 (CH), *123.32 (C), 121.72 (CH), *121.51 (CH), *121.42 (CH), 121.30 (CH), 120.34 (C), *119.84 (CH), *118.62 (CH),

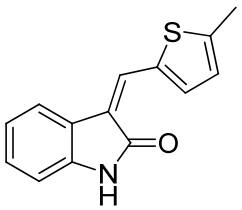
116.89 (CH), *115.02 (CH), 114.71 (CH), 110.20 (CH), *109.82 (CH). HRMS (ESI): Exact mass calcd for $C_{13}H_8N_2O_4$ $[M]^+$: 256.0484. Found: $[M+Na]^+$: 279.0374.



(Z)-3-((5-nitrothiophen-2-yl)methylene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 5-nitro-2-thiophenecarbaldehyde (0.142 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a brown crystalline solid with a trace of the *E* isomer. (162.4 mg, 79% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.89 (s, 1H), 8.15 (s, 1H), 8.12 (d, *J* = 4.2 Hz, 1H), 7.74 (d, *J* = 4.2 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 167.29 (C), 153.19 (C), 142.97 (C), 141.60 (C), 136.11 (CH), 130.43 (CH), 128.77 (CH), 127.10 (C), 126.65 (CH), 123.28 (C), 121.53 (CH), 120.67 (CH), 110.06 (CH). HRMS (ESI): Exact mass calcd for $C_{13}H_8N_2O_3S$ $[M]^+$: 272.0256. Found: $[M+Na]^+$ 295.0148.

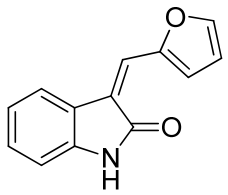


(Z)-3-(5-methylfuran-2-yl)methylene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 5-methylfurfural (0.0896 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with H_2O to provide the title compound as a sandy yellow amorphous solid with trace amounts of the *E* isomer. (117.0 mg, 69% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ *10.54 (s, 1H), 10.50 (s, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), *8.22 (d, *J* = 7.0 Hz, 1H), *7.68 (d, *J* = 7.0 Hz, 1H), *7.60 (s, 1H), 7.23 (m, 2H), 7.17 (d, *J* = 3.1 Hz, 1H), 7.02 (t, *J* = 7.0 Hz, 1H), *6.95 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 6.8 Hz, 1H), *6.82 (d, *J* = 7.0 Hz, 1H), 6.46 (d, *J* = 3.1 Hz, 1H), *6.41 (d, *J* = 7.0 Hz, 1H), 2.52 (s, 3H), *2.39 (s, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.42 (C), 157.22 (C), 149.39 (C), 142.27 (C), 129.17 (CH), 124.34 (CH), 122.57 (CH), 121.47 (C), 121.31 (CH), 120.61 (C), 119.36 (CH), 110.37 (CH), 109.57 (CH), 13.95 (CH3). HRMS (ESI): Exact mass calcd for C14H11NO2 [M]+: 225.0790. Found: $[M+Na]^+$ 248.0681.

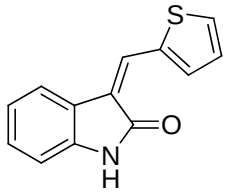


(Z)-3-(5-methylthiophen-2-ylmethylene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and 5-methyl-2-thiophenecarbaldehyde (0.0972 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and

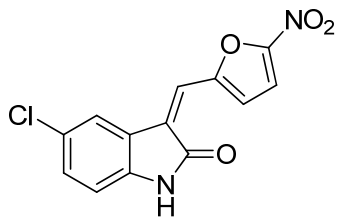
H_2O to provide the title compound as a brown crystalline solid with a trace of the *E* isomer. (141.7 mg, 93% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.56 (s, 1H), 7.98 (s, 1H), 7.72 (d, *J* = 3.6 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.96 (m, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.34 (C), 148.68 (C), 140.21 (C), 138.25 (CH), 135.53 (C), 128.50 (CH), 128.05 (CH), 126.28 (CH), 124.53 (C), 120.83 (CH), 120.21 (C), 119.14 (CH), 109.32 (CH), 15.40 (CH_3). HRMS (ESI): Exact mass calcd for $C_{14}H_{11}NOS$ $[M]^+$: 241.0561. Found: $[M+Na]^+$ 264.0454.



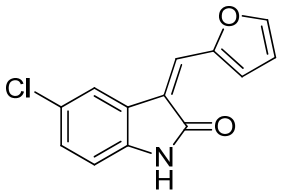
(Z)-3-(furan-2-ylmethylene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and furfural (0.0746 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by flash column chromatography (10-100% Et_2O/hexanes) to provide the title compound as a yellow crystalline solid with trace amounts of the *E* isomer. (139.0 mg, 84% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.56 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.15 (s, 1H), 7.33 (s, 1H), 7.26 (m, 2H), 7.01 (t, *J* = 7.0 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.30 (C), 150.70 (C), 147.26 (CH), 142.58 (C), 129.72 (CH), 124.52 (CH), 122.19 (C), 121.36 (C), 121.27 (CH), 120.81 (CH), 119.33 (CH), 113.54 (CH), 109.74 (CH). HRMS (ESI): Exact mass calcd for C13H9NO2 [M]+: 211.0633. Found: $[M+Na]^+$ 234.0522.



(Z)-3-(thiophen-2-ylmethylene)indolin-2-one: Oxindole (0.100 g, 0.751 mmol) and thenaldehyde (0.0842 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by flash column chromatography (10-100% Et_2O/hexanes) to provide a mixture of *E*/*Z* isomers as a yellow amorphous solid. (170.5 mg, 68% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 10.62 (s, 1H), *10.60 (s, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), *8.10 (s, 1H), 7.98 (d, *J* = 4.8 Hz, 1H), *7.94 (d, *J* = 3.1 Hz, 1H), *7.88 (d, *J* = 4.9 Hz, 1H), 7.81 (d, *J* = 3.3 Hz, 1H), 7.79 (s, 1H), *7.86 (d, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 4.7 Hz, 4.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), *7.23 (m, 1H), *7.19 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), *6.99 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), *6.85 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ *denotes minor isomer 169.17 (C), *167.28 (C), 142.64 (C), *140.45 (C), *137.47 (CH), *137.38 (C), 137.05 (C), 136.02 (CH), *134.23 (CH), 131.93 (CH), 129.84 (CH), *128.63 (CH), *128.44 (CH), 128.09 (CH), *127.47 (CH), 127.13 (CH), *124.35 (C), 123.42 (C), *123.15 (CH), *121.68 (C), 121.20 (CH), *120.94 (CH), 120.66 (C), 119.41 (CH), 110.04 (CH), *109.43 (CH). HRMS (ESI): Exact mass calcd for $C_{13}H_9NOS$ $[M]^+$: 227.0405. Found: $[M+Na]^+$ 250.0298.

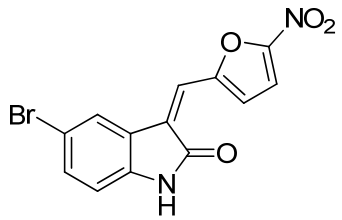


(*Z*)-5-chloro-3-(5-nitrofuran-2-yl)methylene)indolin-2-one: 5-chlorooxindole (0.126 g, 0.751 mmol) and 5-nitrofurfural (0.127 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a sandy yellow amorphous solid with a trace of the *E* isomer. (131.4 mg, 61% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.82 (s, 1H), 8.56 (s, 1H), 7.86 (d, *J* = 3.9 Hz, 1H), 7.52 (d, *J* = 3.7 Hz, 1H), 7.41 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.14 (C), 152.51 (C), 151.89 (C), 142.54 (C), 130.91 (CH), 126.83 (C), 126.00 (C), 125.23 (CH), 122.07 (CH), 121.76 (C), 118.32 (CH), 114.46 (CH), 111.37 (CH). HRMS (ESI): Exact mass calcd for $C_{13}H_7ClN_2O_4$ $[M]^+$: 290.0094. Found: $[M+Na]^+$: 312.9979.

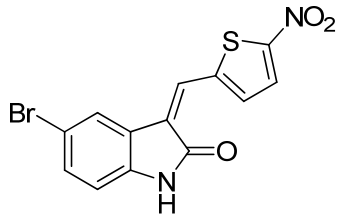


(*Z*)-5-chloro-3-(furan-2-yl)methylene)indolin-2-one: 5-chloro-oxindole (0.126 g, 0.751 mmol) and furfural (0.0746 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room

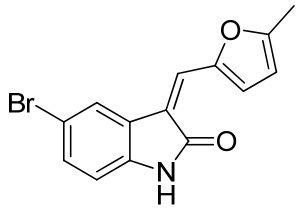
temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a sandy yellow amorphous solid with a trace of the *E* isomer. (191.97 mg, 85% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.70 (s, 1H), 8.30 (d, *J* = 1.2 Hz, 1H), 8.26 (s, 1H), 7.30 (s, 1H), 7.33 (d, *J* = 3.3 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.00 (C), 150.48 (C), 147.99 (CH), 141.26 (C), 129.08 (CH), 125.33 (C), 123.80 (CH), 122.88 (C), 122.14 (CH), 120.96 (C), 120.73 (CH), 113.78 (CH), 111.04 (CH). HRMS (ESI): Exact mass calcd for $C_{13}H_6ClNO_2$ $[M]^+$: 245.0244. Found: $[M+H]^+$: 246.0313.



(Z)-5-bromo-3-((5-nitrofuran-2-yl)methylene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 5-nitro-furfural (0.127 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a fine dark purple amorphous solid. (250.4 mg, 99% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.85 (s, 1H), 8.74 (s, 1H), 7.87 (d, *J* = 3.9 Hz, 1H), 7.53 (d, *J* = 3.7 Hz, 1H), 7.51 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.44 (s, 1H), 6.85 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (176 MHz; DMSO): δ 168.05 (C), 152.54 (C), 151.87 (C), 142.91 (C), 133.78 (CH), 127.97 (CH), 126.68 (C), 122.25 (C), 122.14 (CH), 118.40 (CH), 114.47 (CH), 113.72 (C), 111.92 (CH). HRMS (EI): Exact mass calcd for $C_{13}H_7BrN_2O_4$ [M]+: 333.9589. Found $[M+Na]^+$: 356.9467.

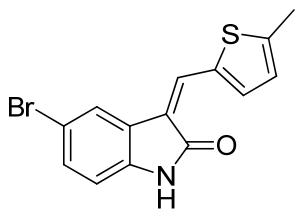


(Z)-5-bromo-3-((5-nitrothiophen-2-yl)methylene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 5-nitro-2-thiophenecarboxaldehyde (0.142 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a fine dark purple amorphous solid with trace amounts of the *E* isomer. (224.5 mg, 85% yield). ^{1}H NMR (700 MHz; DMSO): δ 11.01 (s, 1H), 8.28 (s, 1H), 8.13 (d, *J* = 4.2 Hz, 1H), 7.95 (s, 1H), 7.70 (d, *J* = 4.3 Hz, 1H), 7.43 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (176 MHz; DMSO): δ 166.91 (C), 153.69 (C), 142.50 (C), 140.55 (C), 136.67 (CH), 132.46 (CH), 128.78 (CH), 128.45 (CH), 125.81 (C), 125.53 (C), 123.37 (CH), 113.40 (C), 111.93 (CH). HRMS (EI): Exact mass calcd for $C_{13}H_7BrN_2O_3S$ [M]+: 349.9361. Found $[M+Na]^+$: 372.9243.



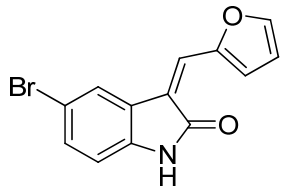
(Z)-5-bromo-3-((5-methylfuran-2-yl)methylene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 5-methylfurfural (0.0896 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150

mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with trace amounts of the *E* isomer as an orange amorphous solid. (172.9 mg, 76% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ *10.67 (s, 1H), 10.66 (s, 1H), 8.46 (d, *J* = 1.6 Hz, 1H), *8.25 (d, *J* = 3.1 Hz, 1H), *7.96 (d, *J* = 1.5 Hz, 1H), *7.76 (s, 1H), 7.40 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.32 (s, 1H), 7.25 (d, *J* = 3.3 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), *6.78 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 3.3 Hz, 1H), *6.45 (d, *J* = 3.4 Hz, 1H), 2.52 (s, 3H), *2.41 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 169.00 (C), *166.75 (C), 157.71 (C), *156.87 (C), *149.67 (C), 149.20 (C), 141.29 (C), *139.25 (C), 131.24 (CH), *130.39 (CH), 126.74 (CH), 123.85 (CH), 123.60 (C), *122.96 (CH), *122.29 (CH), *121.75 (CH), 120.69 (CH), *119.63 (C), 119.39 (C), 112.92 (C), 111.38 (CH), *111.08 (CH), *110.80 (CH), 110.75 (CH). HRMS (EI): Exact mass calcd for $C_{14}H_{10}BrNO_2$ [M]+: 302.9895. Found $[M+Na]^+$: 325.9771.

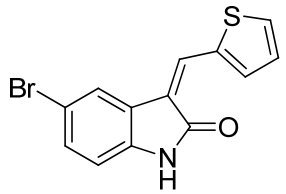


(Z)-5-bromo-3-((5-methylthiophen-2-yl)methylene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 5-methyl-2-thiophenecarboxaldehyde (0.0972 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as fine brown needles

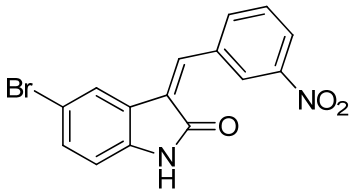
with trace amounts of the *E* isomer. (191.3 mg, 80% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.68 (s, 1H), 8.14 (s, 1H), 7.90 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.32 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (176 MHz; DMSO): δ 167.01 (C), 149.85 (C), 139.14 (CH), 135.38 (C), 130.43 (CH), 130.13 (CH), 126.97 (C), 126.58 (CH), 121.89 (CH), 118.88 (C), 112.88 (C), 111.17 (CH), 15.50 (CH_3). HRMS (EI): Exact mass calcd for $C_{14}H_{10}BrNOS$ [M]+: 318.9666. Found $[M+Na]^+$: 341.9564.



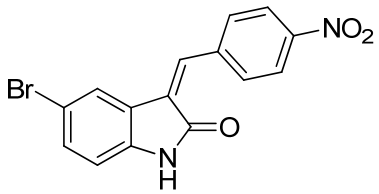
(Z)-5-bromo-3-(furan-2-ylmethylene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and furfural (0.0746 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a brown crystalline solid with trace amounts of the *E* isomer. (194.9 mg, 89% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.71 (s, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 8.25 (d, *J* = 1.3 Hz, 1H), 7.42 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 3.4 Hz, 1H), 6.83 (m, 2H). ^{13}C NMR (176 MHz; DMSO): δ 168.85 (C), 150.47 (C), 147.96 (CH), 141.61 (C), 131.89 (CH), 126.52 (CH), 123.36 (C), 122.16 (CH), 120.81 (C), 120.72 (CH), 113.80 (CH), 113.06 (C), 111.56 (CH). HRMS (EI): Exact mass calcd for $C_{13}H_8BrNO_2$ [M]+: 288.9738. Found $[M+Na]^+$: 311.9617.



(Z)-5-bromo-3-(thiopehn-2-ylmethylene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 2-thiophenecarboxaldehyde (0.0842 mL, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound as a mixture of *E*/*Z* isomers in the form of fine yellow needles. (229.9 mg, 92% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ *10.81 (s, 1H), 10.76 (s, 1H), *8.31 (d, *J* = 1.8 Hz, 1H), 8.30 (s, 1H), *8.09 (d, *J* = 4.9 Hz, 1H), 7.98 (m, 3H), *7.90 (m, 2H), *7.50 (dd, *J* = 8.3, 1.9 Hz, 1H), *7.39 (d, *J* = 1.9 Hz, 1H), 7.38 (m, 1H), 7.29 (dd, *J* = 4.7, 4.0 Hz, 1H), *6.92 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (176 MHz; DMSO): δ *169.71 (C), 167.86 (C), *142.65 (C), 140.34 (C), 139.19 (CH), *138.18 (CH), 138.14 (C), *137.57 (C), 136.14 (CH), *133.86 (CH), *133.00 (CH), 131.47 (CH), 130.97 (CH), *129.86 (CH), *129.73 (CH), 128.61 (CH), 127.69 (C), *126.18 (CH), *123.73 (C), 123.13 (CH), 121.31 (C), 113.89 (C), *113.62 (C), *112.79 (CH), 112.21 (CH). HRMS (EI): Exact mass calcd for $C_{13}H_8BrNOS$ [M]+: 304.9510. Found $[M+Na]^+$: 327.9387.

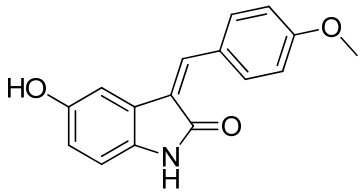


(Z)-5-bromo-3-(3-nitrobenzylidene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 3-nitrobenzaldehyde (0.136 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound with a 66:33 mixture of *Z*/*E* isomers, respectively, as a bright orange amorphous solid. (236.6 mg, 91% yield). ^{1}H NMR (700 MHz; DMSO): *denotes minor isomer. δ 10.85 (s, 1H), *10.83 (s, 1H), 9.38 (s, 1H), 8.65 (d, *J* = 7.8 Hz, 1H), *8.52 (s, 1H), *.8.32 (d, *J* = 8.2 Hz, 1H), 8.28 (m, 1H), *8.14 (d, *J* = 7.2 Hz, 1H), 8.08 (s, 1H), 7.98 (d, *J* = 1.9 Hz, 1H), *7.83 (t, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), *7.76 (s, 1H), 7.43 (m, 1H), 7.40 (dd, *J* = 8.2, 1.9 Hz, 1H), *6.85 (m, 1H), 6.80 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (176 MHz; DMSO): δ *167.76 (C), 166.57 (C), *148.00 (C), 147.68 (C), *142.49 (C), 140.29 (C), 138.00 (CH), 135.76 (CH), *135.71 (C), *134.83 (CH), *133.10 (CH), 131.95 (CH), *130.48 (CH), 129.77 (CH), *128.58 (C), 127.97 (C), 126.62 (C), 126.05 (CH), 124.77 (CH), *124.39 (CH), *123.71 (CH), 123.18 (CH), *122.45 (C), 113.27 (C), *112.77 (C), *112.25 (CH), 111.51 (CH). HRMS (EI): Exact mass calcd for $C_{15}H_9BrN_2O_3$ [M]+: 343.9797. Found $[M+Na]^+$: 366.9673.



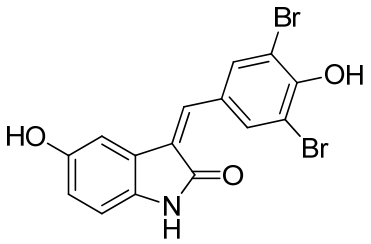
(Z)-5-bromo-3-(4-nitrobenzylidene)indolin-2-one: 5-Bromooxindole (0.159 g, 0.751 mmol) and 4-nitrobenzaldehyde(0.136 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (0.0148 mL, 0.150 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room

temperature, the precipitate was filtered via vacuum filtration and washed with CH_2Cl_2 and H_2O to provide the title compound in a 50:50 mixture of *E*/*Z* isomers as bright red crystals (218.1 mg, 84% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.86 (bs, 1H), 10.85 (bs, 1H), 8.50 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 8.8 Hz), 8.05 (s, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H) 7.43 (m, 3H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (176 MHz; DMSO): δ 168.17 (C), 166.87 (C), 148.23 (C), 148.12 (C), 143.09 (C), 141.39 (C), 141.02 (C), 140.36 (C), 135.92 (CH), 135.33 (CH), 133.80 (CH), 133.17 (CH), 132.78 (CH), 130.97 (CH), 129.48 (C), 129.45 (C), 126.98 (C), 125.42 (CH), 124.44 (CH), 123.94 (CH), 123.71 (CH), 122.86 (C), 113.78 (C), 113.31 (C), 112.77 (CH), 112.04 (CH). HRMS (EI): Exact mass calcd for $C_{15}H_9BrN_2O_3$ [M]+: 343.9797. Found $[M+Na]^+$: 366.9668.



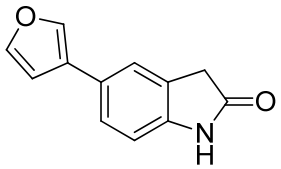
(Z)-methyl 3-((5-nitrofuran-2-yl)methylene)-2-oxoindoline-5-carboxylate: 5-hydroxyoxindole (0.112 g, 0.751 mmol) and 4-methoxybenzaldehyde (0.110 mL, 0.901 mmol) were added to a 1.1:1.3 M NH_4OAc/HOAc solution in ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (14.8 μL, 0.150 mmol) was then added and the tube was sealed and microwaved for 10 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water, DCM, and MeOH to provide the title compound as a brown amorphous solid with a 13:3 mixture of *Z*/*E* isomers. (191.1 mg, 95 % yield). ^{1}H NMR (600 MHz; DMSO): * denotes minor isomer. δ *10.26 (bs, 1H), 10.22 (bs, 1H), *9.87 (s, 1H), 8.96 (s, 1H), *8.48 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), *7.60 (s, 1H), 7.52 (s, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), *7.12 (m, 1H), 7.09 (d, *J* =

8.7 Hz, 2H), *7.02 (d, *J* = 8.9 Hz, 2H), 6.66 (s, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), *6.63 (d, *J* = 2.3 Hz, 1H), *6.61 (m, 1H), 3.85 (s, 3H), *3.83 (s, 3H). ^{13}C NMR (150 MHz; DMSO): δ 168.92 (C), 160.38 (C), 151.78 (CH), *136.15 (CH), 135.35 (CH), *134.15 (CH), 131.08 (CH), 126.40 (C), 126.26 (C), 116.00 (CH), *114.70 (CH), 114.26 (CH), 113.96 (CH), *113.42 (CH), 110.09 (CH), 109.42 (CH), *106.45 (CH), 55.11 (CH_3), *55.09 (CH_3). HRMS (ESI): Exact mass calcd for $C_{16}H_{13}NO_3$ $[M]^+$: 267.0895. Found: $[M+Na]^+$ 290.0424.



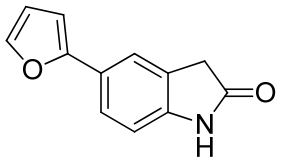
(Z)-3-(3,5-dibromo-4-hydroxybenzylidene)-5-hydroxyindolin-2-one: 5-Hydroxyoxindole (0.112 g, 0.751 mmol) and 3,5-dibromo-4-hydroxybenzaldehyde (0.252 g, 0.901 mmol) were added to ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (6.90 μL, 0.0698 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water, DCM, and EtOH to provide the title compound as a bright orange fluffy solid. (93.5 mg, 87 % yield). ^{1}H NMR (700 MHz; DMSO): δ 10.52 (bs, 1H), 10.26 (s, 1H), 9.04 (s, 1H), 7.85 (s, 2H), 7.41 (s, 1H), 6.94 (s, 1H), 6.66 (m, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 168.42 (C), 151.87 (C), 151.74 (C), 135.40 (C), 133.05 (CH), 132.93 (CH), 132.76 (CH), 132.59 (CH), 128.73 (C), 128.47 (C), 121.37 (C), 111.83 (CH), 111.82 (C). HRMS (ESI): Exact mass calcd for $C_{15}H_9Br_2NO_3$ $[M]^+$: 408.8949 Found: $[M+Na]^+$ 431.8821.

General procedure B (Suzuki Cross-Coupling reaction): To a clean Radley's Carousel Tube charged with a stir bar was added the 5-iodooxindole (1.0 equiv.), boronic acid (1.2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), and anhydrous dimethoxyethane as the solvent. The vial was then sealed and degassed with N_2 for 5 minutes. $NaHCO_3$ (2.0 equiv.) was then added to 1.0 mL dH_2O, dissolved, and added to the parent reaction mixture. The vessel was then sealed and refluxed for 18 hours at 70 °C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography.

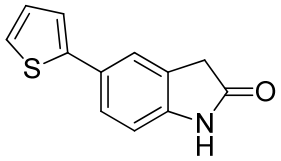


5-(furan-3-yl)indolin-2-one: 5-Iodooxindole (0.111 g, 0.429 mmol), 3-furanylboronic acid or pinacol ester (acid = 57.6 mg, 0.515 mmol, pinacol ester = 99.9 mg, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the title compound as a light brown amorphous solid (acid = 35.5 mg, 42% yield, pinacol ester = 25.8 mg, 30% yield). ^1H NMR (700

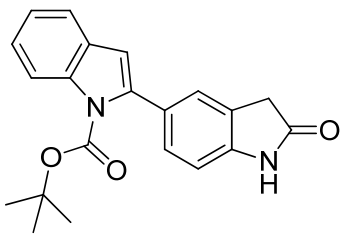
MHz; DMSO): δ 10.40 (s, 1H), 8.06 (s, 1H), 7.69 (d, *J* = 1.2 Hz, 1H), 7.46 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 3.50 (s, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.28 (C), 144.04 (CH), 142.62 (C), 138.12 (CH), 126.46 (C), 125.98 (C), 125.16 (C), 124.73 (CH), 121.81 (CH), 109.24 (CH), 108.61 (CH), 35.75 (CH_2). HRMS (ESI): Exact mass calcd for $C_{12}H_9NO_2$ $[M]^+$: 199.0633 Found: $[M+Na]^+$ 222.0530.



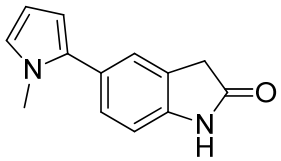
5-(furan-2-yl)indolin-2-one: 5-Iodooxindole (0.111 g, 0.429 mmol), 2-furanylboronic acid (57.6 mg, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the title compound as a light brown amorphous solid (84.7 mg, 99% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.46 (s, 1H), 7.67 (s, 1H), 7.55 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 3.1 Hz, 1H), 6.54 (d, *J* = 1.8 Hz, 1H), 3.52 (s, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.26 (C), 153.45 (C), 143.15 (C), 142.00 (CH), 126.55 (C), 124.01 (C), 122.96 (CH), 119.91 (CH), 111.91 (CH), 109.29 (CH), 103.86 (CH), 35.73 (CH_2). HRMS (ESI): Exact mass calcd for $C_{12}H_9NO_2$ $[M]^+$: 199.0633 Found: $[M+Na]^+$ 222.0531.



5-(thiophen-2-yl)indolin-2-one: 5-Iodooxindole (0.111 g, 0.429 mmol), 2-thienylboronic acid or pinacol ester (acid = 65.9 mg, 0.515 mmol, pinacol ester = 0.108 g, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the title compound as a light brown amorphous solid (acid = 51.4 mg, 56% yield, pinacol ester = 90.2 mg, 99% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.47 (s, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.36 (d, *J* = 3.4 Hz, 1H), 7.09 (t, *J* = 4.2 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 3.52 (s, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.27 (C), 143.90 (C), 143.31 (C), 128.35 (CH), 127.22 (C), 126.80 (C), 124.91 (CH), 124.32 (CH), 122.23 (CH), 121.74 (CH), 109.45 (CH), 35.76 (CH_2). HRMS (ESI): Exact mass calcd for $C_{12}H_9NOS$ $[M]^+$: 215.0405 Found: $[M+Na]^+$ 238.0305.

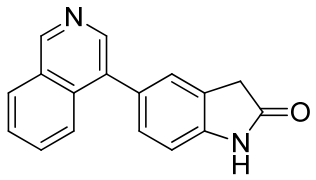


tert-butyl 2-(2-oxoindolin-5-yl)-1H-indole-1-carboxylate: 5-Iodooxindole (0.111 g, 0.429 mmol), N-boc-indole-2-boronic acid (0.134 g, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the title compound as a light brown amorphous solid (108 mg, 69% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.49 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.30 (m, 2H), 7.24 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.63 (s, 1H), 3.53 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.29 (C), 149.56 (C), 143.36 (C), 140.48 (C), 136.66 (C), 128.81 (C), 127.88 (CH), 127.07 (C), 125.34 (C), 124.73 (CH), 124.01 (CH), 122.88 (CH), 120.43 (CH), 114.48 (CH), 108.77 (CH), 108.45 (CH), 83.35 (C), 35.70 (CH_2), 27.14 (CH_3). HRMS (ESI): Exact mass calcd for $C_{21}H_{20}N_2O_3$ $[M]^+$: 364.1423 Found: $[M+Na]^+$ 371.1369.



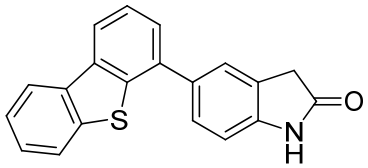
5-(1-methyl-1H-pyrrol-2-yl)indolin-2-one: 5-Iodooxindole (0.111 g, 0.429 mmol), 1-methyl-2-pyrroleboronic acid pinacol ester (0.107 g, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then

dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the title compound as a light brown amorphous solid (31.6 mg, 35% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.41 (s, 1H), 7.25 (s, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.77 (s, 1H), 6.02 (m, 2H), 3.59 (s, 3H), 3.50 (s, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.30 (C), 142.46 (C), 133.75 (C), 127.48 (CH), 126.21 (C), 126.08 (C), 124.44 (CH), 123.42 (CH), 108.97 (CH), 107.57 (CH), 107.14 (CH), 35.82 (CH_2), 34.66 (CH_3). HRMS (ESI): Exact mass calcd for $C_{13}H_{12}N_2O$ $[M]^+$: 212.0950 Found: $[M+Na]^+$ 235.0852.



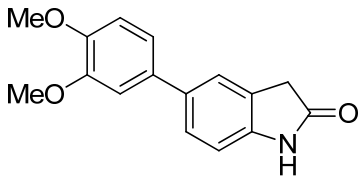
5-(isoquinolin-4-yl)indolin-2-one: 5-Iodooxindole (0.111 g, 0.429 mmol), 4-isoquinolineboronic acid (89.1 mg, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the

title compound as a light brown amorphous solid (51.9 mg, 46% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.55 (s, 1H), 9.30 (s, 1H), 8.4 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.38 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 3.58 (s, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.37 (C), 151.53 (CH), 143.69 (C), 142.36 (CH), 133.36 (C), 132.61 (C), 130.89 (CH), 129.24 (CH), 129.19 (C), 128.06 (C), 128.02 (CH), 127.40 (CH), 126.42 (C), 125.93 (CH), 124.15 (CH), 109.27 (CH), 35.84 (CH_2). HRMS (ESI): Exact mass calcd for $C_{17}H_{12}N_2O$ $[M]^+$: 260.0950 Found: $[M+H]^+$ 261.1019.

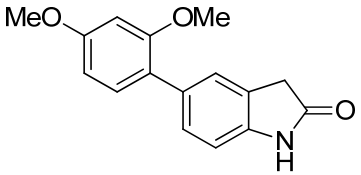


5-(dibenzo[b,d]thiophen-4-yl)indolin-2-one: 5-Iodooxindole (0.111 g, 0.429 mmol), 4-dibenzothienylboronic acid (0.117 g, 0.515 mmol), and $Pd(PPh_3)_4$ (24.8 mg, 0.0215 mmol) were added to a Radley's Carousel Tube with 5 mL dimethoxyethane and degassed with N_2 for five minutes according to general procedure B. $NaHCO_3$ (72.0 mg, 0.858 mmol) was then dissolved in 1 mL dH_2O and syringed into the reaction mixture. The mixture was then sealed and refluxed for 18 hours at 70 °C. Following cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The mixture was then resuspended in H_2O and EtOAc and extracted three times. The organic layers were collected, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the title compound as a pale pink amorphous solid (58.4 mg, 43% yield). ^{1}H NMR (700 MHz; DMSO): δ 10.56 (s, 1H), 8.40 (m, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.01 (m, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.57 (m, 2H), 7.53 (m, 2H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 3.59 (s, 2H). ^{13}C NMR (176.06 MHz; DMSO): δ 176.38 (C), 143.84 (C), 138.44 (C), 137.23 (C), 136.49

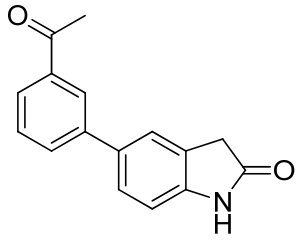
(C), 135.76 (C), 135.33 (C), 132.90 (C), 127.31 (CH), 127.17 (CH), 126.71 (CH), 126.66 (C), 125.61 (CH), 124.79 (CH), 124.06 (CH), 122.82 (CH), 122.20 (CH), 120.58 (CH), 109.37 CH), 35.87 (CH_2). HRMS (ESI): Exact mass calcd for $C_{20}H_{13}NOS$ $[M]^+$: 315.0718 Found: $[M+Na]^+$ 338.063.



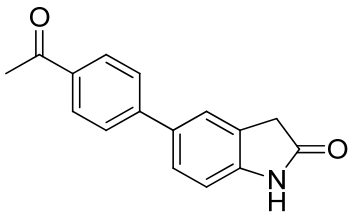
5-(3,4-dimeoxyphenyl)indolin-2-one: 5-iodoindolin-2-one (0.100 g, 0.386 mmol), (3,4-dimeoxyphenyl)boronic acid (0.085 g, 0.463 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.022 g, 0.019 mmol) were dissolved in 5 mL of anhydrous THF in a carousel vial and purged with N_2. Sodium bicarbonate (0.065 g, 0.772 mmol) dissolved in 1 mL of water was added and the reaction vessel sealed. After heating for 24 hours at 70 °C with reflux, THF was evaporated, then diluted with water and extracted with EtOAc. $MgSO_4$ was used to remove residual water then filtered by gravity filtration. The reaction was purified by flash chromatography to give the title compound as an off-white amorphous solid (29.7 mg, 28.5 % yield). ^{1}H NMR (600 MHz; DMSO): δ 10.42 (s, 1H), 7.49 (s, 1H), 7.44 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.10 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.35 (s, 2H). ^{13}C NMR (150 MHz; DMSO) δ 176.42 (C), 149.02 (C), 147.96 (C), 142.69 (C), 133.55 (C), 133.30 (C), 126.47 (C), 125.61 (CH), 122.62 (CH), 118.19 (CH), 112.22 (CH), 110.05 (CH), 109.28 (CH), 55.56 (CH_3) 55.50 (CH_3) 35.90 (CH_2). HRMS (ESI): Exact mass calcd for $C_{16}H_{15}NO_3$ $[M]^+$: 269.1052. Found $[M+H]^+$: 270.1148.



5-(2,4-dimeoxyphenyl)indolin-2-one: 5-iodoindolin-2-one (0.100 g, 0.386 mmol), (2,4-dimeoxyphenyl)boronic acid (0.085 g, 0.463 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.022 g, 0.019 mmol) were dissolved in 5 mL of anhydrous THF in a carousel vial and purged with N_2. Sodium bicarbonate (0.065 g, 0.772 mmol) dissolved in 1 mL of water was added and the reaction vessel sealed. After heating for 24 hours at 70 °C with reflux, THF was evaporated, then diluted with water and extracted with EtOAc. $MgSO_4$ was used to remove residual water then filtered by gravity filtration. The reaction was purified by flash chromatography to give the title compound as an off-white amorphous solid (55.2 mg, 53.3 % yield). ^{1}H NMR (600 MHz; DMSO): δ 10.36 (s, 1H), 7.25 (s, 1H), 7.19 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.57(dd, *J* = 8.4 Hz, 2.5 Hz, 1H) 3.79 (s, 3H), 3.74 (s, 3H), 3.48 (s, 2H). ^{13}C NMR (150 MHz; DMSO) δ 176.40 (C), 159.64 (C), 156.99 (C), 142.16 (C), 131.17 (C), 130.61 (CH), 128.23 (CH), 125.36 (C), 125.30 (CH), 122.70 (C), 108.61 (CH), 105.15 (CH), 98.92 (CH), 55.48 (CH_3) 55.22 (CH_3) 35.84 (CH_2). HRMS (ESI): Exact mass calcd for $C_{16}H_{15}NO_3$ $[M]^+$: 269.1052. Found $[M+H]^+$: 270.1156.

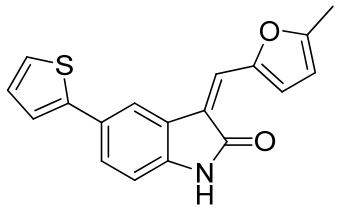


5-(3-acetylphenyl)indolin-2-one: 5-iodoindolin-2-one (0.119 g, 0.460 mmol), (3-acetylphenyl)boronic acid (0.091 g, 0.552 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.023 mmol) were dissolved in 5 mL of anhydrous THF in a carousel vial and purged with N_2. Sodium bicarbonate (0.077 g, 0.920 mmol) dissolved in 1 mL of water was added and the reaction vessel sealed. After heating for 24 hours at 70 °C with reflux, THF was evaporated, then diluted with water and extracted with EtOAc. $MgSO_4$ was used to remove residual water then filtered by gravity filtration. The reaction was purified by flash chromatography to give the title compound as an off-white amorphous solid (21.6 mg, 18.7 % yield). ^{1}H NMR (600 MHz; DMSO): δ 10.49 (s, 1H), 8.12 (t, *J* = 1.6 Hz, 1H), 7.88 (dt, *J* = 7.7 Hz, 1.3 Hz, 1.3 Hz, 1H), 7.86 (m, 1H), 7.60 (s, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.55 (m, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 3.55 (s, 2H), 2.64 (s, 3H). ^{13}C NMR (150 MHz; DMSO) δ 198.04 (C), 176.40 (C), 143.68 (C), 140.77 (C), 137.43 (C), 132.49 (C), 130.77 (CH), 129.29 (CH), 126.77 (C), 126.38 (CH), 126.25 (CH), 125.76 (CH), 123.01 (CH), 109.48 (CH), 35.86 (CH_2), 26.89 (CH_3). HRMS (ESI): Exact mass calcd for $C_{16}H_{13}NO_2$ $[M]^+$: 251.0942. Found $[M+H]^+$: 252.1031.



5-(4-acetylphenyl)indolin-2-one: 5-iodoindolin-2-one (0.119 g, 0.460 mmol), (4-acetylphenyl)boronic acid (0.091 g, 0.552 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.023 mmol) were dissolved in 5 mL of anhydrous THF in a carousel vial and purged with N_2. Sodium bicarbonate (0.077 g, 0.920 mmol) dissolved in 1 mL of water was added and the reaction vessel sealed. After heating for 24 hours at 70 °C with reflux, THF was evaporated,

then diluted with water and extracted with EtOAc. $MgSO_4$ was used to remove residual water then filtered by gravity filtration. The reaction was purified by flash chromatography to give the title compound as a an off-white amorphous solid (25.3 mg, 25.3 % yield). ^{1}H NMR (600 MHz; DMSO): δ 10.53 (s, 1H), 7.99 (m, 2H), 7.75 (m, 2H), 7.60 (s, 1H), 7.57 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 3.55 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (150 MHz; DMSO) δ 197.33 (C), 176.40 (C), 144.74 (C), 144.19 (C), 134.92 (C), 131.98 (C), 128.91 (CH), 126.82 (CH), 126.50 (C), 126.11 (CH), 23.06 (CH), 109.54 (CH), 35.82 (CH_2), 26.67 (CH_3). HRMS (ESI): Exact mass calcd for $C_{16}H_{13}NO_2$ $[M]^+$: 251.0942. Found $[M+H]^+$: 252.1034.



(Z)-3-((5-methylfuran-2-yl)methylene)-5-(thiophen-2-yl)indolin-2-one: 5-(thiophen-2-yl)indolin-2-one (0.0750 g, 0.349 mmol) and 5-methylfurfural (41.7 μL, 0.419 mmol) were added to a 1.1:1.3 M NH_4OAc/HOAc solution in ethanol (3 mL) in a microwave tube charged with a stir bar as per general procedure A. Piperidine (6.90 μL, 0.0698 mmol) was then added and the tube was sealed and microwaved for 30 minutes. After cooling to room temperature, the precipitate was filtered via vacuum filtration and washed with water, DCM, and EtOH to provide the title compound as an orange amorphous solid. (93.5 mg, 87 % yield). ^{1}H NMR (700 MHz; DMSO): δ 10.64 (bs, 1H), 8.66 (s, 1H), 7.60 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.49 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.42 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 3.4 Hz, 1H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.52 (dd, *J* = 3.3, 0.9 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (176.06 MHz; DMSO): δ 169.44 (C), 157.39 (C), 149.43 (C), 144.30 (C), 141.77 (C), 128.52 (CH),

127.17 (C), 126.34 (CH), 124.41 (CH), 123.37 (CH), 122.14 (C), 122.01 (CH), 121.65 (CH), 120.17 (C), 120.00 (CH), 110.69 (CH), 110.01 (CH), 14.26 (CH_3). HRMS (ESI): Exact mass calcd for $C_{18}H_{13}NO_2S$ $[M]^+$: 307.0667 Found: $[M+H]^+$ 308.0737.

Chapter 3: Library of APH(2")Id and ANT(2")Ia Inhibitors

3.1 Inhibitors of APH(2")-IVa and ANT(2")Ia as Antibiotic Adjuvants

The aminoglycoside nucleotidyltransferases (ANTs) are a subclass of aminoglycoside modifying enzymes that allow for adenylation of an antibiotic such as gentamicin. Recently, the Wright lab (2015, unpublished results) identified two quinazolines (figure 3.1) capable of inhibiting APH(2")Id and ANT(2")Ia. Notably, APH(2")Id and ANT(2")Ia confer resistance towards gentamicin by phosphorylating or adenylating the antibiotic, respectively.[117]

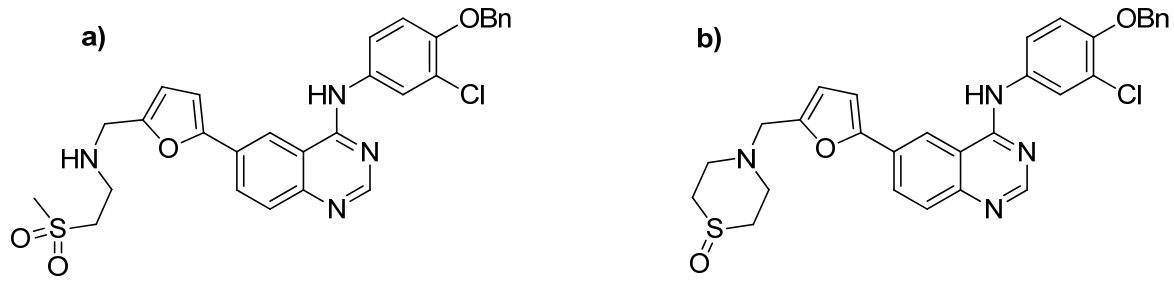


Figure 3.1. Leads generated from a high-throughput screen of a GSK PKIS library for inhibitors of APH(2")Id and ANT(2")Ia.

The leads identified are based off the 4-anilinoquinazoline scaffold common in many tyrosine kinase and EGFR inhibitors such as Lapatinib, a drug currently on the market as a treatment for breast cancer. Lapatinib has been previously shown to competitively bind to the ATP-binding site of tyrosine kinase ErbB4.[118] Interestingly, a co-crystallization study conducted by the Wright lab (2015, unpublished results), found that Lapatinib (structurally similar to the leads generated from the HTS screen) bound to the ATP-binding site of APH(2")Id; consistent with the binding observed by Qiu *et al*.

[117] Tsai, S.F.; Zervos, M.J.; Clewell, D.B.; Donabedian, S.M.; Sahm, D.F.; Chow, J.W. *Antimicrob. Agents Chemother.* **1998**, *42* (5), 1229-1232.
[118] Qiu, C.; Tarrant, M.K.; Choi, S.H.; Sathyamurthy, A.; Bose, R.; Banjade, S.; Pal, A.; Bornmann, W.G.; Lemmon, M.A.; Cole, P.A.; Leahy, D.J. *Structure*, **2008**, *16* (3), 460-467.

3.2 General Strategies for 4-Anilinoquinazoline Libraries

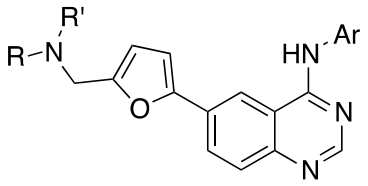


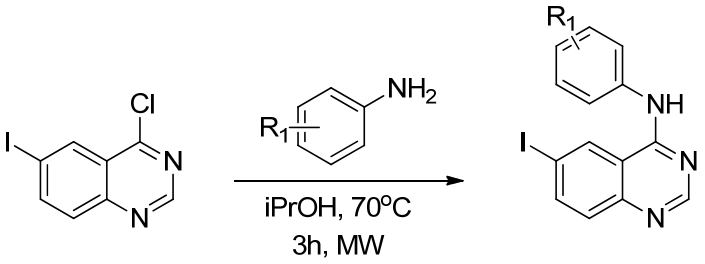
Figure 3.2. General scaffold for the quinazoline library synthesis.

In order to further probe these leads, a small library was prepared to determine which parts of the molecule are required for biological activity. Synthetically, installation of the aniline moiety at the 4-position (Figure 3.2) was envisioned to proceed via an S_nAr reaction while addition of the furanyl vector at the 6-positon could be prepared *via* a Suzuki reaction. Finally, the amino fragment pendant off the furan could be synthesized *via* a reductive amination. A survey of chemical suppliers, revealed that the ideal scaffolds for this chemistry, 4-chloro-6-iodoquinazoline and (5-formylfuran-2-yl)boronic acid, were commercially available.

3.3 4-Anilinoquinazoline Library Synthesis

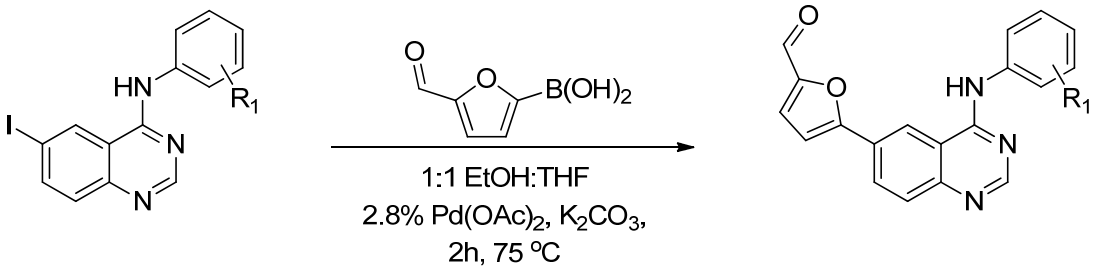
The S_NAr reaction was conducted using a modified version of a known procedure under microwave irradiation (scheme 3.1).[119] The reaction proceed smoothly and allowed for the installation of 4-(benzyloxy)-3-chloroaniline or 4-(benzyloxy)aniline in good yields (>85%). These particular vectors were introduced in an attempt to determine if the chloride found in the lead compounds was a necessary part of the molecule.

[119] Gaul, M.D.; Guo, Y.; Affleck, K.; Cockerill, G.S.; Gilmer, T.M.; Griffin, R.J.; Guntrip, S.; Keith, B.R.; Knight, W.B.; Mullin, R.J.; Murray, D.M.; Rusnak, D.W.; Smith, K.; Tadepalli, S.; Wood, E.R.; Lackey, K. *Bioorg. Med. Chem. Lett.* **2003**, *13* (4), 637-640.



Scheme 3.1. Installation of the anilino fragment at the 4-position using an S_NAr reaction.

Addition of the furaldehyde boronic acid via a Suzuki cross-coupling reaction was carried out successfully using another known literature procedure (Scheme 3.2)[120] in a 65% yield. It should be noted that future work should involve the introduction of other heterocycles in order to determine the necessity or function of the furanyl fragment.

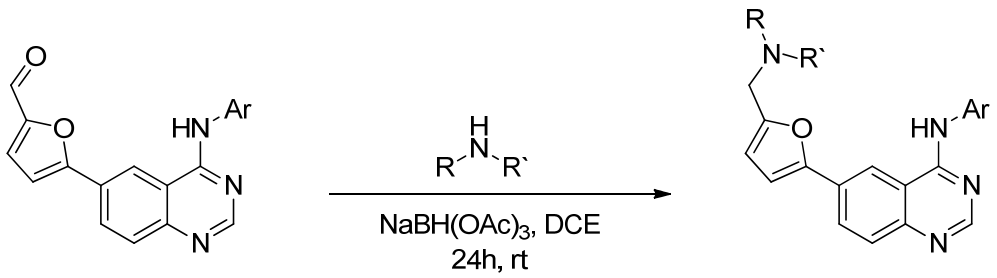


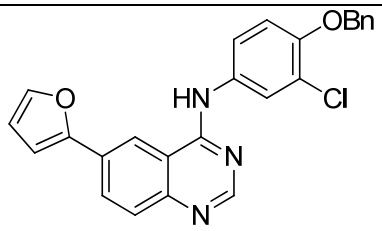
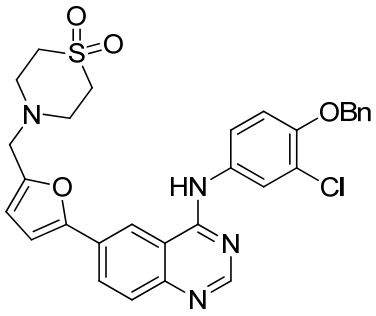
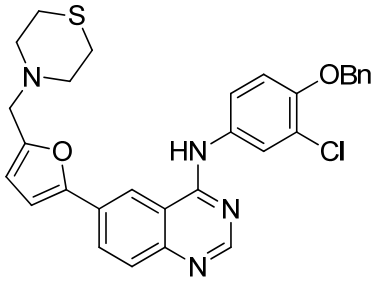
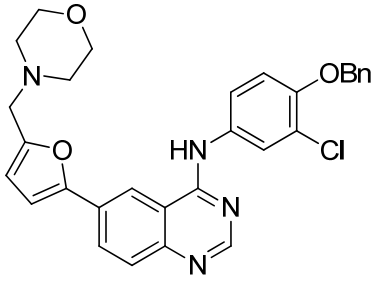
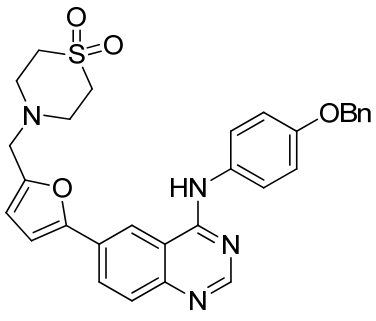
Scheme 3.2. Installation of the furanyl moiety at position-6 via a Suzuki reaction.

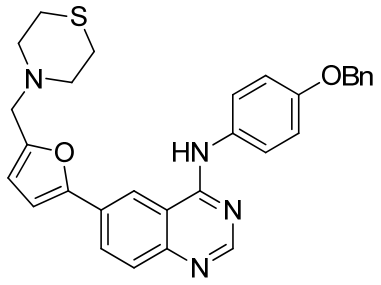
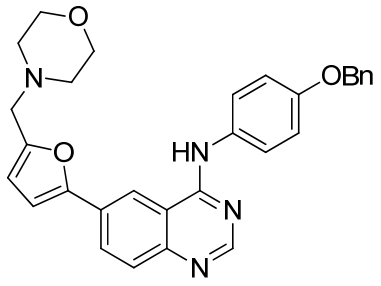
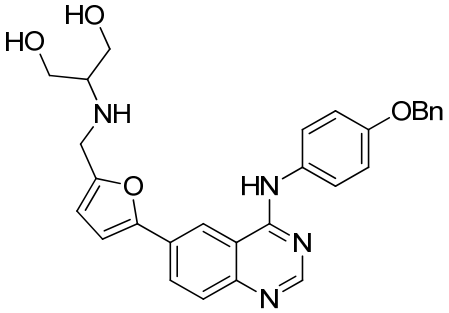
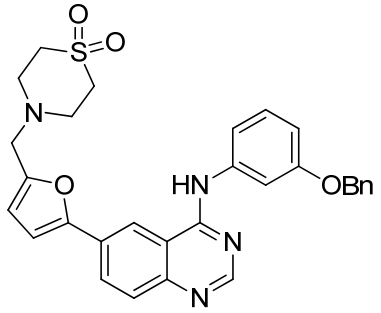
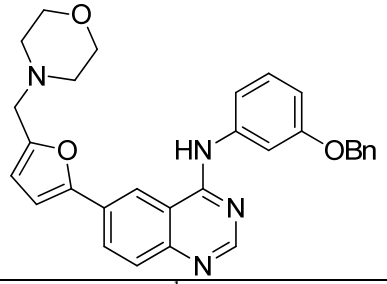
Finally, a reductive amination reaction based once again off a known literature procedure[121] was used to generate the pendant amino group off the furanyl moeity. The members of the completed quinazoline library appear in Table 3.1. While at first glance it appears that these substitutions serve the purpose of improving solubility of the compound, it is also likely they could be playing a key role in binding to the target protein.

Table 3.1. Completed quinazoline library.

[120] Zhang, L.; Fan, C.; Guo, Z.; Li, Y.; Zhao, S.; Yang, S.; Yang, Y.; Zhu, J.; Lin, D. *Eur. J. Med. Chem.* **2013**, *69*, 833-841.
[121] Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996**, *61* (11), 3849-3862.



Entry	Product	Yield (%)[a]
1[b]		71
2		81
3		71
4		81
5		82

6		79
7		88
8		35
9		84
10		82

[a]Yields are for reductive amination step only. [b]Yield is for the coupling step as no reductive amination was conducted on this product.

The compounds present in table 3.1 are currently being assessed for their biological activity. Since the chemical modification of gentamicin by APH(2")Id and ANT(2")Ia is ATP-

dependent, the APH activity is monitored by measuring the release of ADP coupled with pyruvate kinase/lactate dehydrogenase activity.[122] Activity of ANT enzymes is monitored using a colorimetric stopped assay by the addition of pyrophosphatase and posphomolybdic acid and measurement of free phosphate.

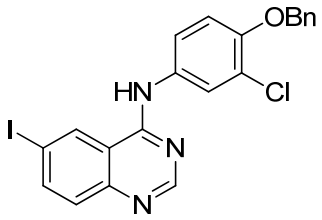
Questions that will be addressed by the library include: whether the substitution on the furan is necessary and the impact it has on binding (entry 1), whether the benzoxyl group is required at the 4-position or is tolerated elsewhere (entries 2 and 9, respectfully), and whether the chloride is required on the aniline moiety (entry 5). As previously stated, based on the HTS "hits" it is likely that the furanyl substitutions were likely to improve solubility and/or cell permeability, so variations of this substitution should help elucidate this phenomenon. Finally, the chemistry developed in this chapter should be applicable to future iterations of the 4-anilinoquinazoline library.

3.4 Experimental

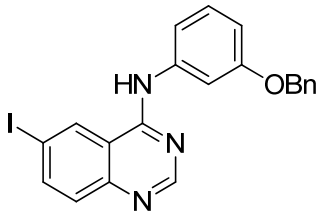
Microwave reactions were performed in 2.0 – 5.0 mL microwave vials, sealed under ambient atmosphere, and loaded to a CEM Discover SP-D 80 Microwave Reactor (100 W, < 100 psi). Heated non-microwave reactions were performed in a temperature-controlled oil bath. TLC was performed on F-254 (0.25 mm) precoated silica gel (Merck) and visualized under UV, aqueous KMnO4, or aqueous ninhydrin stain. Flash column chromatography purifications were performed using a normal phase Teledyne Isco CombiFlash® Rf 200 with standard RediSep RF 12 g silica columns.

[122] Pon, N.G.; Bondar, R.J. *Anal. Biochem.* **1967**, *19*, 272-279.

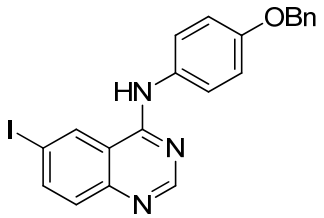
Compounds were characterized by ^{1}H NMR, ^{13}C NMR, DEPT Q, ESI-MS, and HRMS. NMR spectra were obtained from a Bruker AvanceIII 700 (700 MHz). Chemical shifts are reported as ppm, coupling constants in Hz, and peaks were calibrated to the solvent residual peak ($CDCl^3$ = 7.27 (^{1}H), 77.16 (^{13}C), DMSO = 2.50 (^{1}H), 39.51 (^{13}C)). Mass spectrometry was conducted with a Bruker Maxis 4G/TOF in either positive or negative ion mode with direct infusion.



N-(4-(benzyloxy)-3-chlorophenyl)-6-iodoquinazolin-4-amine: 4-Chloro-6-iodoquinazoline (0.500 g, 1.72 mmol) and 4-(benzyloxy)-3-chloroaniline (0.442 g, 1.89 mmol) were added to a clean, oven-dried microwave vial. Isopropanol was then added (10 mL) and the vessel was then sealed with a microwave cap and irradiated at 70 °C for 3 hours. The precipitate was then collected via filtration and washed with copious amounts of cold isopropanol, yielding the title compound as a yellow-green amorphous solid (0.721 g, 86% yield). ^{1}H NMR (700 MHz; DMSO) δ 11.69 (bs, 1H), 9.34 (d, *J* = 1.3 Hz, 1H), 8.95 (s, 1H), 8.36 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.90 (d, *J* = 2.5 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.50 (m, 2H), 7.43 (m, 2H), 7.35 (m, 2H), 5.27 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 158.23 (C), 151.99 (C), 151.20 (CH), 144.12 (CH), 138.36 (C), 136.41 (C), 132.94 (CH), 130.11 (C), 128.53 (CH), 128.03 (CH), 127.53 (CH), 126.10 (CH), 124.40 (CH), 121.73 (CH), 121.12 (C), 115.18 (C), 114.14 (CH), 94.13 (C), 70.25 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{21}H_{15}ClIN_3O$ $[M]^+$: 486.9948. Found $[M+H]^+$: 488.0039.

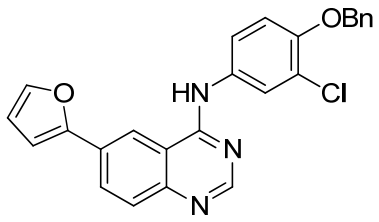


N-(3-(benzyloxy)phenyl)-6-iodoquinazolin-4-amine: 4-Chloro-6-iodoquinazoline (0.500 g, 1.72 mmol) and 3-(benzyloxy)aniline (0.377 g, 1.89 mmol) were added to a clean, oven-dried microwave vial. Isopropanol was then added (10 mL) and the vessel was then sealed with a microwave cap and irradiated at 70 °C for 3 hours. The precipitate was then collected via filtration and washed with copious amounts of cold isopropanol, yielding the title compound as a gray crystalline solid (0.702 g, 90% yield). ^{1}H NMR (700 MHz; DMSO) δ 11.53 (bs, 1H), 9.33 (d, *J* = 0.9 Hz, 1H), 8.94 (s, 1H), 8.37 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.49 (m, 3H), 7.41 (td, *J* = 7.8, 5.2 Hz, 3H), 7.35 (m, 2H), 7.00 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.14 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 158.47 (C), 158.33 (C), 151.22 (CH), 144.07 (CH), 137.75 (C), 136.81 (C), 132.88 (CH), 129.60 (CH), 128.47 (CH), 127.93 (CH), 127.76 (CH), 116.84 (CH), 115.27 (C), 112.78 (CH), 111.37 (CH), 94.11 (C), 69.43 (CH_2).HRMS (ESI-MS): Exact mass calcd for $C_{21}H_{16}IN_3O$ $[M]^+$: 453.0338. Found $[M+H]^+$: 455.0441.



N-(4-(benzyloxy)phenyl)-6-iodoquinazolin-4-amine: 4-Chloro-6-iodoquinazoline (0.500 g, 1.72 mmol) and 4-(benzyloxy)aniline (0.377 g, 1.89 mmol) were added to a clean, oven-dried microwave vial. Isopropanol was then added (10 mL) and the vessel was then sealed with a

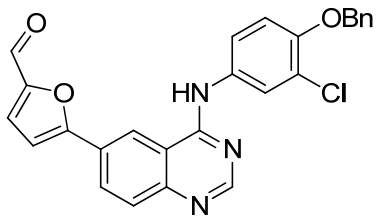
microwave cap and irradiated at 70 °C for 3 hours. The precipitate was then collected via filtration and washed with copious amounts of cold isopropanol, yielding the title compound as a yellow-green amorphous solid (0.643 g, 83% yield). ^{1}H NMR (700 MHz; DMSO) δ 11.62 (bs, 1H), 9.31 (d, *J* = 1.2 Hz, 1H), 8.89 (s, 1H), 8.35 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.63 (m, 2H), 7.47 (m, 2H), 7.41 (t, 2H), 7.34 (m, 1H), 7.13 (m, 2H), 5.16 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 158.10 (C), 156.84 (C), 151.04 (CH), 144.02 (CH), 138.08 (C), 136.89 (C), 132.91 (CH), 129.41 (C), 128.46 (CH), 127.89 (CH), 127.72 (CH), 126.00 (CH), 121.51 (CH), 115.13 (C), 114.86 (CH), 93.97 (C), 69.44 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{21}H_{16}IN_3O$ $[M]^+$: 453.0338. Found $[M+H]^+$: 455.0443.



N-(4-(benzyloxy)-3-chlorophenyl)-6-(furan-2-yl)quinazolin-4-amine: N-(4-(benzyloxy)-3-chlorophenyl)-6-iodoquinazolin-4-amine (0.100 g, 0.205 mmol), 2-furanylboronic acid (0.0260 g, 0.232 mmol), $Pd(OAc)_2$ (1.29 mg, 0.00574 mmol), and K_2CO_3 (0.0793 g, 0.574 mmol) were added to an oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube with 5 mL of a 1:1 solution of anhydrous THF and ethanol according to a known procedure.[123] The vessel was then sealed and purged with N_2 for an additional 5 minutes, and then allowed to reflux at 75 °C for 2 hours. After cooling to room temperature, the mixture was filtered through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (30-100% EtOAc/hexanes) to yield the title compound as a slightly yellow amorphous solid (61.5 mg, 71%

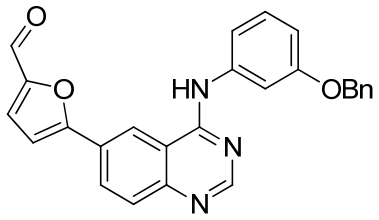
[123] Zhang, L.; Fan, C.; Guo, Z.; Li, Y.; Zhao, S.; Yang, S.; Yang, Y.; Zhu, J.; Lin, D. *Eur. J. Med. Chem.* **2013**, *69*, 833-841.

yield). ^{1}H NMR (700 MHz; DMSO) δ 9.93 (s, 1H), 8.80 (d, *J* = 1.6 Hz, 1H), 8.56 (s, 1H), 8.19 (dd, *J* = 8.7, 1.9 Hz, 1H), 8.01 (d, *J* = 2.7 Hz, 1H), 7.88 (dd, *J* = 1.7, 0.5 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.75 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.50 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.35 (m, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.13 (dd, *J* = 3.4, 0.5 Hz, 1H), 6.71 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.24 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 157.58 (C), 154.35 (CH), 152.48 (C), 149.98 (C), 148.98 (C), 143.59 (CH), 136.69 (C), 132.90 (C), 128.82 (CH), 128.52 (CH), 128.48 (CH), 128.19 (C), 127.93 (CH), 127.51 (CH), 124.23 (CH), 122.42 (CH), 120.98 (C), 116.69 (CH), 115.31 (C), 114.26 (CH), 112.47 (CH), 107.21 (CH), 70.23 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{25}H_{18}ClN_3O_2$ $[M]^+$: 427.1088. Found $[M+H]^+$: 428.1197.



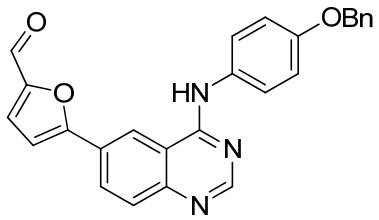
5-(4-((4-(benzyloxy)-3-chlorophenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde: N-(4-(benzyloxy)-3-chlorophenyl)-6-iodoquinazolin-4-amine (0.300 g, 0.615 mmol), 5-formyl-2-furanylboronic acid (0.0972 g, 0.695 mmol), $Pd(OAc)_2$ (3.86 mg, 0.0172 mmol), and K_2CO_3 (0.237 g, 1.72 mmol) were added to an oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube with 5 mL of a 1:1 solution of anhydrous THF and ethanol according to a known procedure.[123] The vessel was then sealed and purged with N_2 for an additional 5 minutes, and then allowed to reflux at 75 °C for 2 hours. After cooling to room temperature, the mixture was filtered through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (30-100% EtOAc/hexanes) to yield the title compound as a yellow amorphous solid (157.7 mg, 56% yield). ^{1}H NMR (700 MHz; DMSO) δ 10.11 (s, 1H), 9.68 (s, 1H), 8.98 (d,

J = 1.6 Hz, 1H), 8.59 (s, 1H), 8.31 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 3.7 Hz, 1H), 7.70 (m, 1H), 7.50 (m, 2H), 7.43 (m, 3H), 7.35 (m, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 5.24 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 177.85 (CH), 157.87 (C), 157.62 (C), 155.33 (CH), 152.09 (C), 150.23 (C), 150.19 (C), 136.66 (C), 132.58 (C), 129.63 (CH), 128.82 (CH), 128.48 (CH), 127.94 (CH), 127.51 (CH), 126.33 (C), 124.63 (CH), 122.84 (CH), 121.00 (C), 119.49 (CH), 115.30 (C), 114.25 (CH), 109.80 (CH), 70.23 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{26}H_{18}ClN_3O_3$ $[M]^+$: 455.1037. Found $[M+H]^+$: 456.1111.



5-(4-((3-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde: N-(3-(benzyloxy)phenyl)-6-iodoquinazolin-4-amine (0.279 g, 0.615 mmol), 5-formyl-2-furanylboronic acid (0.0972 g, 0.695 mmol), $Pd(OAc)_2$ (3.86 mg, 0.0172 mmol), and K_2CO_3 (0.237 g, 1.72 mmol) were added to an oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube with 5 mL of a 1:1 solution of anhydrous THF and ethanol according to a known procedure.[123] The vessel was then sealed and purged with N_2 for an additional 5 minutes, and then allowed to reflux at 75 °C for 2 hours. After cooling to room temperature, the mixture was filtered through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (30-100% EtOAc/hexanes) to yield the title compound as a yellow amorphous solid (140.9 mg, 54% yield). ^{1}H NMR (700 MHz; DMSO) δ 10.08 (s, 1H), 9.68 (s, 1H), 9.02 (d, *J* = 1.6 Hz, 1H), 8.62 (s, 1H), 8.31 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 3.7 Hz, 1H), 7.65 (t, *J* = 2.1 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.42 (m, 4H), 7.34 (m, 2H), 6.84

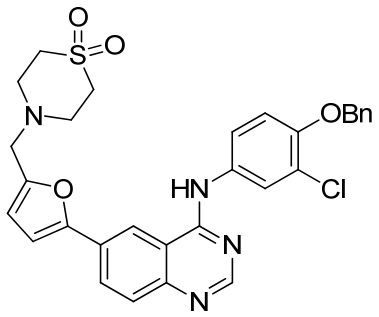
(dd, J = 8.1, 2.1 Hz, 1H), 5.15 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 177.86 (CH), 158.46 (C), 157.89 (C), 157.64 (C), 155.29 (CH), 152.09 (C), 150.26 (C), 140.05 (C), 137.09 (C), 129.56 (CH), 129.23 (CH), 128.85 (CH), 128.43 (CH), 127.82 (CH), 127.70 (CH), 126.35 (C), 119.66 (CH), 115.45 (C), 115.23 (CH), 110.24 (CH), 109.84 (CH), 109.58 (CH), 69.27 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{26}H_{19}N_3O_3$ $[M]^+$: 421.1426. Found $[M+H]^+$: 422.1495.



5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde: N-(4-(benzyloxy)phenyl)-6-iodoquinazolin-4-amine (0.279 g, 0.615 mmol), 5-formyl-2-furanylboronic acid (0.0972 g, 0.695 mmol), $Pd(OAc)_2$ (3.86 mg, 0.0172 mmol), and K_2CO_3 (0.237 g, 1.72 mmol) were added to an oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube with 5 mL of a 1:1 solution of anhydrous THF and ethanol according to a known procedure.[123] The vessel was then sealed and purged with N_2 for an additional 5 minutes, and then allowed to reflux at 75 °C for 2 hours. After cooling to room temperature, the mixture was filtered through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (30-100% EtOAc/hexanes) to yield the title compound as a brown crystalline solid (111.0 mg, 43% yield). ^{1}H NMR (700 MHz; DMSO) δ 10.05 (s, 1H), 9.67 (s, 1H), 8.99 (d, J = 1.8 Hz, 1H), 8.52 (s, 1H), 8.28 (dd, J = 8.8, 1.9 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 3.7 Hz, 1H), 7.66 (m, 2H), 7.48 (m, 2H), 7.41 (m, 3H), 7.34 (m, 1H), 7.08 (m, 2H), 5.14 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 177.80 (CH), 158.10 (C), 157.73 (C), 155.53 (CH), 155.21 (C), 152.04 (C), 150.21 (C), 137.15 (C), 131.74 (C), 129.40 (CH), 128.73 (CH), 128.42 (CH), 127.80

(CH), 127.68 (CH), 126.15 (C), 124.88 (CH), 119.64 (CH), 115.33 (C), 114.68 (CH), 109.66 (CH), 69.39 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{26}H_{19}N_3O_3$ $[M]^+$: 421.1426. Found $[M+H]^+$: 422.1495.

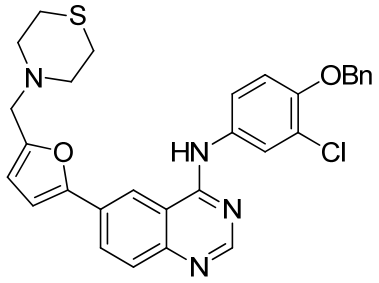
General procedure C (reductive amination of quinazolines): To an oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube was added the quinazoline furaldehyde (1.0 equiv.), amine (1.0 equiv.), and $NaBH(OAc)_3$ (3.0 equiv.) with 5 mL of dichloroethane according to a known procedure.[124] The vessel was then purged with N_2 for an additional 5 minutes and was allowed to stir at room temperature overnight. Saturated $NaHCO_3$ was then added to quench the reaction and the mixture was stirred for 15 minutes. The mixture was then extracted with CH_2Cl_2, dried with $NaSO_4$, concentrated under reduced pressure, and purified by column chromatography to yield the corresponding title compound.



4-((5-(4-((4-(benzyloxy)-3-chlorophenyl)amino)quinazolin-6-yl)furan-2-yl)methyl)thiomorpholine 1,1-dioxide: 5-(4-((4-(benzyloxy)-3-chlorophenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.108 g, 0.237 mmol), thiomorpholine-1,1-dioxide (32.0 mg, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with

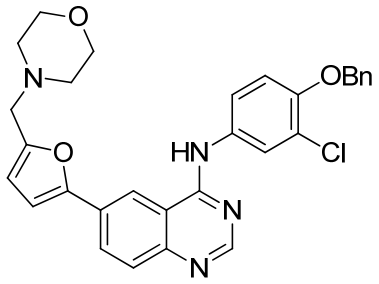
[124] Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996**, *61* (11), 3849-3862.

CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a dark yellow oil (110.6 mg, 81% yield). ^{1}H NMR (700 MHz; $CDCl_3$) δ 8.64 (s, 1H), 8.37 (s, 1H), 7.95 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.83 (m, 2H), 7.52 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.32 (m, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.78 (d, *J* = 3.3 Hz, 1H), 6.31 (d, *J* = 3.3 Hz, 1H), 5.11 (s, 2H), 3.72 (s, 2H), 3.05 (m, 8H). ^{13}C NMR (176 MHz; $CDCl_3$) δ 157.85 (C), 154.02 (CH), 152.50 (C), 151.52 (C), 151.42 (C), 147.79 (C), 136.31 (C), 131.66 (C), 129.16 (CH), 128.98 (C), 128.59 (CH), 128.04 (CH), 127.10 (CH), 125.12 (CH), 123.22 (C), 122.35 (CH), 115.48 (CH), 115.12 (C), 114.18 (CH), 111.79 (CH), 107.74 (CH), 71.11 (CH_2), 53.74 (CH_2), 51.29 (CH_2), 50.28 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{27}ClN_4O_4S$ $[M]^+$: 574.1442. Found $[M+H]^+$: 575.1507.



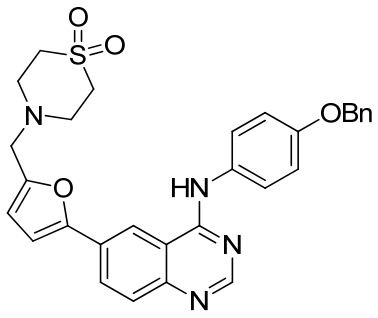
N-(4-(benzyloxy)-3-chlorophenyl)-6-(5-(thiomorpholinomethyl)furan-2-yl)quinazolin-4-amine: 5-(4-((4-(benzyloxy)-3-chlorophenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.108 g, 0.237 mmol), thiomorpholine (23.8 μL, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a dark yellow oil (90.4 mg, 71% yield). ^{1}H NMR (700 MHz; $CDCl_3$) δ 8.68 (s, 1H), 8.41 (s, 1H), 8.21 (bs, 1H), 7.94 (dd, *J* = 8.8, 1.6 Hz, 1H),

7.88 (d, *J* = 2.1 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.54 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.33 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.70 (d, *J* = 3.1 Hz, 1H), 6.35 (d, *J* = 3.3 Hz, 1H), 5.13 (s, 2H), 3.66 (s, 2H), 2.82 (m, 4H), 2.74 (m, 4H). ^{13}C NMR (176 MHz; $CDCl_3$) δ 157.75 (C), 154.68 (CH), 152.79 (C), 151.26 (C), 151.26 (C), 150.59 (C), 149.09 (C), 136.45 (C), 132.06 (C), 128.85 (CH), 128.76 (CH), 128.64 (C), 128.56 (CH), 127.97 (CH), 127.09 (CH), 124.84 (CH), 123.32 (C), 121.97 (CH), 115.31 (CH), 115.27 (C), 114.32 (CH), 112.12 (CH), 107.09 (CH), 71.16 (CH_2), 55.66 (CH_2), 54.55 (CH_2), 27.42 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{27}ClN_4O_2S$ $[M]^+$: 542.1543. Found $[M+H]^+$: 543.1622.



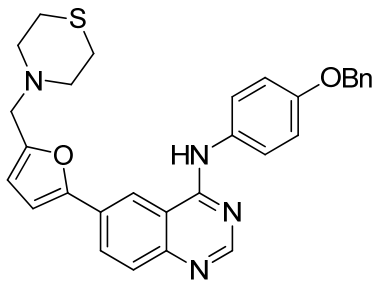
N-(4-(benzyloxy)-3-chlorophenyl)-6-(5-(morpholinomethyl)furan-2-yl)quinazolin-4-amine: 5-(4-((4-(benzyloxy)-3-chlorophenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.108 g, 0.237 mmol), morpholine (20.5 μL, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a pale yellow amorphous solid (100.0 mg, 81% yield). ^{1}H NMR (700 MHz; DMSO) δ 9.94 (bs, 1H), 8.72 (dd, *J* = 1.0 Hz, 1H), 8.54 (s, 1H), 8.14 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.35 (m, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.06 (d, *J* = 3.1

Hz, 1H), 6.52 (d, *J* = 3.3 Hz, 1H), 5.23 (s, 2H), 3.59 (m, 6H), 2.45 (m, 4H). ^{13}C NMR (176 MHz; DMSO) δ 157.63 (C), 154.30 (CH), 152.20 (C), 152.02 (C), 150.04 (C), 148.92 (C), 136.68 (C), 132.85 (C), 128.72 (CH), 128.52 (CH), 128.49 (CH), 128.22 (C), 127.94 (CH), 127.52 (CH), 124.43 (CH), 122.65 (CH), 120.99 (C), 116.48 (CH), 115.34 (C), 114.26 (CH), 111.68 (CH), 107.88 (CH), 70.24 (CH_2), 66.10 (CH_2), 54.58 (CH_2), 52.89 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{27}ClN_4O_3$ $[M]^+$: 526.1772. Found $[M+H]^+$: 527.1842.

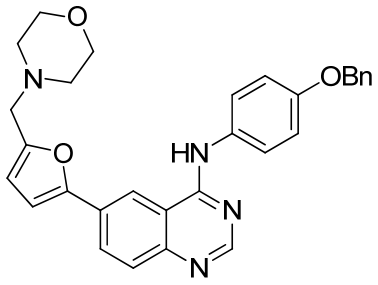


4-((5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-yl)methyl)thiomorpholine 1,1-dioxide: 5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.100 g, 0.237 mmol), thiomorpholine-1,1-dioxide (32.0 mg, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a pale yellow amorphous solid (104.6 mg, 82% yield). ^{1}H NMR (700 MHz; DMSO) δ 9.98 (bs, 1H), 8.77 (d, *J* = 1.5 Hz, 1H), 8.50 (s, 1H), 8.14 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.48 (m, 2H), 7.41 (m, 2H), 7.34 (m, 1H), 7.07 (m, 3H), 6.58 (d, *J* = 3.3 Hz, 1H), 5.14 (s, 2H), 3.83 (s, 2H), 3.15 (m, 4H), 2.98 (m, 4H). ^{13}C NMR (176 MHz; DMSO) δ 157.97 (C), 155.17 (C), 154.31 (CH), 152.21 (C), 151.93 (C), 148.26 (C), 137.15 (C), 131.80 (C), 128.60 (CH), 128.43 (CH), 128.10 (C),

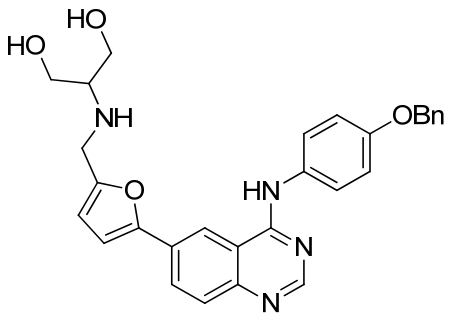
127.96 (CH), 127.81 (CH), 127.68 (CH), 124.83 (CH), 116.88 (CH), 115.28 (C), 114.68 (CH), 111.88 (CH), 107.79 (CH), 69.38 (CH_2), 52.26 (CH_2), 50.25 (CH_2), 49.96 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{28}N_4O_4S$ $[M]^+$: 540.1831. Found $[M+H]^+$: 542.1940.



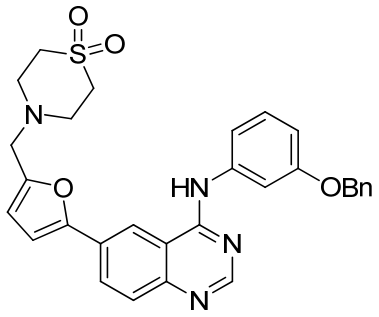
N-(4-(benzyloxy)phenyl)-6-(5-(thiomorpholinomethyl)furan-2-yl)quinazolin-4-amine: 5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.100 g, 0.237 mmol), thiomorpholine (23.8 μL, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a pale yellow amorphous solid (94.4 mg, 79% yield). ^{1}H NMR (700 MHz; $CDCl_3$) δ 8.68 (s, 1H), 8.30 (bs, 1H), 7.98 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.91 (bs, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.45 (m, 2H), 7.40 (m, 2H), 7.34 (m, 1H), 7.03 (m, 2H), 6.72 (d, *J* = 3.3 Hz, 1H), 6.36 (d, *J* = 3.3 Hz, 1H), 5.08 (s, 2H), 3.68 (s, 2H), 2.83 (m, 4H), 2.76 (m, 4H). ^{13}C NMR (176 MHz; $CDCl_3$) δ 158.00 (C), 156.17 (C), 154.98 (CH), 152.82 (C), 151.04 (C), 149.23 (C), 136.91 (C), 131.15 (C), 129.04 (CH), 128.78 (CH), 128.60 (C), 128.58 (CH), 127.97 (CH), 127.46 (CH), 124.49 (CH), 115.32 (CH), 115.30 (C), 115.02 (CH), 112.03 (CH), 107.09 (CH), 70.29 (CH_2), 55.73 (CH_2), 54.57 (CH_2), 27.58 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{28}N_4O_2S$ $[M]^+$: 508.1933. Found: 509.2011.



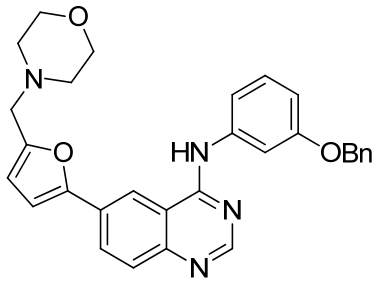
N-(4-(benzyloxy)phenyl)-6-(5-(morpholinomethyl)furan-2-yl)quinazolin-4-amine: 5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.100 g, 0.237 mmol), morpholine (20.5 μL, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a pale yellow amorphous solid (102.4 mg, 88% yield). ^1H NMR (700 MHz; $CDCl_3$) δ 8.68 (s, 1H), 8.29 (bs, 1H), 7.99 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.85 (s, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.46 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.34 (m, 1H), 7.04 (m, 2H), 6.73 (d, *J* = 3.3 Hz, 1H), 6.39 (d, *J* = 3.3 Hz, 1H), 5.09 (s, 2H), 3.79 (t, *J* = 4.4 Hz, 4H), 3.68 (s, 2H), 2.58 (m, 4H). ^{13}C NMR (176 MHz; $CDCl_3$) δ 157.98 (C), 156.18 (C), 154.99 (CH), 152.90 (C), 149.26 (C), 136.93 (C), 131.15 (C), 129.09 (CH), 128.82 (CH), 128.59 (CH), 128.60 (C), 127.99 (CH), 127.47 (CH), 124.47 (CH), 115.34 (CH), 115.28 (C), 114.94 (CH), 112.09 (CH), 107.11 (CH), 70.31 (CH_2), 66.54 (CH_2), 55.40 (CH_2), 53.28 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{28}N_4O_3$ $[M]^+$: 492.2161. Found $[M+H]^+$: 493.2230.



2-(((5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-yl)methyl)amino)propane-1,3-diol: 5-(4-((4-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.100 g, 0.237 mmol), serinol (21.6 mg, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-20% CH_3OH/CH_2Cl_2) to yield the title compound as a pale pink amorphous solid (40.9 mg, 35% yield). ^{1}H NMR (700 MHz; $CDCl_3$ (spiked with two drops of CD_3OD for solubility)) δ 8.57 (bs, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 7.67 (m, 1H), 7.63 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.39 (m, 2H), 7.36 (m, 2H), 7.30 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 3.0 Hz, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 4.97 (s, 2H), 3.85 (bs, 2H), 3.73 (m, 2H), 3.63 (m, 2H), 2.84 (m, 1H). ^{13}C NMR (176 MHz; $CDCl_3$ (spiked with two drops of CD_3OD for solubility)) δ 158.03 (C), 155.92 (C), 154.62 (CH), 152.29 (C), 148.47 (C), 136.85 (C), 131.42 (C), 128.55 (CH), 128.33 (CH), 128.17 (C), 127.97 (CH), 127.44 (CH), 124.35 (CH), 115.59 (CH), 115.26 (C), 115.03 (CH), 110.03 (CH), 106.97 (CH), 70.19 (CH_2), 61.66 (CH_2), 59.21 (CH), 43.54 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{29}H_{28}N_4O_4$ $[M]^+$: 496.2111. Found $[M+H]^+$: 497.2190.



4-((5-(4-((3-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-yl)methyl)thiomorpholine 1,1-dioxide: 5-(4-((3-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.100 g, 0.237 mmol), thiomorpholine-1,1-dioxide (32.0 mg, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a pale yellow amorphous solid (107.9 mg, 84% yield). ^{1}H NMR (700 MHz; DMSO) δ 10.16 (bs, 1H), 8.84 (d, *J* = 1.3 Hz, 1H), 8.61 (s, 1H), 8.18 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.83 (d, *J*= 8.7 Hz, 1H), 7.65 (s, 1H), 7.48 (m, 2H), 7.42 (m, 3H), 7.34 (m, 2H), 7.13 (d, *J* = 3.3 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 5.14 (s, 2H), 3.85 (s, 2H), 3.15 (m, 4H), 2.99 (m, 4H). ^{13}C NMR (176 MHz; DMSO) δ 158.47 (C), 157.92 (C), 153.77 (CH), 152.07 (C), 147.46 (C), 139.92 (C), 137.07 (C), 129.26 (CH), 128.99 (CH), 128.45 (C), 128.44 (CH), 127.84 (CH), 127.71 (CH), 127.48 (CH), 117.02 (CH), 115.37 (CH), 115.33 (C), 111.95 (CH), 110.38 (CH), 109.75 (CH), 108.15 (CH), 69.29 (CH_2), 52.23 (CH_2), 50.23 (CH_2), 49.96 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{28}N_4O_4S$ $[M]^+$: 540.1831. Found $[M+H]^+$: 541.1902.



N-(3-(benzyloxy)phenyl)-6-(5-(morpholinomethyl)furan-2-yl)quinazolin-4-amine: 5-(4-((3-(benzyloxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde (0.100 g, 0.237 mmol), morpholine (20.5 μL, 0.237 mmol), and $NaBH(OAc)_3$ (0.151 g, 0.711 mmol) were added to a Radley's Carousel 12 Plus reaction tube according to general procedure D and allowed to stir overnight. Following quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2, the mixture was purified by column chromatography (0-5% CH_3OH/CH_2Cl_2) to yield the title compound as a pale yellow amorphous solid (95.3 mg, 82% yield). ^{1}H NMR (700 MHz; $CDCl_3$) δ 8.73 (s, 1H), 8.33 (bs, 1H), 7.99 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.95 (bs, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.40 (m, 2H), 7.32 (m, 3H), 6.81 (m, 1H), 6.73 (d, *J* = 3.3 Hz, 1H), 6.39 (d, *J* = 3.3 Hz, 1H), 5.12 (s, 2H), 3.79 (t, *J* = 4.6 Hz, 4H), 3.68 (s, 2H), 2.59 (bs, 4H). ^{13}C NMR (176 MHz; $CDCl_3$) δ 159.35 (C), 157.54 (C), 154.74 (CH), 152.82 (C), 150.92 (C), 149.34 (C), 139.45 (C), 136.90 (C), 129.70 (CH), 129.16 (CH), 128.85 (CH), 128.72 (C), 128.55 (CH), 127.96 (CH), 127.53 (CH), 115.43 (C), 114.88 (CH), 114.42 (CH), 112.08 (CH), 111.01 (CH), 108.84 (CH), 107.18 (CH), 70.10 (CH_2), 66.52 (CH_2), 55.42 (CH_2), 53.28 (CH_2). HRMS (ESI-MS): Exact mass calcd for $C_{30}H_{28}N_4O_3$ $[M]^+$: 492.2161. Found $[M+H]^+$: 493.2229.

Chapter 4: Phospha-adamantanes as Ligands for Palladium Catalyzed Cross-Coupling Chemistry: Synthesis and Application of a Robust Catalyst for use in the Sonogashira Reaction

4.1 Sonogashira reactions using coupling partners containing hetero atoms.

In Chapter 2, we described the development of synthetic methods for the derivatization of oxindoles with the 3-position acting as the site for an aldol / dehydration reaction and a halogen at the 5-position allowing for organopalladium cross-coupling chemistry. A series of Suzuki reactions were carried out and presented in table 2.5.

In order to increase the structural diversity of our oxindole library, we considered carrying out other organopalladium cross-coupling chemistry; specifically, Sonogashira reactions. The Sonogashira coupling of aryl or vinyl halides with terminal acetylenes has been used effectively in the synthesis of complex natural products[125] and polymeric materials[126] as well as generating one the partners required for a typical Click reaction.[127] Attempts at coupling phenyl acetylene with 5-iodo-oxindole under standard Sonogashira reaction conditions failed. Interestingly, a survey of the chemical literature revealed surprisingly few examples of Sonogashira reactions carried out with hetero atom containing substrates. As seen often, many of the popular catalytic systems used in palladium catalyzed cross-coupling reactions are poisoned by substrates containing heteroatoms (especially nitrogen).[128]

The Capretta group has shown that ligands based on the phospha-adamantane (PA) skeleton incorporated into catalytic systems allow a variety of Suzuki, Sonogashira, ketone arylation and amination reactions to proceed at room temperature in a few hours, even with less-

[125] D. Wang, S. Gao, *Org. Chem. Front.* **2014**, *1*, 556-566.
[126] M. Trunk, A. Herrmann, H. Bildirir, A. Yassin, J. Schmidt, A. Thomas, *Chem. Eur. J.* **2016**, *22*, 7179-7183.
[127] J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249-1262.
[128] V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellogg, *Org. Process Res. Dev.* **2009**, *14*, 30-47.

reactive substrates.[129] ,[130] In addition, new reaction sequences incorporating these catalytic systems aimed at the parallel synthesis of small molecule libraries have been described allowing for the synthesis of flavones,[131] isoquinolines,[132] pyrazolo[3,4-*d*]pyrimidines,[133] and maleimides.[134] The PA/Pd-catalytic systems are ideal platforms for library generation, as they allow for convergent strategies in high yields; their efficacy allows for low catalyst loadings and cost effective library synthesis; and they are easy to use as they do not require any special handling. The present chapter describes the synthesis, characterization and application of a new catalyst (PA-Ph$(OMe)_2)_2Pd\cdot O_2$, **2**, figure 4.1) for use in Sonogashira coupling.

4.2 New Pd-Phosphaadamantane-based Catalyst: (PA-Ph$(OMe)_2)_2PdO_2$

Previous work in the Capretta group allowed for the preparation and characterization of palladium complexes of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph), namely Pd(PA-Ph)$_2\cdot$dba and Pd(PA-Ph)$_2\cdot O_2$.[135] While the latter complex provided crystals suitable for x-ray analysis, the former complex was shown to be an effective catalyst for use in the Sonogashira reaction. Unfortunately, attempts to employ this chemistry in the Sonogashira coupling of phenyl acetylene with 5-iodo-oxindole were unsuccessful.

In 2004, the Capretta group described the synthesis and screening of a library of PA ligands and noted that the 2,4-dimethoxyphenyl variant of the PA-Ph ligand, namely PA-

[129] Adjabeng, G.; Brenstrum, T.; Wilson, J.; Frampton, C.S.; Robertson, A.J.; Hillhouse, J.; McNulty, J.; Capretta, A. *Org. Lett.* **2003**, *5* (6), 953-955.
[130] Gerristma, D.; Brenstrum, T.; McNulty, J.; Capretta, A. *Tet. Lett.* **2004**, *45* (45), 8319-8321.
[131] E. Awuah, A. Capretta, *Org. Lett.* **2009**, *11*, 3210-3213.
[132] E. Awuah, A. Capretta, *J. Org. Chem.* **2010**, *75*, 5627-5634.
[133] N. Todorovic, E. Awuah, T. Shakya, G. D. Wright, C. A., *Tetrahedron Lett.* **2011**, *52*, 5761 – 5763.
[134] E. Awuah, A. Capretta, *J. Org. Chem.* **2011**, *76*, 3122-3130.
[135] Adjabeng, G.; Brenstrum, T.; Frampton, C.S.; Robertson, A.J.; Hillhouse, J.; McNulty, K.; Capretta, A. *J. Org. Chem.* **2004**, *69* (15), 5082-5086.

$Ph(OMe)_2$ (**1**), facilitated a number of reactions wherein the PA-Ph ligand was less effective.[136] Given this precedent, we attempted to couple phenyl acetylene with 5-iodo-oxindole in the presence of 1 mol% $Pd_2(dba)_3$ and 2 mol% PA-Ph$(OMe)_2$. Unfortunately these conditions also failed to achieve coupling. At this point, we questioned whether the heterocyclic systems were likely poisoning the formation of our active catalyst *in situ* and set about to synthesize a preassociated Pd complex containing the PA-Ph$(OMe)_2$ ligand.

Palladium complexes of PA-Ph$(OMe)_2$ were readily prepared by dissolving **1** and $Pd_2(dba)_3$ in toluene and stirring the resultant solution at room temperature for 2 h before diluting with hexane (a 10-fold volume). The crystals obtained were subjected to NMR and mass spectrometry analysis and allowed us to characterize the complex as $(PA\text{-}Ph(OMe)_2)_2Pd\cdot O_2$ **2** (figure 4.1). Interestingly, unlike the complexes made in a similar fashion with PA-Ph, a complex with dba was not generated. Furthermore, attempts to analyze complex **2** via x-ray crystallography failed due to crystal quality.

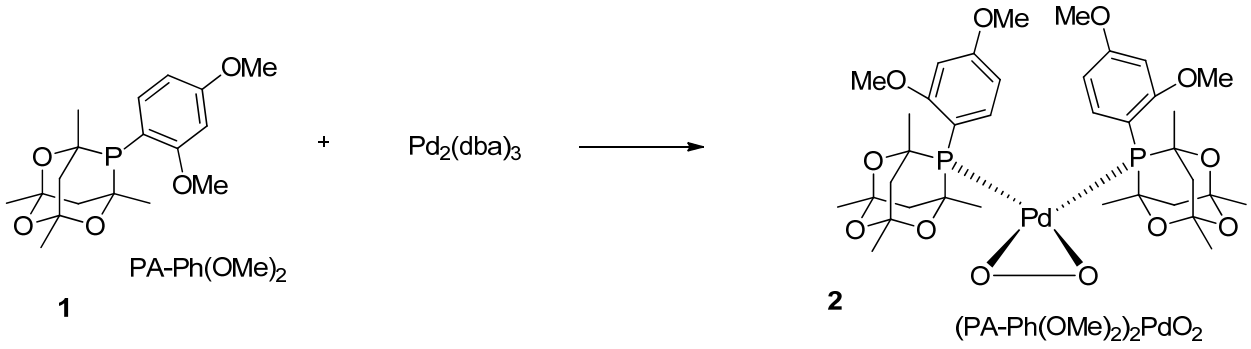
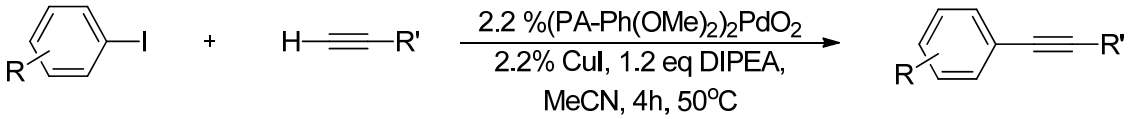
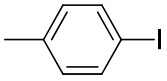
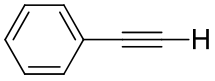
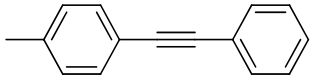
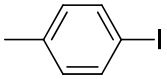
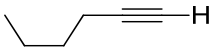
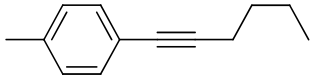
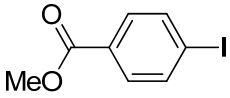
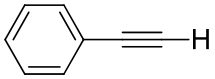
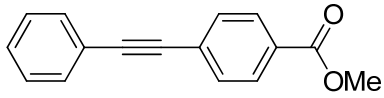
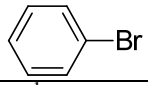
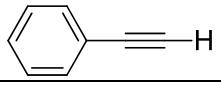
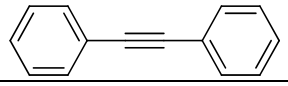


Figure 4.1. Synthesis of the catalytic palladium complex.

[136] Brenstrum, T.; Gerristma, D.A.; Adjabeng, G.M.; Frampton, C.S.; Britten, J. Robertson, A.J.; McNulty, J.; Capretta, A.; *J. Org. Chem.* **2004**, *69*, 7635-7639.

Table 4.1. Previously reported Sonogashira couplings using the $(PA\text{-}Ph(OMe)_2)_2Pd\cdot O_2$ catalyst.



Entry	Aryl Halide	Alkyne	Product	Yield (%)[a]
1				60
2				31
3				44
4[b]				55

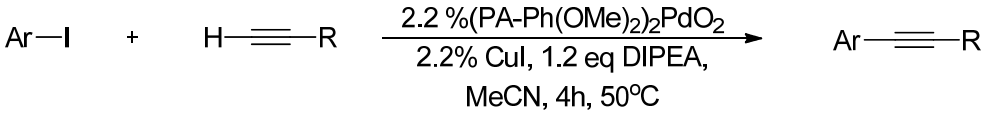
[a] Isolated yield. [b] 1.5 eq Cs_2CO_3, no CuI.

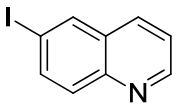
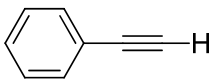
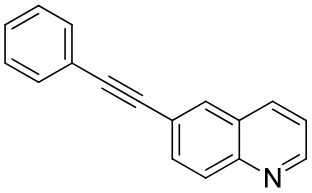
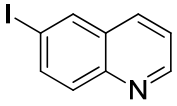
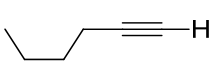
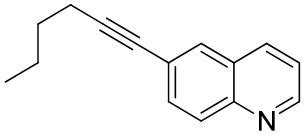
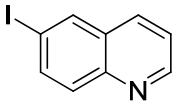
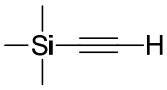
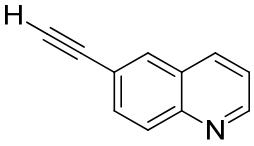
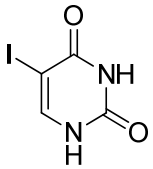
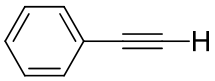
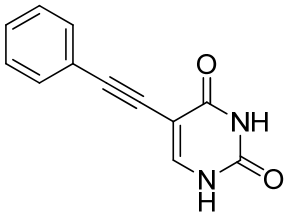
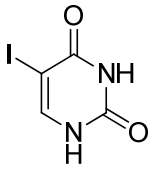
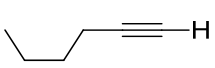
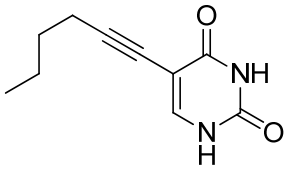
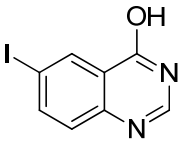
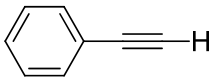
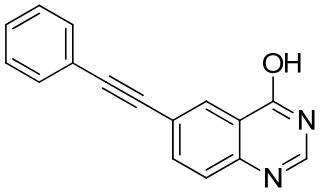
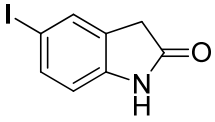
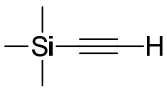
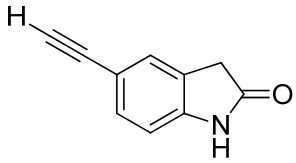
Our initial efforts focussed on the ability of complex **2** to facilitate the Sonogashira reaction as compared to the previously reported $Pd(PA\text{-}Ph)_2\cdot dba$ catalyst.[136] The results are presented in table 4.1. Exploratory experiments revealed that the reaction mixture utilizing **2** required heating to 50 °C to allow reductive elimination of O_2 and activate the catalyst. As a result, the coupling of aryl iodides with $Pd(PA\text{-}Ph)_2\cdot dba$ could be carried out at room temperature while $(PA\text{-}Ph(OMe)_2)_2Pd\cdot O_2$ necessitated elevated temperatures. Attempts to activate the complex **2** at 50°C then cooling the reaction mixture to room temperature (in the presence of coupling partners or with addition of coupling partners after cooling to room temperature) failed to achieve cross-coupling. As was previously noted,[136] reactions involving aryl iodides required the use of CuI as a co-catalyst while the use of copper (I) iodide was detrimental to the coupling of aryl bromides. Overall, it was determined that the $Pd(PA\text{-}Ph)_2\cdot dba$ generally gave better isolated yields of the coupled products.

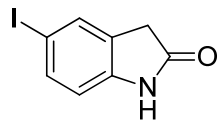
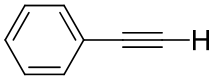
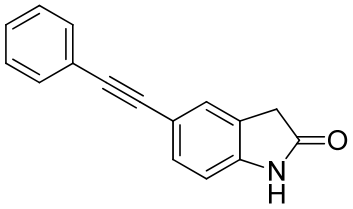
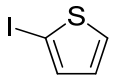
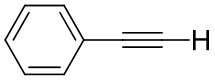
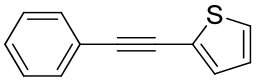
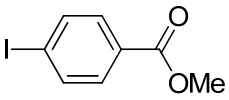
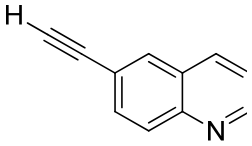
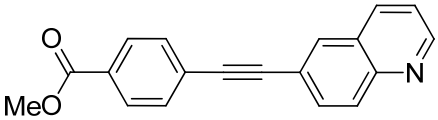
We next examined the effectiveness of complex **2** in the Sonogashira coupling of substrates possessing hetero atoms. Satisfyingly, complex **2** succeeded where the other Pd-PA

complexes failed (see table 4.2). Most striking was the ability of complex **2** to carry out couplings previously reported in the literature that required forcing conditions and longer reaction times.

Table 4.2. Sonogashira coupling reactions on various heterocycles



Entry	Aryl Iodide	Alkyne	Product	Yield (%)[a]
1				99
2				70
3[b]				82
4				79
5				21
6				81
7[b]				73

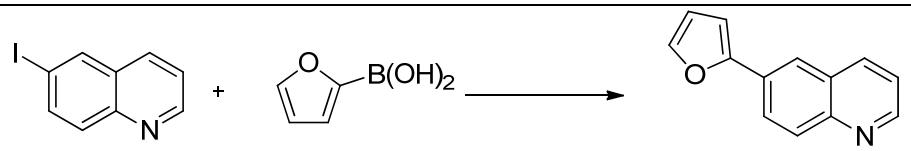
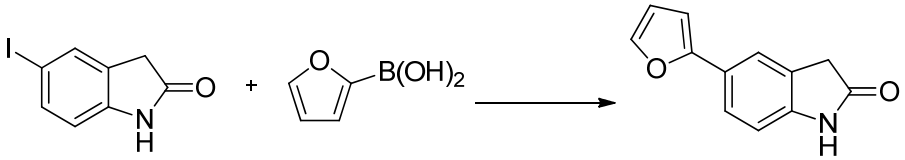
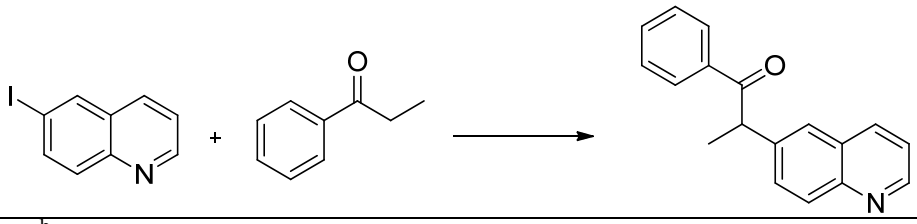
8				92
9				62
10				92

[a] Isolated yield. [b] Deprotection of TMS was conducted on crude product with 1.5 equivalents of TBAF (1.0 M in THF); yields are isolated yields.

For example, while previously reported Sonogashira reactions involving 5-iodooxindole (table 4.2, entries 7 and 8) required solid support and a 72 hour reaction time at room temperature,[137] complex **2** allowed for Sonogashira coupling at 50°C in 2 hours. Excellent yields were observed for the coupling of phenylacetylene (table 4.2, entry 8) and TMS-acetylene following deprotection with TBAF (table 4.2, entry 7). Also interesting were the results obtained with quinazolines[138,139] (entry 6) with previously reported procedures requiring longer reaction times and resulting in substantially lower yields. Known procedures for uracils and quinolines, however, currently surpass our conditions.[140,141]

[137] Lo, M.M.-C.; Neumann, C.S.; Nagayama, S.; Perlstein, E.O.; Schreiber, S.L. *J. Am. Chem. Soc.* **2004**, *126* (49), 16077-16086.
[138] Khabnadideh, S.; Pez, D.; Musso, A.; Brun, R.; Ruiz Perez, L.M.; Gonzalez-Pacanowska, D., Gilbert, I.H. *Bioorg. Med. Chem.* **2005**, *13* (7), 2637-2649.
[139] Harris, N.V.; Smith, C.; Bowden, K. *Synlett*, **1990**, *10*, 577-578.
[140] Cristofoli, W.A.; Wiebe, L.I.; Clercq, E.D.; Andrei, G.; Snoeck, R.; Balzarini, J.; Knaus, E.E. *J. Med. Chem.* **2007**, *50* (12), 2851-2857.
[141] Reddy, E.A.; Islam, A.; Mukkanti, K.; Bandameedi, V.; Bhowmik, D.R.; Pal, M. *Beilstein J. Org. Chem.* **2009**, *5* (32), 1-6.

Table 4.3. Additional cross-coupling reactions performed.

Entry	Reaction	Yield (%)[a]
1[b]		94
2[b]		11[c]
3[d]		28

[a] Isolated yield. [b] Conditions: 1.2 eq boronic acid, 1.5 eq Cs_2CO_3, 2.2% $(PA\text{-}Ph(OMe)_2)_2PdO_2$, toluene, 18h, 50 °C. [c] Product co-elutes with starting material; yield is calculated by comparison to starting material through ^1H NMR. [d] Conditions: 1.1 eq propiophenone, 1.5 eq NaO^tBu, 2% $(PA\text{-}Ph(OMe)_2)_2PdO_2$, toluene, 18h, 50 °C.

Following the success of $(PA\text{-}Ph(OMe)_2)_2PdO_2$ as a catalyst for heterocyclic Sonogashira couplings, we explored the ability of this system to catalyze other palladium cross-coupling reactions. While an excellent yield was observed for the Suzuki coupling on quinoline (table 4.3, entry 1), the same could not be said for the oxindole (table 4.3, entry 2), where a significant amount of starting material was observed in the ^1H NMR spectrum. The attempted α-keto arylation reaction also did not yield optimal results as the reaction also did not go to completion.

These results further support the notion that a "one-size-fits-all" ligand does not really exist.[136] A review of the chemical literature reveals that while certain phosphines accelerate a particular reaction, the same phosphine may have little effect on a different palladium-catalyzed cross-coupling reaction. Although some phosphines show a greater versatility than others, a ligand that can successfully be employed in all organopalladium coupling reactions has yet to be described. Capretta's PA library approach seems to be a more practical solution. Having

generated a collection of phospha-adamantanes with variable aryl or alkyl moiety at the phosphorous, each tertiary phosphine member has different electronic and steric properties. Parallel screening of the phospha-adamantane library quickly establishes the superior ligand to be used for the optimization of the particular reaction.

Heterocycles are the foundation of the majority of pharmaceuticals,[142] so it was surprising to notice the scarcity of literature in heterocyclic Sonogashira chemistry. The (PA-$Ph(OMe)_2)_2PdO_2$ catalyst demonstrates the potential to catalyze Sonogashira reactions on heterocyclic systems. It benefits from being easy to synthesize from commercially-available materials and is air-stable. In some cases, (PA-$Ph(OMe)_2)_2PdO_2$ outperformed current procedures found in the literature and could provide facile access to alkynes on a number of drug scaffolds.

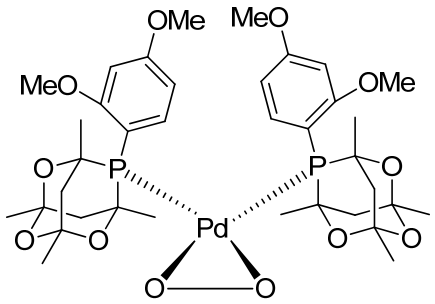
4.3 Experimental

Heated reactions were performed in a temperature-controlled oil bath with an oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube. TLC was performed on F-254 (0.25 mm) precoated silica gel (Merck) and visualized under UV, aqueous KMnO4, or aqueous ninhydrin stain. Flash column chromatography purifications were performed using a normal phase Teledyne Isco CombiFlash® Rf 200 with standard RediSep RF 12 g silica columns.

Compounds were characterized by ^1H NMR, ^{13}C NMR, DEPT Q, ESI-MS, and HRMS. NMR spectra were obtained from a Bruker AvanceIII 700 (700 MHz). Chemical shifts are reported as ppm, coupling constants in Hz, and peaks were calibrated to the solvent residual peak ($CDCl_3$ = 7.27 (^1H), 77.16 (^{13}C), DMSO = 2.50 (^1H), 39.51 (^{13}C)). Mass spectrometry was

[142] Gomtsyan, A. *Chem. Heterocycl. Compd.* **2011**, *48* (1), 7-10.

conducted with a Bruker Maxis 4G/TOF in either positive or negative ion mode with direct infusion.



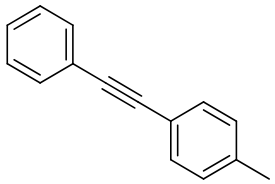
(PA-Ph(OMe)$_2$)$_2$PdO$_2$: The ligand 8-(2,4-dimethoxyphenyl)-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (PA-Ph(OMe)$_2$) was synthesized and purified according to a known procedure.[143] The title compound was then synthesized by dissolving PA-Ph(OMe)$_2$ (1.06 g, 3.00 mmol) to 30 mL anhydrous toluene in an oven-dried and N_2-purged round bottom flask which was then degassed for 10 minutes with N_2. $Pd_2(dba)_3$ (0.344 g, 0.376 mmol) was then added under positive N_2 flow to the reaction mixture, and the vessel was sealed and allowed to stir for 2 hours. A distinct colour change from dark red to dark yellow/orange occurred during this time. After 2 hours, the reaction mixture was added to 300 mL of hexanes and allowed to sit overnight. The following morning, an amorphous solid was observed in the mixture. This precipitate was then filtered, washed with hexanes, and dried under vacuum to yield the final product as a grey-green amorphous solid (0.298 g, 94% yield). ^{1}H NMR (700 MHz; CD_3OD) δ 7.91 (m, 2H), 6.66 (s, 2H), 6.61 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 6H), 3.85 (s, 6H), 2.63 (d, *J* = 13.3 Hz, 2H), 1.77 (d, *J* = 13.8 Hz, 2H), 1.59 (m, 2H), 1.52 (m, 2H), 1.41 (m, 12H), 1.25 (m, 6H), 0.83 (m, 6H). ^{13}C NMR (176 MHz; CD_3OD) δ 166.11 (C), 164.71 (C), 135.54 (CH), 107.92 (C), 107.36 (CH), 99.97 (CH), 97.86 (C), 97.37 (C), 76.44 (C), 75.19 (C), 56.27 (CH_3), 55.68 (CH_3), 45.46 (CH_2),

[143] Brenstrum, T.; Gerristma, D.A.; Adjabeng, G.M.; Frampton, C.S.; Britten, J.; Robertson, A.J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635-7639.

39.55 (CH_2), 28.06 (CH_3), 27.94 (CH_3), 27.45 (CH_3), 25.61 (CH_3) ^{31}P NMR (283 MHz, CD_3OD) δ 3.94. HRMS (ESI): Exact mass calcd for $C_{36}H_{50}O_{12}P_2Pd$ $[M]^+$: 842.1812. Found $[M+H]^+$: 843.1952.

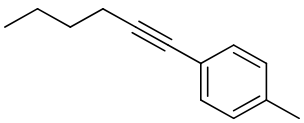
General procedure D ((PA-Ph(OMe)$_2$)$_2$PdO$_2$ catalysis):

To a clean oven-dried and N_2-purged Radley's Carousel 12 Plus reaction tube was added the aryl halide (1.0 equiv.), alkyne (1.5 equiv.), catalyst (2.2%), CuI (2.2%), stir bar, and 5 mL anhydrous CH_3CN. The vessel was then degassed for 5 minutes. DIPEA was then added (1.2 equiv.) and the vessel was purged for an additional 2 minutes before being sealed and allowed to stir for 4 hours at 50 °C. The mixture was then removed from heat, diluted with CH_2Cl_2, filtered through a pad of silica, concentrated under reduced pressure, and the product was purified by column chromatography.

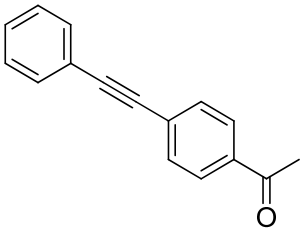


1-methyl-4-(phenylethynyl)benzene: 1-iodo-4-methylbenzene (0.100 g, 0.459 mmol), phenylacetylene (76.0 μL, 0.688 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (8.53 mg, 0.0101 mmol), and CuI (1.92 mg, 0.0101 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (96.3 μL, 0.550 mmol) and heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-20% Et_2O/hexanes) to yield the final product as a white amorphous solid (54.4 mg, 60% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.55 (m, 2H), 7.45 (d, *J* =

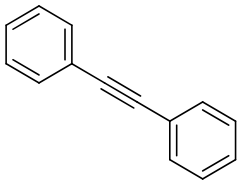
8.1 Hz, 2H), 7.35 (m, 3H), 7.18 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 138.34 (C), 131.52 (CH), 131.47 (CH), 129.09 (CH), 128.28 (CH), 128.04 (CH), 123.46 (C), 120.17 (C), 89.54 (C), 88.70 (C), 21.47 (CH_3). HRMS (ESI): Exact mass calcd for $C_{15}H_{12}$ $[M]^+$: 192.0939. Found $[M+H]^+$: 193.1030.



1-(hex-1-yn-1-yl)-4-methylbenzene: 1-iodo-4-methylbenzene (0.100 g, 0.459 mmol), 1-hexyne (79.0 μL, 0.688 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (8.53 mg, 0.0101 mmol), and CuI (1.92 mg, 0.0101 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (96.3 μL, 0.550 mmol) and heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-20% Et_2O/hexanes) to yield the final product as a yellow oil (24.4 mg, 31% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.32 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.62 (m, 2H), 1.52 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 137.37 (C), 131.38 (CH), 128.91 (CH), 120.99 (C), 89.55 (C), 80.52 (C), 30.90 (CH_2), 22.00 (CH_2), 21.37 (CH_3), 19.10 (CH_2), 13.64 (CH_3). HRMS (EI-MS): Exact mass calcd for $C_{13}H_{16}$ $[M]^+$: 172.1252 Found $[M]^+$: 172.1264.

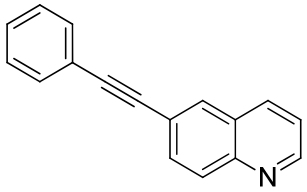


1-(4-(phenylethynyl)phenyl)ethanone: 1-iodo-4-acetyllbenzene (0.113 g, 0.459 mmol), phenylacetylene (76.0 μL, 0.688 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (8.53 mg, 0.0101 mmol), and CuI (1.92 mg, 0.0101 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (96.3 μL, 0.550 mmol) and heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-20% Et_2O/hexanes) to yield the final product as a yellow oil (24.4 mg, 44% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.32 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.62 (m, 2H), 1.52 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 137.37 (C), 131.38 (CH), 128.91 (CH), 120.99 (C), 89.55 (C), 80.52 (C), 30.90 (CH_2), 22.00 (CH_2), 21.37 (CH_3), 19.10 (CH_2), 13.64 (CH_3). HRMS (ESI-MS): Exact mass calcd for $C_{16}H_{12}O$ $[M]^+$: 220.0888 Found $[M+H]^+$: 221.0994.

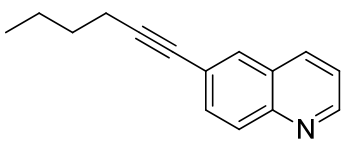


1,2-diphenylethyne: Bromobenzene (49.0 μL, 0.459 mmol), phenylacetylene (76.0 μL, 0.688 mmol), and (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (8.53 mg, 0.0101 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added Cs_2CO_3 (0.224 g, 0.689 mmol) and heated at 50 °C for 24 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-20% Et_2O/hexanes) to yield the final product as a yellow oil (45.4 mg, 55% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.57 (m, 2H), 7.38 (m, 3H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 131.59 (CH),

128.32 (CH), 128.23 (CH), 123.26 (C), 89.35 (C). HRMS (EI-MS): Exact mass calcd for $C_{14}H_{10}$ $[M]^+$: 178.0783. Found: 178.0780.

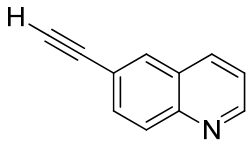


6-(phenylethynyl)quinoline: 6-iodoquinoline (0.100 g, 0.392 mmol), phenylacetylene (65.0 μL, 0.588 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (7.29 mg, 0.00863 mmol), and CuI (1.64 mg, 0.00863 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (82.4 μL, 0.470 mmol) and heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a light brown amorphous solid (88.5mg, 99% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 8.94 (bs, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.04 (s, 1H), 7.83 (dd, J = 8.6, 1.6 Hz, 1H), 7.59 (m, 2H), 7.44 (m, 1H), 7.38 (m, 3H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 150.86 (CH), 147.83 (C), 135.74 (C), 132.20 (CH), 131.73 (CH), 131.15 (CH), 129.72 (CH), 128.61 (CH), 128.46 (CH), 122.95 (C), 121.90 (CH), 121.66 (C), 90.70 (C), 88.98 (C). HRMS (ESI): Exact mass calcd for $C_{17}H_{11}N$ $[M]^+$: 229.0892. Found $[M+H]^+$: 230.0963.



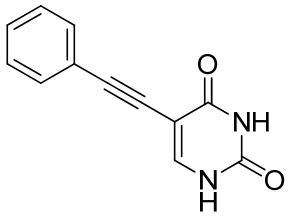
6-(hex-1-yn-1-yl)quinoline: 6-iodoquinoline (0.100 g, 0.392 mmol), 1-hexyne (68.0 μL, 0.588 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (7.29 mg, 0.00863 mmol), and CuI (1.64 mg, 0.00863 mmol) were

added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (82.4 µL, 0.470 mmol) and heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a yellow oil (74.0, 70% yield). ^{1}H NMR (600 MHz; $CDCl_3$): *indicates residual starting material that co-eluted δ 8.91 (br. s, 1H), *8.17 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 8.00 (m, 1H), *7.98 (m, 1H), *7.92 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 7.86 (s, 1H), *7.81 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.37 (m, 1H), 2.45 (t, *J* = 7.1 Hz, 2H), 1.61 (m, 2H), 1.50 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$) δ *150.76 (C), 150.37(C), 147.32(C), *147.11(C), *138.05 (CH), *136.43(CH), 135.43 (CH), *134.68(CH), 132.40 (CH), *131.08 (CH), 130.57 (CH), 129.29 (CH), *127.98 (CH), 122.38 (CH), 121.64 (C), 121.51 (CH), 91.90 (C), 80.17 (C), 30.67 (CH_2), 21.96 (CH_2), 19.11 (CH_2), 13.57 (CH_3). HRMS (ESI): Exact mass calcd for $C_{15}H_{15}N$ $[M]^+$: 209.1205. Found $[M+H]^+$: 210.1278.



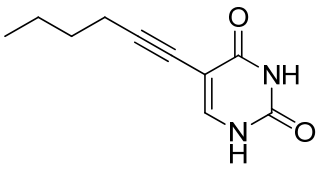
6-ethynylquinoline: 6-iodoquinoline (0.100 g, 0.392 mmol), ethynyltrimethylsilane (83.0 µL, 0.588 mmol), $(PA\text{-}Ph(OMe)_2)_2PdO_2$ (7.29 mg, 0.00863 mmol), and CuI (1.64 mg, 0.00863 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (82.4 µL, 0.470 mmol) and heated at 50 °C for 4 hours. The mixture was then cooled to room temperature and partitioned in H_2O/CH_2Cl_2. The CH_2Cl_2 fraction was dried with $MgSO_4$, concentrated under

reduced pressure, and suspended in anhydrous THF in a Radley's 12 Plus Carousel vial and degassed with N_2 for 5 minutes while cooling to 0 °C. A 1 M solution of tetra-n-butylammonium fluoride in THF (0.784 mL 0.781 mmol) was then added dropwise over 10 minutes. Following completion of the addition, the mixture was allowed to warm to room temperature for 4 hours. The mixture was then concentrated under reduced pressure and purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a light brown solid (49.0 mg, 82% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 8.91 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.1 (dd, *J* = 8.3, 0.4 Hz, 1H), 8.05 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.75 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.3 Hz, 1H), 3.20 (s, 1H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 151.15 (CH), 147.78 (C), 135.84 (CH), 132.33 (CH), 132.03 (CH), 129.63 (CH), 127.84 (C), 121.80 (CH), 120.44 (C), 83.17 (C), 78.48 (CH). HRMS (ESI): Exact mass calcd for $C_{11}H_7N$ $[M]^+$: 153.0579. Found $[M+H]^+$: 154.0656.

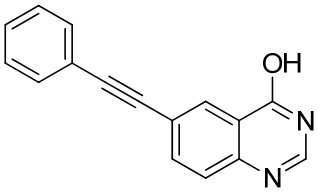


5-(phenylethynyl)pyrimidine-2,4(1H,3H)-dione: 5-Iodouracil (0.184 g, 0.772 mmol), phenylacetylene (127 μL, 1.16 mmol), $(PA\text{-}Ph(OMe)_2)_2PdO_2$ (14.4 mg, 0.0170 mmol), and CuI (3.23 mg, 0.0170 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (161 μL, 0.926 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-20% CH_3OH/CH_2Cl_2) to yield the

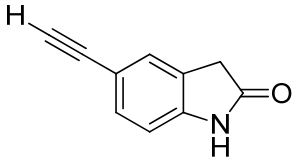
final product as a light brown amorphous solid (64.4 mg, 40% yield). ^{1}H NMR (700 MHz; DMSO). * Denotes minor tautomer: δ 11.42 (bs, 1H), 11.36 (bs, 1H), *11.24 (bs, 1H), *11.17 (bs, 1H), 7.89 (s, 1H), *7.65 (d, *J* = 5.5 Hz, 1H), 7.45 (m, 2H), 7.39 (m, 4H), *7.33 (m, 3H), 6.47 (s, 1H). ^{13}C NMR (176 MHz; DMSO) δ 162.47 (C), *151.26 (C), 150.41 (C), 145.82 (CH), *145.60 (C), *142.74 (CH), *138.63 (C), *131.07 (CH), 131.04 (CH), *128.78 (CH), 128.70 (CH), 128.46 (CH), *128.33 (CH), *126.18 (CH), 122.59 (C), *110.16 (C), *108.69 (CH), 96.82 (C), *94.77 (C), 91.52 (C), *88.70 (C), 82.68 (C). HRMS (ESI): Exact mass calcd for $C_{12}H_8N_2O_2$ $[M]^+$: 212.0586. Found $[M+Na]^+$: 235.0503.



5-(hex-1-yn-1-yl)pyrimidine-2,4(1H,3H)-dione: 5-Iodouracil (0.184 g, 0.772 mmol), 1-hexyne (133 µL, 1.16 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (14.4 mg, 0.0170 mmol), and CuI (3.23 mg, 0.0170 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (161 µL, 0.926 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-20% CH_3OH/CH_2Cl_2) to yield the final product as a light brown amorphous solid (30.8 mg, 21% yield). ^{1}H NMR (700 MHz; DMSO) δ 11.95 (bs, 1H), 8.14 (s, 1H), 6.37 (s, 1H), 2.64 (t, *J* = 7.3 Hz, 2H), 1.60 (quin, *J* = 7.5, 2H), 1.35 (m, 2H), 0.91 (t, *J* = 7.4, 3H). ^{13}C NMR (176 MHz; DMSO) δ 172.09 (C), 157.75 (C), 155.83 (C), 105.99 (CH), 99.61 (C), 99.47 (C), 28.45 (CH_2), 27.00 (CH_2), 21.51 (CH_2) 13.57 (CH_3). HRMS (ESI): Exact mass calcd for $C_{10}H_{12}N_2O_2$ $[M]^+$: 192.0899. Found $[M+Na]^+$: 215.0793.

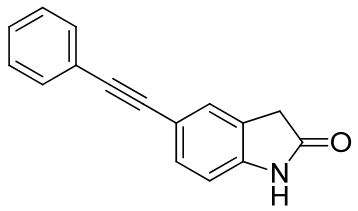


6-(phenylethynyl)quinazolin-4-ol: 6-iodoquinazolin-4-ol (0.210 g, 0.772 mmol), phenylacetylene (127 μL, 1.16 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (14.4 mg, 0.0170 mmol), and CuI (3.23 mg, 0.0170 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (161 μL, 0.926 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a fluffy light brown amorphous solid (153 mg, 81% yield). ^{1}H NMR (700 MHz; DMSO) δ 12.40 (bs, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.14 (s, 1H), 7.93 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.61 (m, 2H), 7.46 (m, 3H). ^{13}C NMR (176 MHz; DMSO) δ 159.99 (C), 148.59 (C), 146.29 (CH), 136.58 (CH), 131.51 (CH), 129.08 (CH), 128.79 (CH), 127.91 (CH), 122.89 (C), 121.91 (C), 120.44 (C), 90.48 (C), 88.36 (C). HRMS (ESI): Exact mass calcd for $C_{16}H_{10}N_2O$ $[M]^+$: 246.0793. Found $[M+H]^+$: 247.0863.



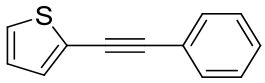
5-ethynylindolin-2-one: 5-iodooxindole (0.200 g, 0.772 mmol), ethynyltrimethylsilane (164 μL, 1.16 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (14.4 mg, 0.0170 mmol), and CuI (3.23 mg, 0.0170 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General

Procedure D. Following degassing with N_2 was added DIPEA (161 μL, 0.926 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature and partitioned in H_2O/CH_2Cl_2. The CH_2Cl_2 fraction was dried with $MgSO_4$, concentrated under reduced pressure, and suspended in anhydrous THF in a Radley's 12 Plus Carousel vial and degassed with N_2 for 5 minutes while cooling to 0 °C. A 1 M solution of tetra-n-butylammonium fluoride in THF (0.654 mL, 0.654 mmol) was then added dropwise over 10 minutes. Following completion of the addition, the mixture was allowed to warm to room temperature for 4 hours. The mixture was then concentrated under reduced pressure and purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a brown amorphous solid (87.1 mg, 73%).^{1}H NMR (700 MHz; DMSO) δ 10.54 (bs, 1H), 7.29 (m, 2H), 6.79 (d, J = 7.9 Hz, 1H), 3.99 (s, 1H), 3.47 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 176.75 (C), 144.82 (C), 132.13 (CH), 128.08 (CH), 126.82 (C), 114.64 (C), 109.71 (CH), 84.52 (C), 79.39 (C), 35.96 (CH_2). HRMS (ESI): Exact mass calcd for $C_{10}H_6NO$ $[M]^+$: 157.0528. Found $[M+Na]^+$: 180.0436.

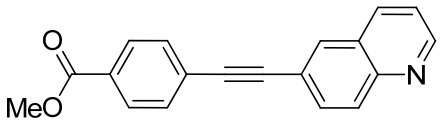


5-(phenylethynyl)indolin-2-one: 5-Iodouracil (0.183 g, 0.707 mmol), phenylacetylene (116 μL, 1.06 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (13.2 mg, 0.0156 mmol), and CuI (2.97 mg, 0.0156 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (148 μL, 0.848 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and

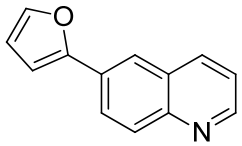
purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a brown amorphous solid (161.4 mg, 98% yield). ^{1}H NMR (700 MHz; DMSO) δ 10.58 (bs, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.40 (m, 5H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.51 (s, 2H). ^{13}C NMR (176 MHz; DMSO) δ 176.26 (C), 144.29 (C), 131.35 (CH), 131.13 (CH), 128.70 (CH), 128.36 (CH), 127.34 (CH), 126.46 (C), 122.71 (C), 114.67 (C), 109.35 (CH), 90.02 (C), 87.79 (C), 35.51 (CH_2). HRMS (ESI): Exact mass calcd for $C_{16}H_{11}NO$ $[M]^+$: 233.0841. Found $[M+Na]^+$: 256.0751.



2-(phenylethynyl)thiophene: 2-Iodothiophene (85.3 μL, 0.772 mmol), phenylacetylene (127 μL, 1.16 mmol), $(PA\text{-}Ph(OMe)_2)_2PdO_2$ (14.4 mg, 0.0170 mmol), and CuI (3.23 mg, 0.0170 mmol) were added to a clean, oven-dried reaction tube in 5 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (161 μL, 0.926 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-10% Et_2O/hexanes) to yield the final product as a white crystalline solid (87.7 mg, 62% yield). ^{1}H NMR (700 MHz; DMSO) δ 7.67 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.54 (m, 2H), 7.43 (m, 4H), 7.13 (dd, *J* = 5.2, 3.7 Hz, 1H). ^{13}C NMR (176 MHz; DMSO) δ 132.68 (CH), 131.15 (CH), 128.96 (CH), 128.80 (CH), 127.79 (CH), 121.85 (C), 121.77 (C), 92.78 (C), 82.60 (C). HRMS (EI-MS): Exact mass calcd for $C_{12}H_8S$ $[M]^+$: 184.0347. Found $[M]^+$: 184.0347.

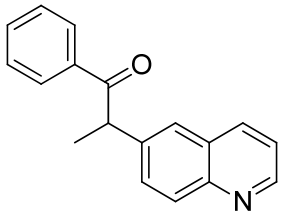


Methyl 4-(quinolin-6-ylethynyl)benzoate: 2-Iodothiophene (70.0, 0.267 mmol), 6-ethynylquinoline (61.4 mg, 0.401 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (6.1 mg, 0.00587 mmol), and CuI (1.0 mg, 0.00534 mmol) were added to a clean, oven-dried reaction tube in 3 mL of anhydrous CH_3CN as per General Procedure D. Following degassing with N_2 was added DIPEA (55.8 μL, 0.320 mmol) and the vessel was heated at 50 °C for 4 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-100% Et_2O/hexanes) to yield the final product as a yellow amorphous solid (70.5 mg, 91% yield). ^{1}H NMR (700 MHz; DMSO) δ 9.03 (bs, 1H), 8.41 (d, *J* = 8.1 Hz, 1H), 8.31 (s, 1H), 8.07 (s, 1H), 8.01 (d, *J* = 7.7 Hz, 2H), 7.88 (d, *J* = 6.2 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 6.4 Hz, 1H), 3.85 (s, 1H). ^{13}C NMR (176 MHz; DMSO) δ 165.56 (C), 151.56 (C), 147.32 (C), 135.93 (C), 131.93 (C), 131.75 (CH), 131.57 (C), 129.61 (CH), 129.44 (CH), 127.88 (CH), 126.73 (CH), 122.59 (CH), 119.67 (CH), 91.87 (CH), 89.35 (CH), 52.31 (CH_3). HRMS (ESI-MS): Exact mass calcd for $C_{19}H_{13}NO_2$ $[M]^+$: 287.0946. Found $[M+Na]^+$: 310.0849.



6-(furan-2-yl)quinoline: 6-iodoquinoline (0.100 g, 0.392 mmol), furan-2ylboronic acid (0.065 g, 0.588 mmol) and the (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (7.29 mg, 0.00863 mmol) were dissolved in 5 mL of anhydrous CH_3CN in a carousel vial and purged with N_2. Cs_2CO_3 (0.307 g, 0.941 mmol) was added and the reaction vessel was sealed. After heating for 18 hours at 50 °C, the reaction was

filtered through a pad of silica, concentrated under reduced pressure, and purified by flash chromatography (0-100% EtOAc/hexanes) to give the title compound as a yellow solid (72.0 mg, 94% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 8.87 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.11 (m, 2H), 7.85 (m, 3H), 7.53 (t, *J* = 1.6 Hz, 1H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.81 (dd, *J* = 1.7, 0.9 Hz, 1H). ^{13}C NMR (150 MHz; $CDCl_3$) δ 149.95 (CH), 147.48 (C), 143.98 (CH), 139.15 (CH), 135.75 (CH), 130.56 (C), 129.86 (CH), 128.50 (C), 127.99 (CH), 125.79 (C), 123.51 (CH), 121.44 (CH), 108.71 (CH). HRMS (ESI): Exact mass calcd for $C_{13}H_9NO$ $[M]^+$: 195.06841. Found $[M+H]^+$ 196.0759.



1-phenyl-2-(quinolin-6-yl)propan-1-one: 6-iodoquinoline (0.150 g, 0.588 mmol), phenylproprione (86.0 μL, 0.647 mmol), (PA-Ph(OMe)$_2$)$_2$PdO$_2$ (9.95 mg, 0.0118 mmol), and 5 mL of anhydrous toluene were added to a clean, oven-dried reaction tube as per General Procedure D. Following degassing with N_2 was added NaO*t*Bu (84.8 mg, 0.882 mmol) and the vessel was heated at 50 °C for 18 hours. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, passed through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (0-100% EtOAc/hexanes) to yield the final product as a fluffy light brown amorphous solid (42.8 mg, 28% yield). ^{1}H NMR (700 MHz; DMSO) δ 8.83 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.30 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.53 (m, 1H), 7.46 (m, 3H), 5.18 (q, *J* = 6.7 Hz, 1H), 1.51 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (176 MHz; DMSO) δ 199.89

(C), 150.37 (CH), 146.68 (C), 139.78 (C), 135.88 (C), 135.75 (CH), 133.10 (CH), 129.68 (CH), 129.50 (CH), 128.69 (CH), 128.60 (CH), 127.95 (C), 126.36 (CH), 121.62 (CH), 46.22 (CH), 19.08 (CH_3). HRMS (ESI): Exact mass calcd for $C_{18}H_{15}NO$ $[M]^+$: 261.1154. Found $[M+H]^+$: 262.1233.

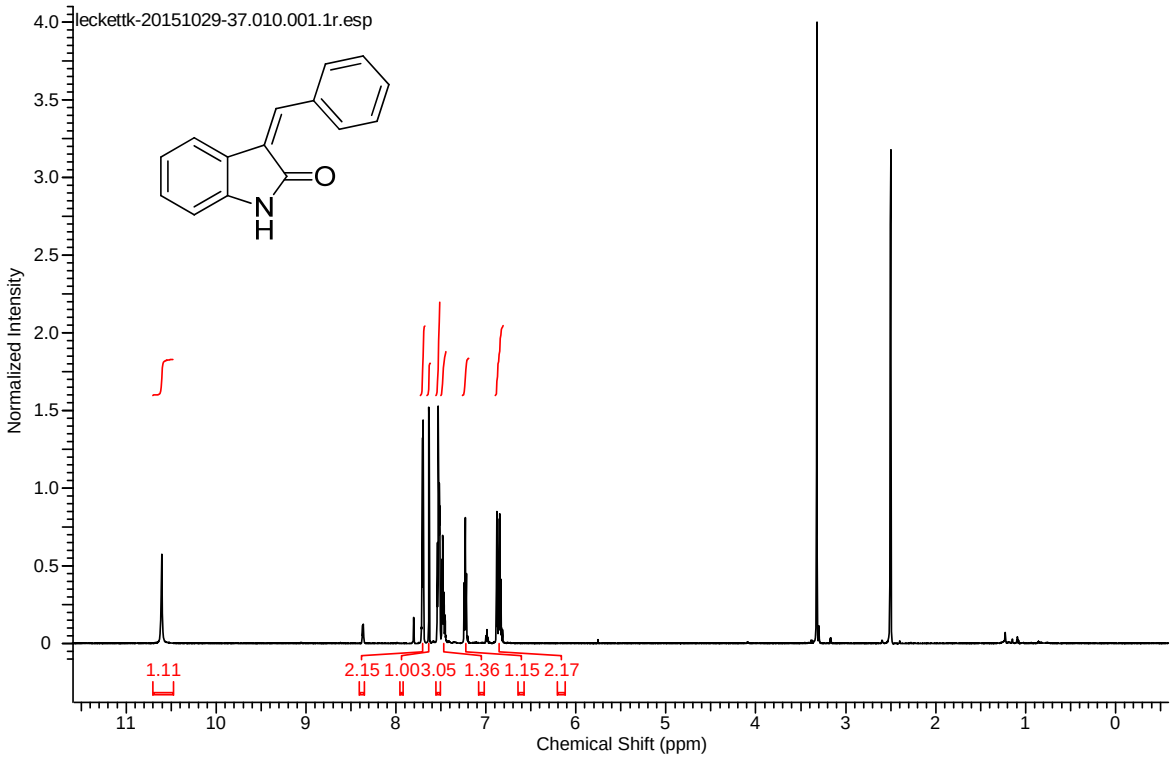
Chapter 5: Conclusions

Throughout the course of the work presented in this thesis, new methodology including microwave-assisted Knoevenagel condensations and Pd-catalyzed cross-coupling reactions has been developed that can facilitate the rapid generation of structurally diverse substituted oxindole and quinazoline libraries. The leads generated for APH, ANT, and AAC inhibitors could potentially provide new options when dealing with the growing threat of antibiotic resistance.

Chapter 6: Future Work

Unfortunately, due to time constraints, the results of the biological assays could not be completed in time to address in this thesis. This is a key step towards understanding the pharmacophore in the case of both the oxindole and quinazoline libraries. Once these biological assays are completed, SAR studies can then be conducted and the most promising lead molecules could be further optimized to improve potency, solubility, and bioavailability. Further, given the novel potential of the $(PA\text{-}Ph(OMe)_2)_2PdO_2$ catalyst, terminal alkyne moieties could be installed on the promising lead compounds produced from the biological assays in order to enable Click-chemistry studies which could provide further insight into the activity of these leads.

Appendix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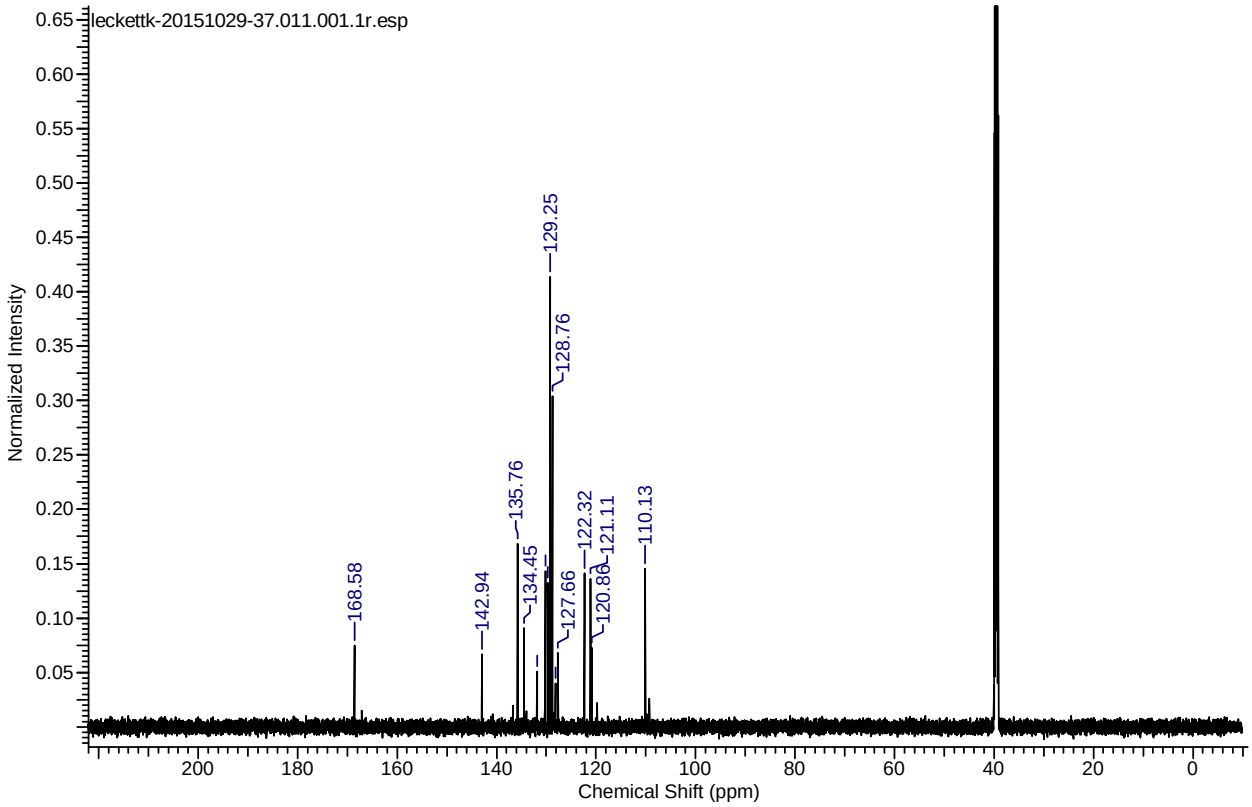
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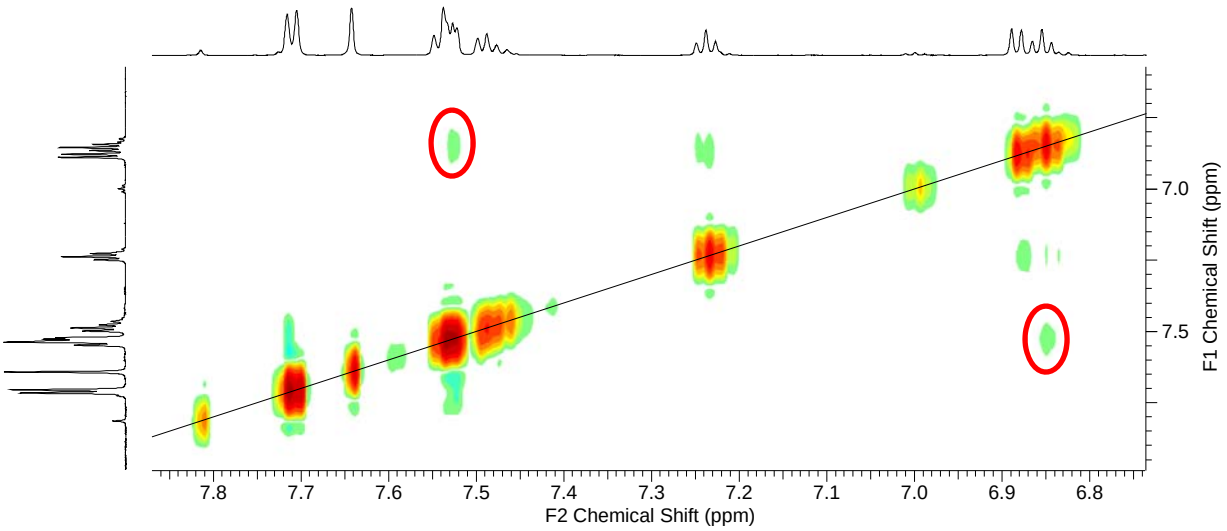
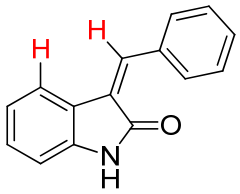
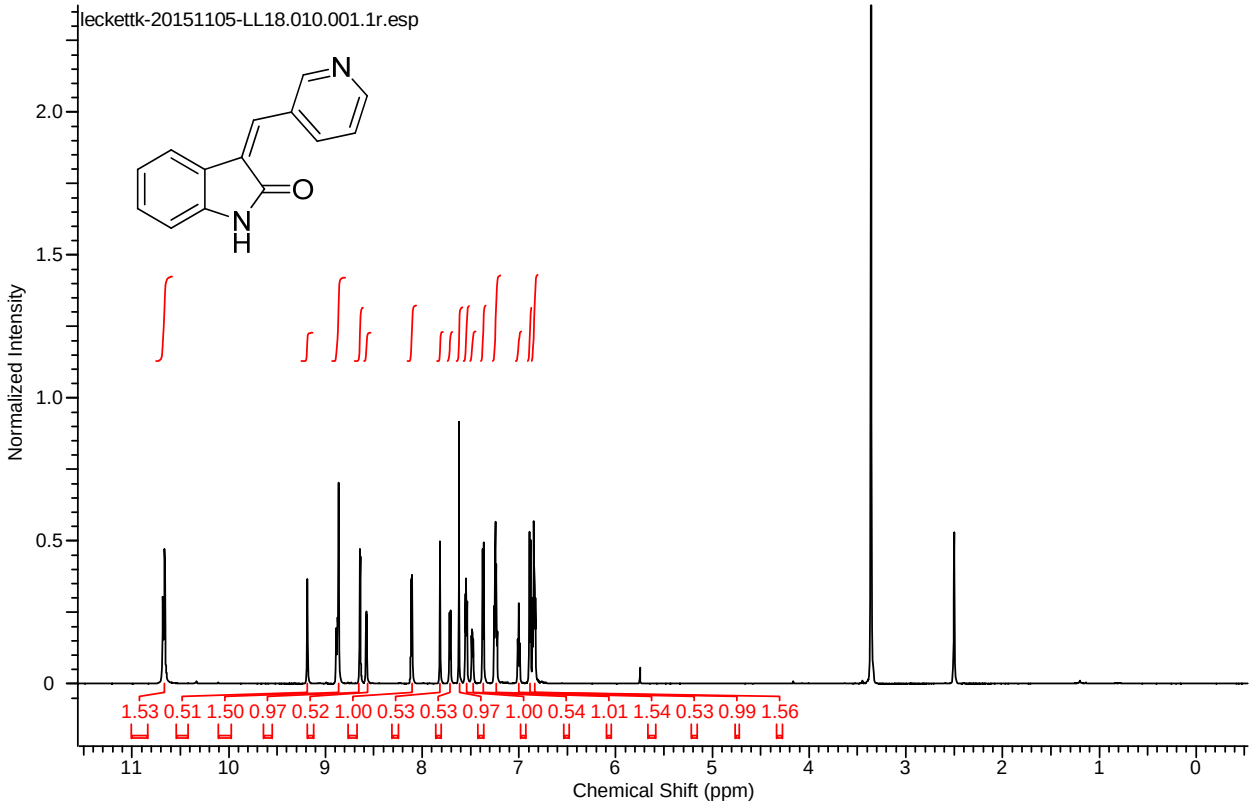




Sample NOESY spectrum of previous molecule. Peaks highlighted in red circles illustrate the two protons listed above, and provide the NOE signal indicative of the *Z* isomer.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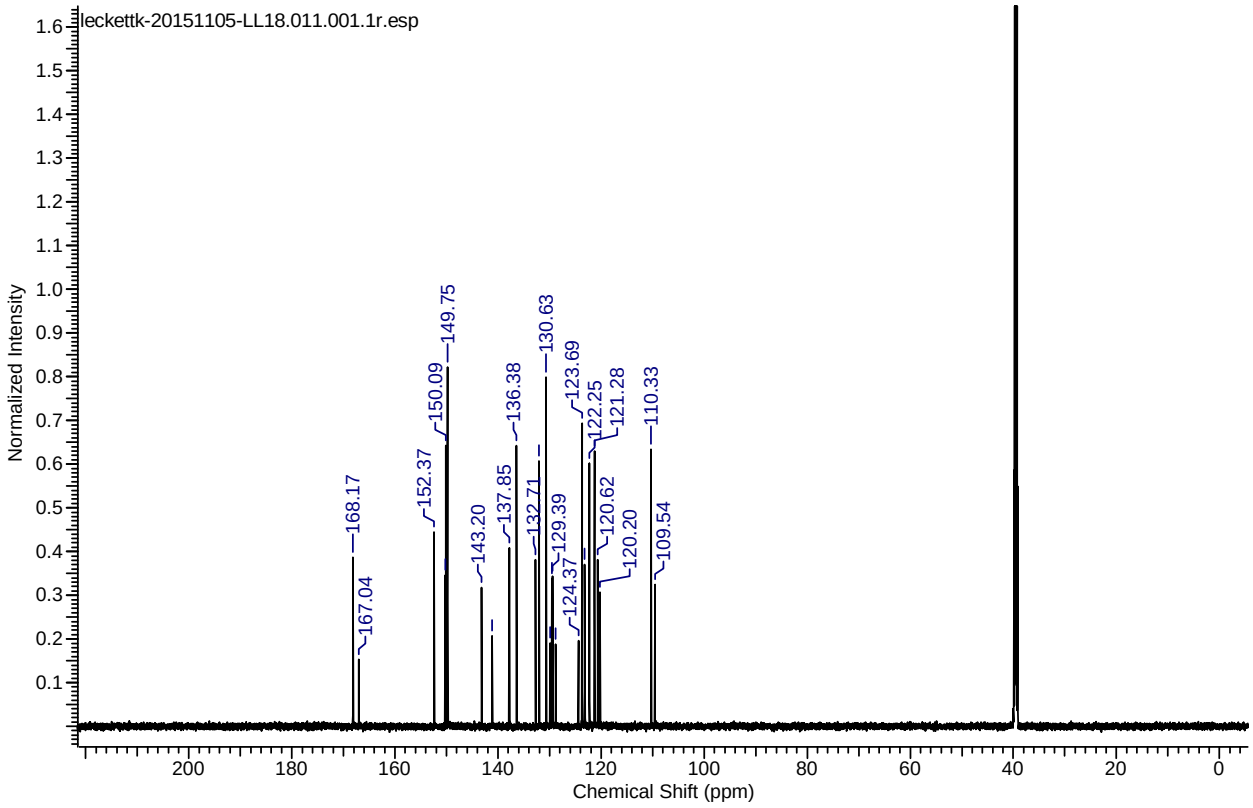
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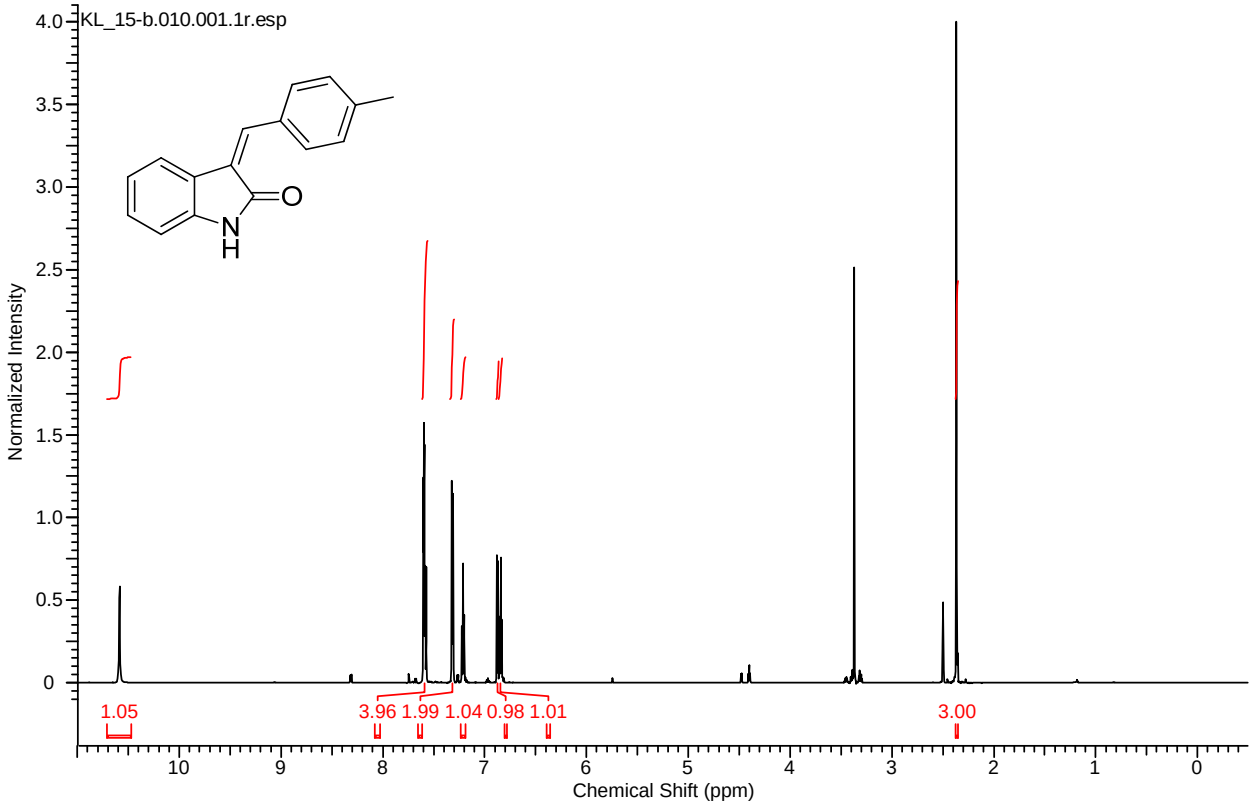
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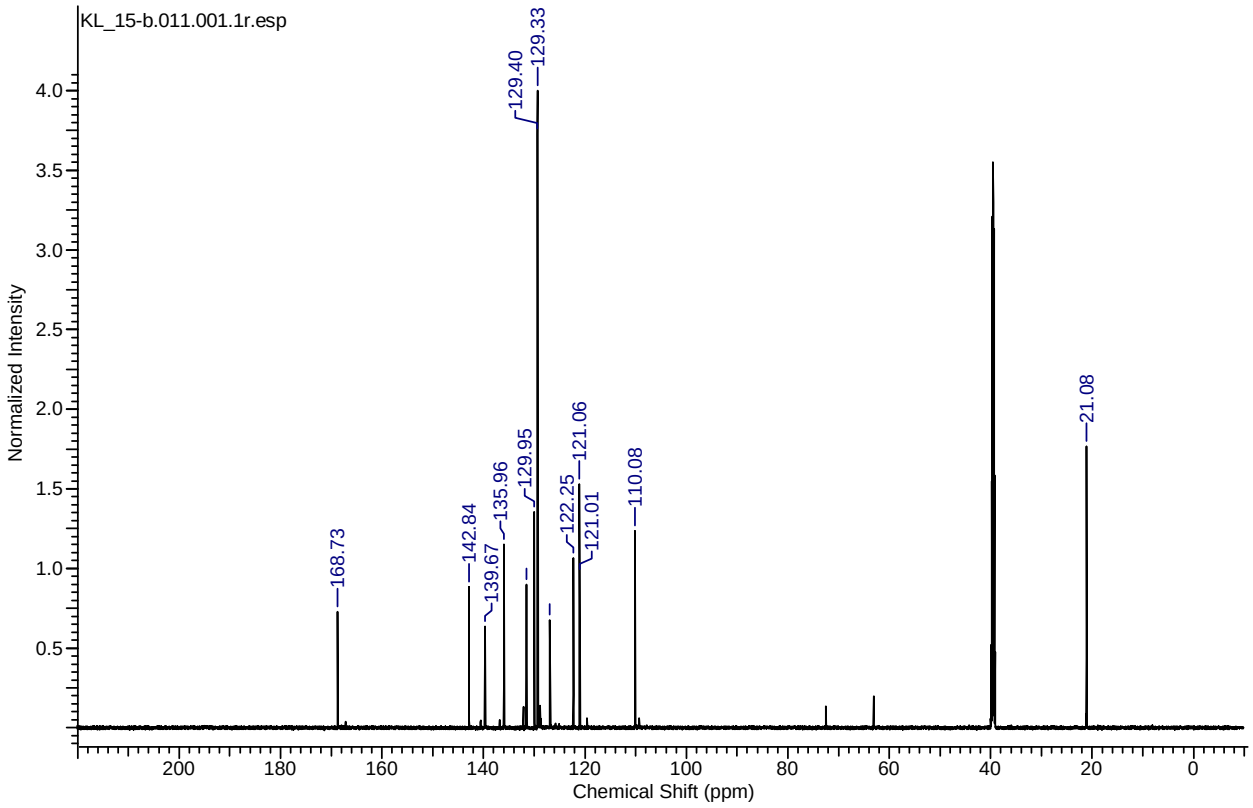
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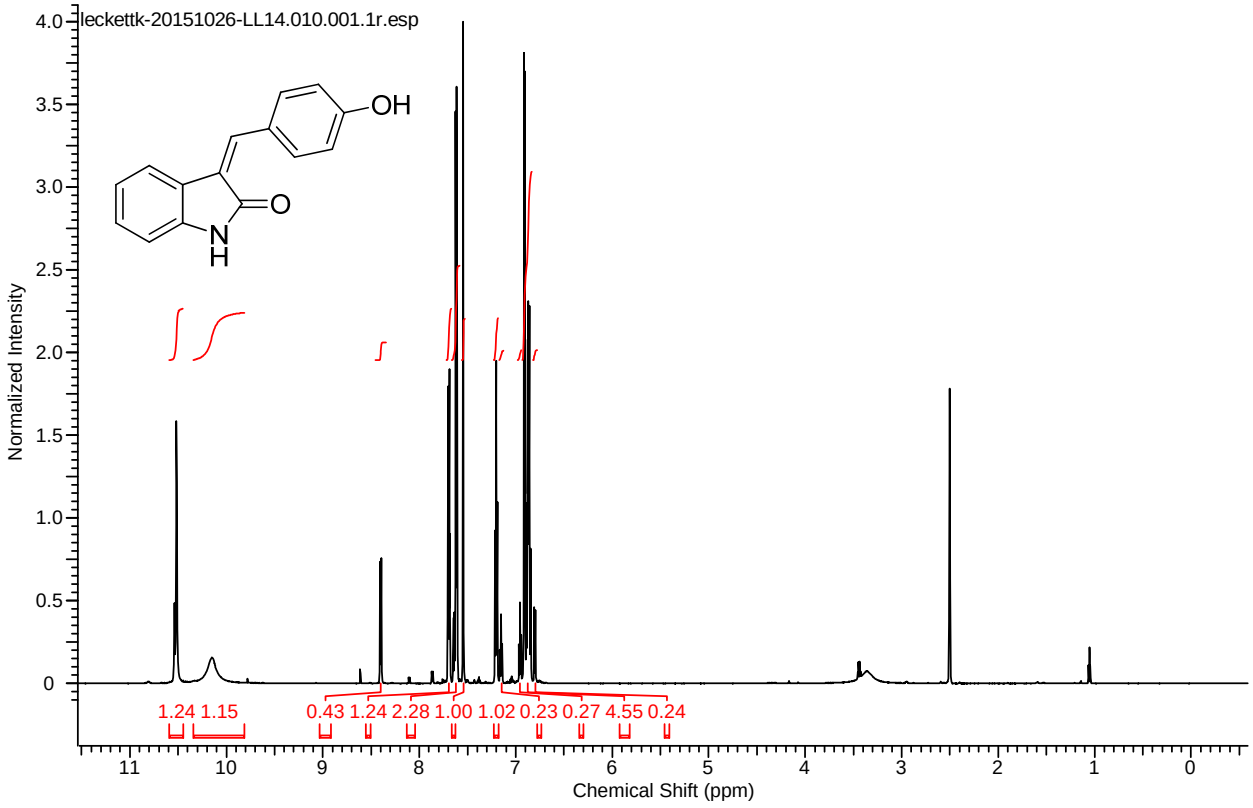
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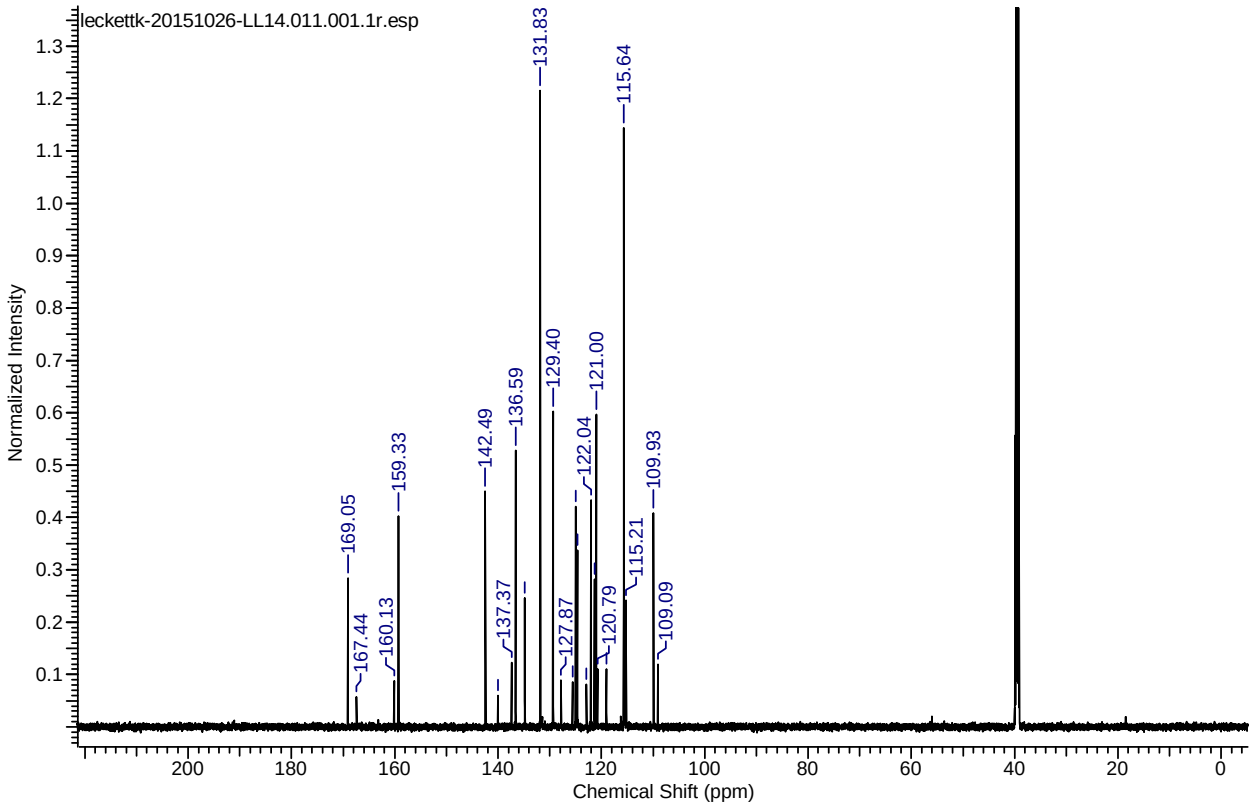
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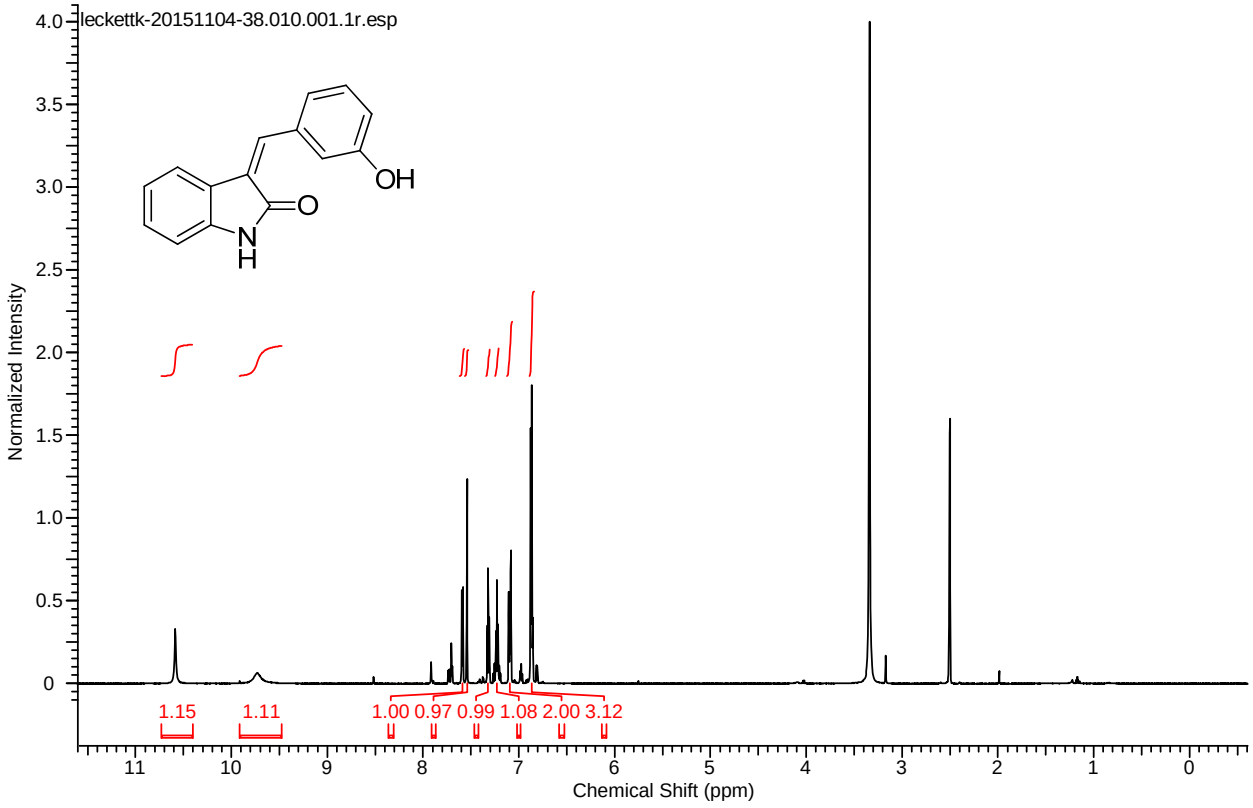
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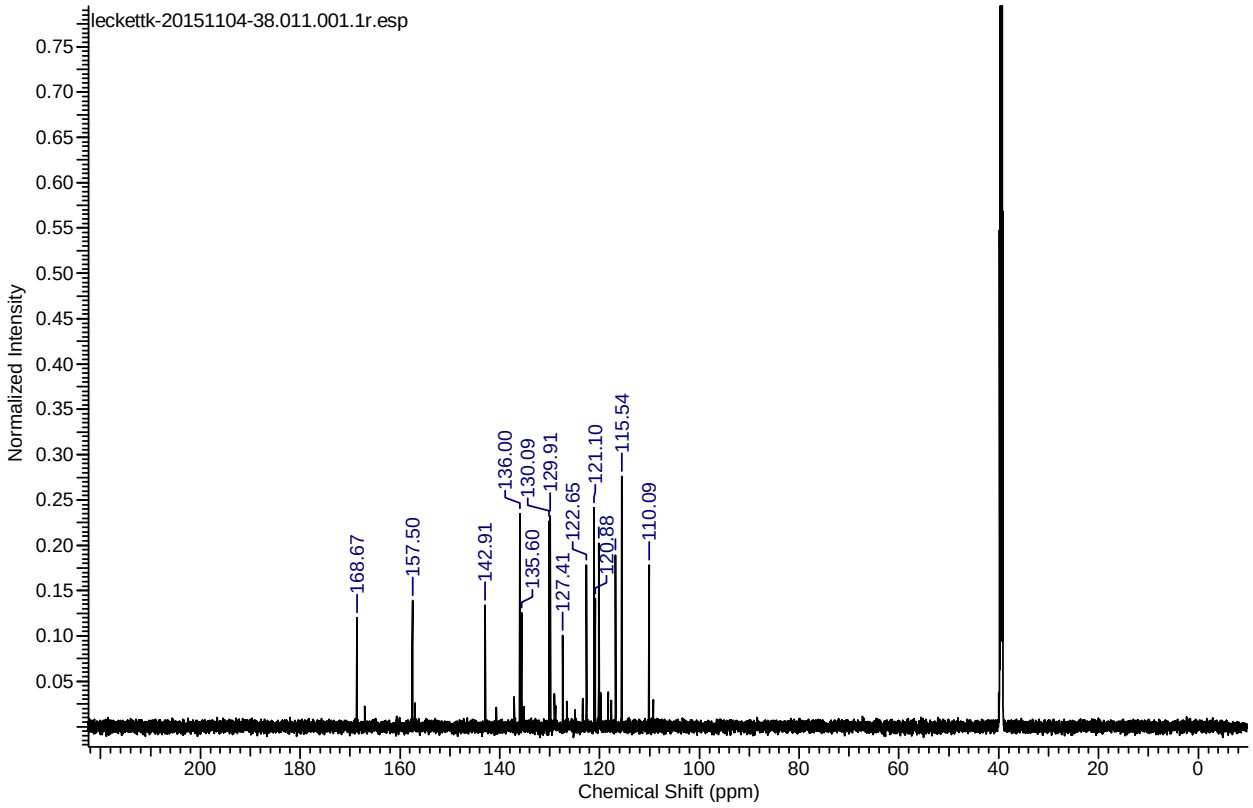
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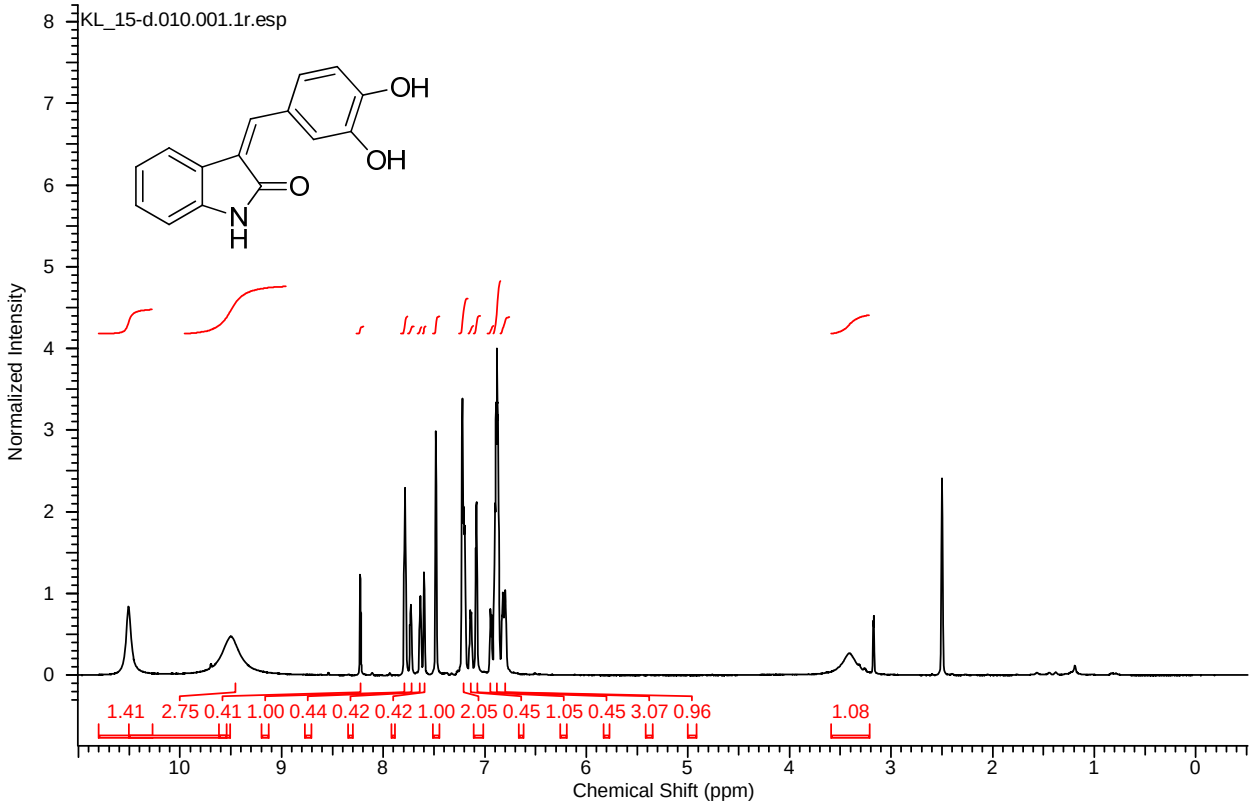
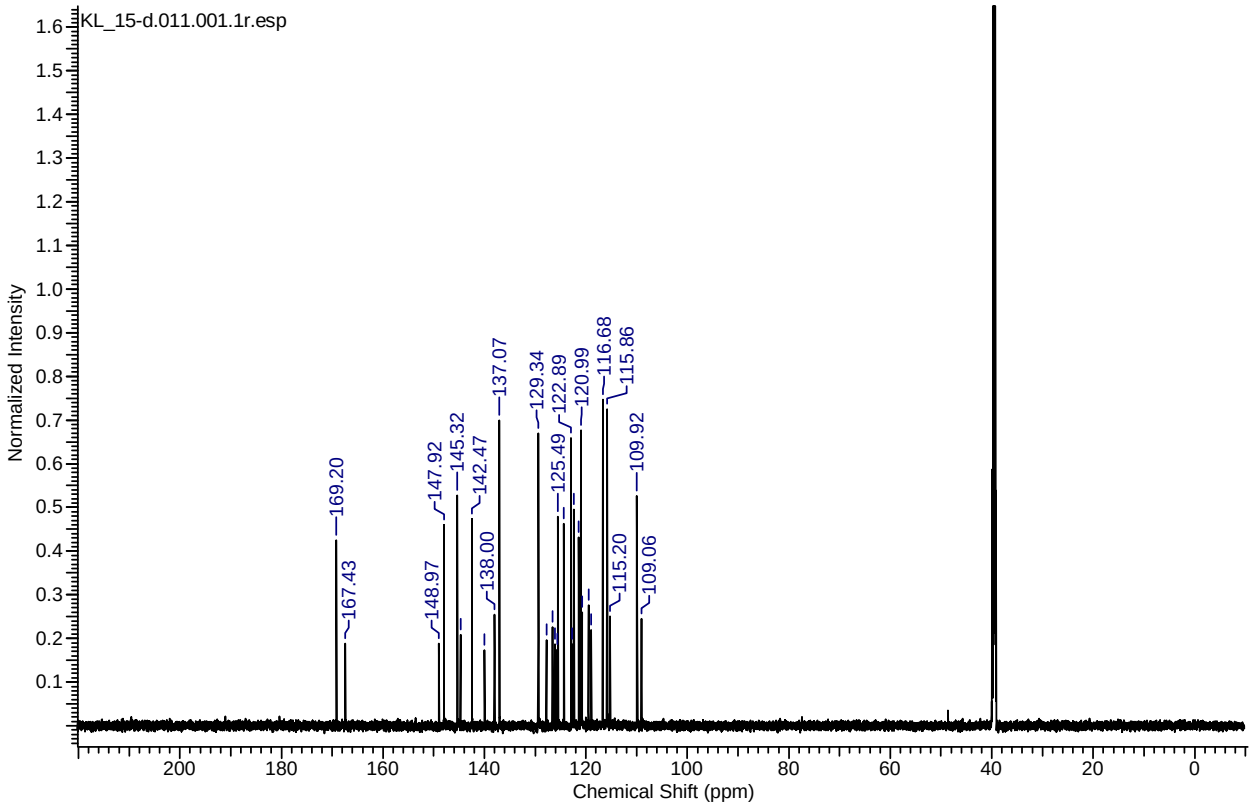
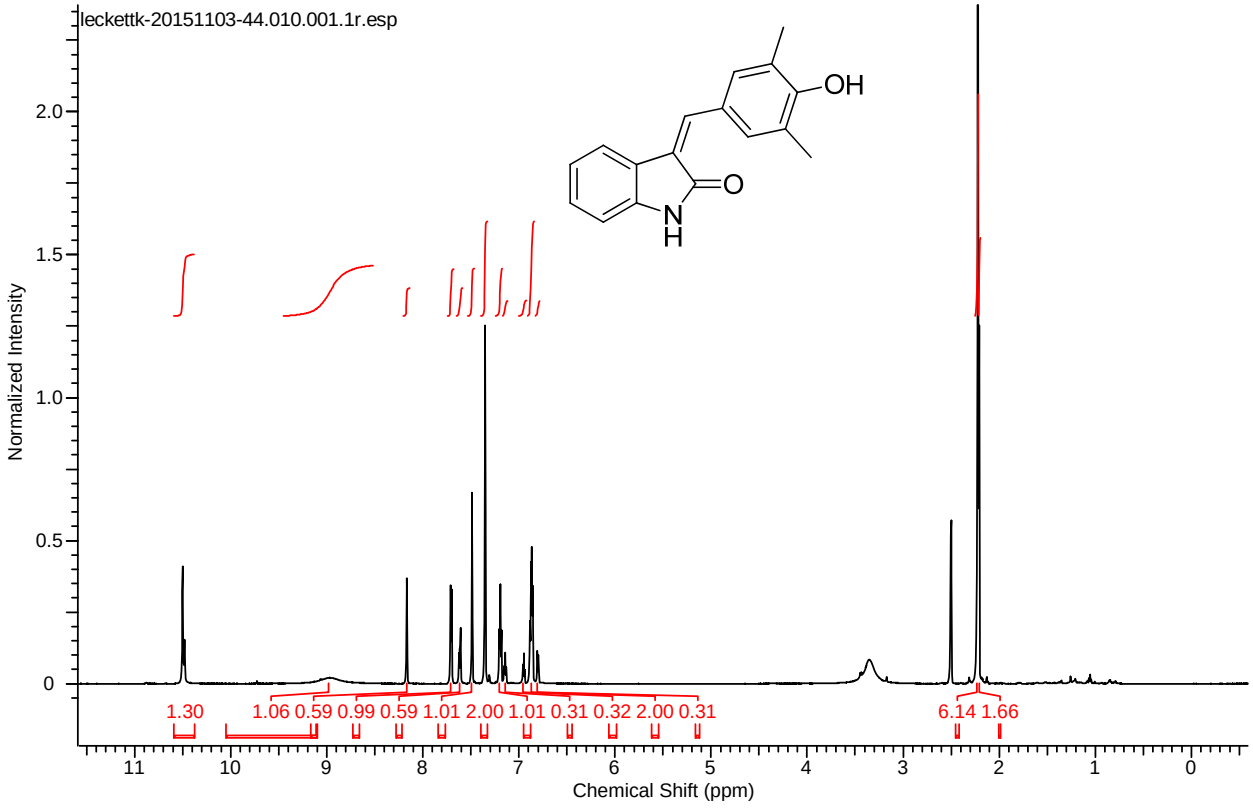
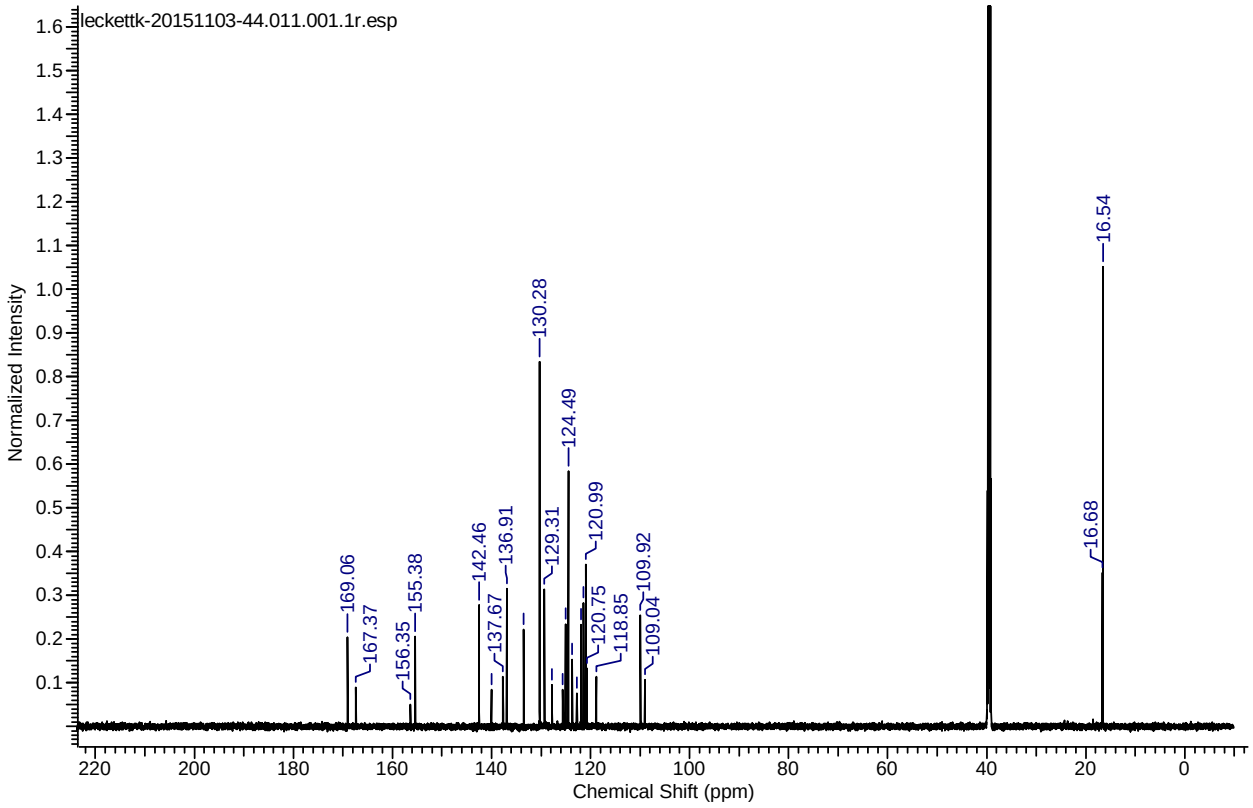
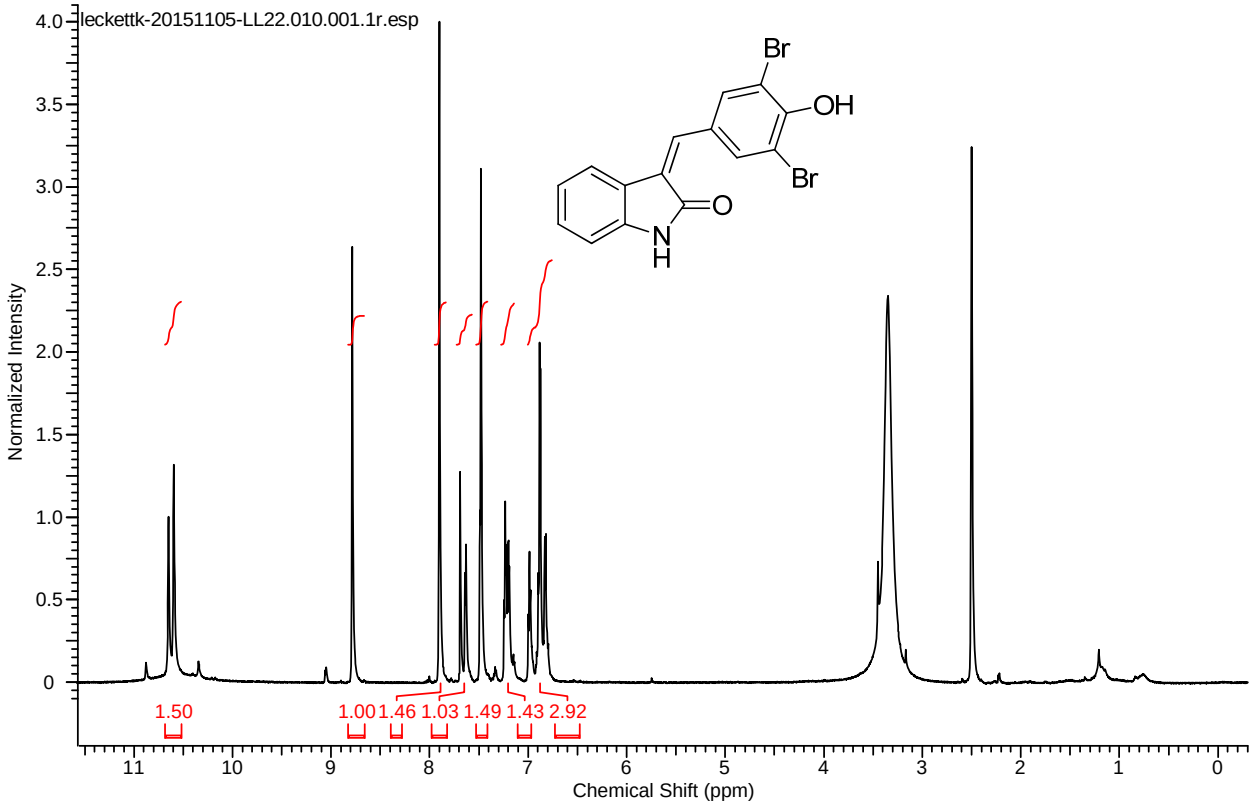
136.00
135.60
130.09
129.91
127.41
122.65
121.10
120.88
115.54
110.09

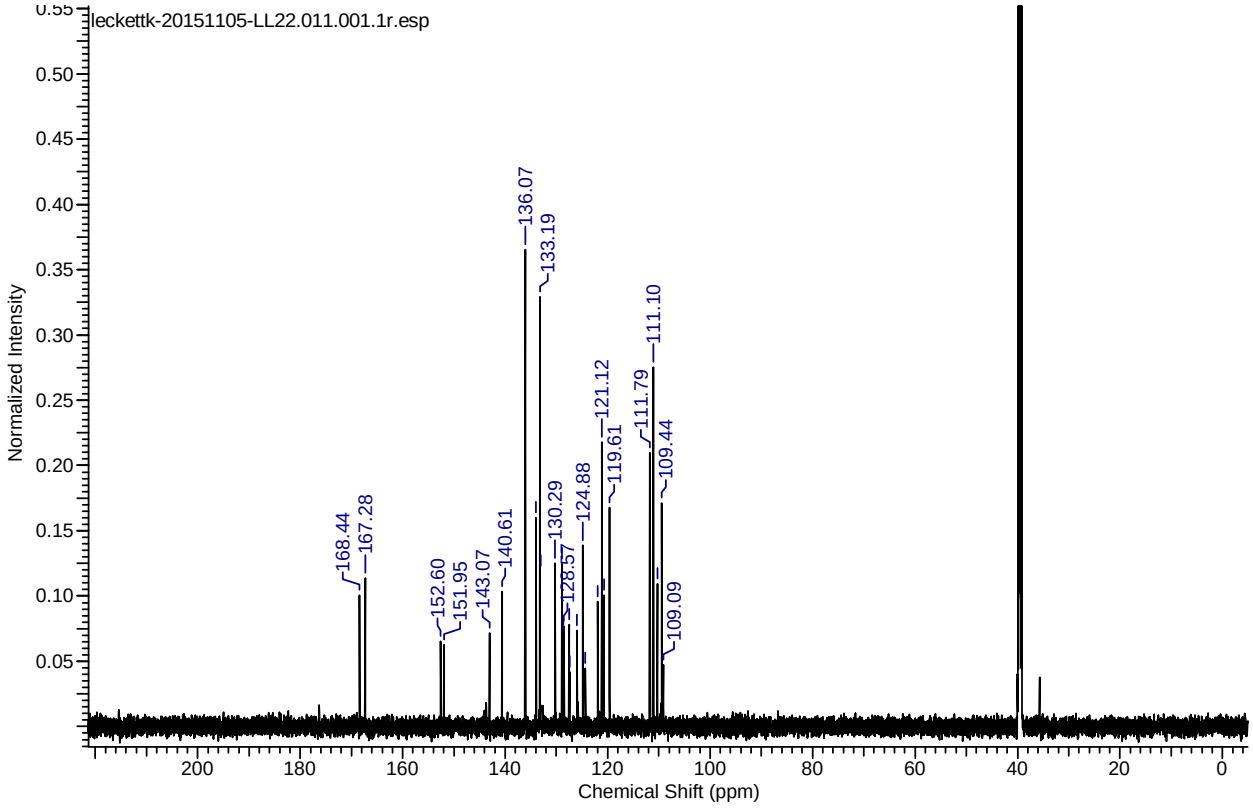

KL_15-d.010.001.1r.esp
OH
OH
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.41
2.75
0.41
1.00
0.44
0.42
0.42
1.00
2.05
0.45
1.05
0.45
3.07
0.96
1.08

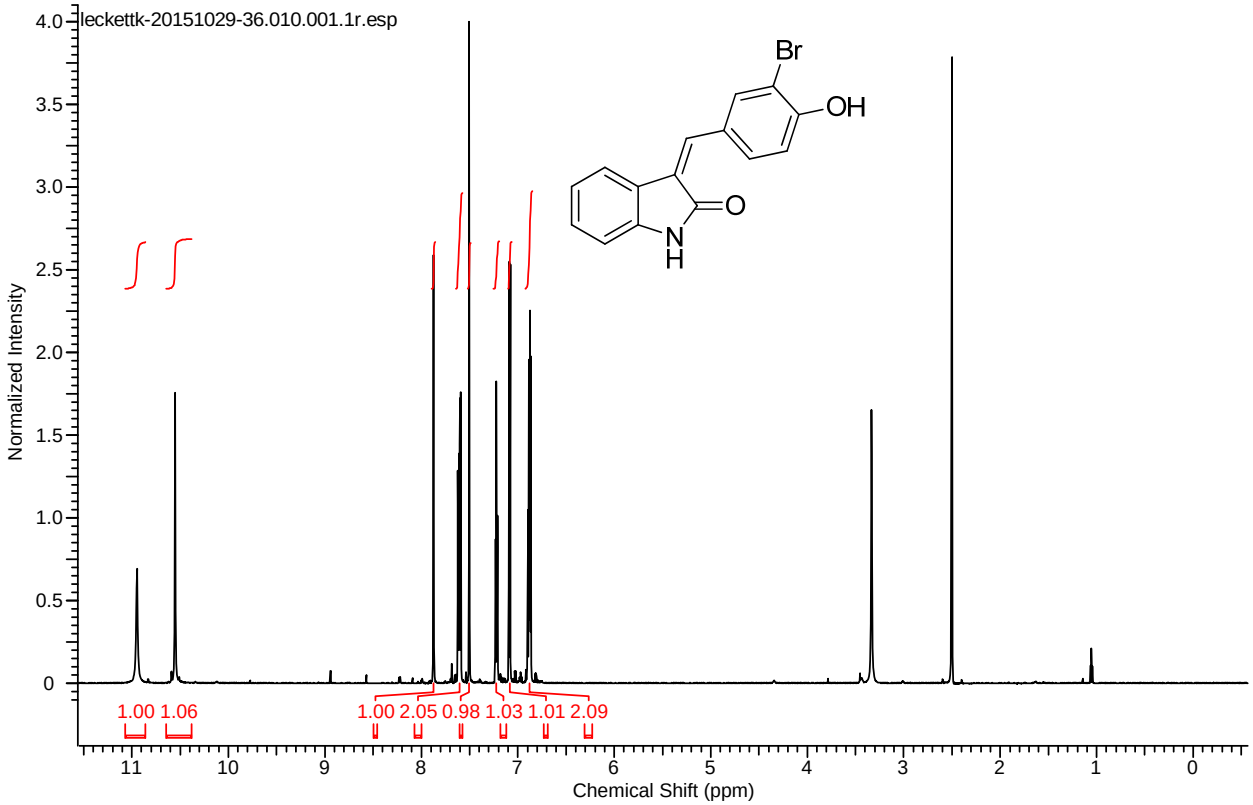

KL_15-d.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.20
167.43
148.97
147.92
145.32
142.47
138.00
137.07
129.34
125.49
122.89
120.99
116.68
115.86
115.20
109.92
109.06

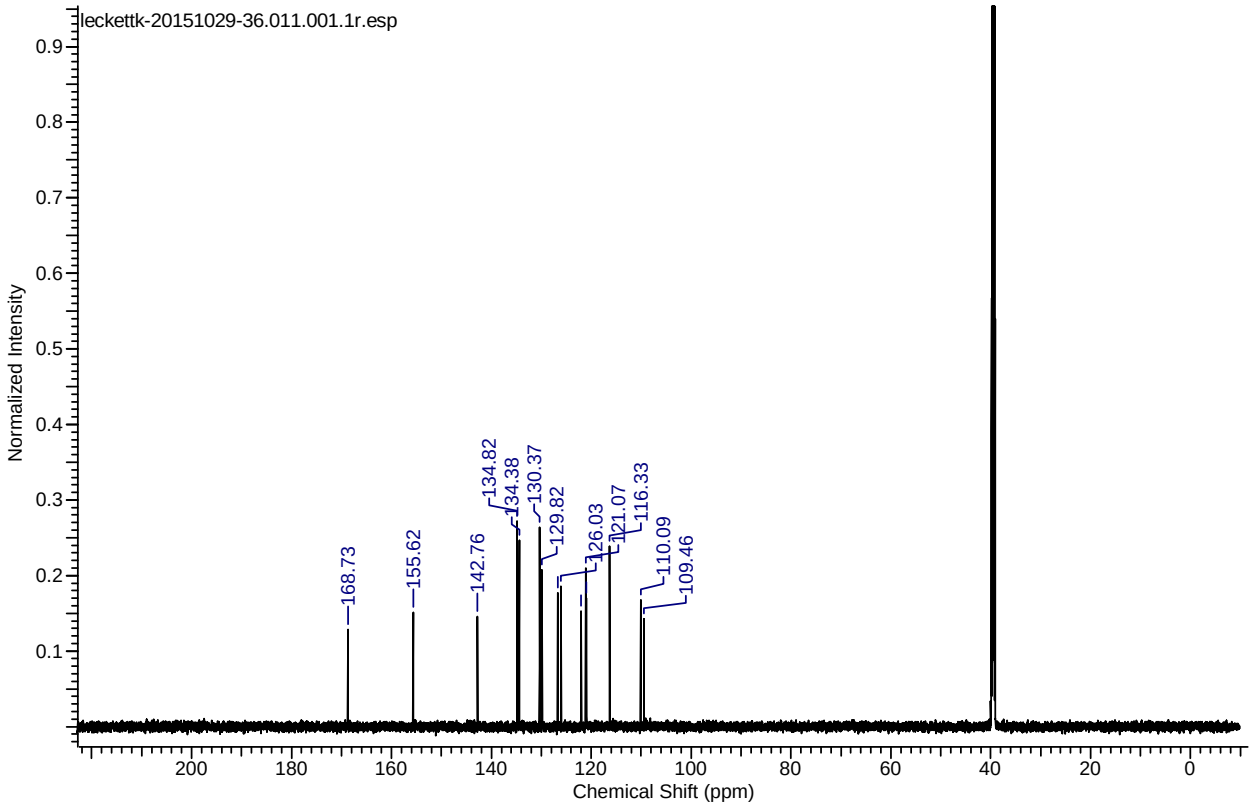

leckettk-20151103-44.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OH
O
N
H
1.30
1.06 0.59 0.99 0.59 1.01 2.00 1.01 0.31 0.32 2.00 0.31
6.14 1.66

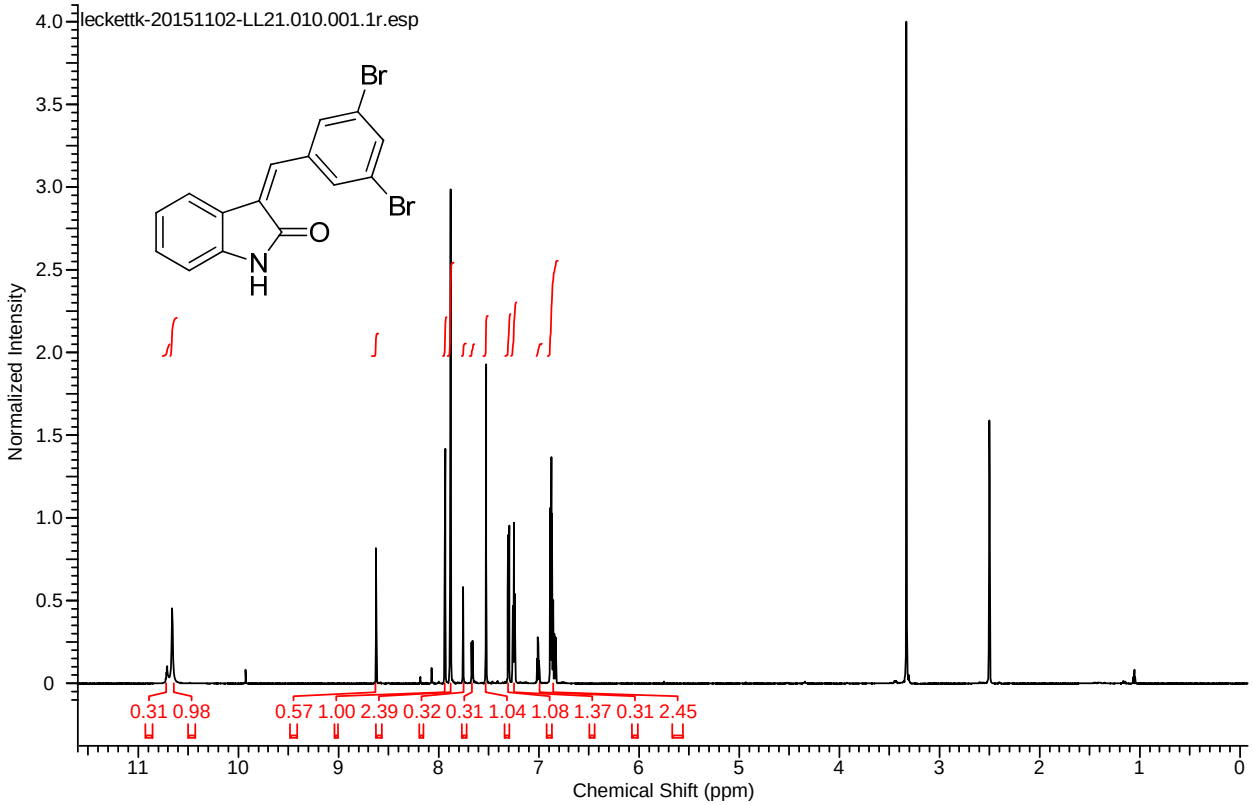

leckettk-20151103-44.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.06
167.37
156.35
155.38
142.46
137.67
136.91
130.28
129.31
124.49
120.99
120.75
118.85
109.92
109.04
16.68
16.54

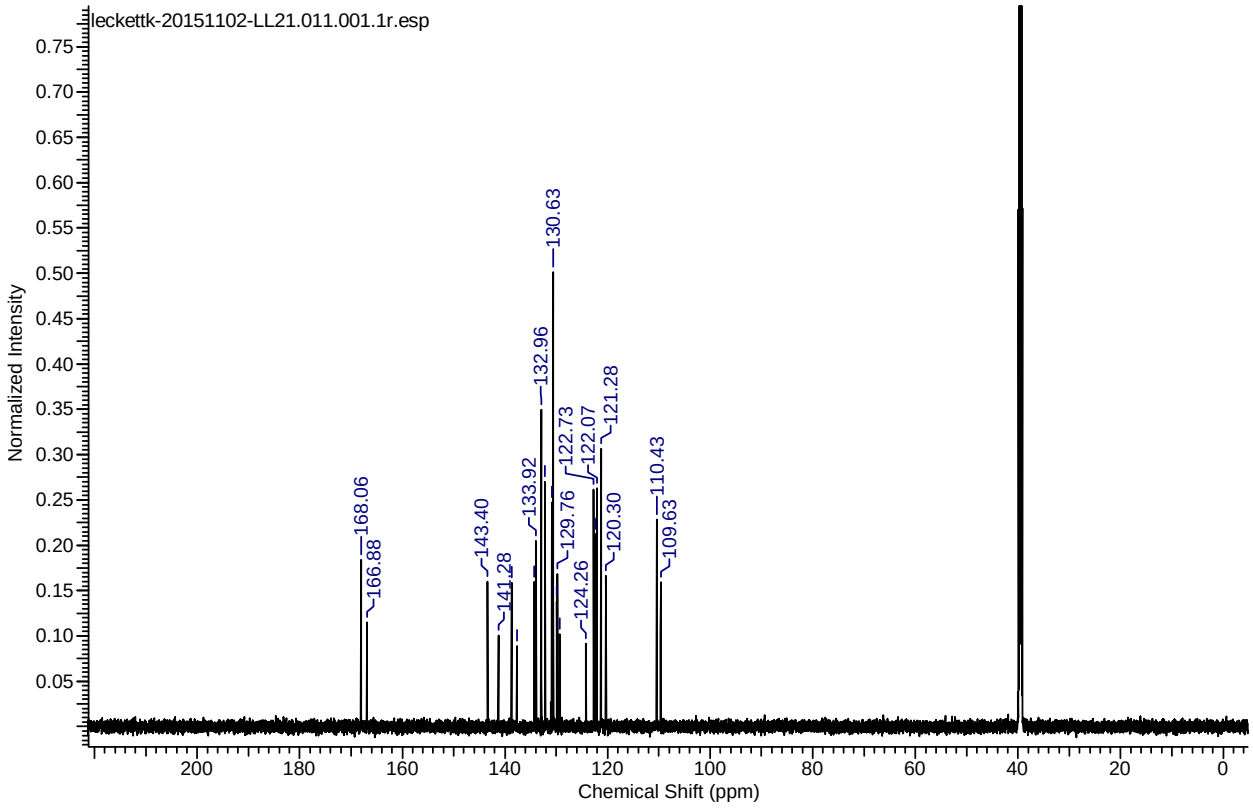

leckettk-20151105-LL22.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
OH
Br
O
N
H
1.50
1.00
1.46
1.03
1.49
1.43
2.92

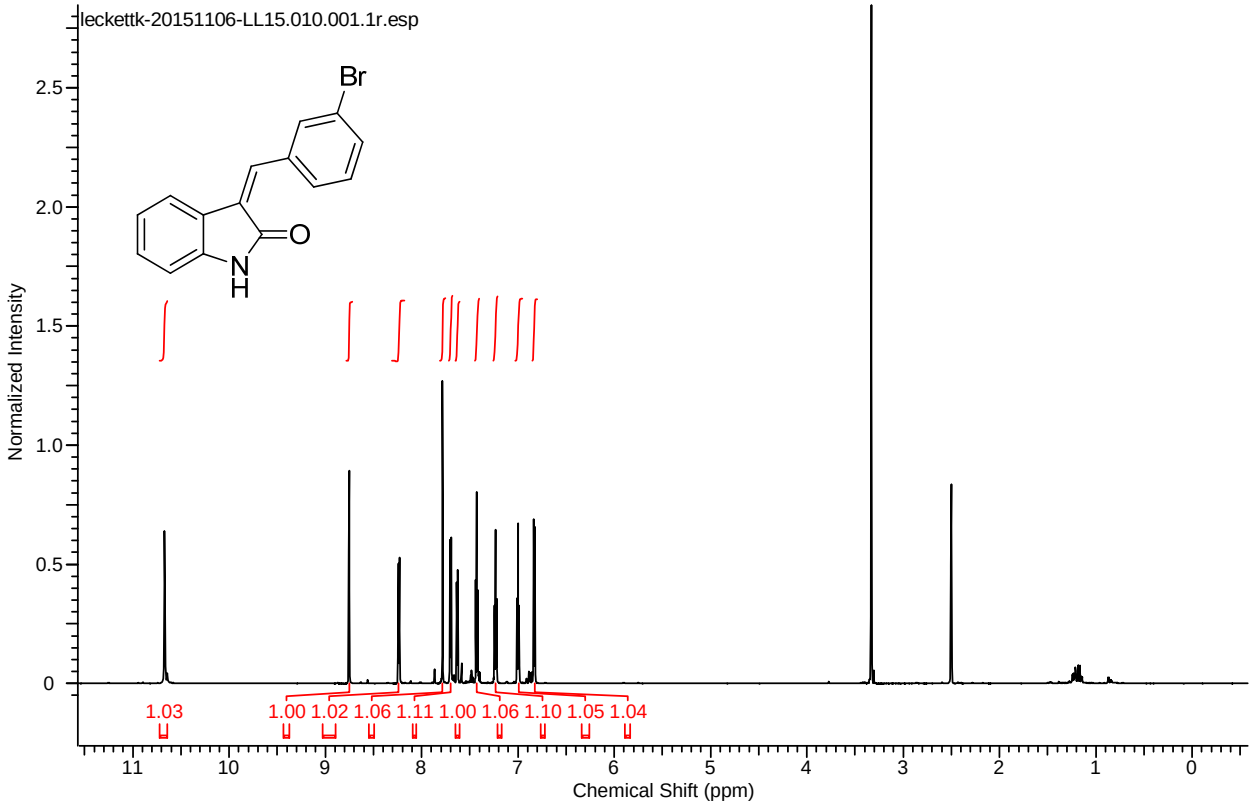

leckettk-20151105-LL22.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.44
167.28
152.60
151.95
143.07
140.61
136.07
133.19
130.29
128.57
124.88
121.12
119.61
111.79
111.10
109.44
109.09

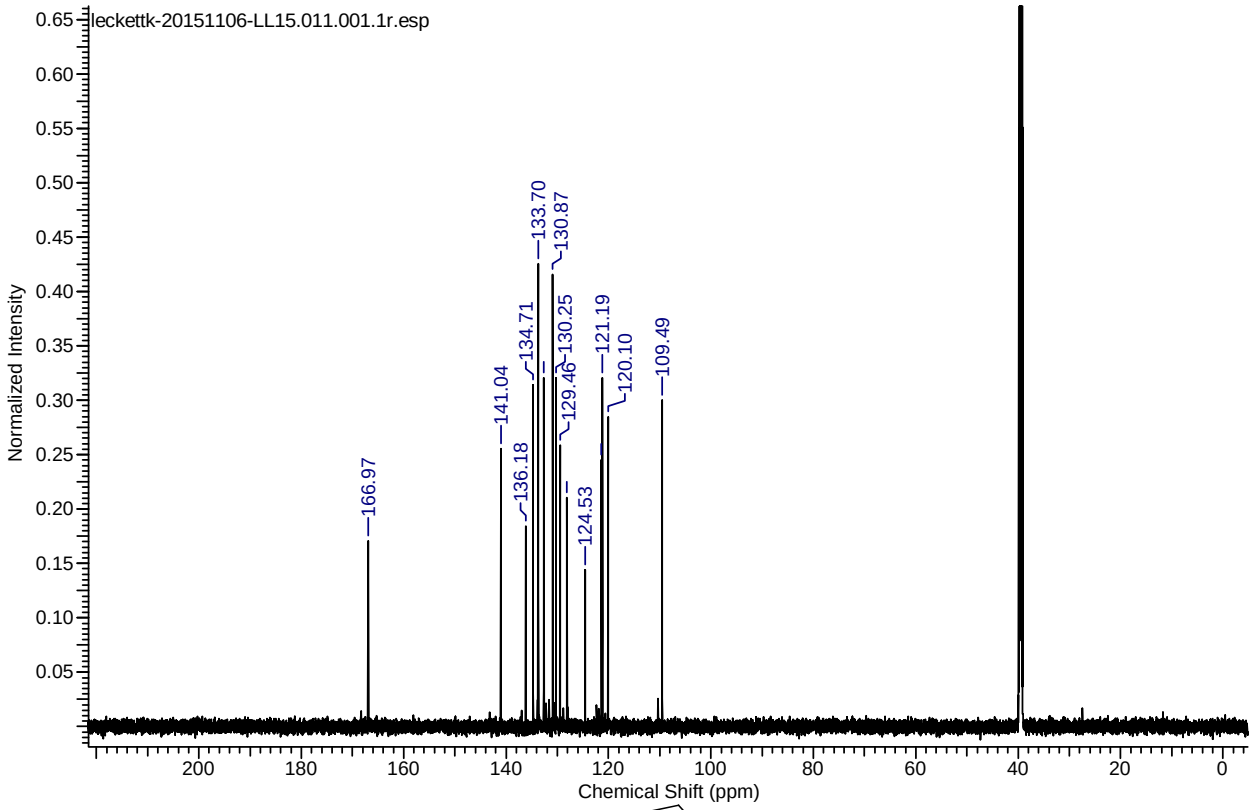

leckettk-20151029-36.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
OH
O
N
H
1.00 1.06
1.00 2.05 0.98 1.03 1.01 2.09

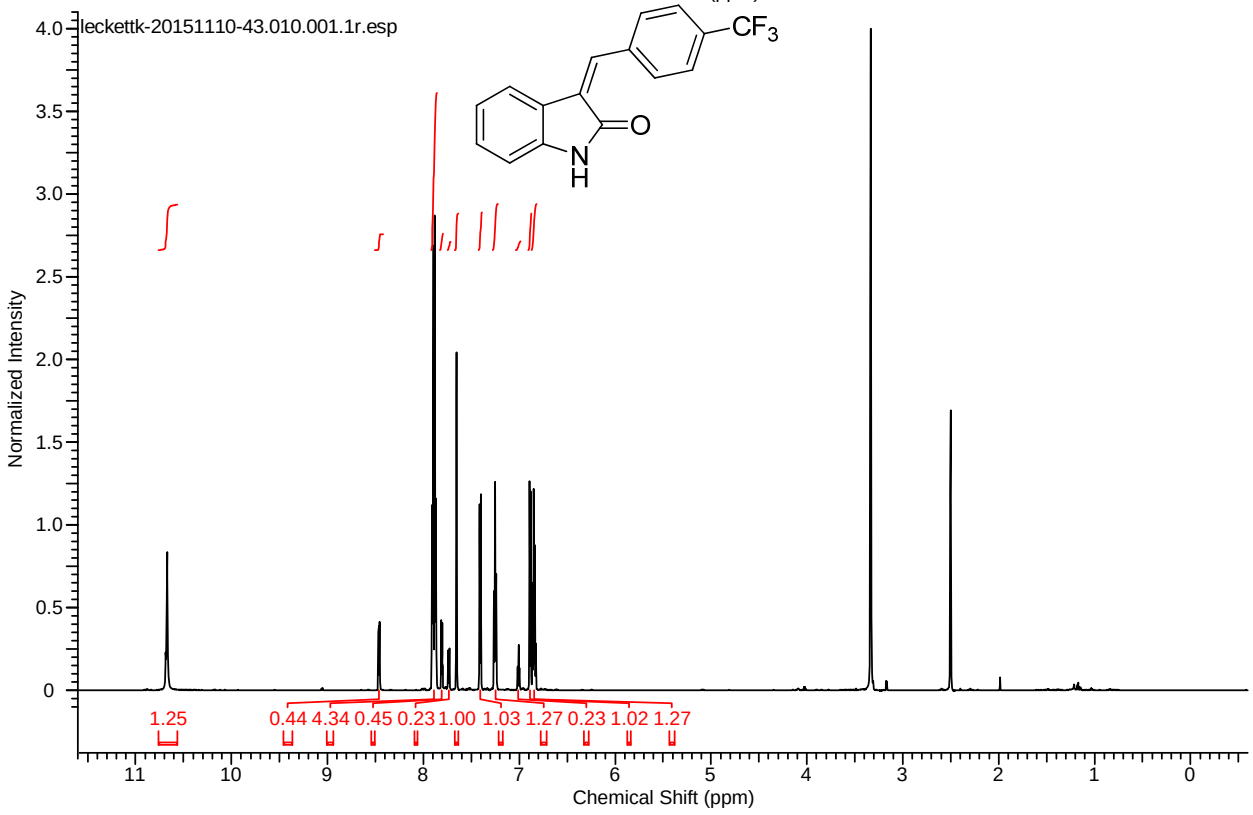

leckettk-20151029-36.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.73
155.62
142.76
134.82
134.38
130.37
129.82
126.03
121.07
116.33
110.09
109.46

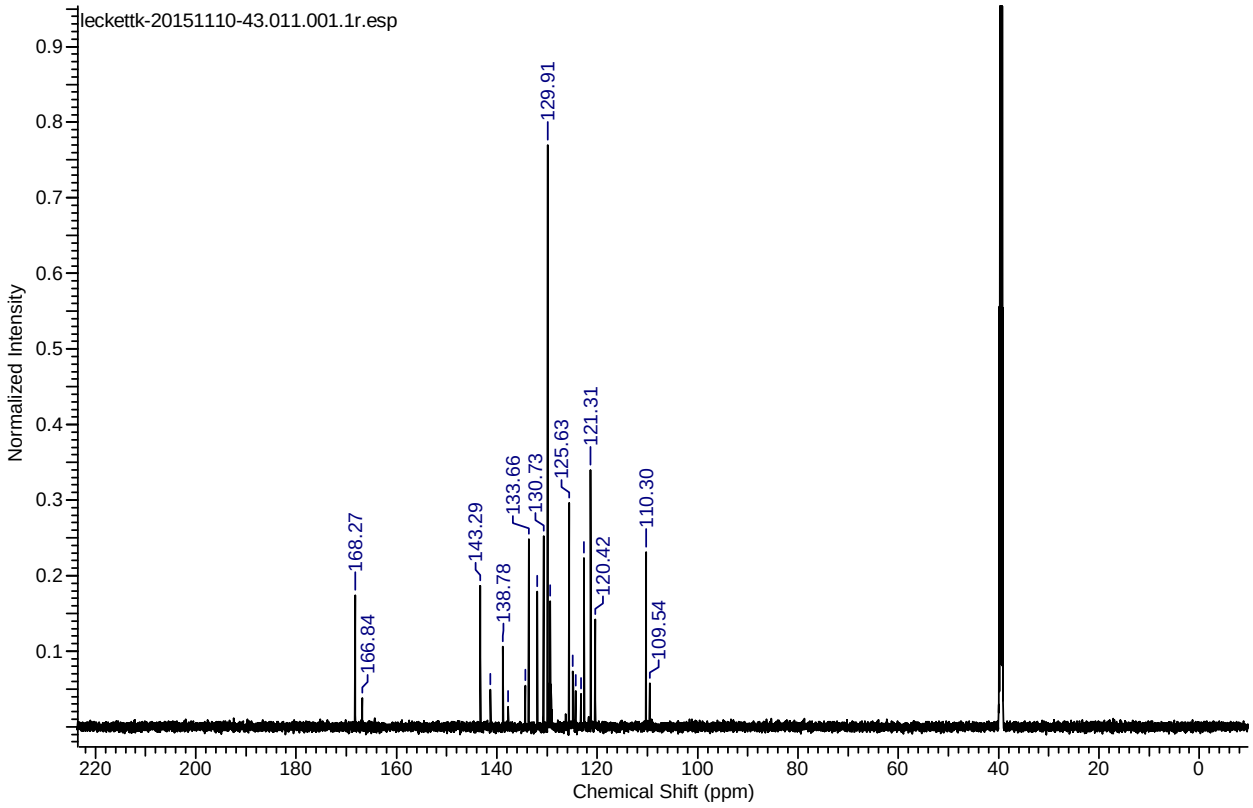

leckettk-20151102-LL21.010.001.1r.esp
Br
Br
O
N
H
Normalized Intensity
Chemical Shift (ppm)
0.31 0.98
0.57 1.00 2.39 0.32 0.31 1.04 1.08 1.37 0.31 2.45

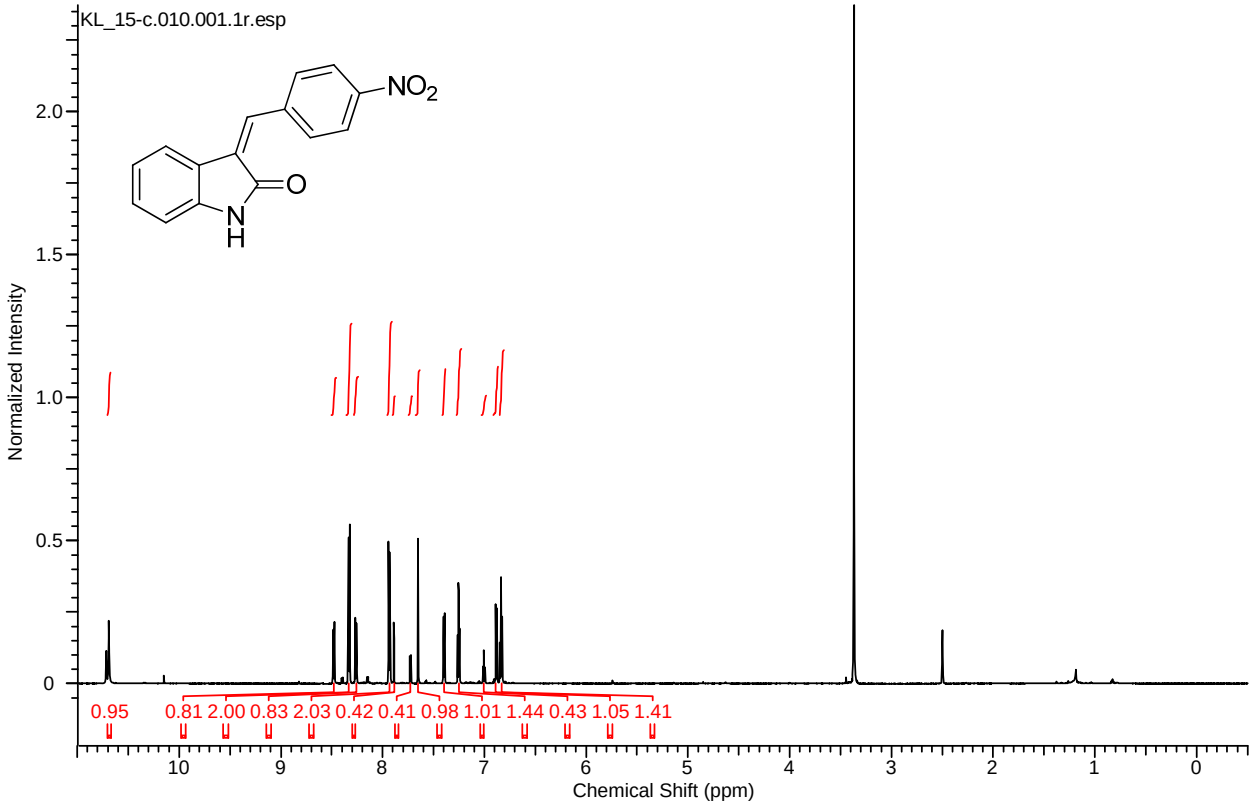

leckettk-20151102-LL21.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.06
166.88
143.40
141.28
133.92
132.96
130.63
129.76
124.26
122.73
122.07
121.28
120.30
110.43
109.63

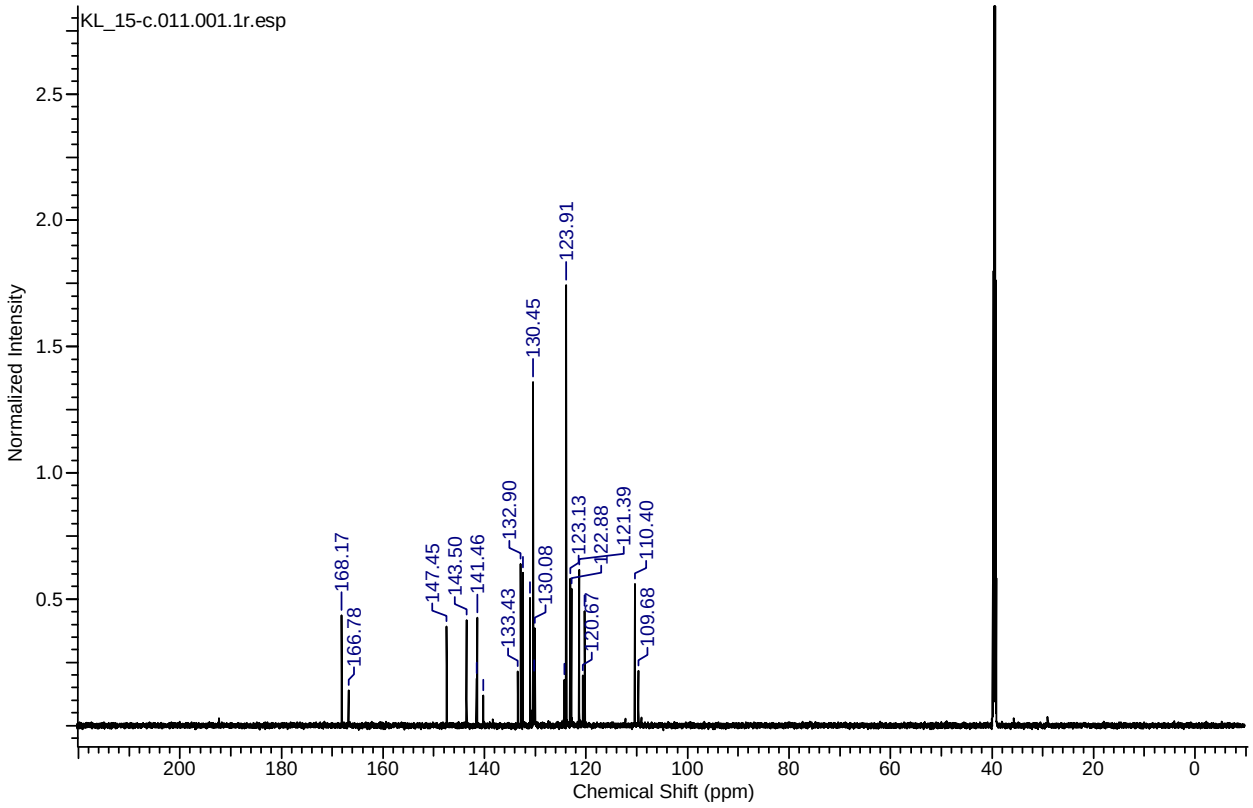

leckettk-20151106-LL15.010.001.1r.esp
Br
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.03
1.00 1.02 1.06 1.11 1.00 1.06 1.10 1.05 1.04

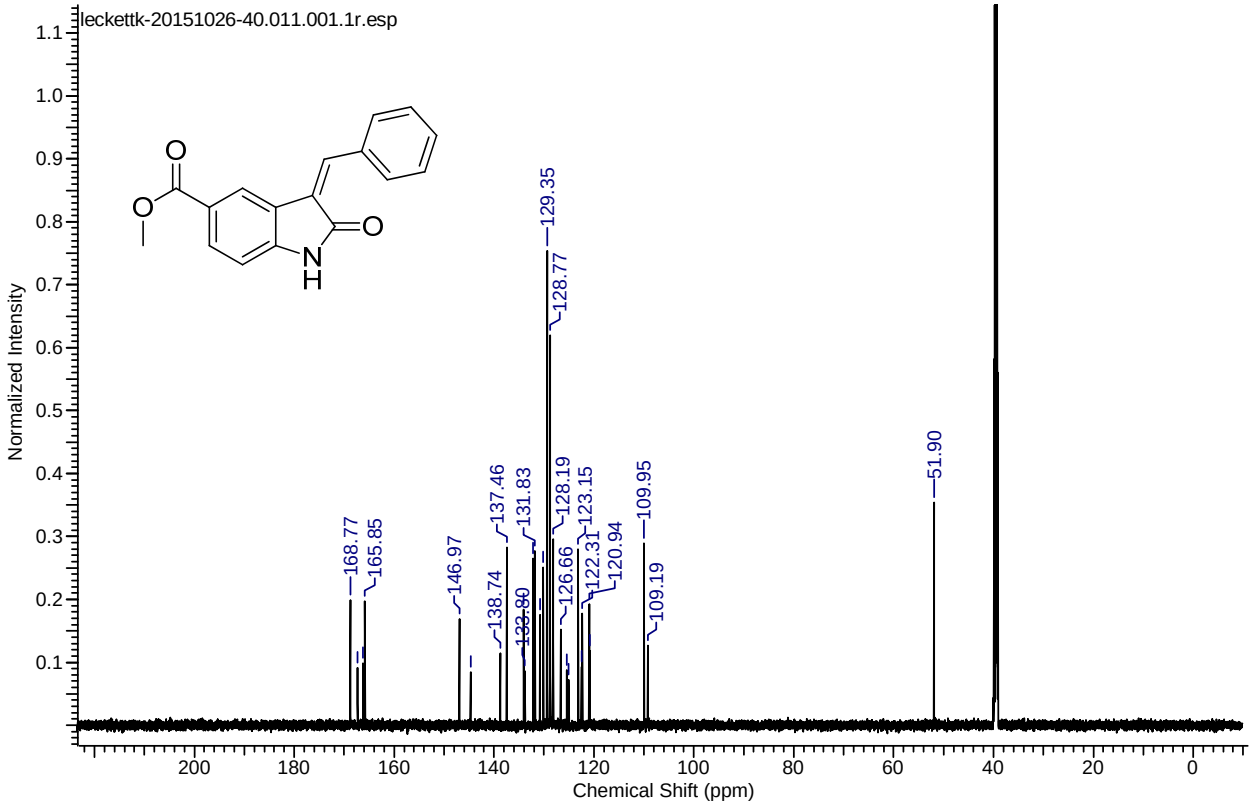

leckettk-20151106-LL15.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
166.97
141.04
136.18
134.71
133.70
130.87
130.25
129.46
124.53
121.19
120.10
109.49

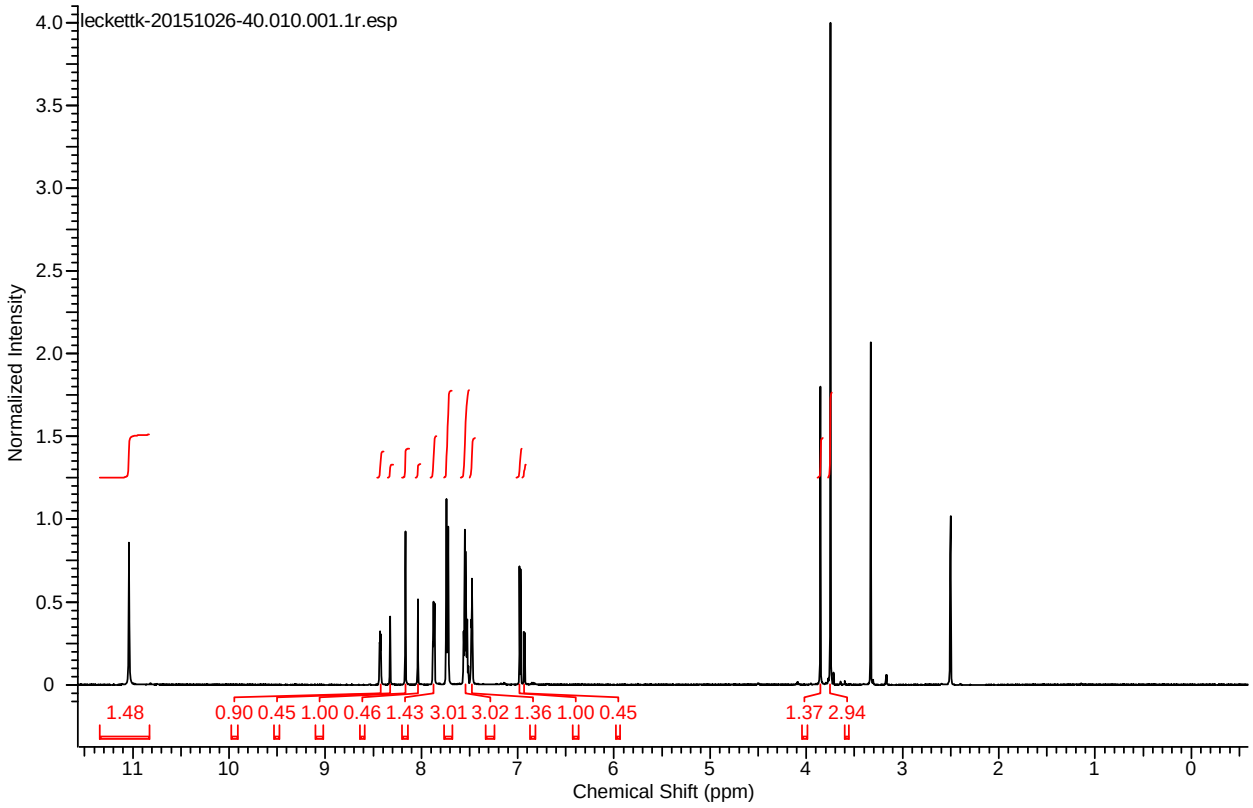

leckettk-20151110-43.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
CF3
O
N
H
1.25
0.44 4.34 0.45 0.23 1.00 1.03 1.27 0.23 1.02 1.27

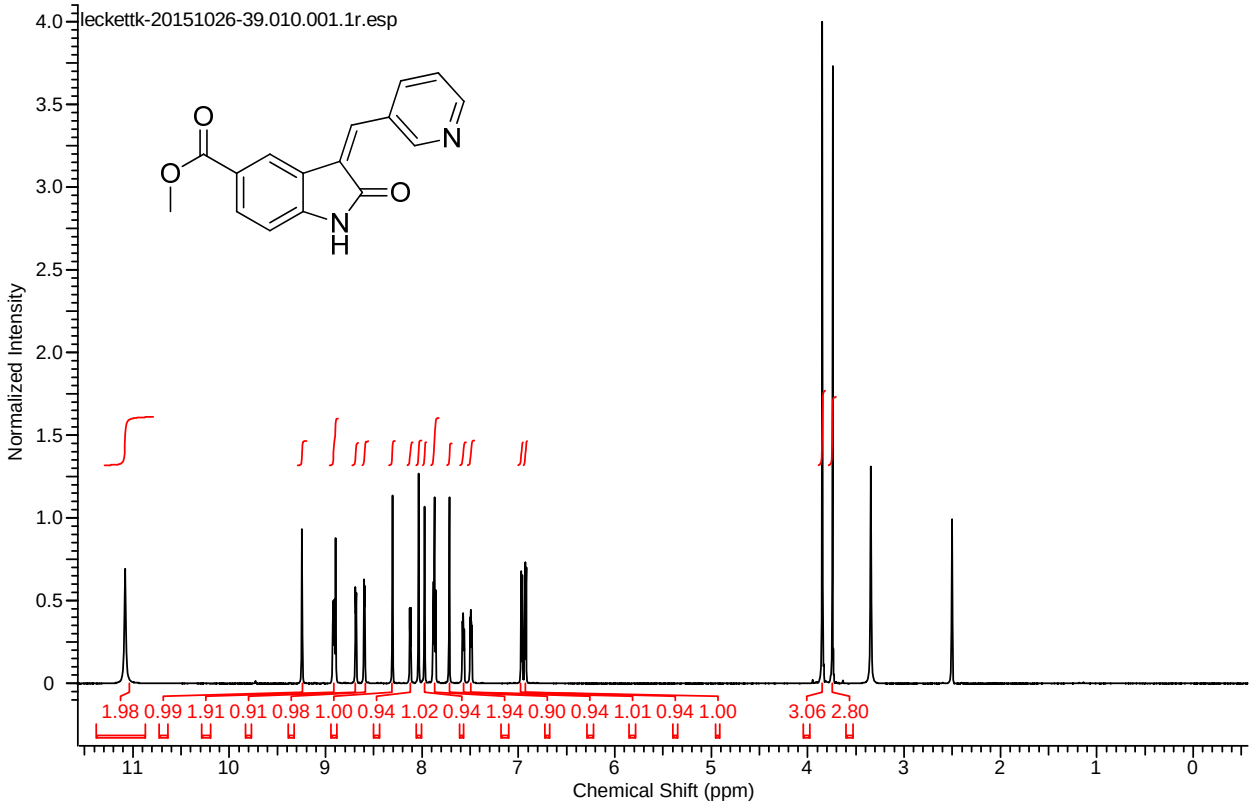

leckettk-20151110-43.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.27
166.84
143.29
138.78
133.66
130.73
129.91
125.63
121.31
120.42
110.30
109.54

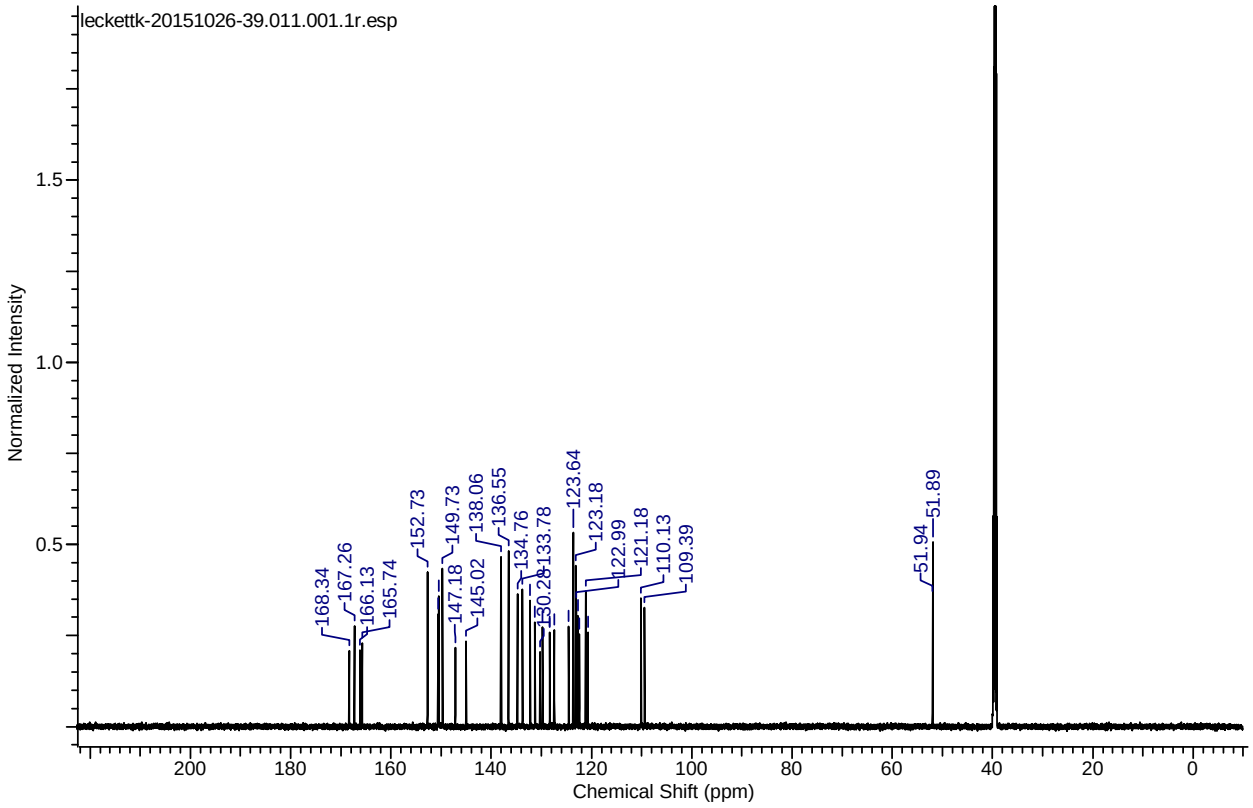

KL_15-c.010.001.1r.esp
NO2
O
N
H
Normalized Intensity
Chemical Shift (ppm)
0.95
0.81 2.00 0.83 2.03 0.42 0.41 0.98 1.01 1.44 0.43 1.05 1.41

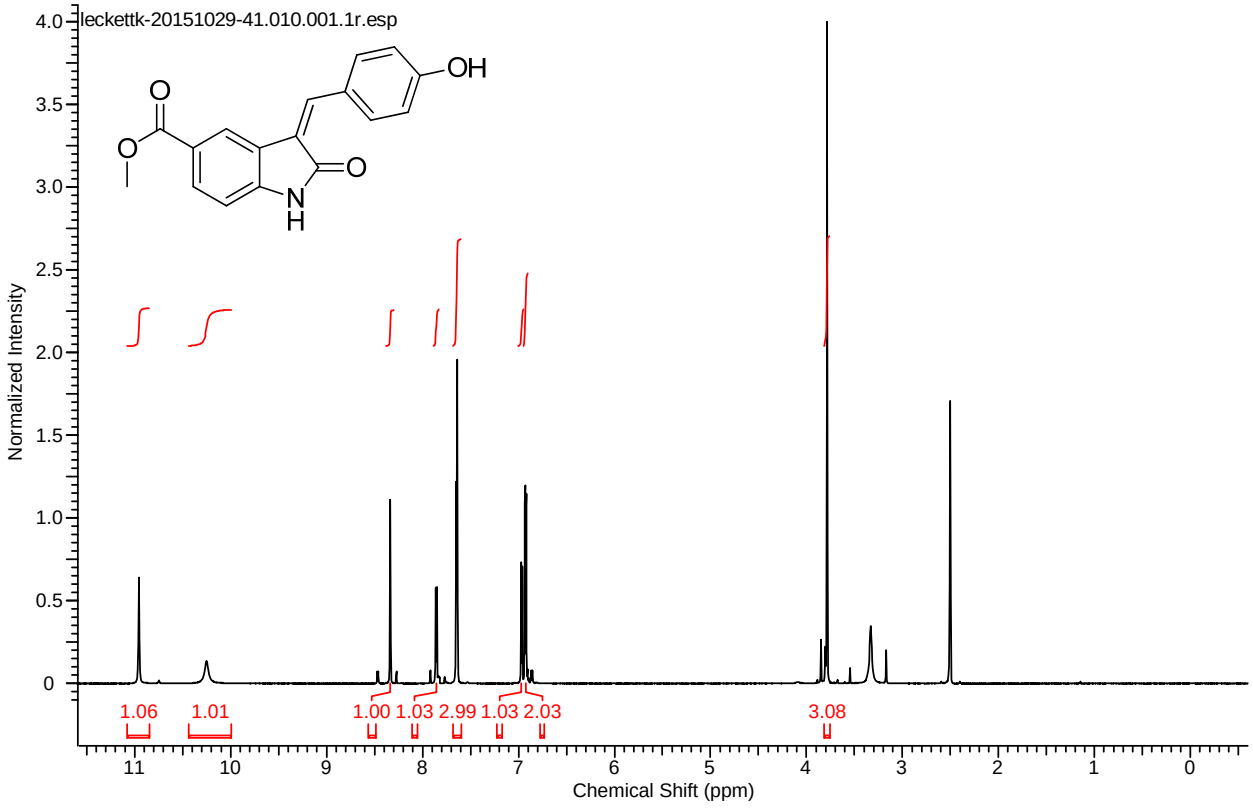

KL_15-c.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.17
166.78
147.45
143.50
141.46
133.43
132.90
130.45
130.08
123.91
123.13
122.88
121.39
120.67
110.40
109.68

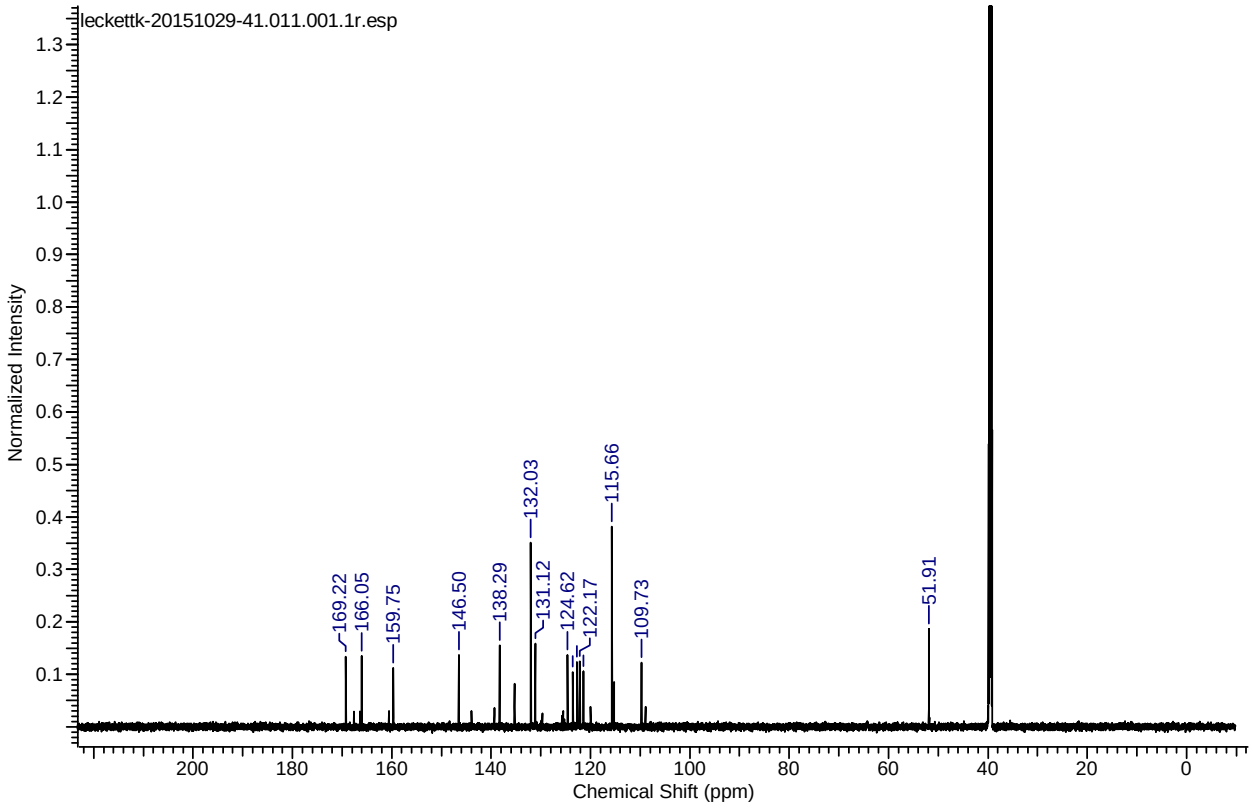

leckettk-20151026-40.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
O
N
H
168.77
165.85
146.97
138.74
137.46
131.83
129.35
128.77
128.19
126.66
123.15
122.31
120.94
109.95
109.19
51.90

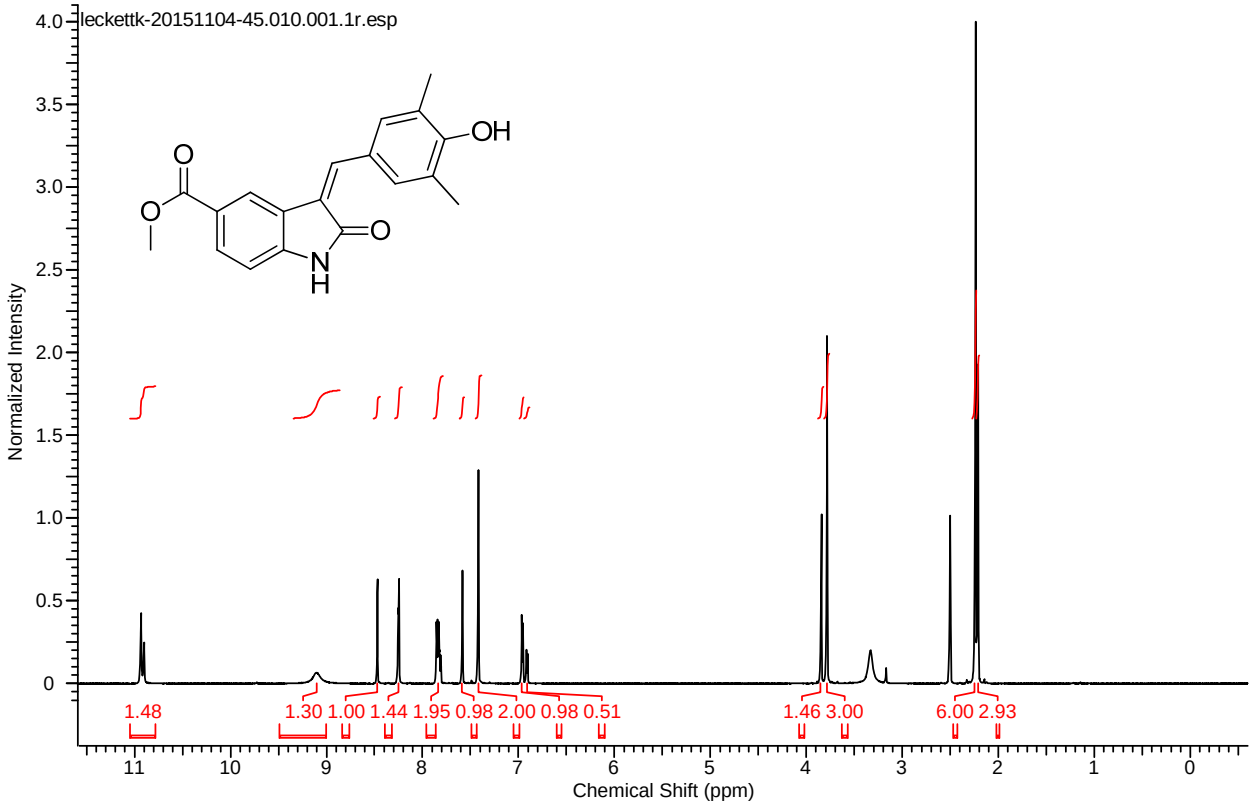

leckettk-20151026-40.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
1.48
0.90 0.45 1.00 0.46 1.43 3.01 3.02 1.36 1.00 0.45
1.37 2.94

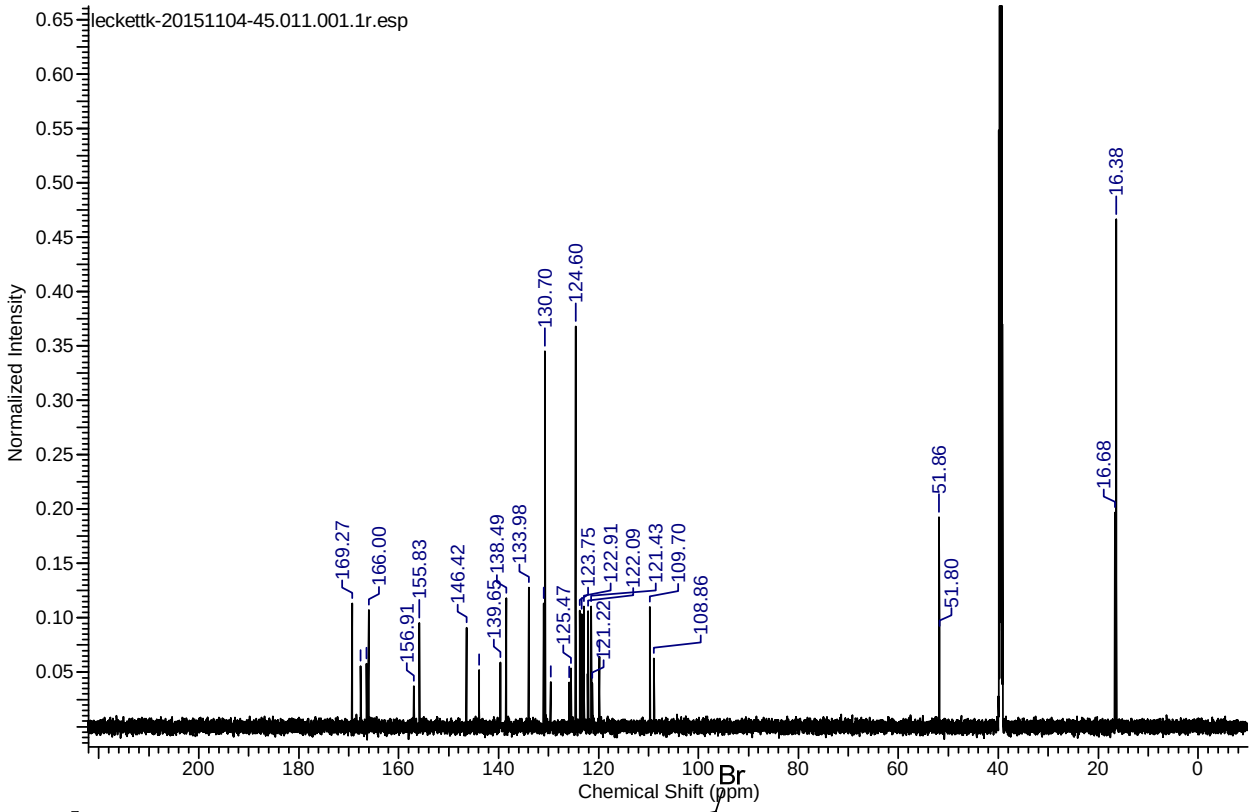

leckettk-20151026-39.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
N
O
N
H
1.98 0.99 1.91 0.91 0.98 1.00 0.94 1.02 0.94 1.94 0.90 0.94 1.01 0.94 1.00
3.06 2.80

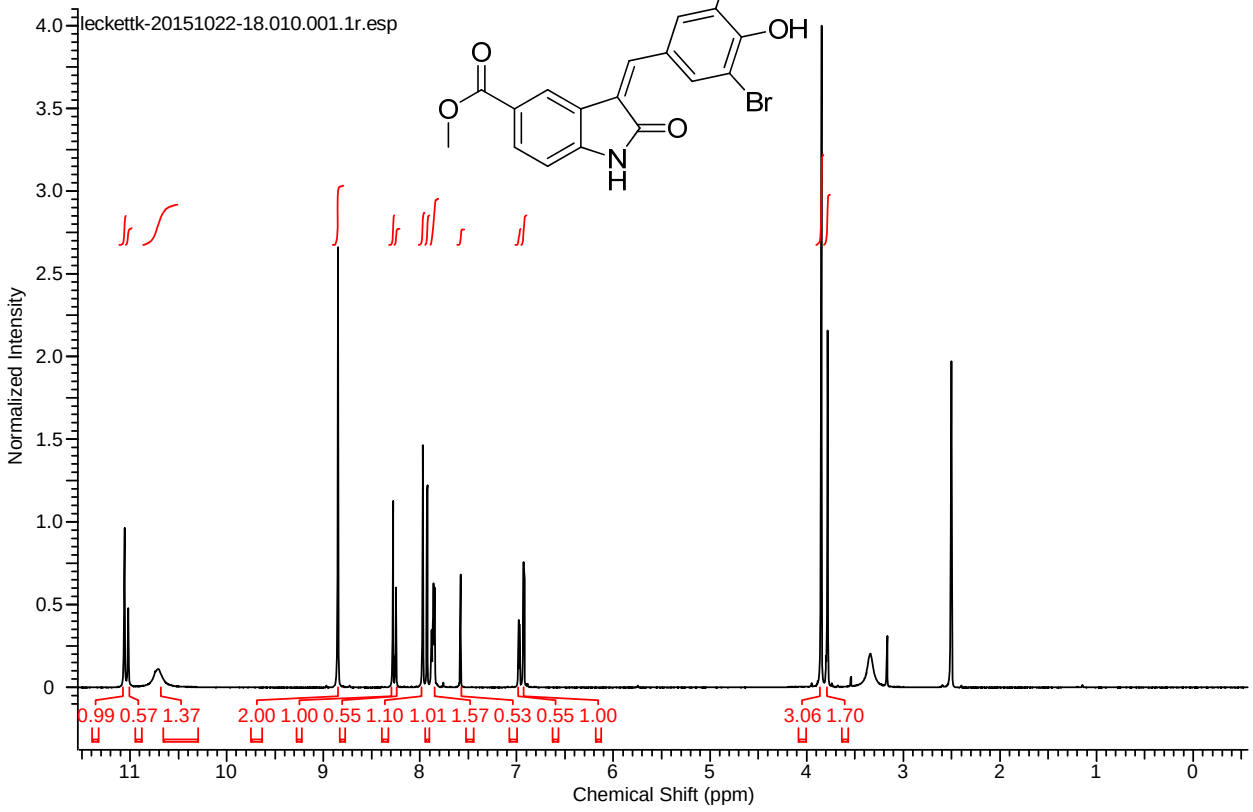

leckettk-20151026-39.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.34
167.26
166.13
165.74
152.73
149.73
147.18
145.02
138.06
136.55
134.76
133.78
130.28
123.64
123.18
122.99
121.18
110.13
109.39
51.94
51.89

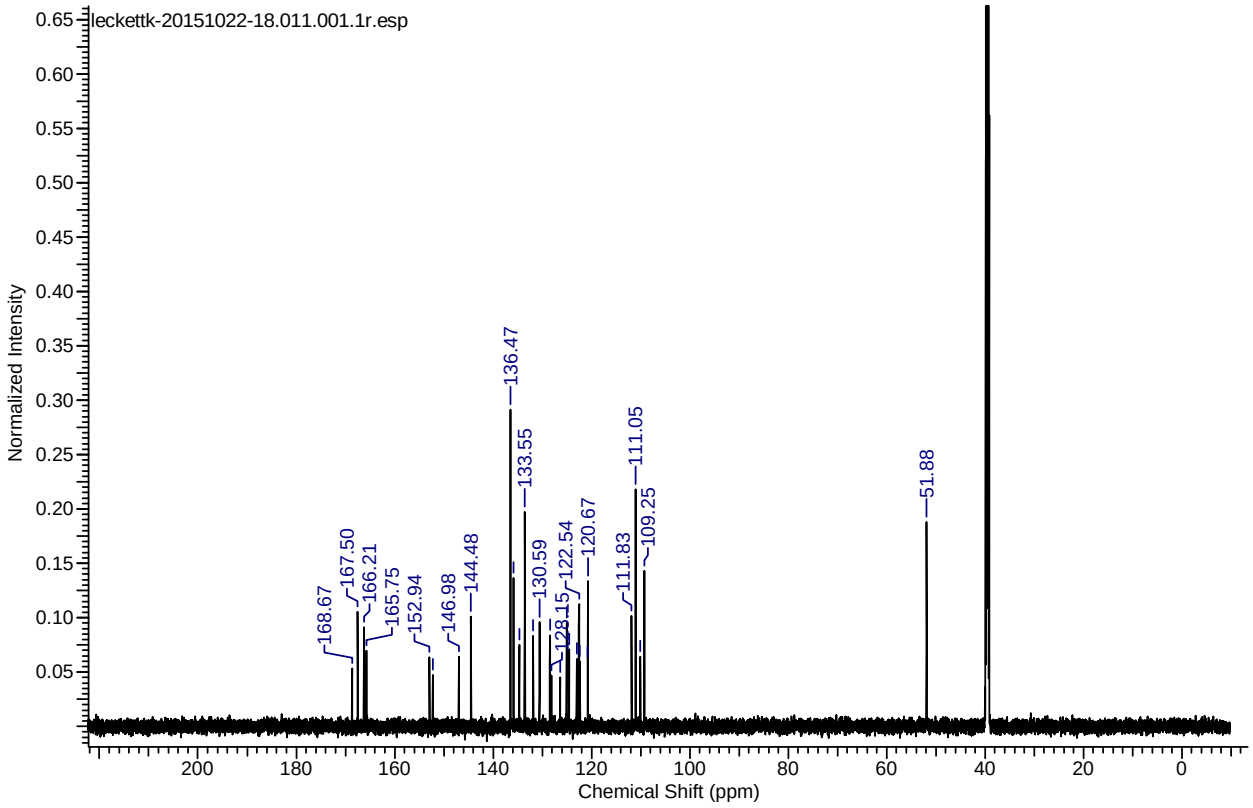

leckettk-20151029-41.010.001.1r.esp
OH
O
O
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.06
1.01
1.00
1.03
2.99
1.03
2.03
3.08

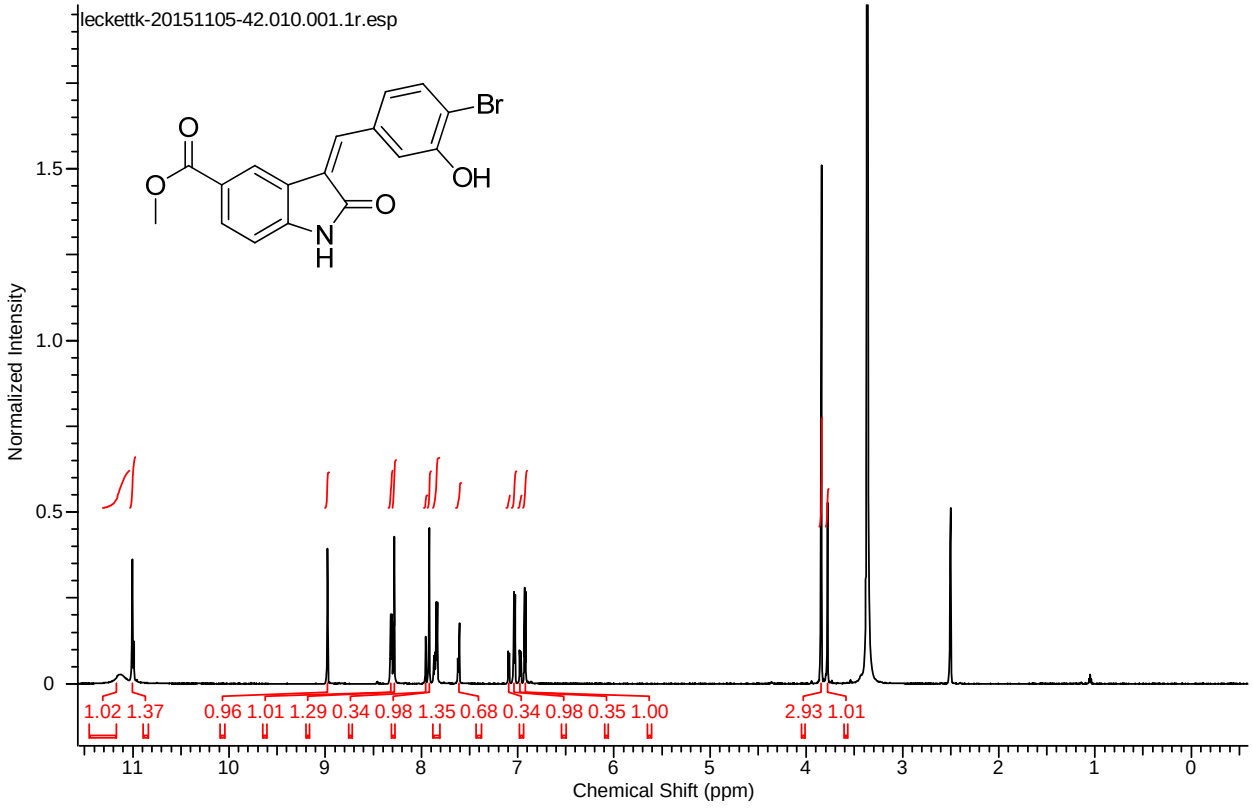

leckettk-20151029-41.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.22
166.05
159.75
146.50
138.29
132.03
131.12
124.62
122.17
115.66
109.73
51.91

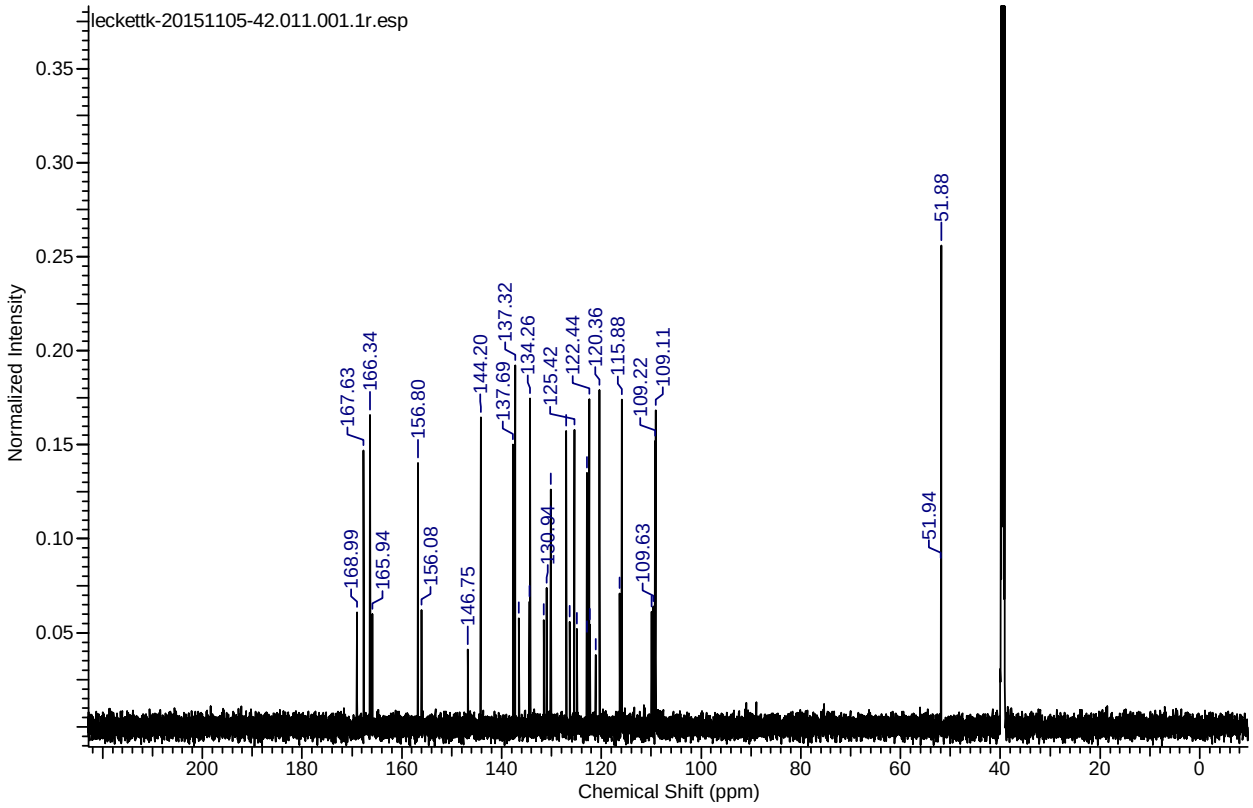

leckettk-20151104-45.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OH
O
O
O
N
H
1.48
1.30 1.00 1.44 1.95 0.98 2.00 0.98 0.51
1.46 3.00
6.00 2.93

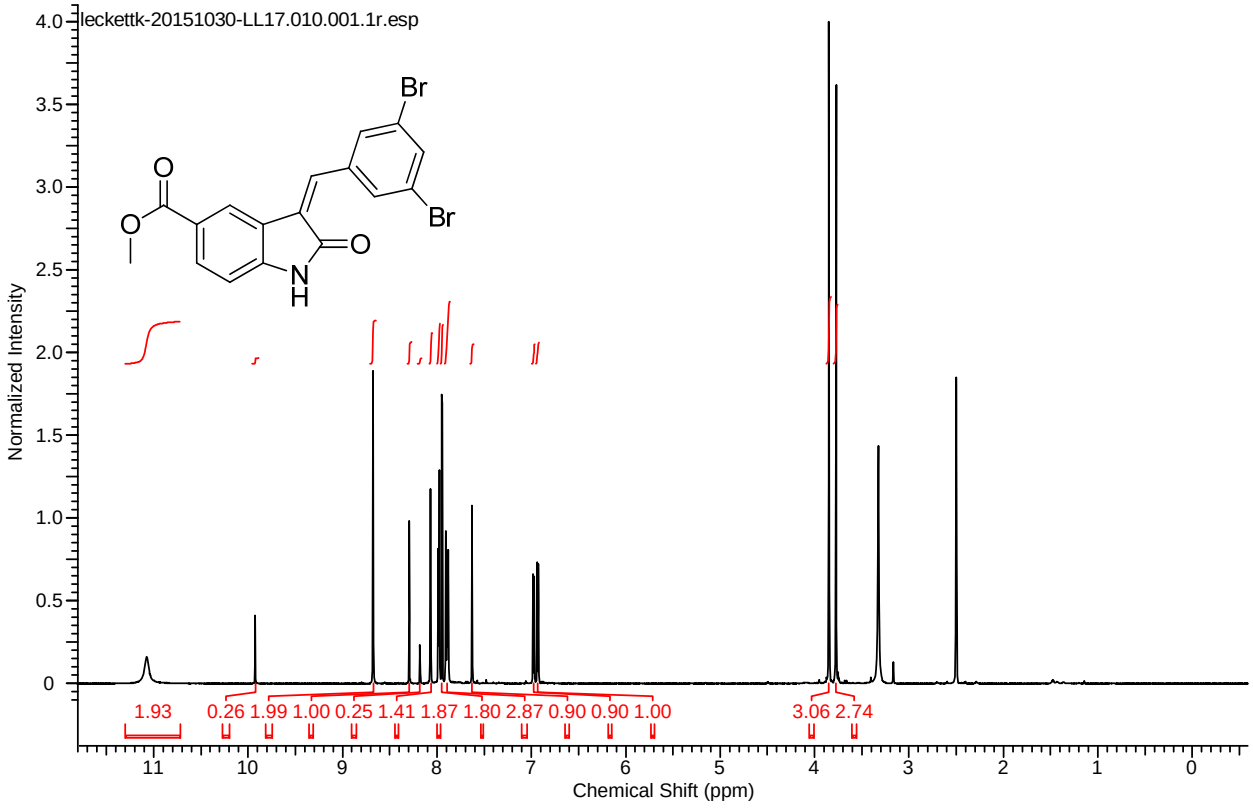

leckettk-20151104-45.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.27
166.00
155.83
146.42
139.65
138.49
133.98
130.70
125.47
124.60
123.75
122.91
122.09
121.43
121.22
109.70
108.86
51.86
51.80
16.68
16.38

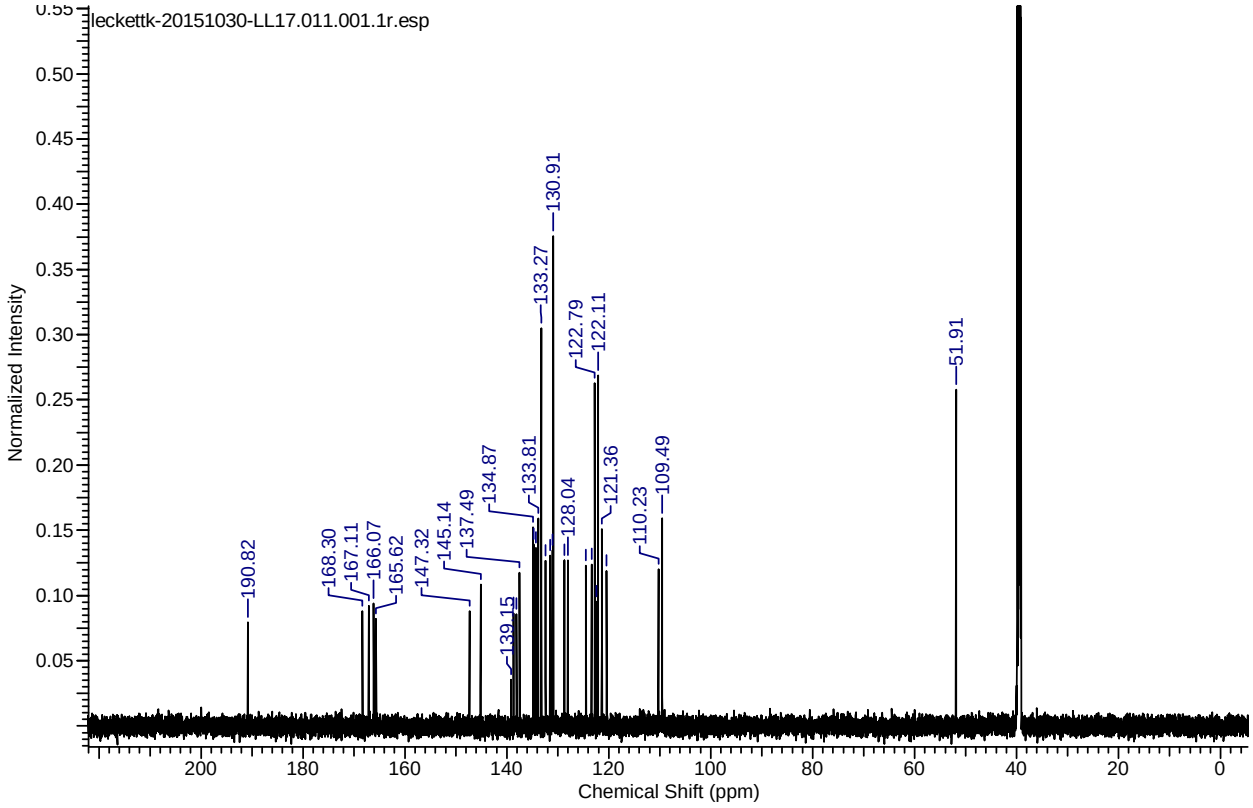

leckettk-20151022-18.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OH
Br
O
O
N
H
0.99 0.57 1.37
2.00 1.00 0.55 1.10 1.01 1.57 0.53 0.55 1.00
3.06 1.70

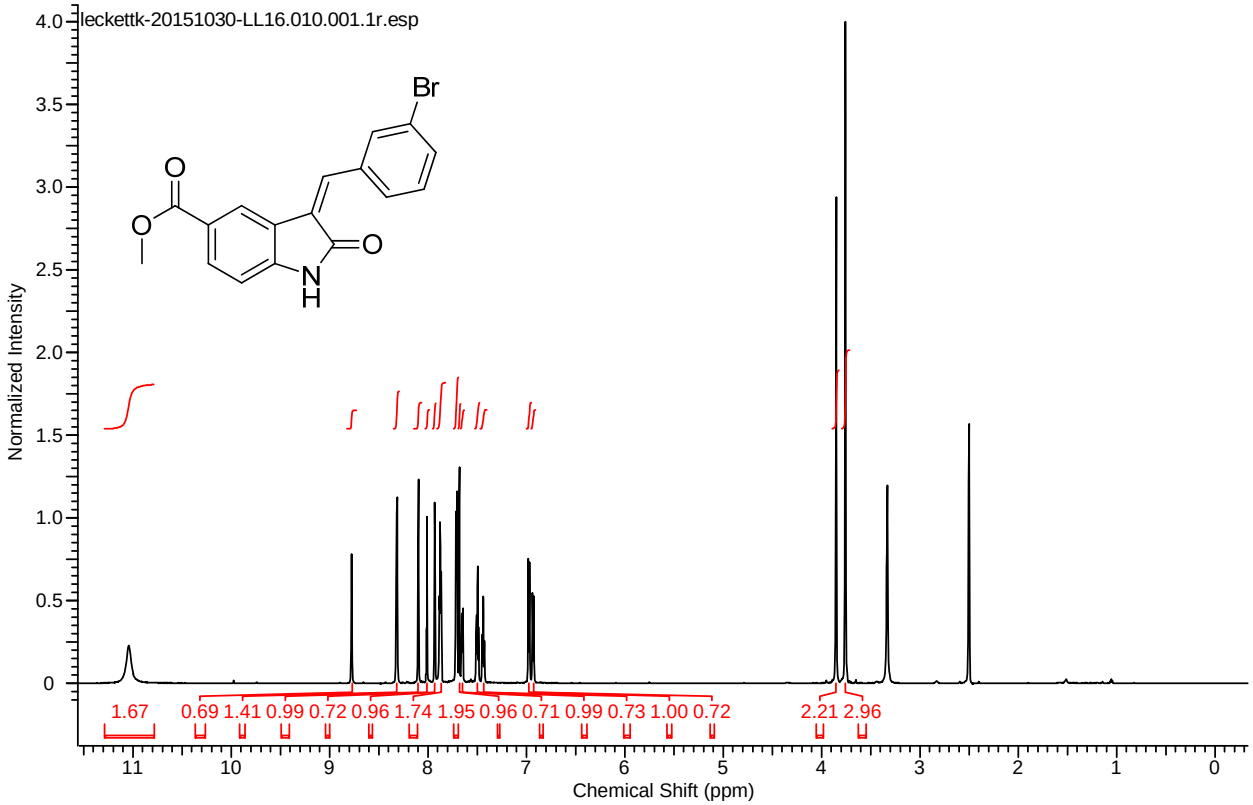

leckettk-20151022-18.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.67
167.50
166.21
165.75
152.94
146.98
144.48
136.47
133.55
130.59
128.15
122.54
120.67
111.83
111.05
109.25
51.88

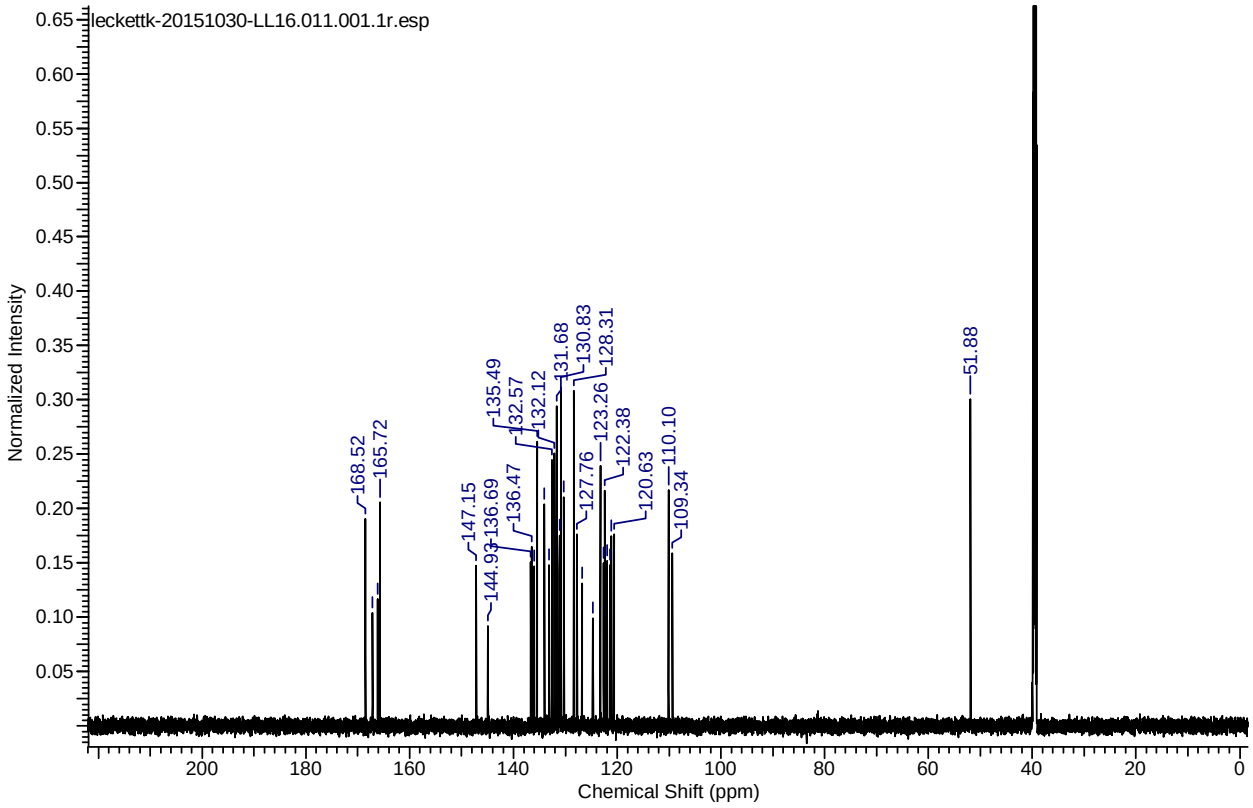

leckettk-20151105-42.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
OH
O
O
O
N
H
1.02 1.37
0.96 1.01 1.29 0.34 0.98 1.35 0.68 0.34 0.98 0.35 1.00
2.93 1.01

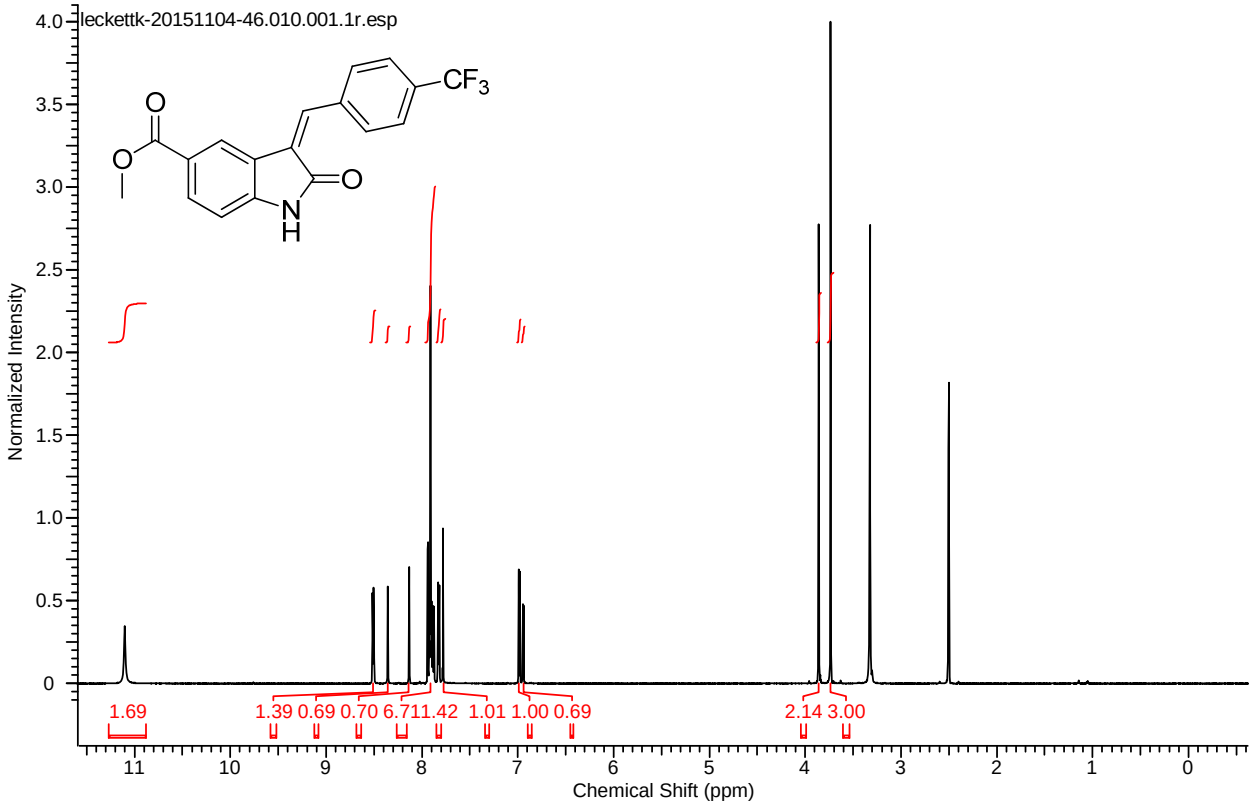

leckettk-20151105-42.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
167.63
166.34
156.80
144.20
137.69
137.32
134.26
125.42
122.44
120.36
115.88
109.22
109.11
51.88
168.99
165.94
156.08
146.75
130.94
109.63
51.94

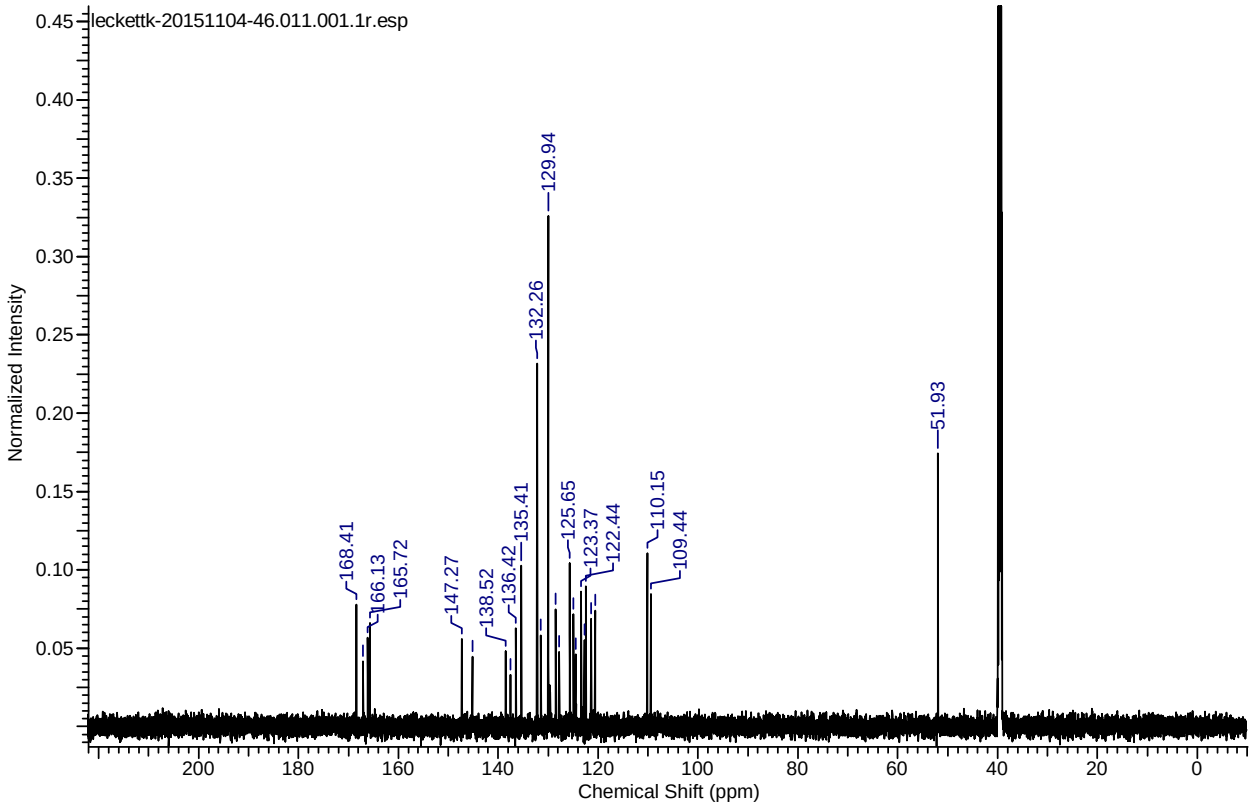

leckettk-20151030-LL17.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
Br
O
O
O
N
H
1.93
0.26 1.99 1.00 0.25 1.41 1.87 1.80 2.87 0.90 0.90 1.00
3.06 2.74

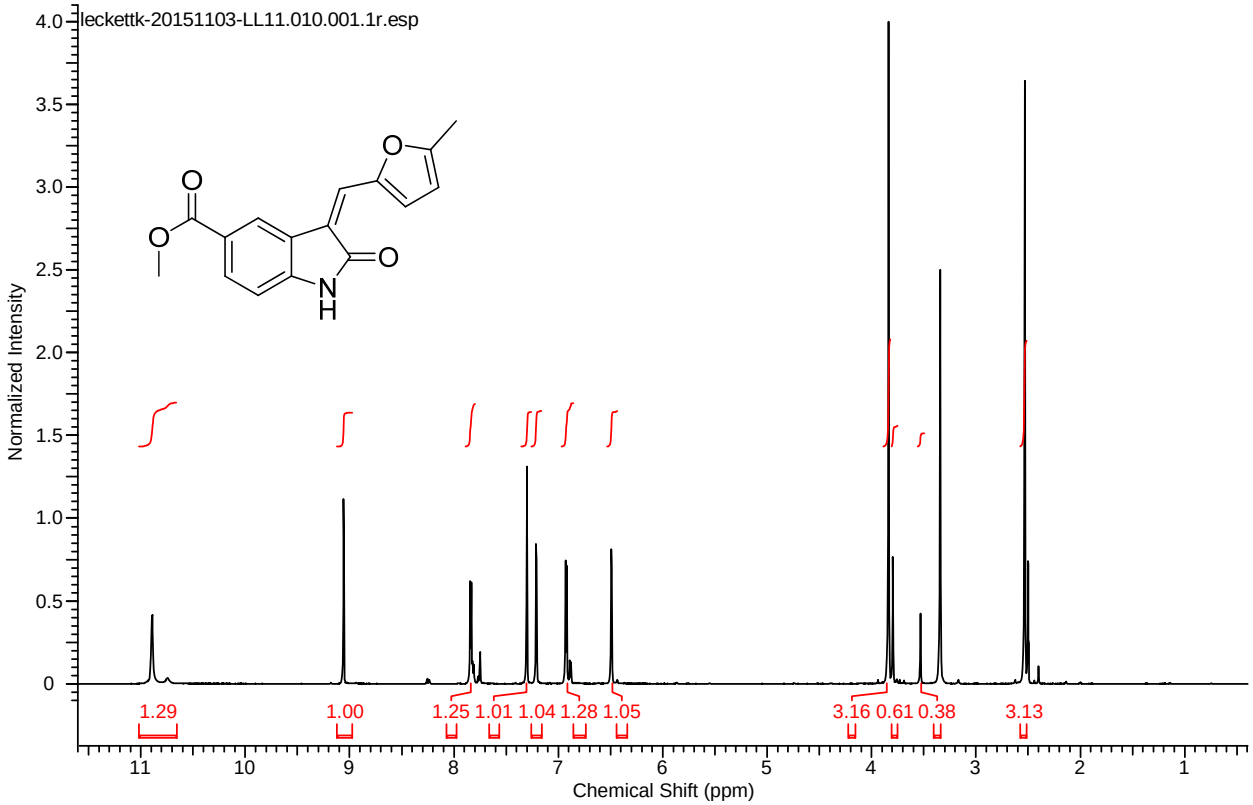

leckettk-20151030-LL17.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
190.82
168.30
167.11
166.07
165.62
147.32
145.14
137.49
134.87
139.15
133.81
133.27
130.91
128.04
122.79
122.11
121.36
110.23
109.49
51.91

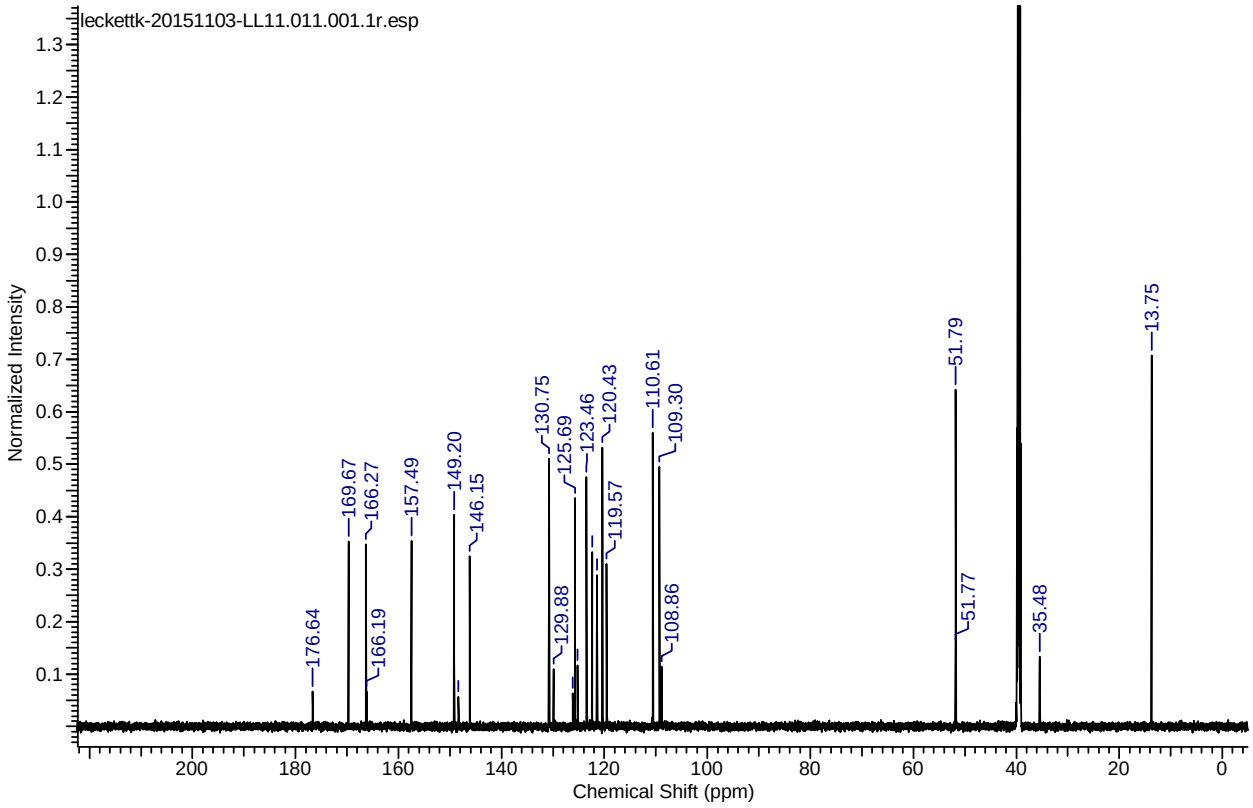

leckettk-20151030-LL16.010.001.1r.esp
Br
O
O
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.67
0.69 1.41 0.99 0.72 0.96 1.74 1.95 0.96 0.71 0.99 0.73 1.00 0.72
2.21 2.96

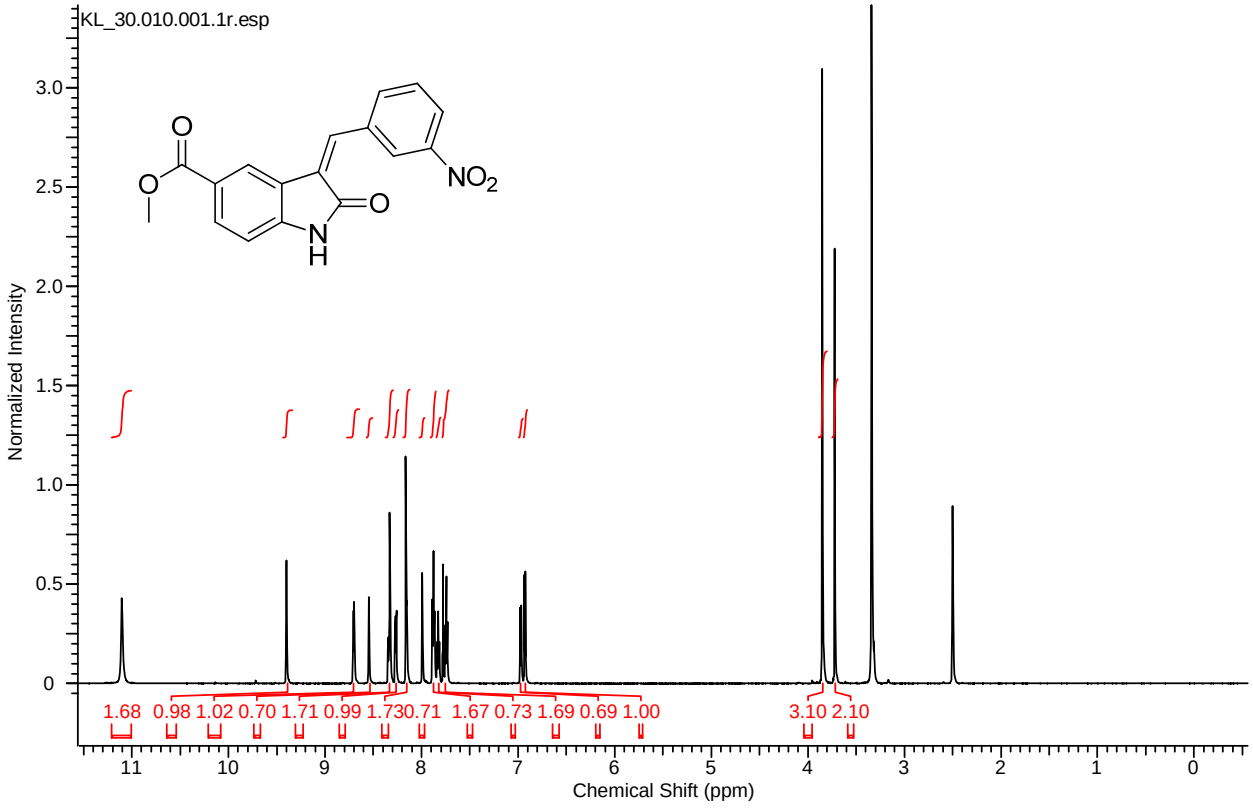

leckettk-20151030-LL16.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.52
165.72
147.15
144.93
136.69
136.47
135.49
132.57
132.12
131.68
130.83
128.31
127.76
123.26
122.38
120.63
110.10
109.34
51.88

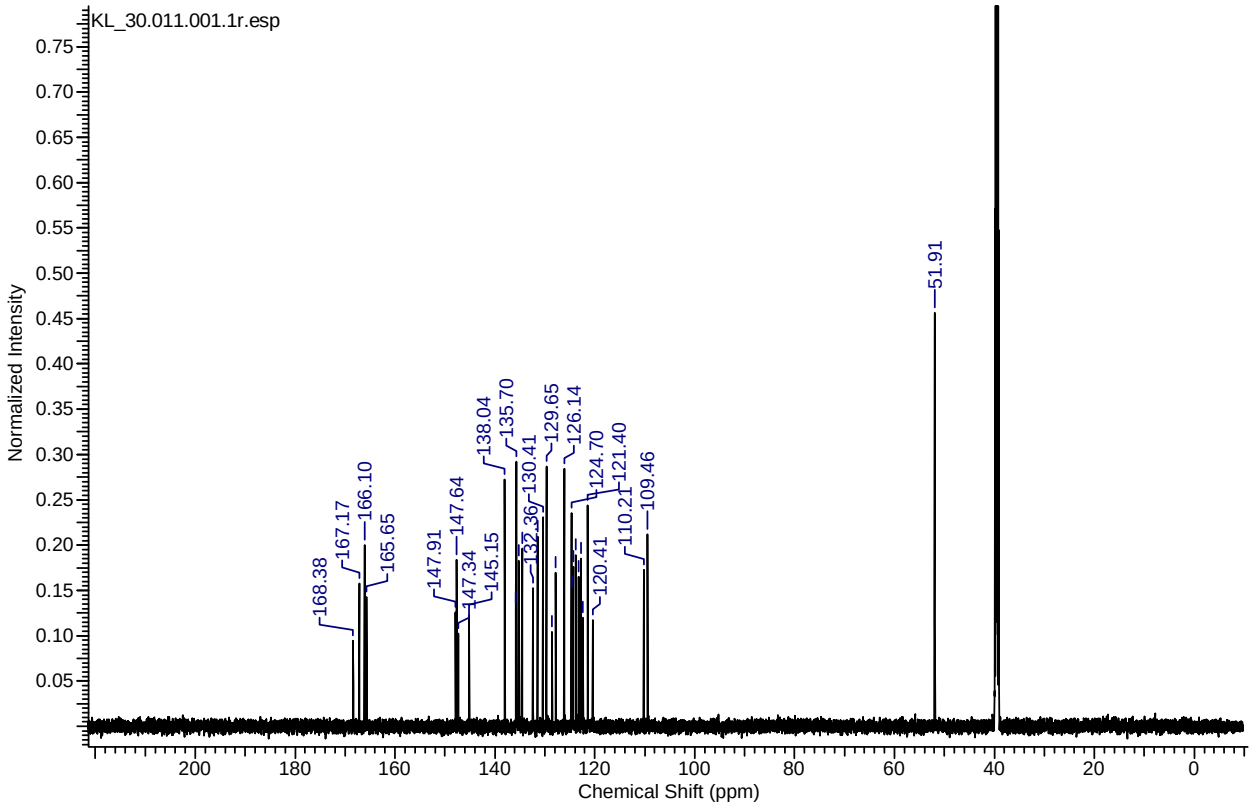

leckettk-20151104-46.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
CF3
O
O
O
N
H
1.69
1.39 0.69 0.70 6.71 1.42 1.01 1.00 0.69
2.14 3.00

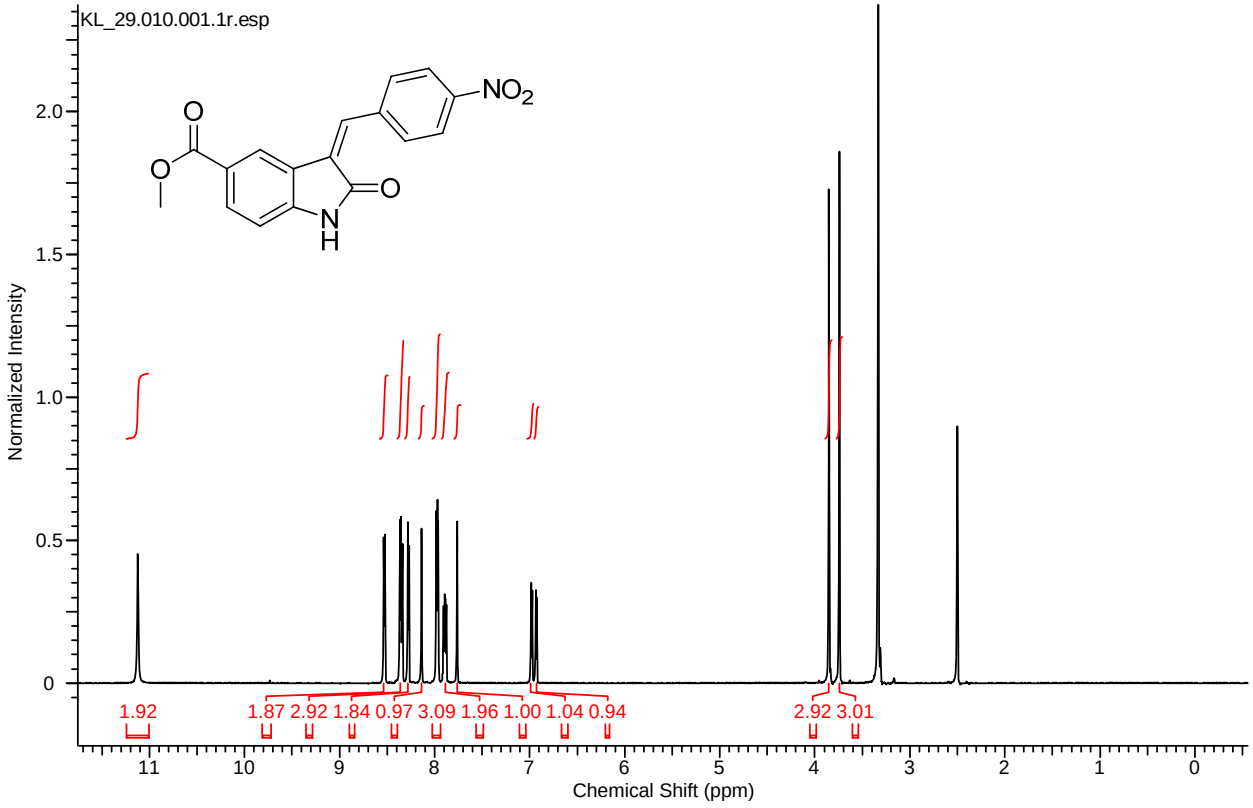

leckettk-20151104-46.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.41
166.13
165.72
147.27
138.52
136.42
135.41
132.26
129.94
125.65
123.37
122.44
110.15
109.44
51.93

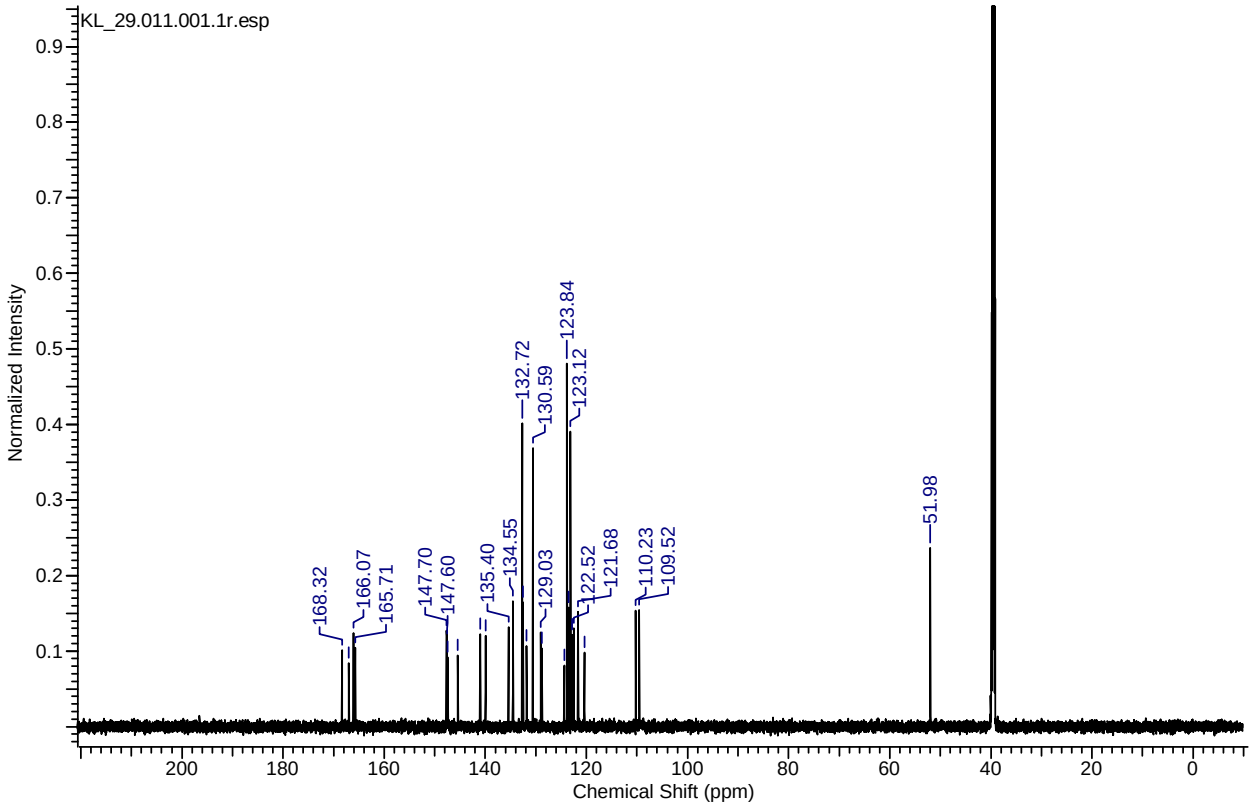

leckettk-20151103-LL11.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
1.29
1.00
1.25 1.01 1.04 1.28 1.05
3.16 0.61 0.38
3.13

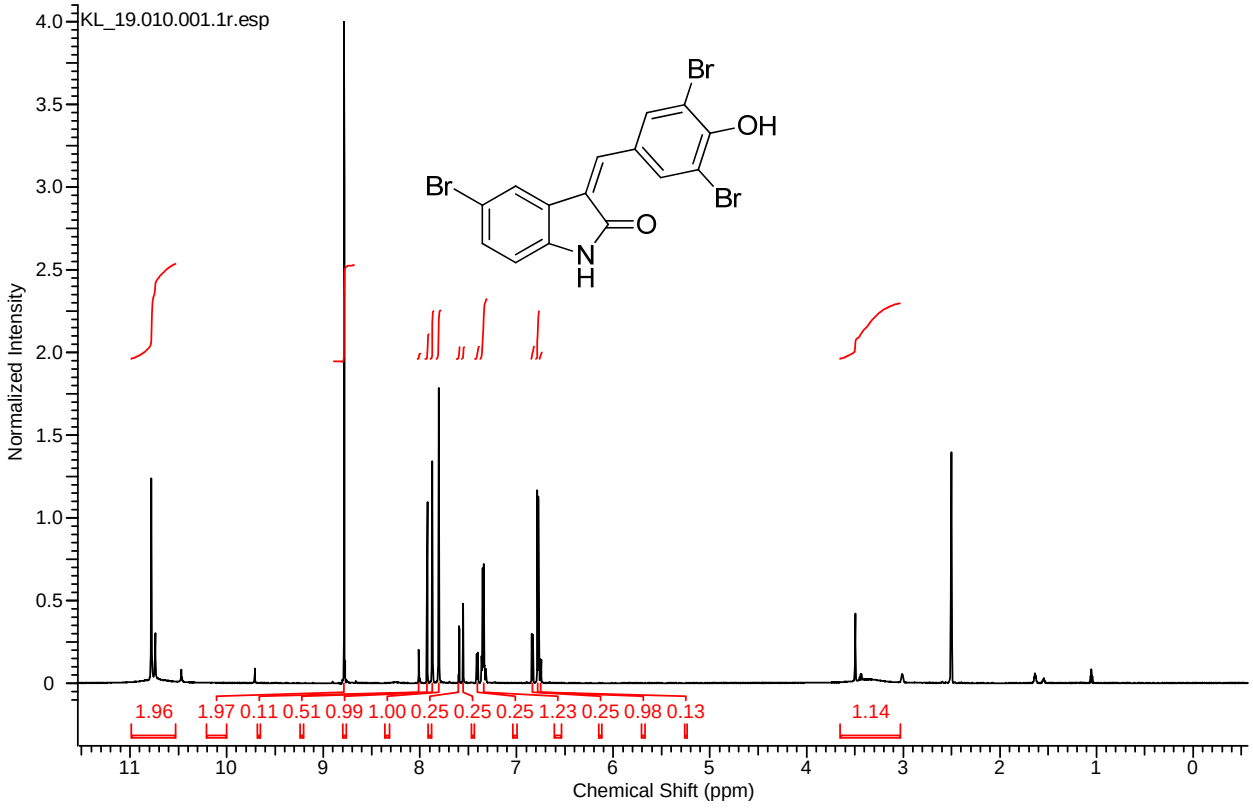

leckettk-20151103-LL11.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.64
169.67
166.27
166.19
157.49
149.20
146.15
130.75
129.88
125.69
123.46
120.43
119.57
110.61
109.30
108.86
51.79
51.77
35.48
13.75

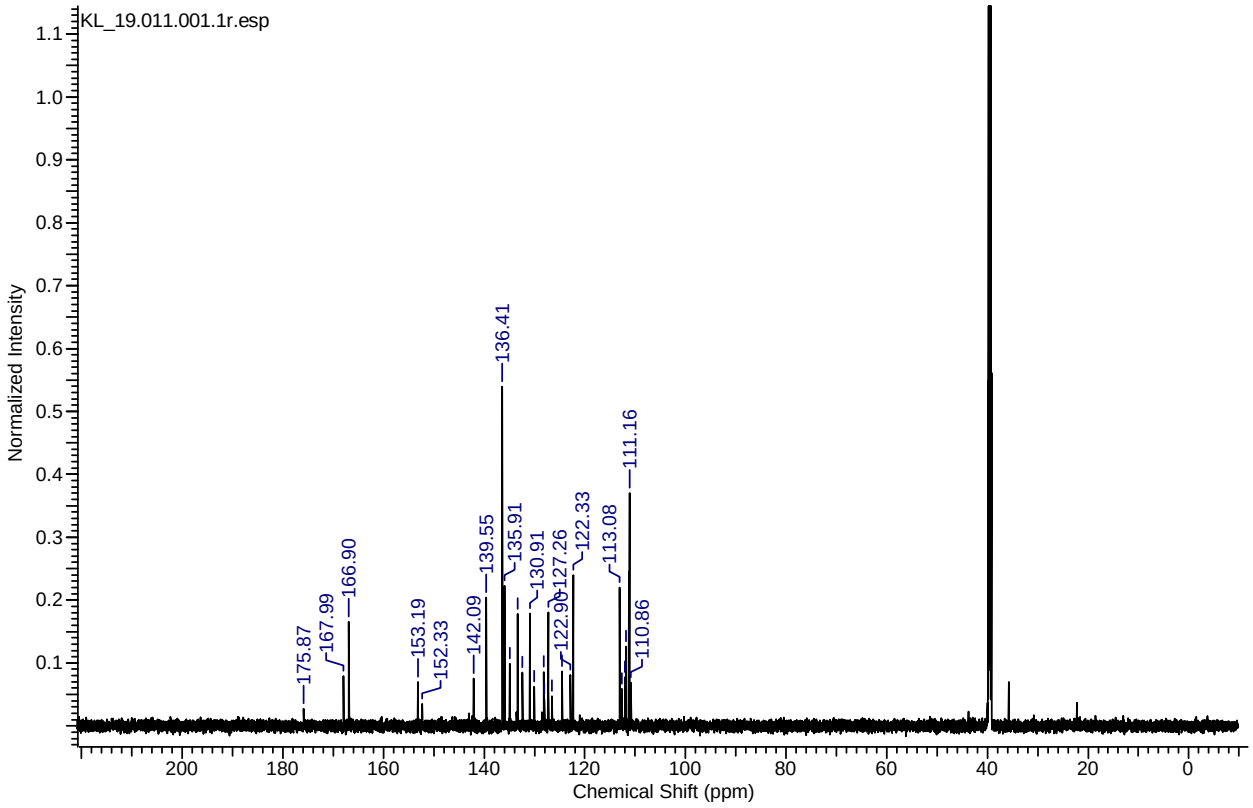

KL_30.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
NO2
O
N
H
1.68 0.98 1.02 0.70 1.71 0.99 1.73 0.71 1.67 0.73 1.69 0.69 1.00
3.10 2.10

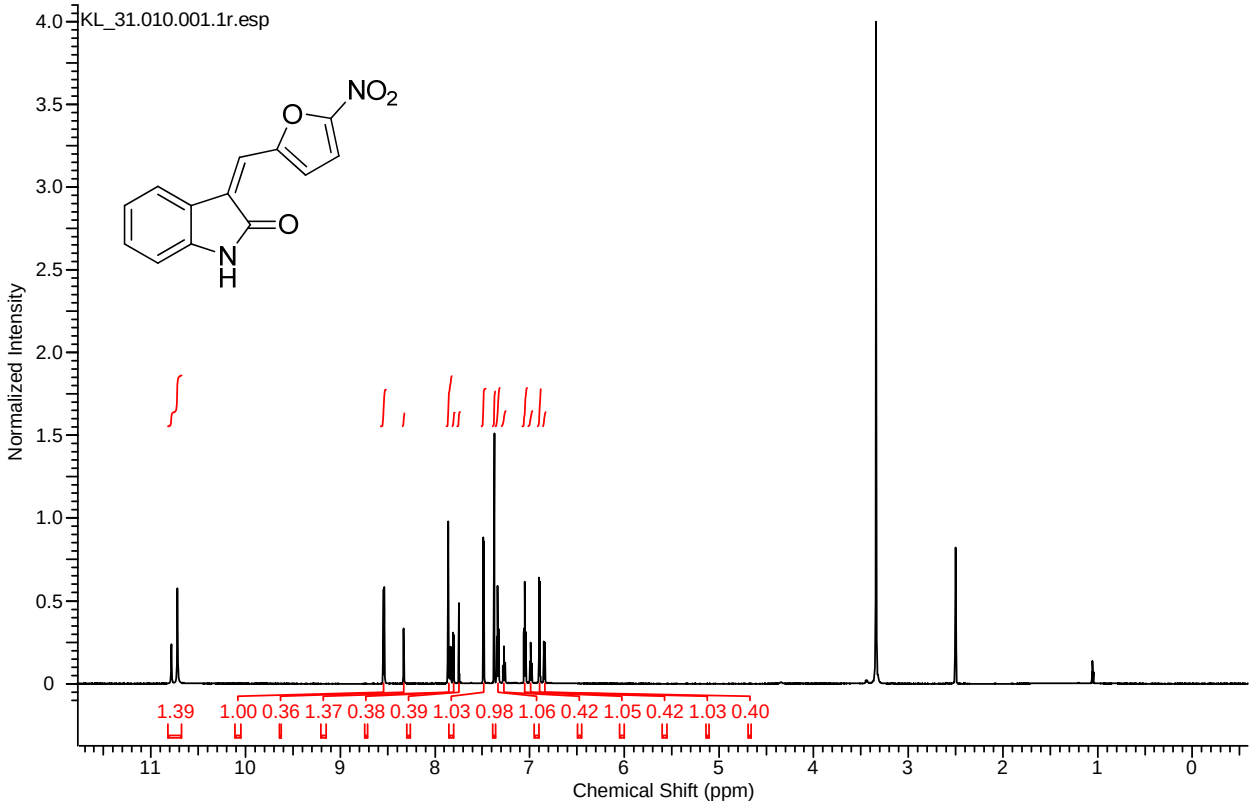

KL_30.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.38
167.17
166.10
165.65
147.91
147.64
147.34
145.15
138.04
135.70
132.36
130.41
129.65
126.14
124.70
121.40
120.41
110.21
109.46
51.91

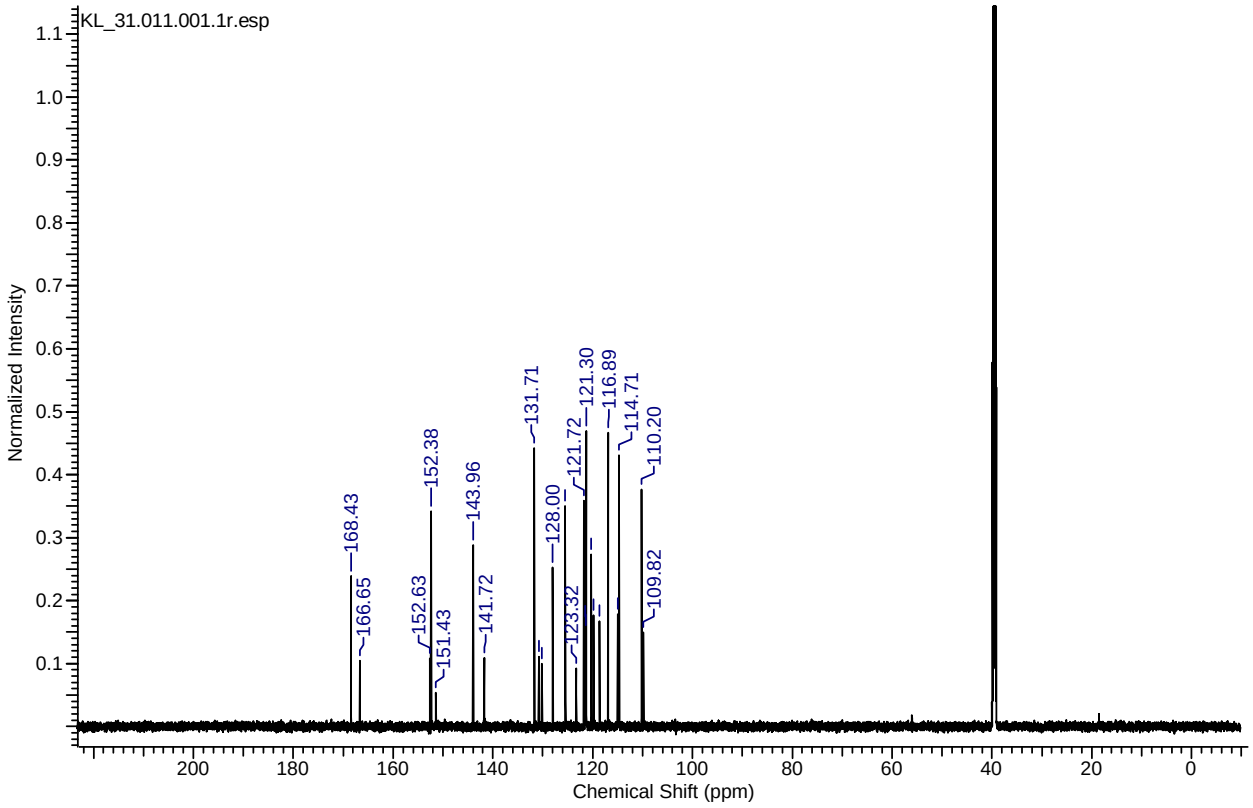

KL_29.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
NO2
O
O
O
N
H
1.92
1.87 2.92 1.84 0.97 3.09 1.96 1.00 1.04 0.94
2.92 3.01

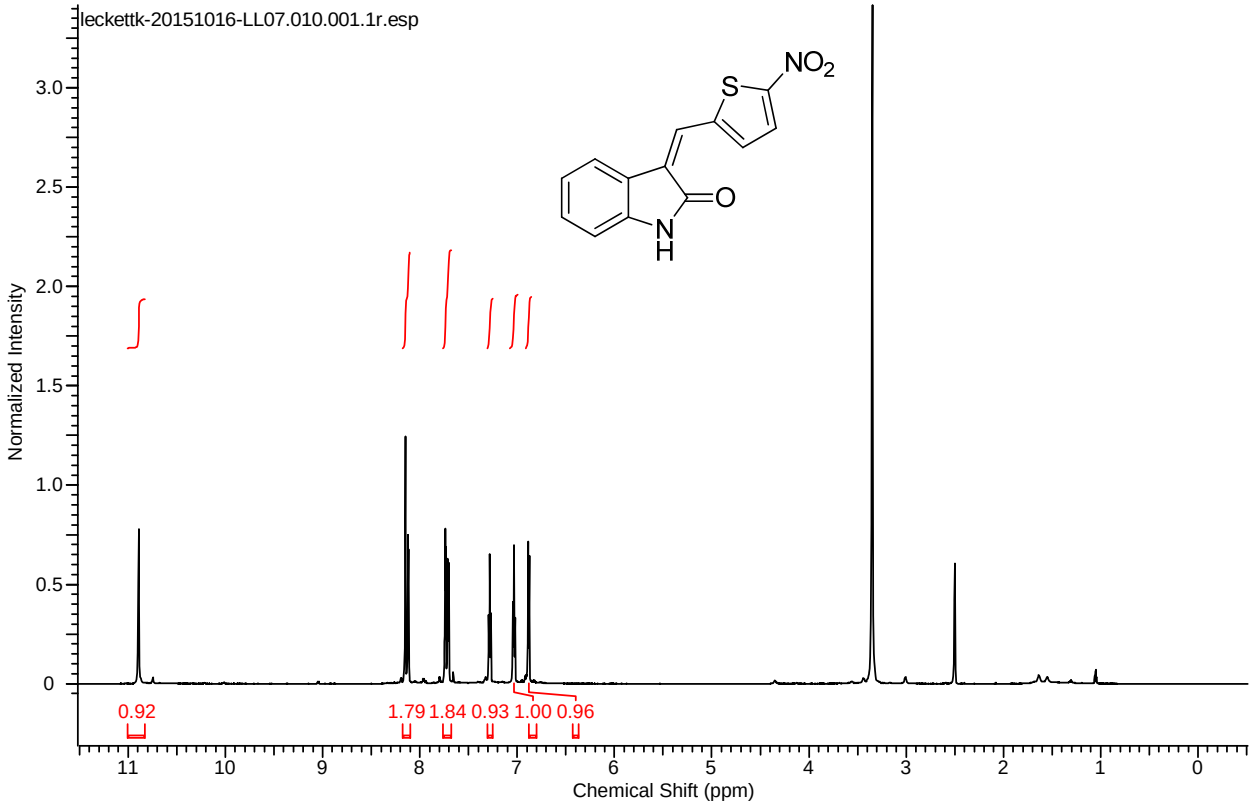

KL_29.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.32
166.07
165.71
147.70
147.60
135.40
134.55
132.72
130.59
129.03
123.84
123.12
122.52
121.68
110.23
109.52
51.98

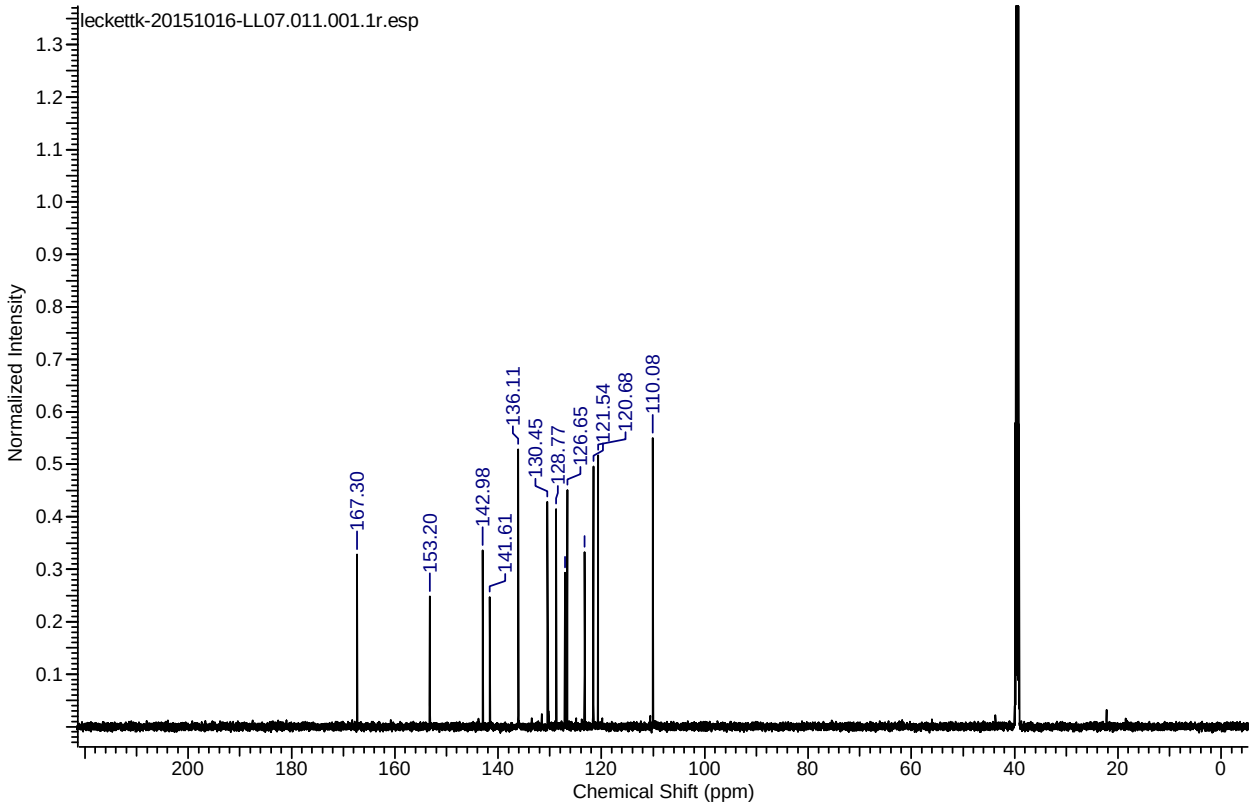

KL_19.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
OH
Br
Br
O
N
H
1.96
1.97
0.11
0.51
0.99
1.00
0.25
0.25
0.25
1.23
0.25
0.98
0.13
1.14

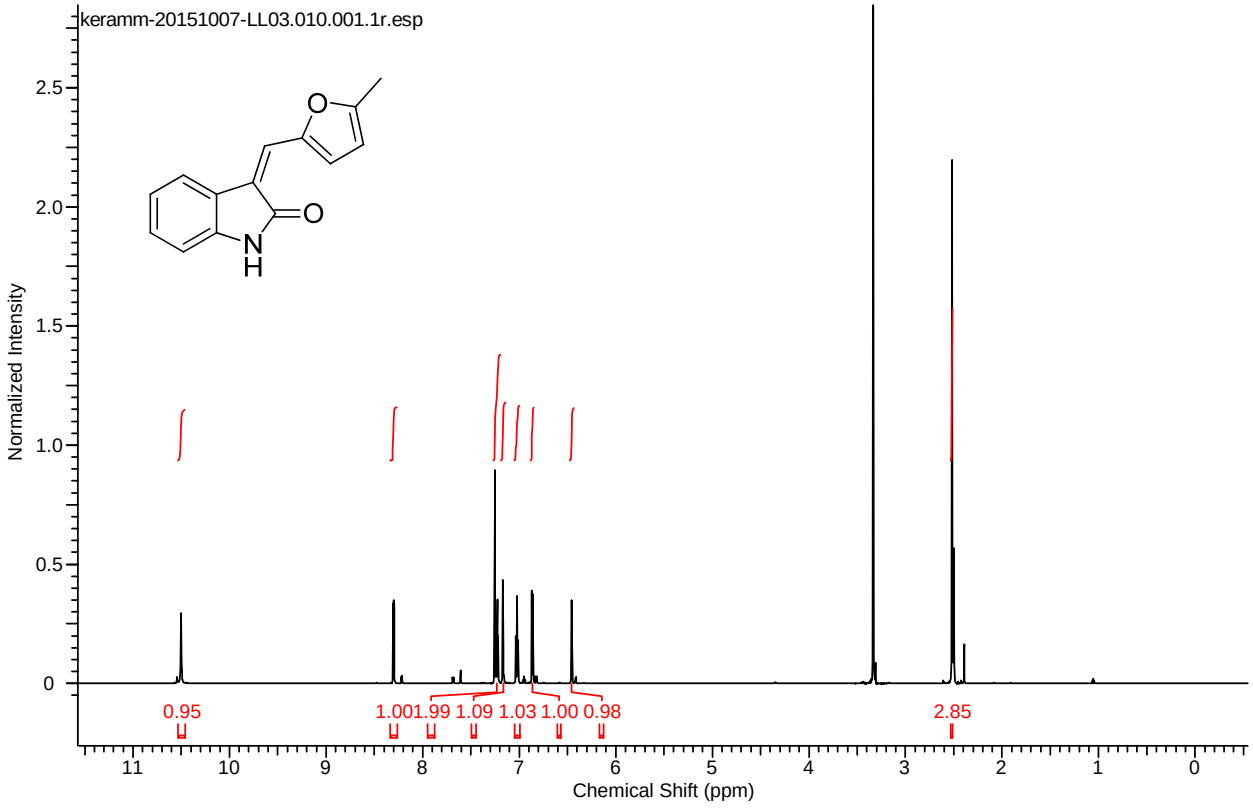

KL_19.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
175.87
167.99
166.90
153.19
152.33
142.09
139.55
136.41
135.91
130.91
127.26
122.90
122.33
113.08
111.16
110.86

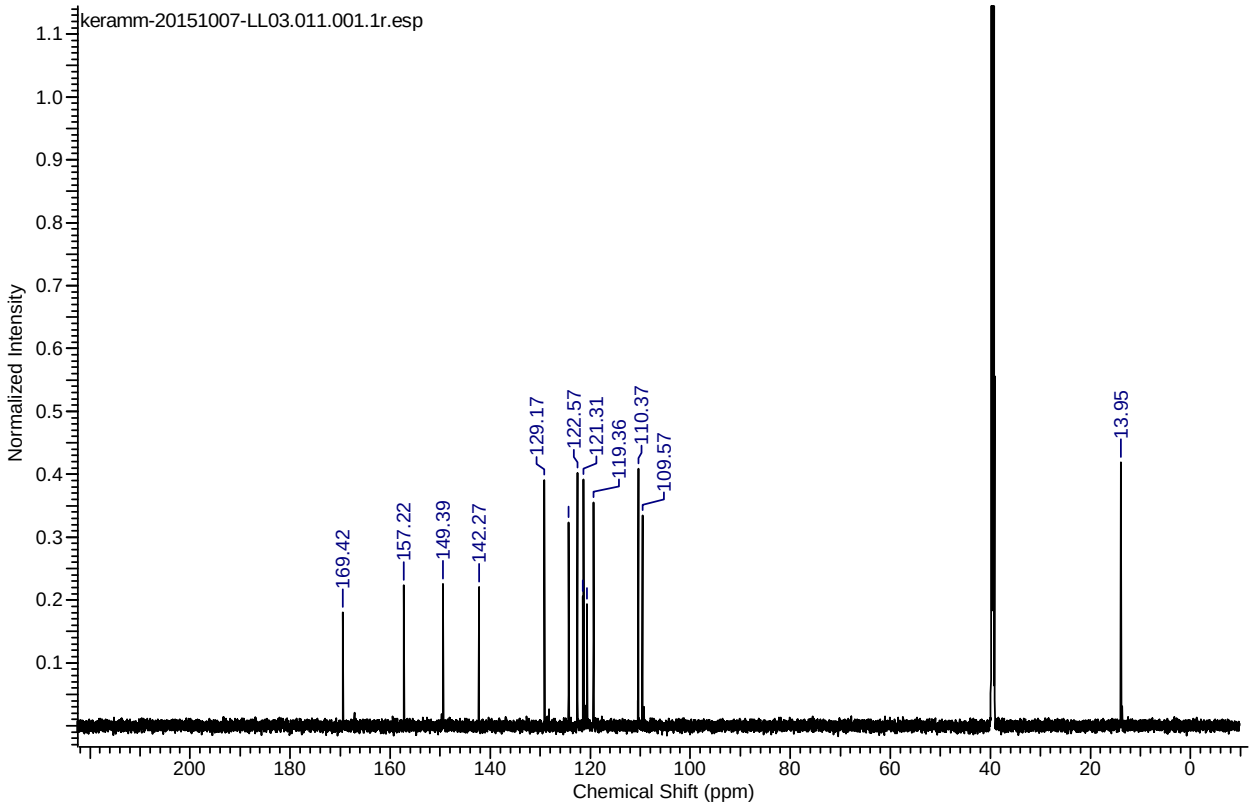

KL_31.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
NO2
O
O
N
H
1.39
1.00 0.36 1.37 0.38 0.39 1.03 0.98 1.06 0.42 1.05 0.42 1.03 0.40

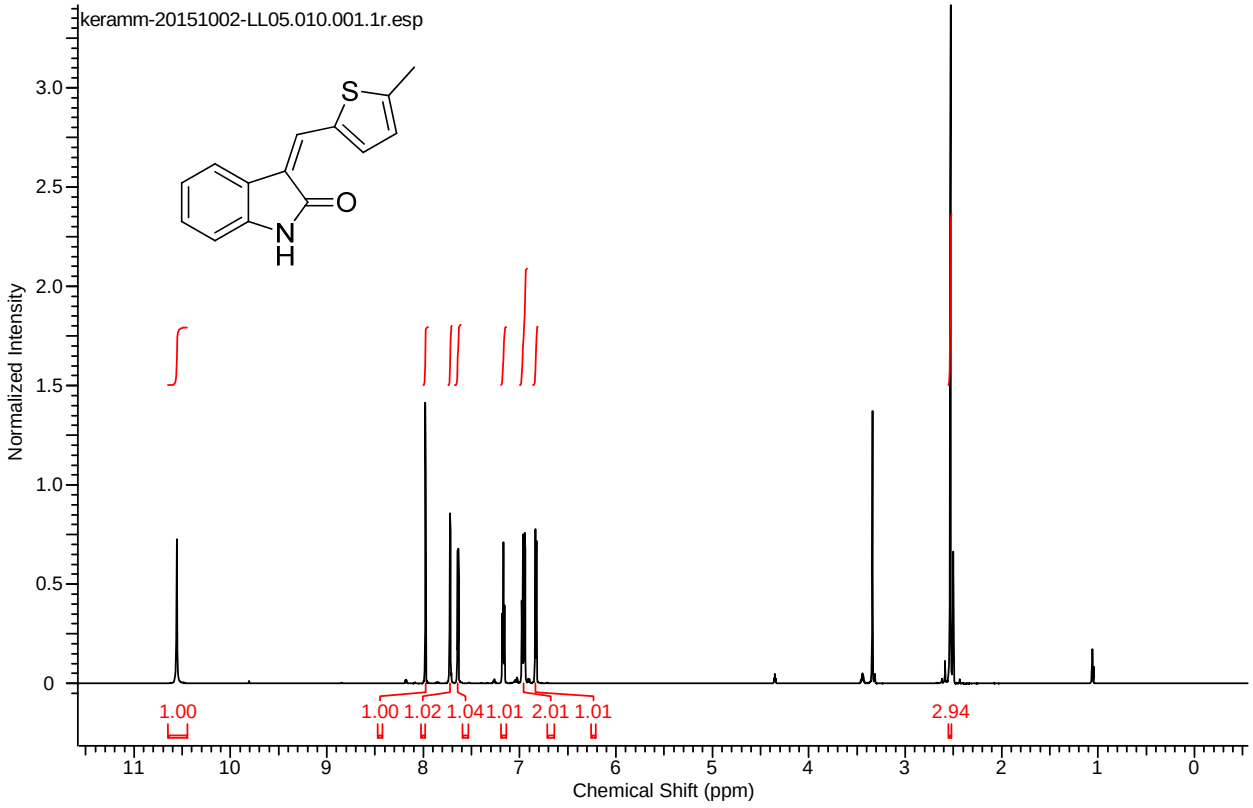

KL_31.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.43
166.65
152.63
152.38
151.43
143.96
141.72
131.71
128.00
123.32
121.72
121.30
116.89
114.71
110.20
109.82

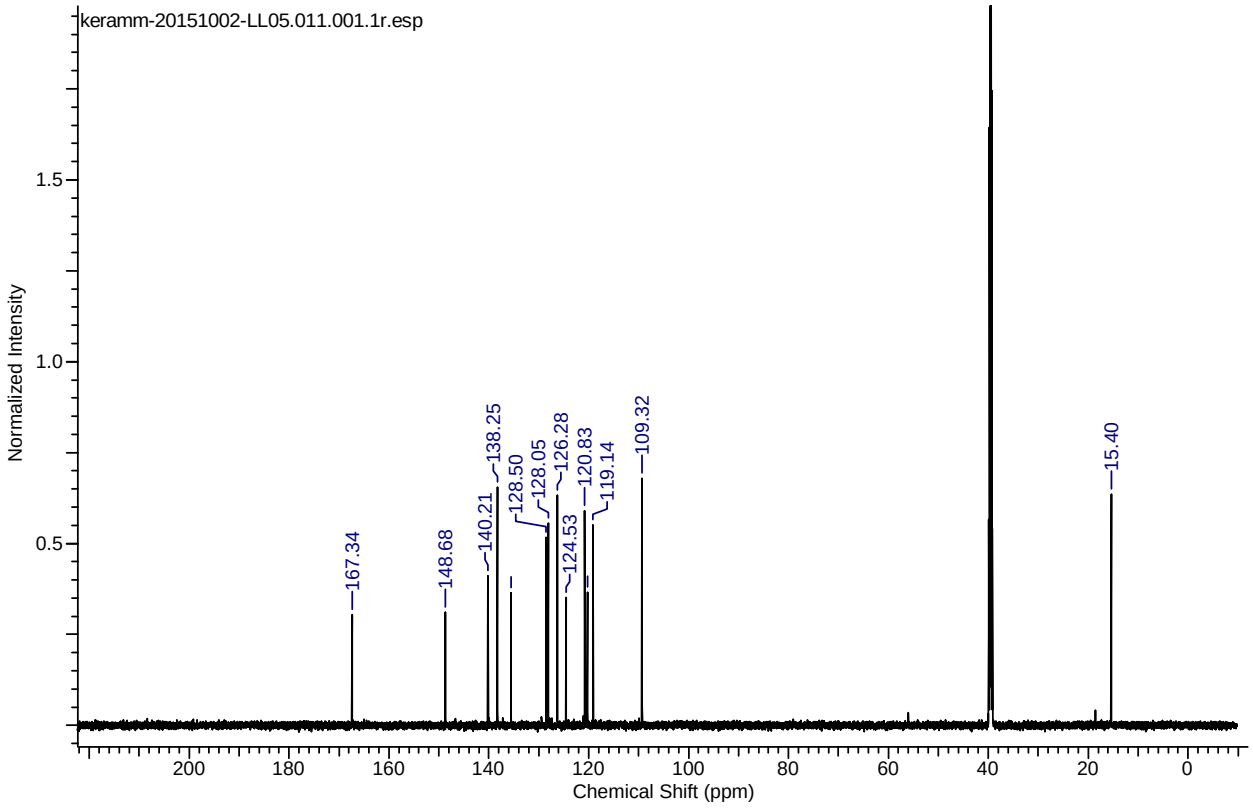

leckettk-20151016-LL07.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
NO2
S
O
N
H
0.92
1.79
1.84
0.93
1.00
0.96

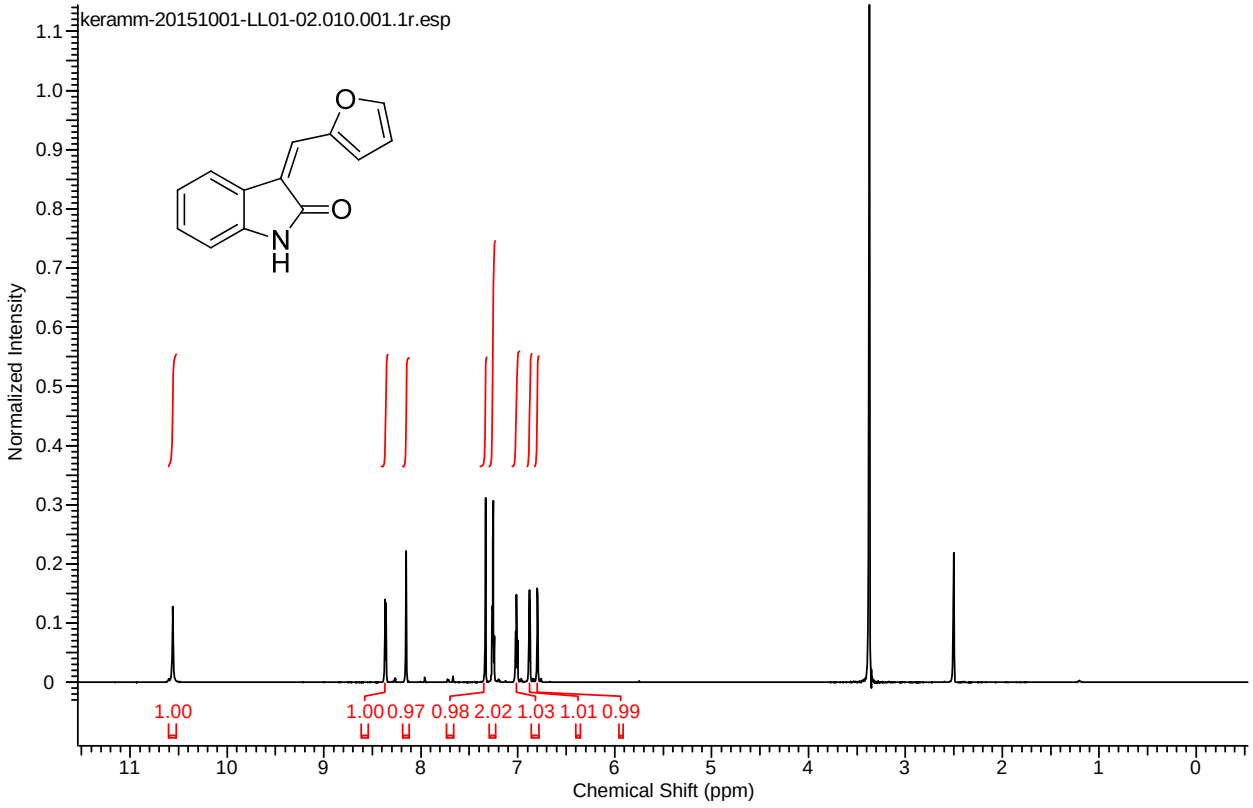

leckettk-20151016-LL07.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
167.30
153.20
142.98
141.61
136.11
130.45
128.77
126.65
121.54
120.68
110.08

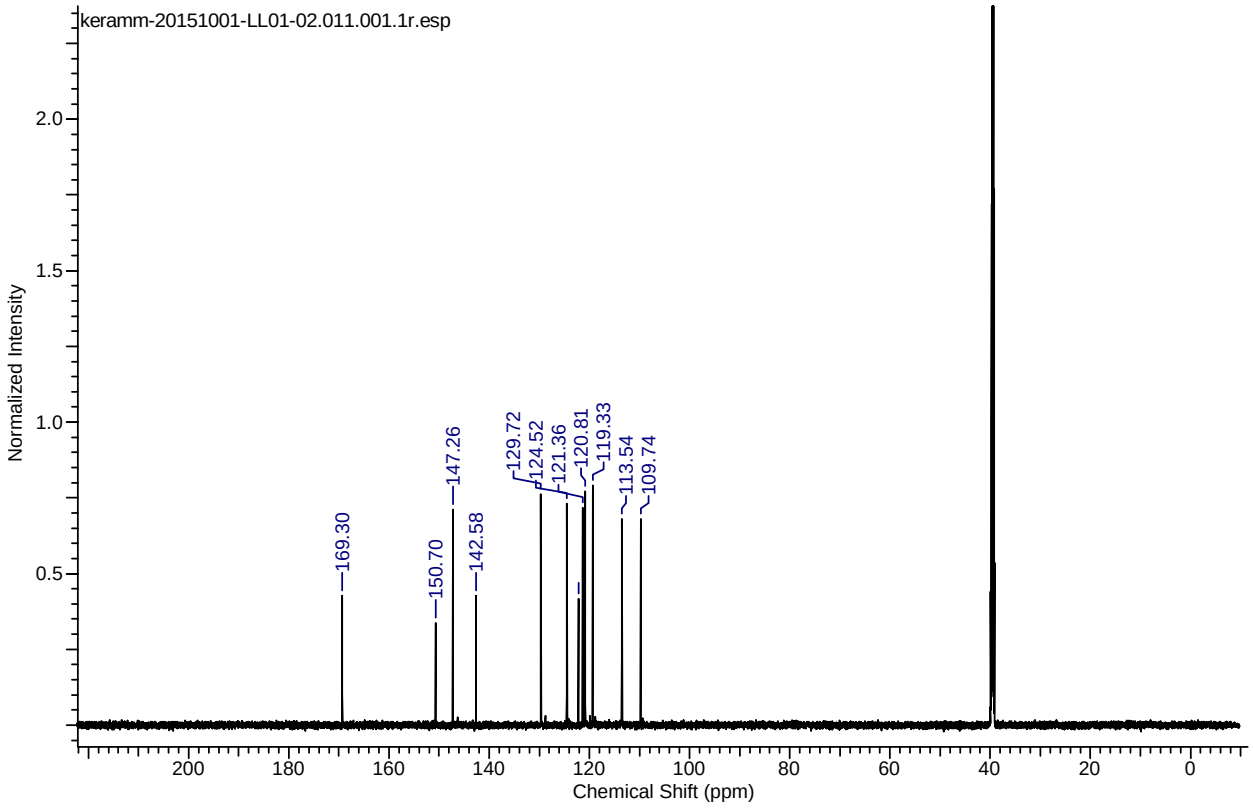

keramm-20151007-LL03.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
N
H
0.95
1.00
1.99
1.09
1.03
1.00
0.98
2.85

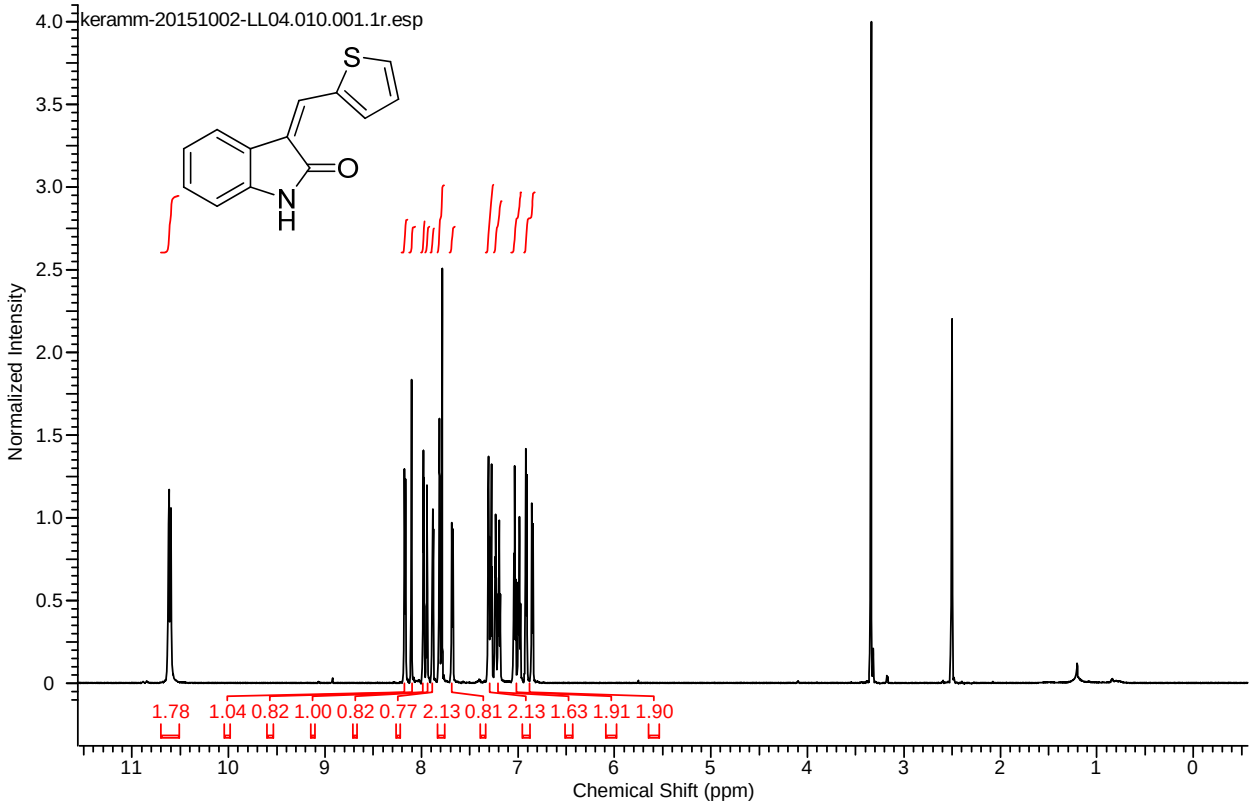

keramm-20151007-LL03.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.42
157.22
149.39
142.27
129.17
122.57
121.31
119.36
110.37
109.57
13.95

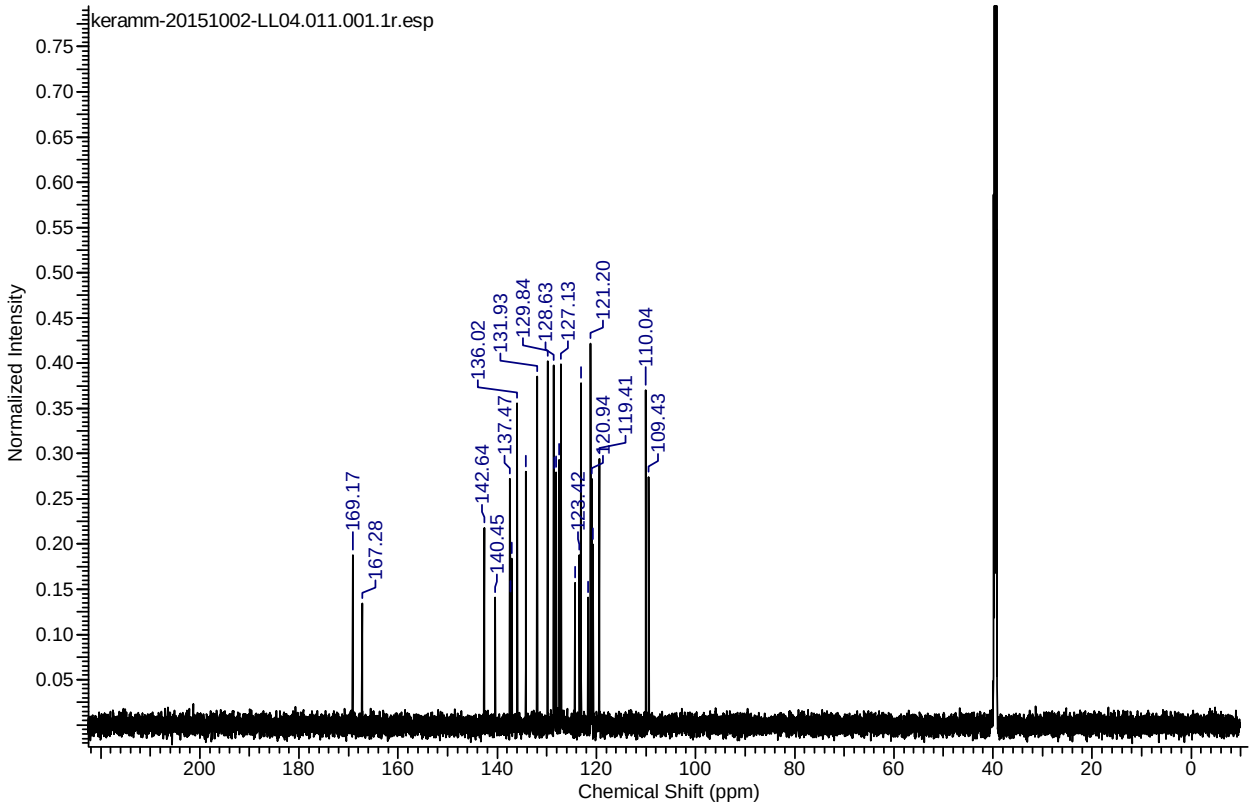

keramm-20151002-LL05.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
O
N
H
1.00
1.00 1.02 1.04 1.01 2.01 1.01
2.94

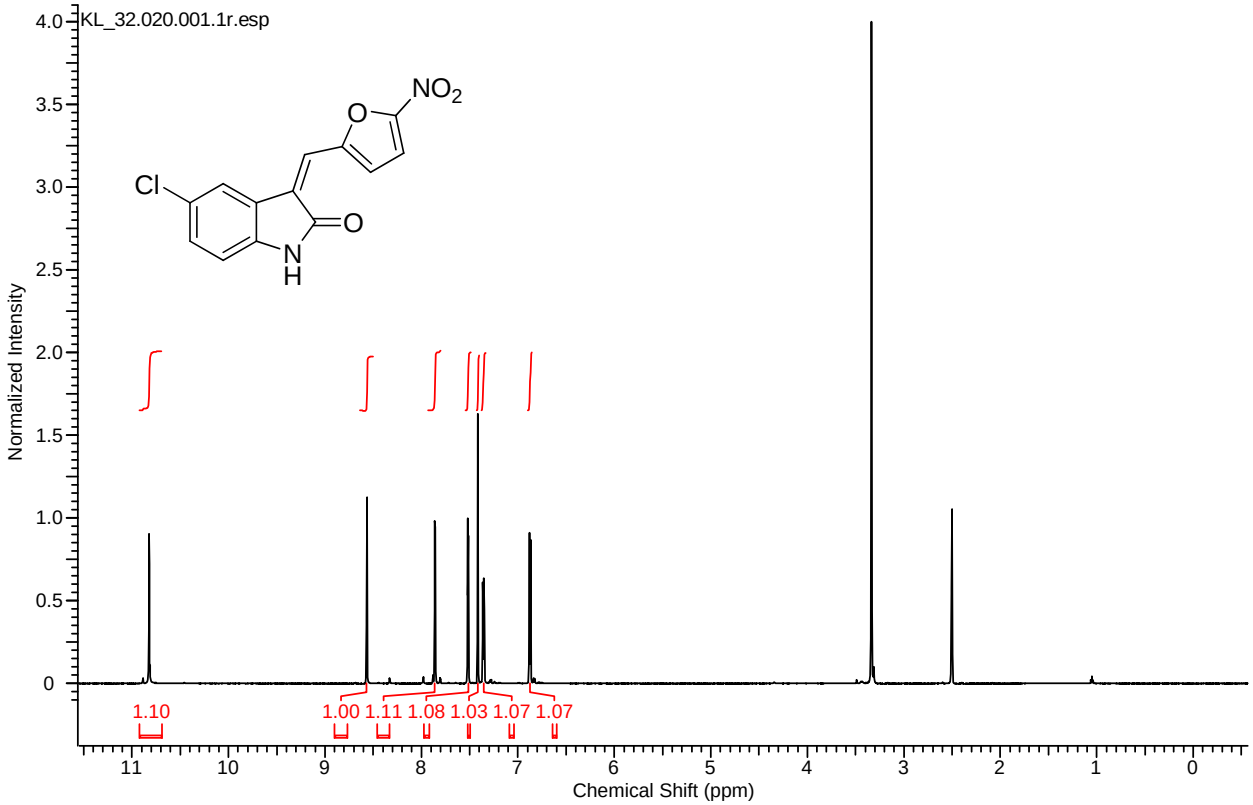

keramm-20151002-LL05.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
167.34
148.68
140.21
138.25
128.50
128.05
126.28
124.53
120.83
119.14
109.32
15.40

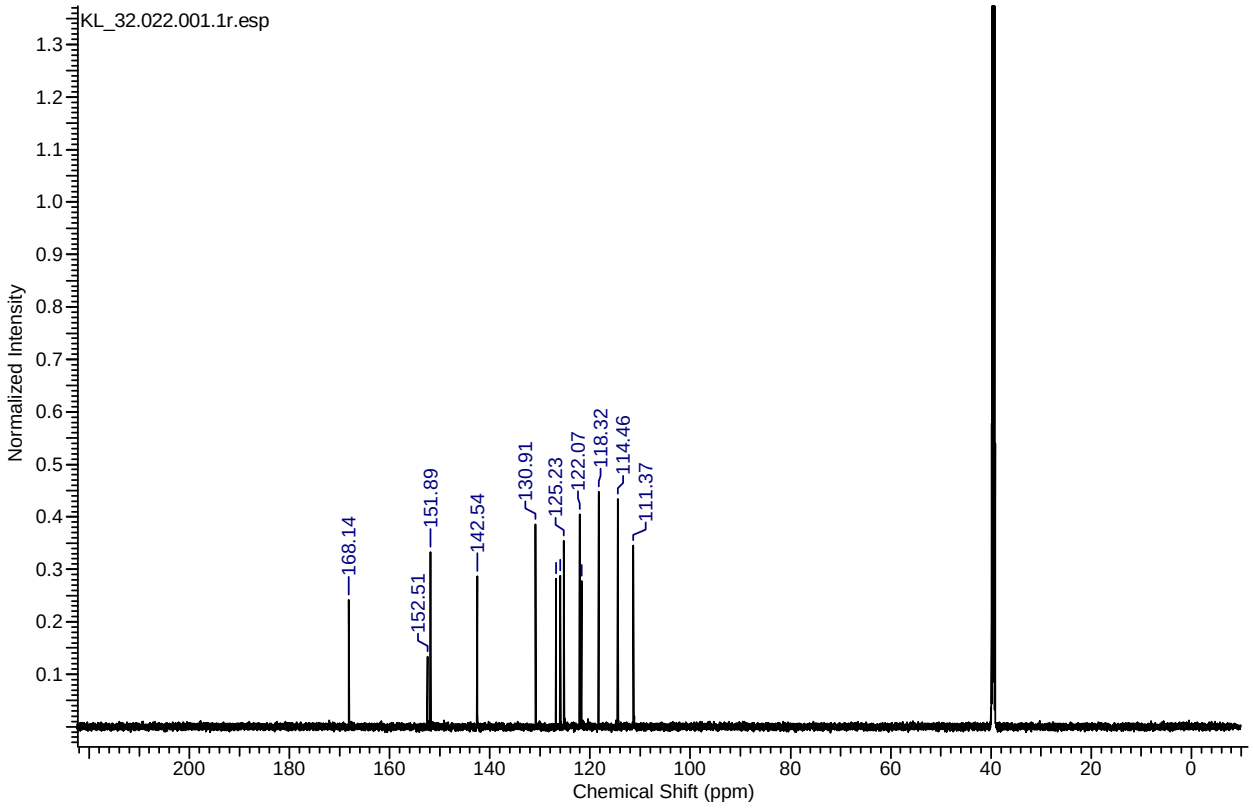

keramm-20151001-LL01-02.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.00 0.97 0.98 2.02 1.03 1.01 0.99

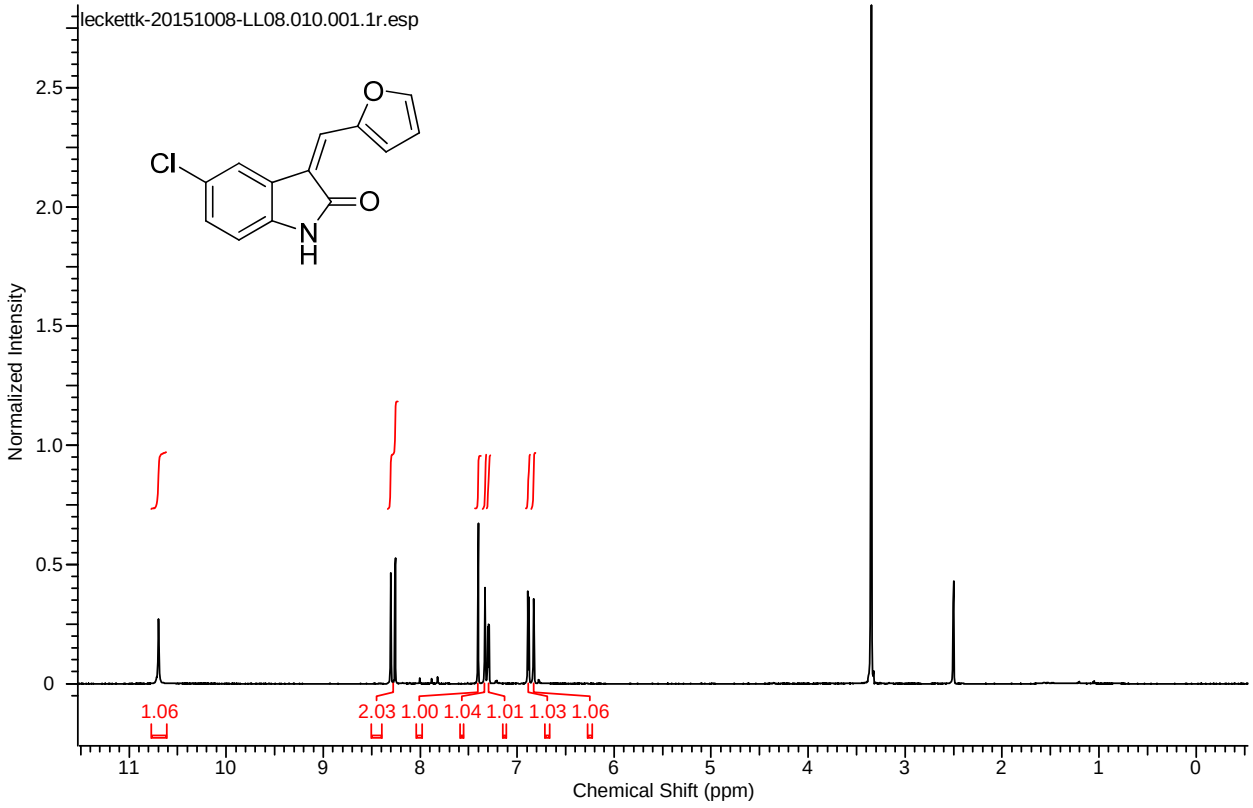

keramm-20151001-LL01-02.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.30
150.70
147.26
142.58
129.72
124.52
121.36
120.81
119.33
113.54
109.74

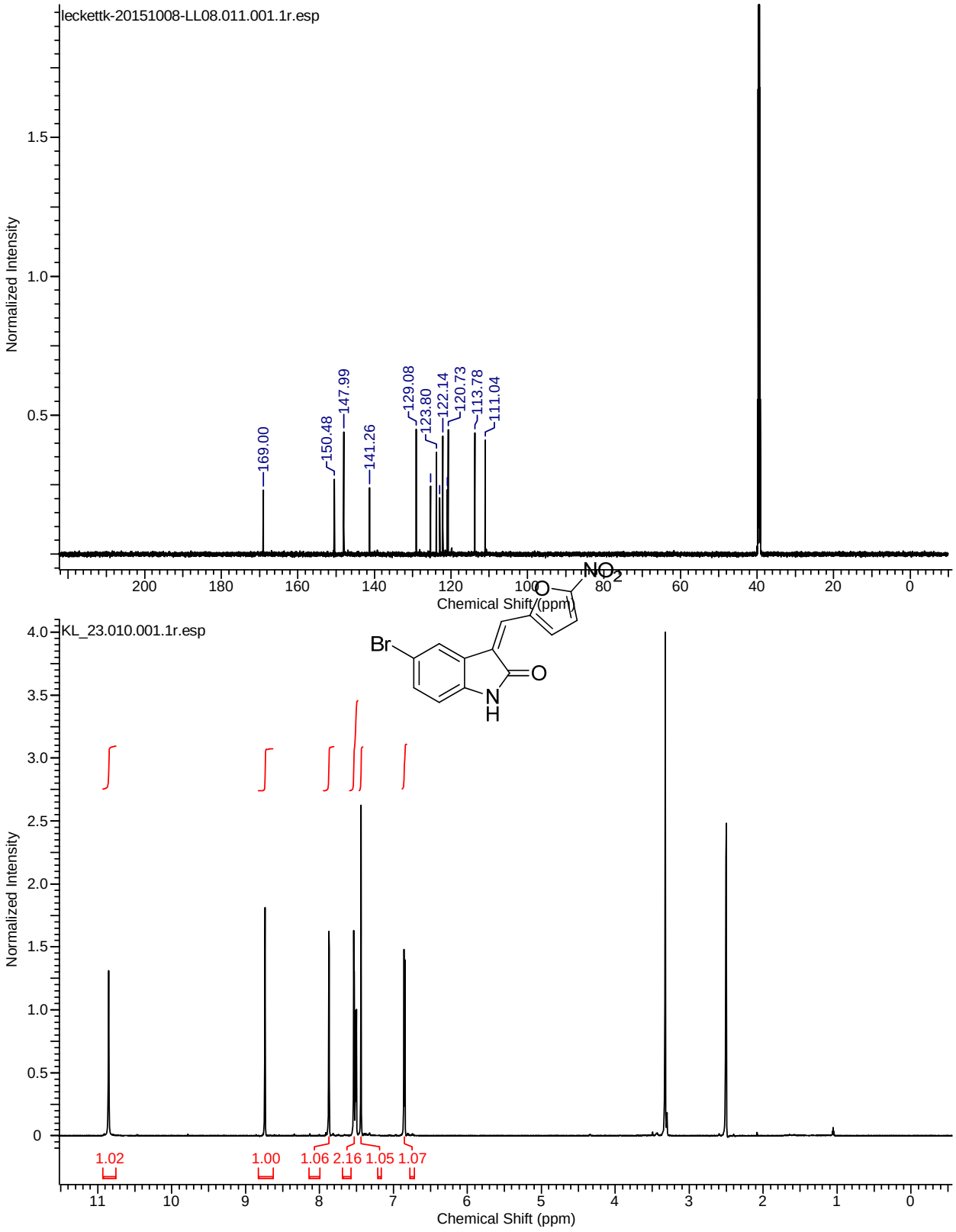

keramm-20151002-LL04.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
O
N
H
1.78
1.04
0.82
1.00
0.82
0.77
2.13
0.81
2.13
1.63
1.91
1.90

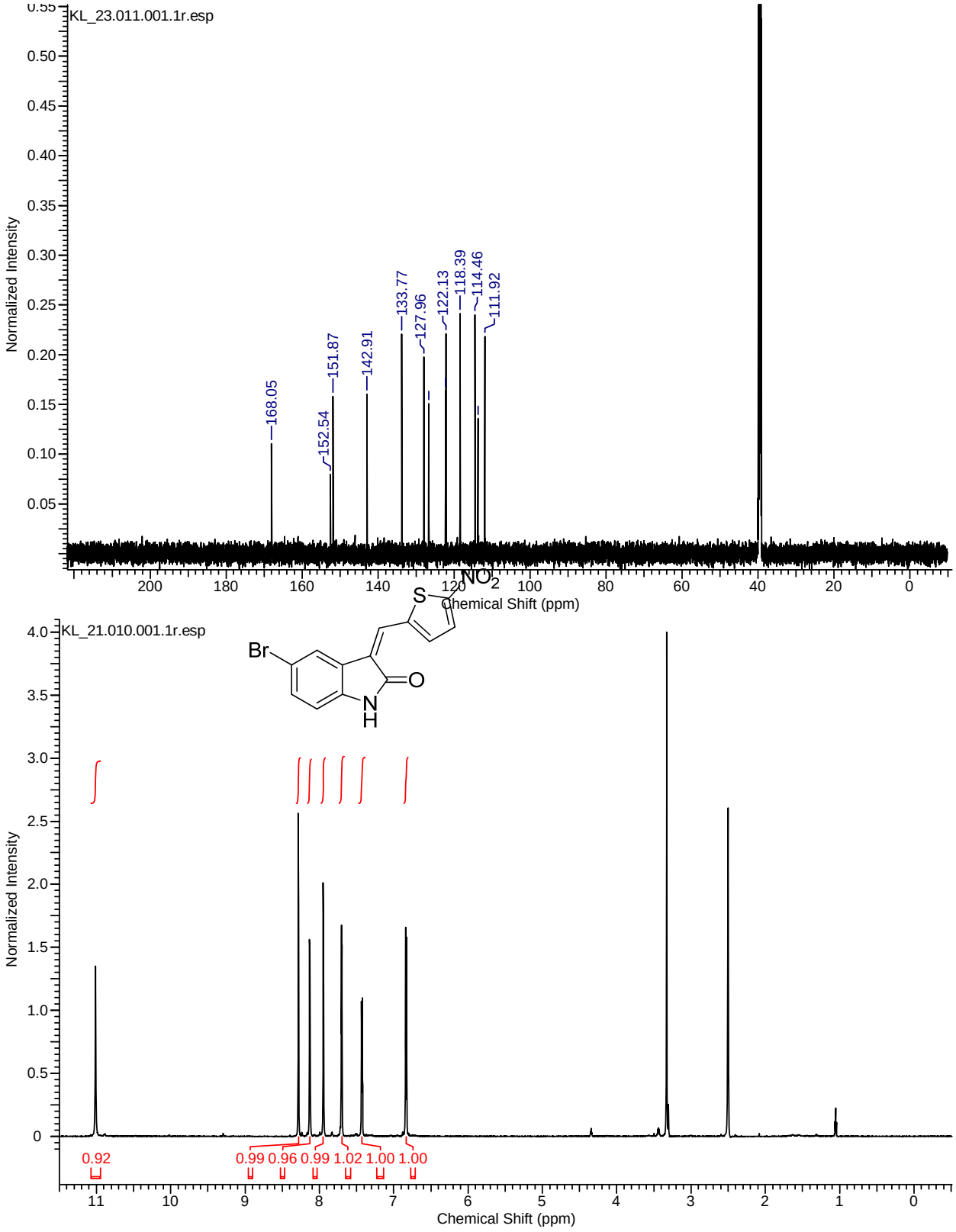

keramm-20151002-LL04.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.17
167.28
142.64
140.45
137.47
136.02
131.93
129.84
128.63
127.13
123.42
121.20
120.94
119.41
110.04
109.43

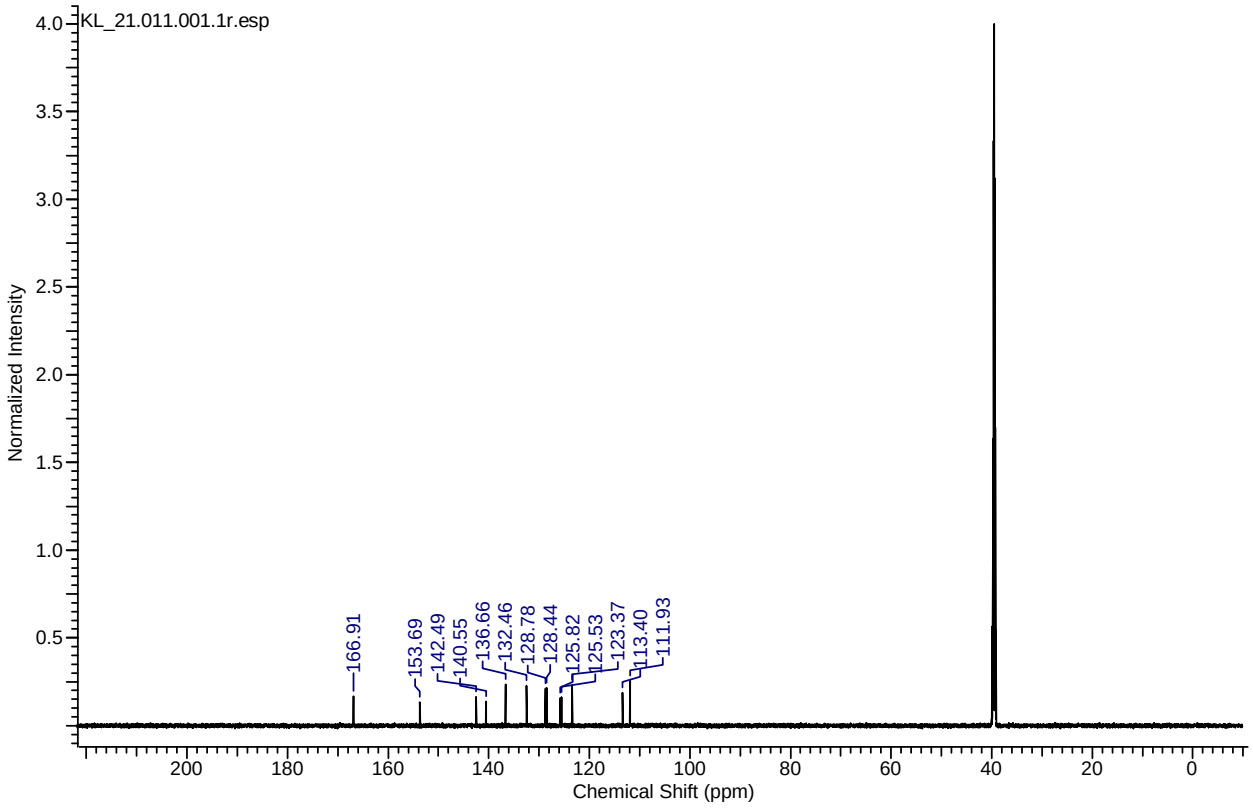

KL_32.020.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
NO2
O
Cl
O
N
H
1.10
1.00 1.11 1.08 1.03 1.07 1.07

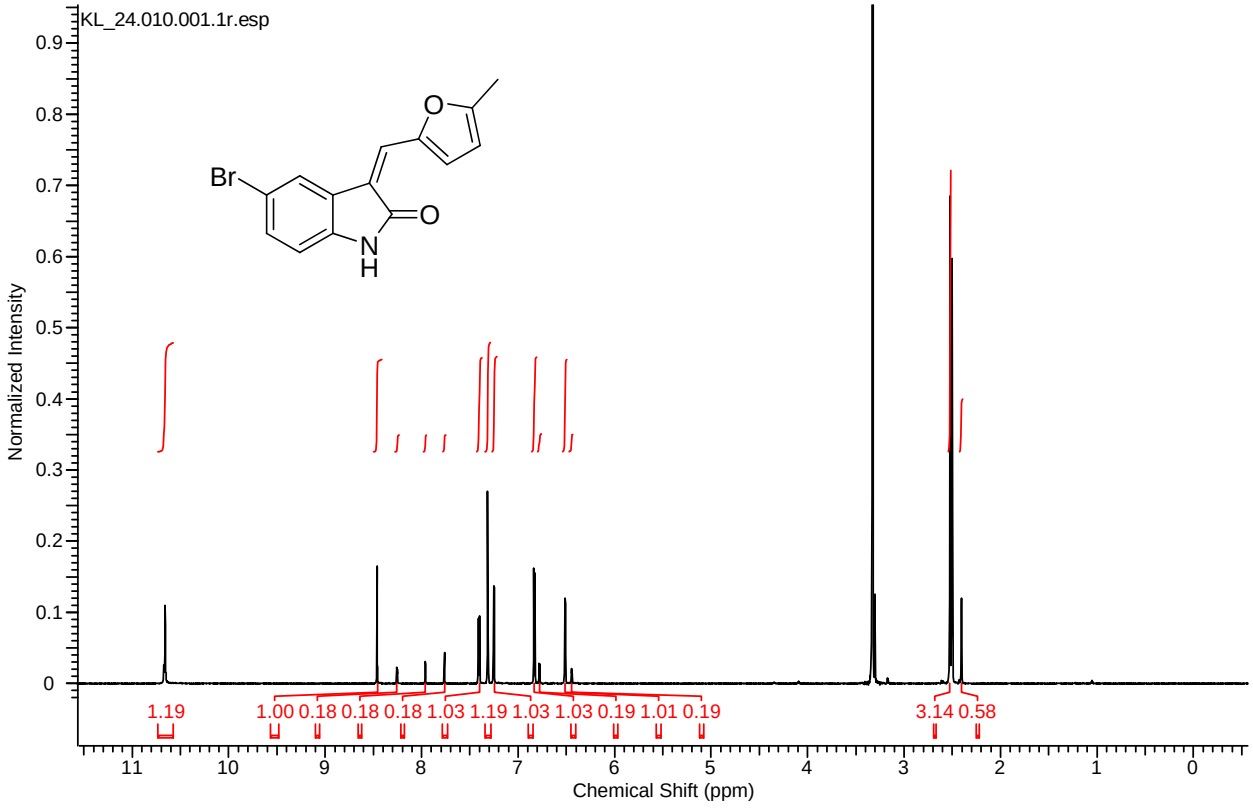

KL_32.022.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.14
152.51
151.89
142.54
130.91
125.23
122.07
118.32
114.46
111.37

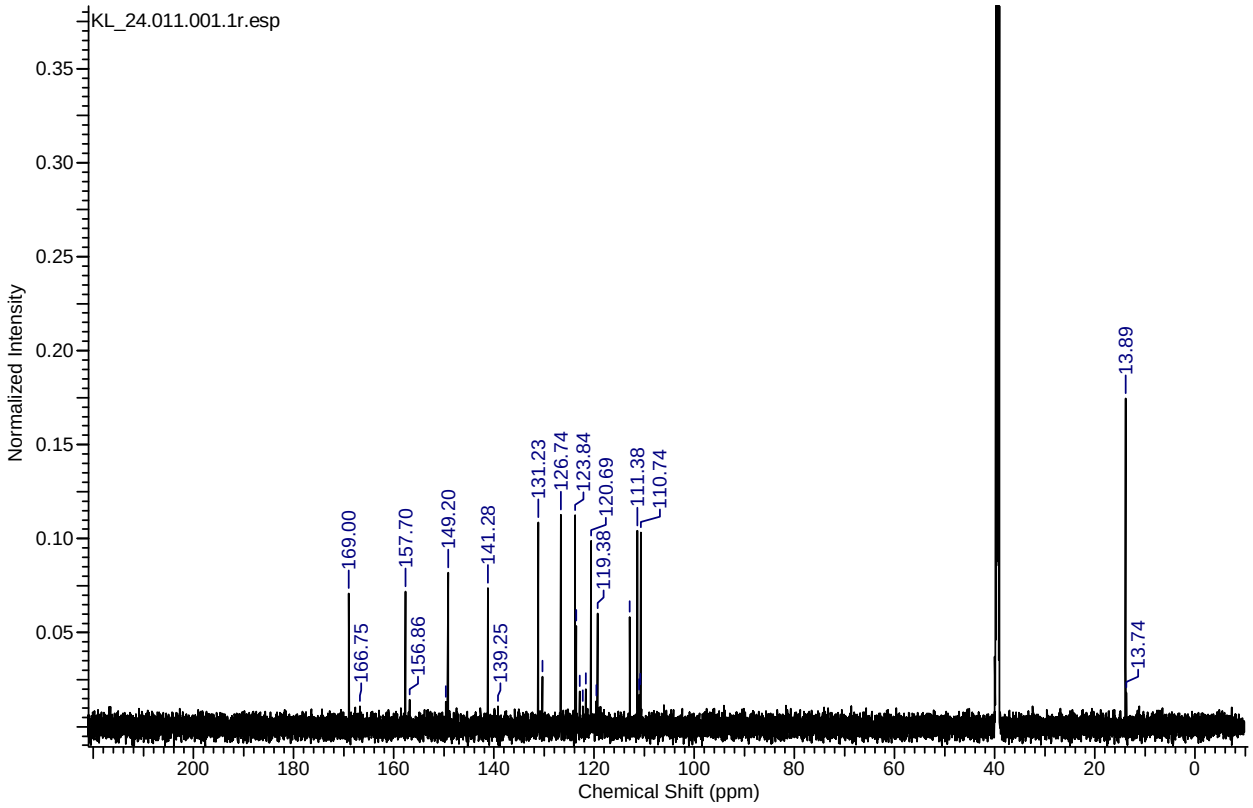

leckettk-20151008-LL08.010.001.1r.esp
Cl
O
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.06
2.03 1.00 1.04 1.01 1.03 1.06

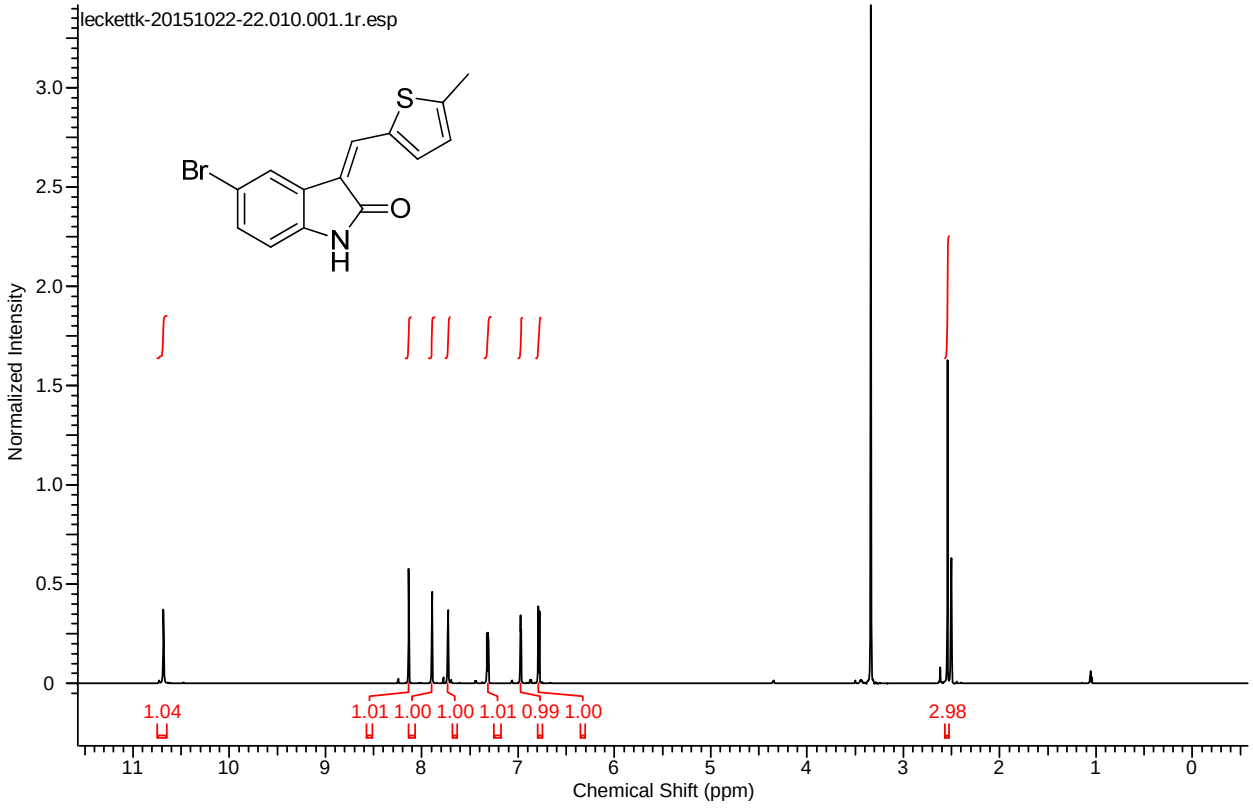

leckettk-20151008-LL08.011.001.1r.esp
Normalized Intensity
169.00
150.48
147.99
141.26
129.08
123.80
122.14
120.73
113.78
111.04
Chemical Shift (ppm)
KL_23.010.001.1r.esp
Br
O
N
H
O
NO2
1.02
1.00
1.06
2.16
1.05
1.07
Normalized Intensity
Chemical Shift (ppm)

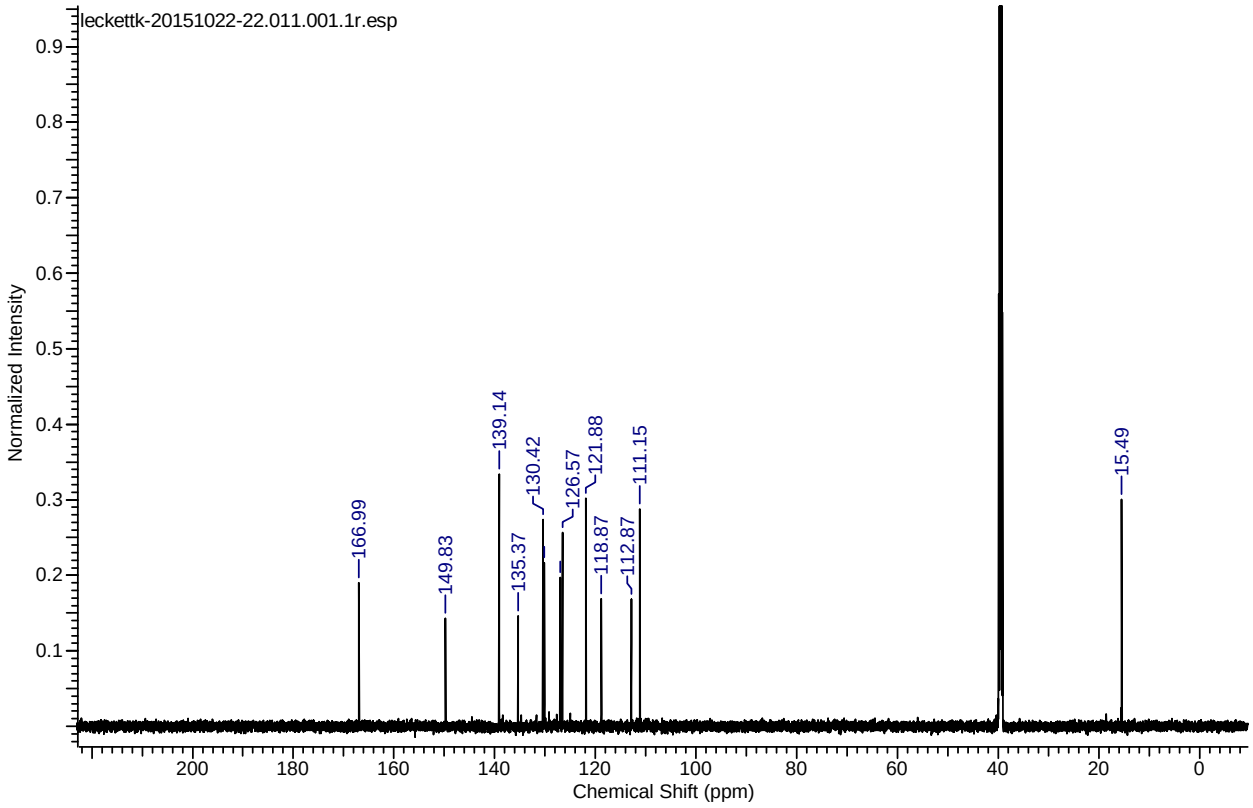

KL_23.011.001.1r.esp
Normalized Intensity
168.05
152.54
151.87
142.91
133.77
127.96
122.13
118.39
114.46
111.92
Chemical Shift (ppm)
KL_21.010.001.1r.esp
Br
S
O
N
H
NO2
0.92
0.99 0.96 0.99 1.02 1.00 1.00
Normalized Intensity
Chemical Shift (ppm)

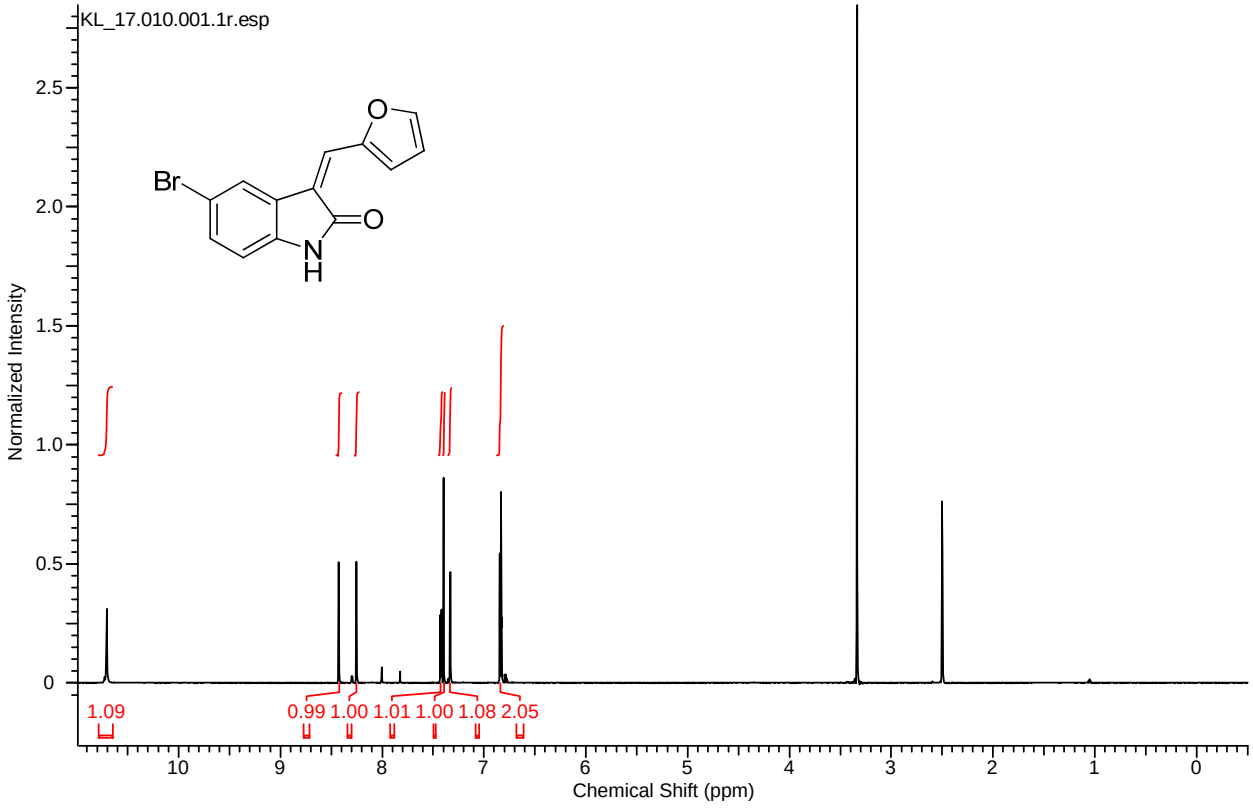

KL_21.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
166.91
153.69
142.49
140.55
136.66
132.46
128.78
128.44
125.82
125.53
123.37
113.40
111.93

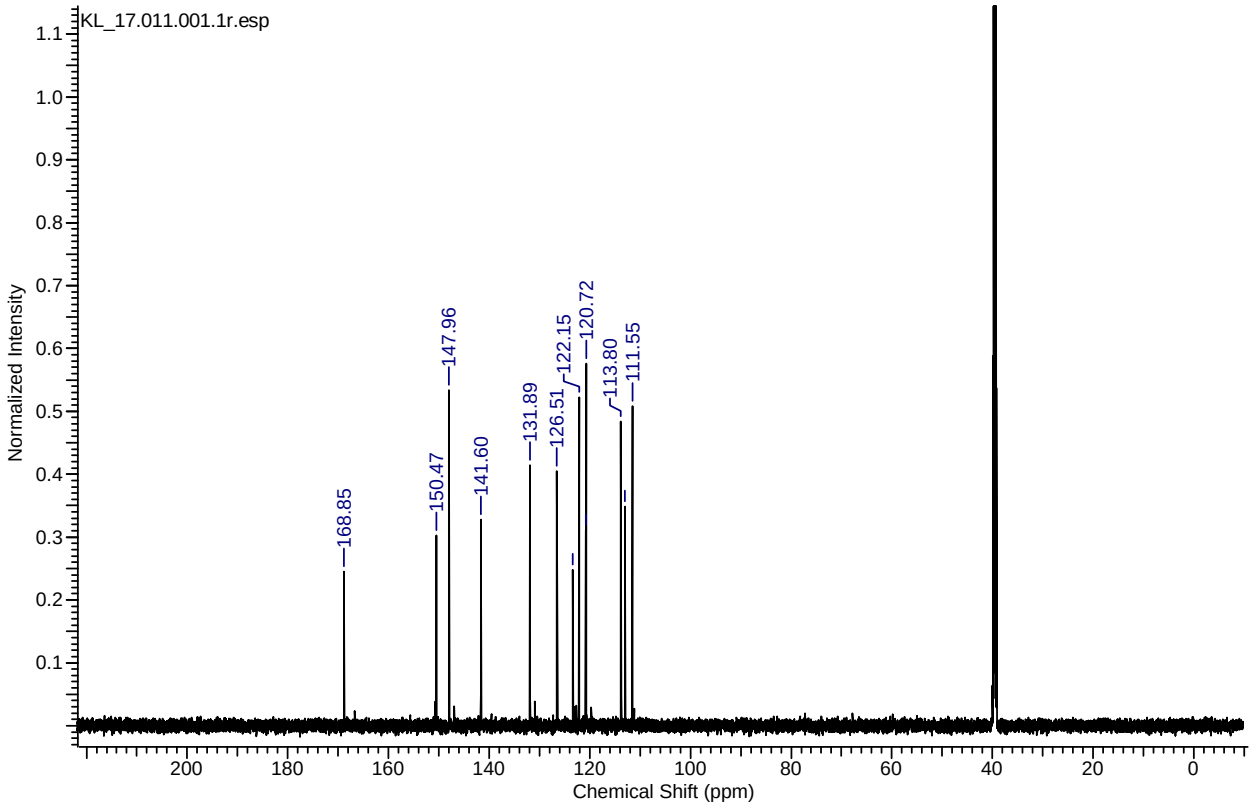

KL_24.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
O
O
N
H
1.19
1.00 0.18 0.18 0.18 1.03 1.19 1.03 1.03 0.19 1.01 0.19
3.14 0.58

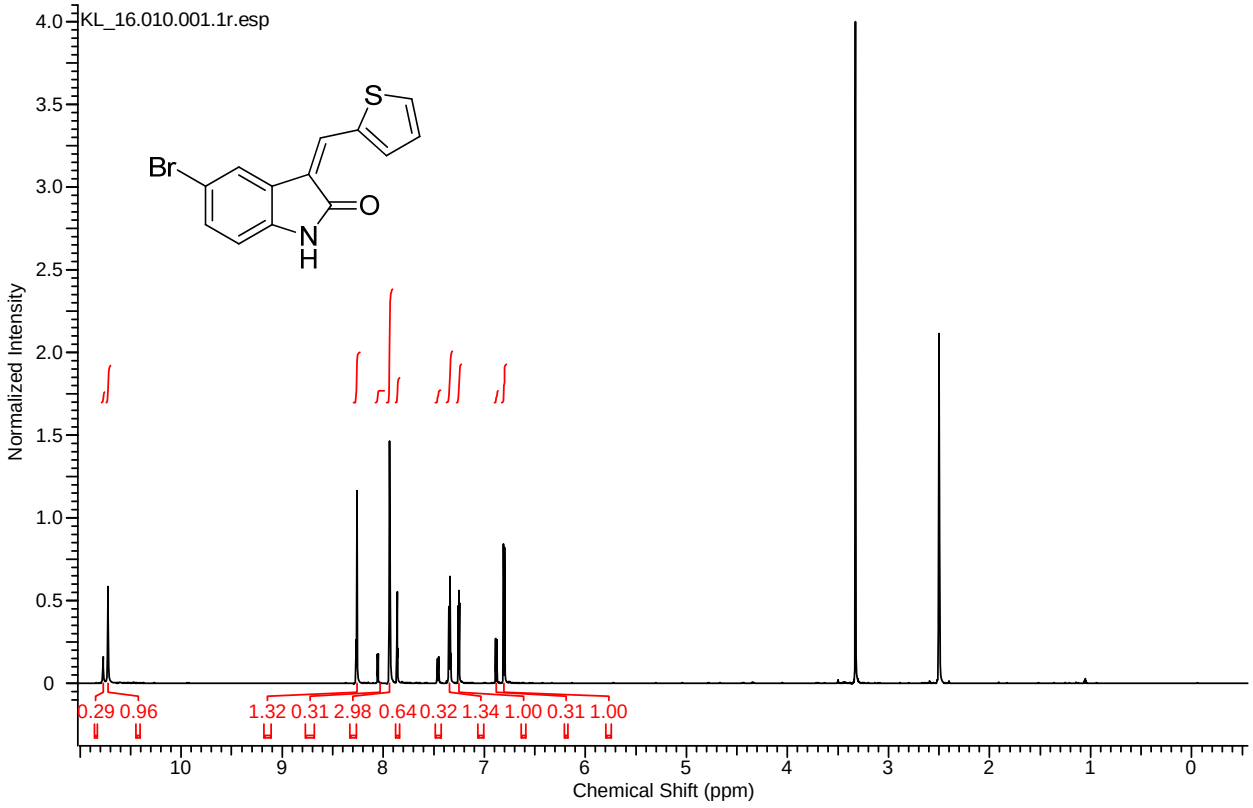

KL_24.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.00
166.75
157.70
156.86
149.20
141.28
139.25
131.23
126.74
123.84
120.69
119.38
111.38
110.74
13.89
13.74

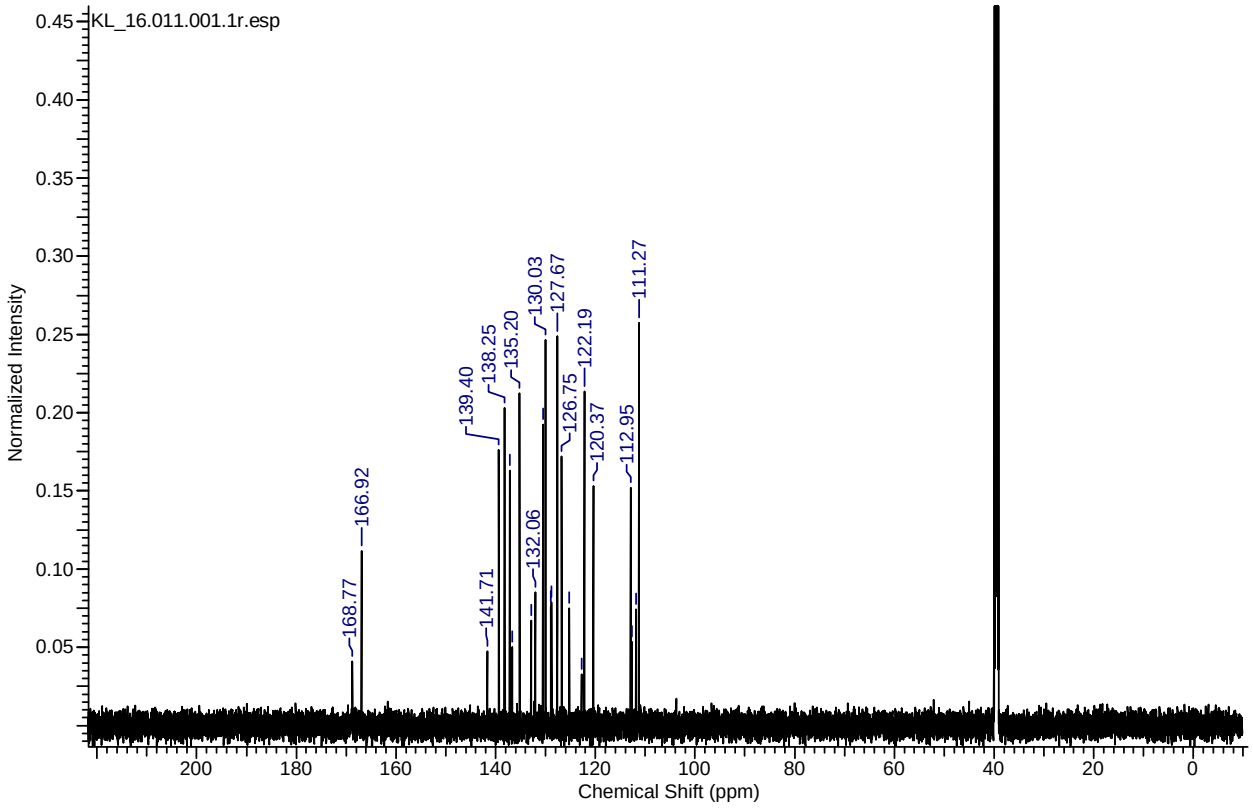

leckettk-20151022-22.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
S
O
N
H
1.04
1.01
1.00
1.00
1.01
0.99
1.00
2.98

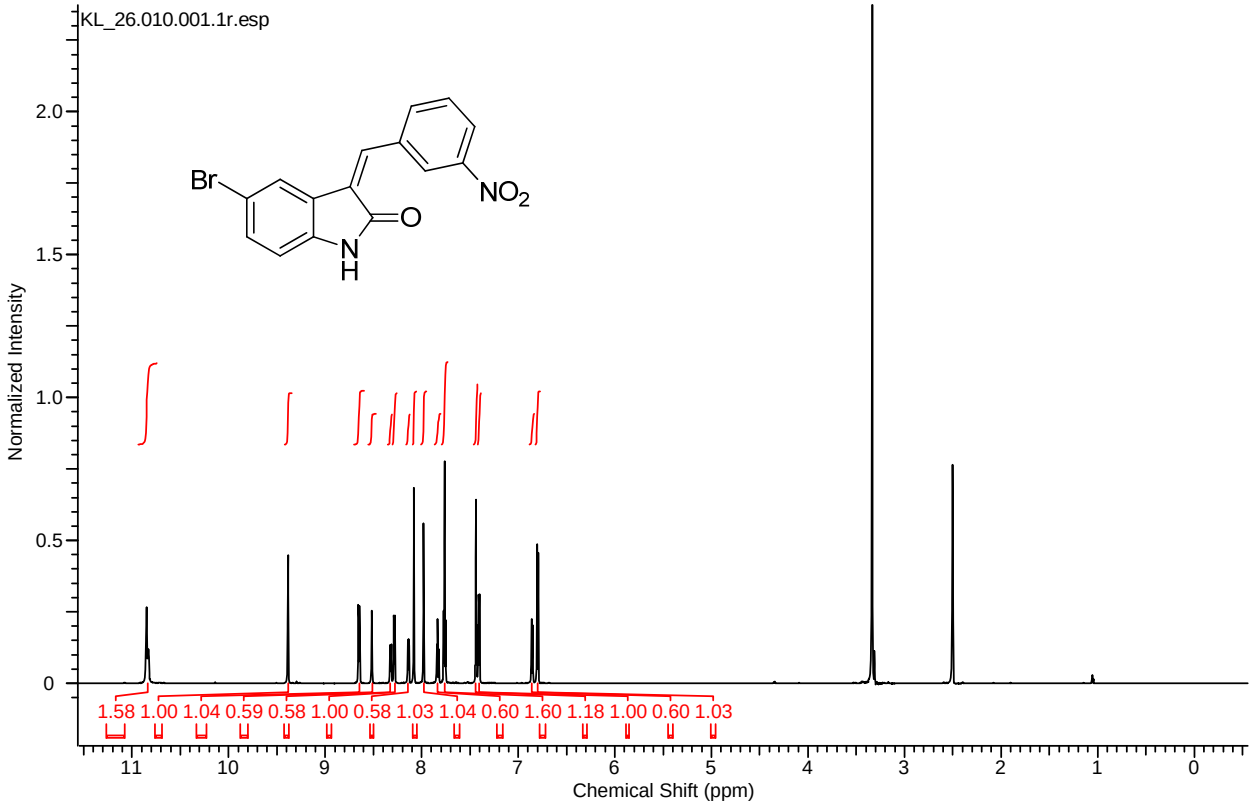

leckettk-20151022-22.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
166.99
149.83
139.14
135.37
130.42
126.57
121.88
118.87
112.87
111.15
15.49

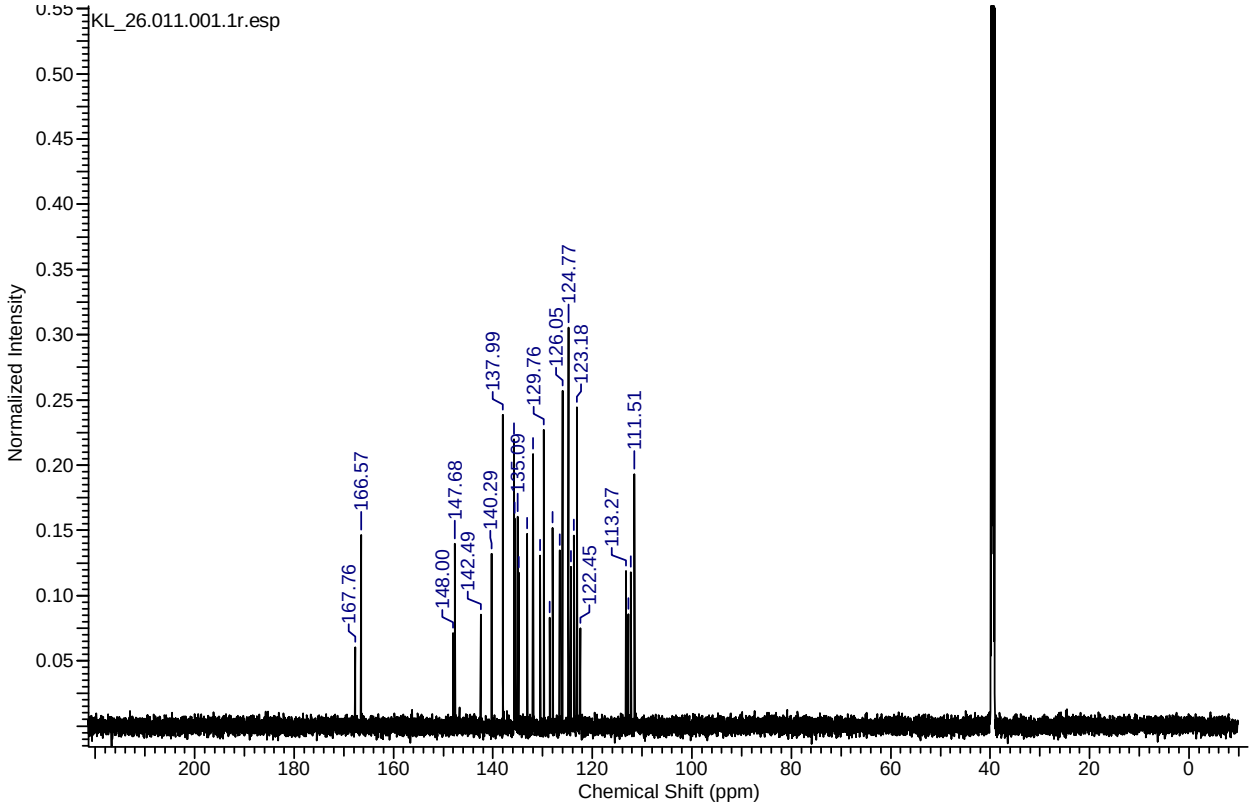

KL_17.010.001.1r.esp
Br
O
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.09
0.99
1.00
1.01
1.00
1.08
2.05

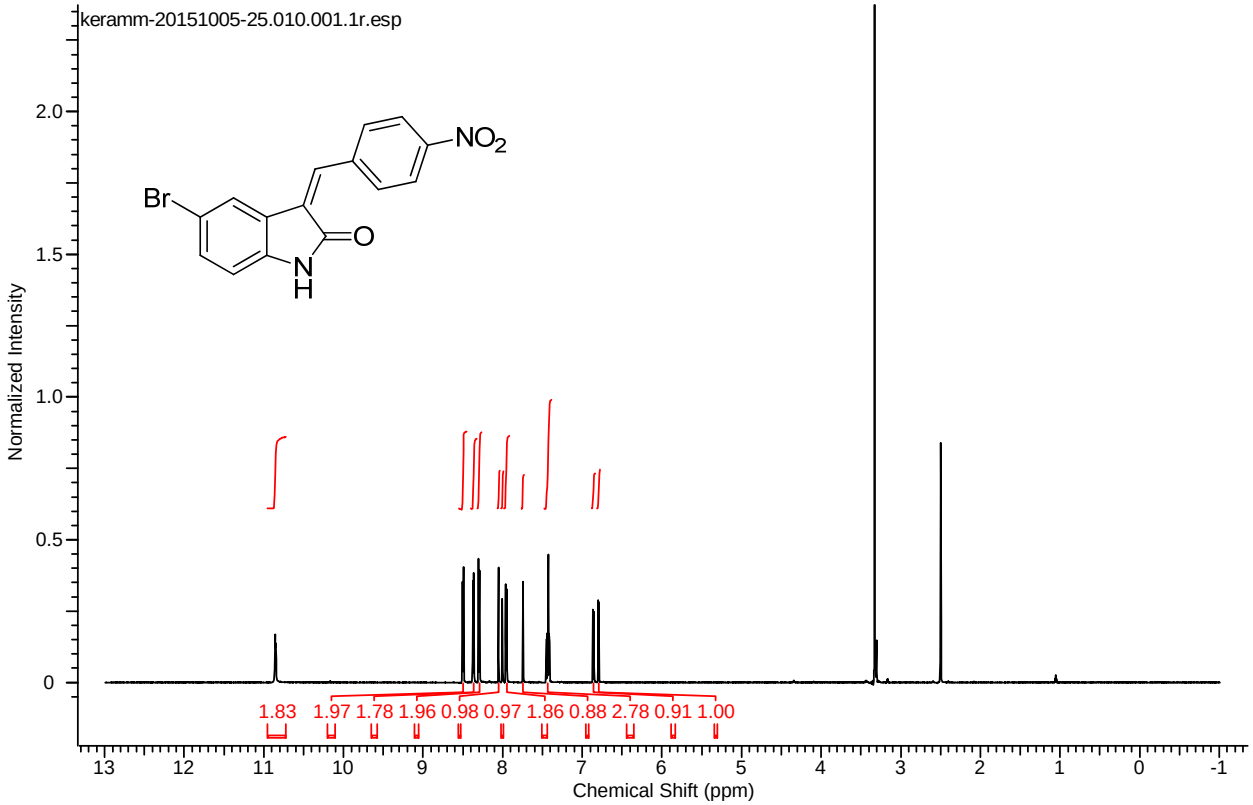

KL_17.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.85
150.47
147.96
141.60
131.89
126.51
122.15
120.72
113.80
111.55

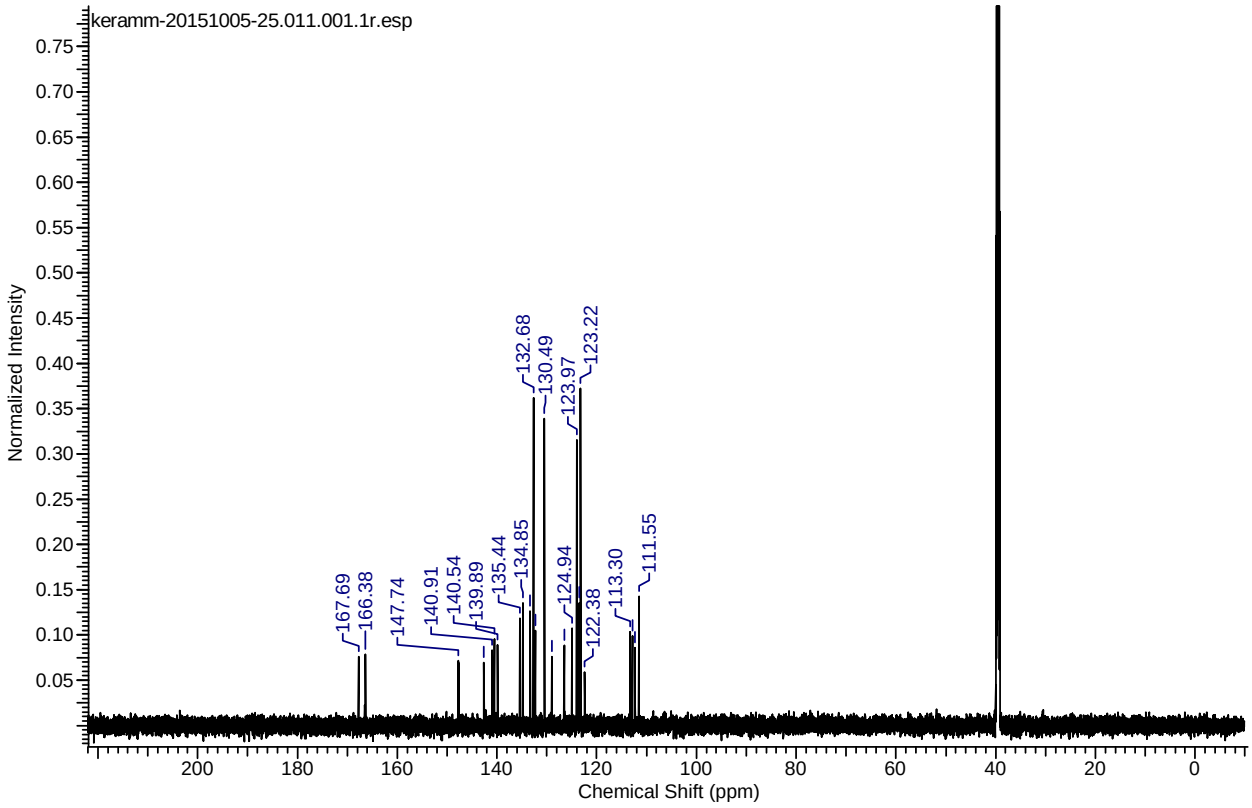

KL_16.010.001.1r.esp
Br
S
O
N
H
Normalized Intensity
Chemical Shift (ppm)
0.29 0.96
1.32 0.31 2.98 0.64 0.32 1.34 1.00 0.31 1.00

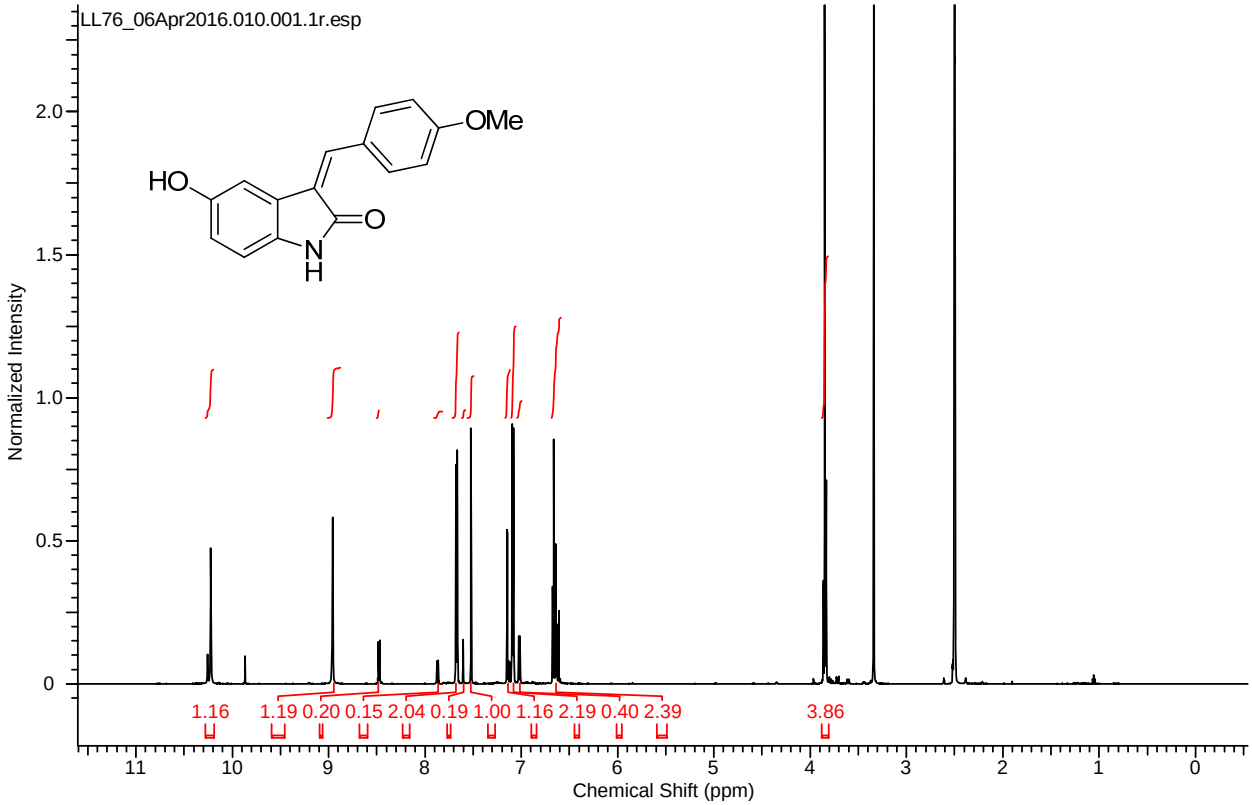

KL_16.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.77
166.92
141.71
139.40
138.25
135.20
132.06
130.03
127.67
126.75
122.19
120.37
112.95
111.27

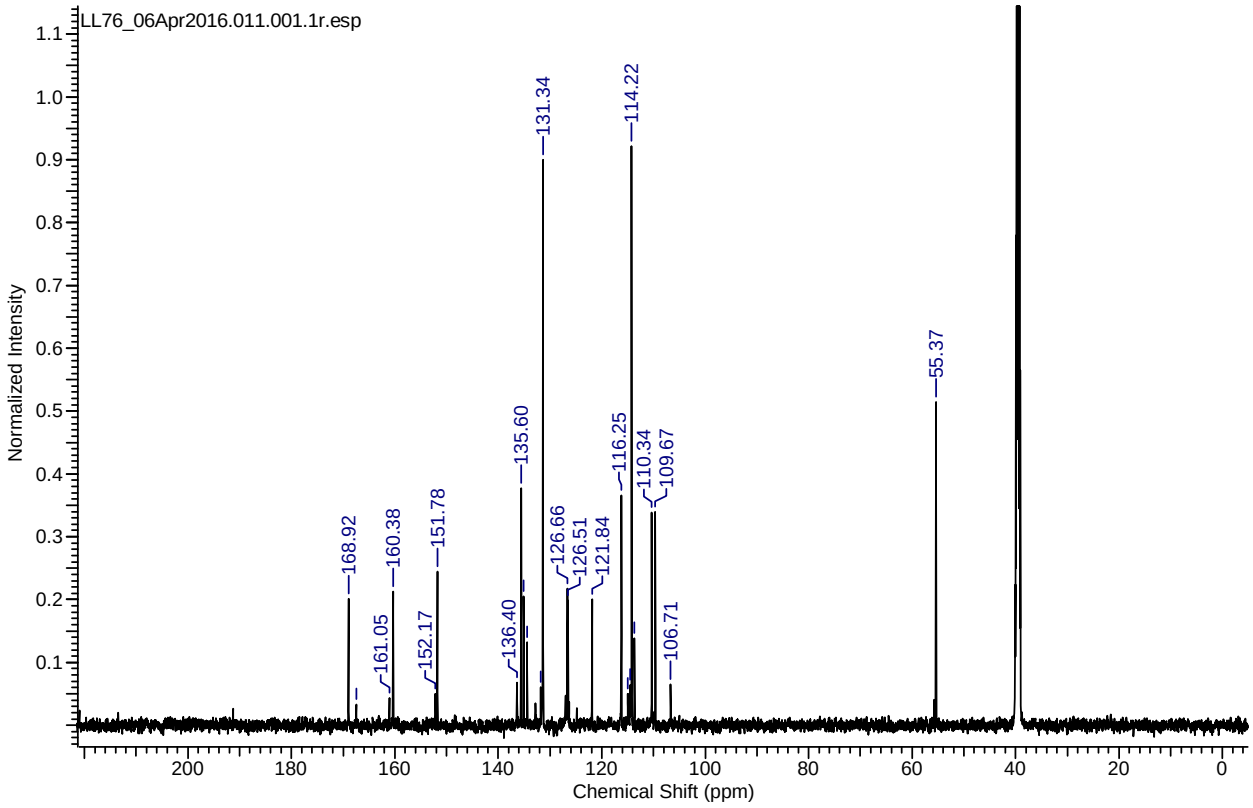

KL_26.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
NO2
O
N
H
1.58 1.00 1.04 0.59 0.58 1.00 0.58 1.03 1.04 0.60 1.60 1.18 1.00 0.60 1.03

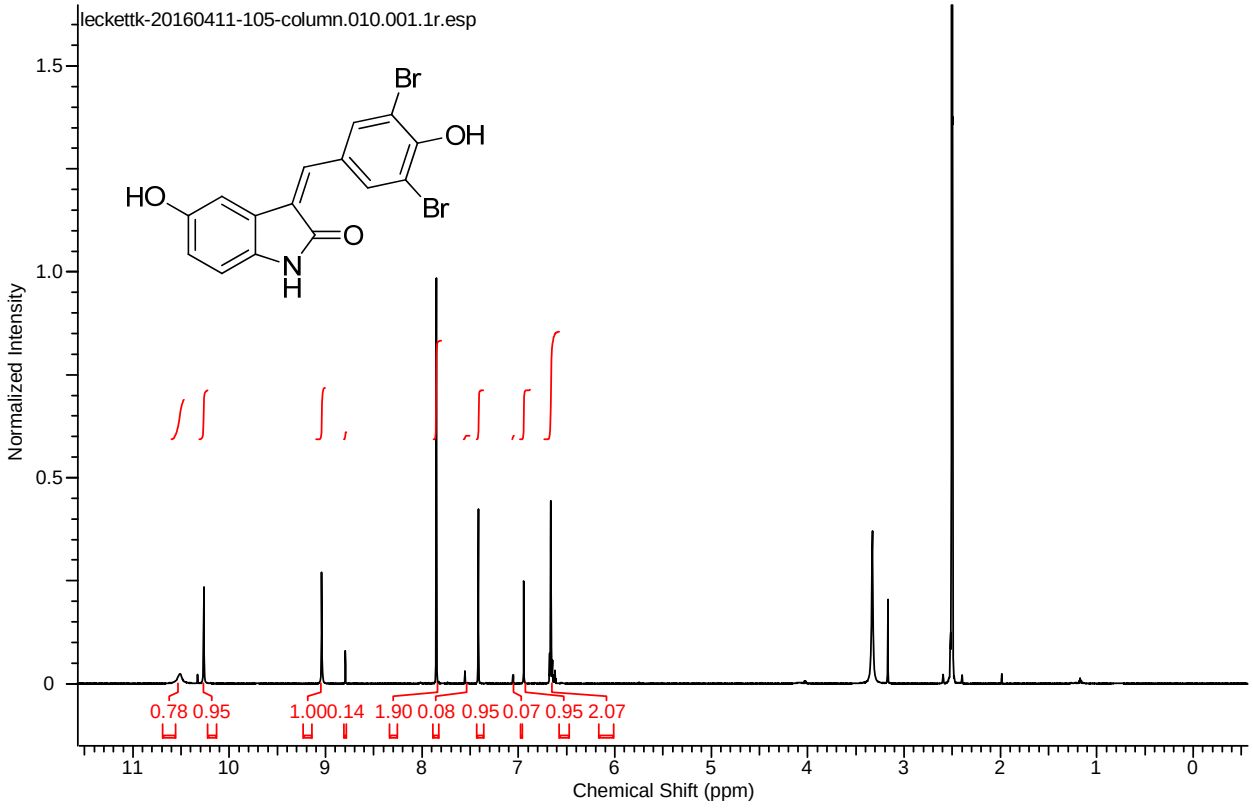

KL_26.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
167.76
166.57
148.00
147.68
142.49
140.29
137.99
135.09
129.76
126.05
124.77
123.18
122.45
113.27
111.51

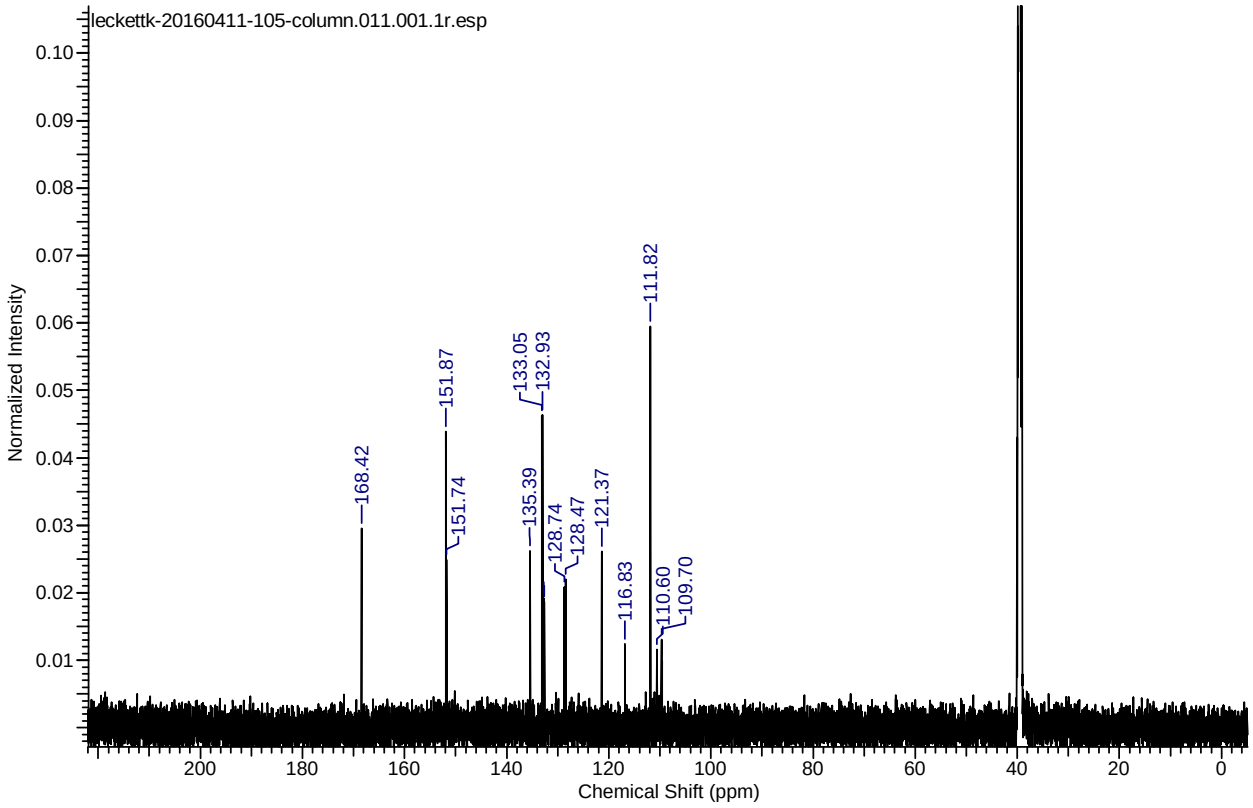

keramm-20151005-25.010.001.1r.esp
Br
NO2
O
N
H
Normalized Intensity
Chemical Shift (ppm)
1.83 1.97 1.78 1.96 0.98 0.97 1.86 0.88 2.78 0.91 1.00

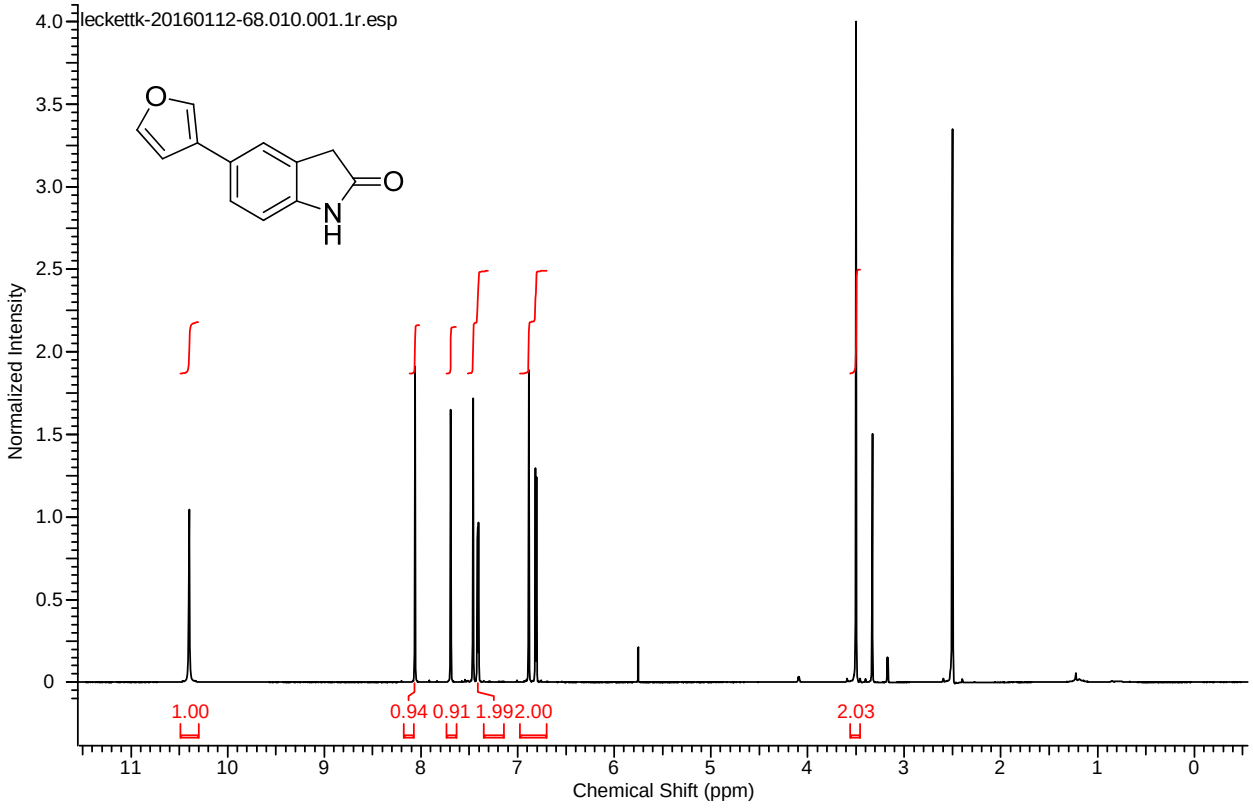

keramm-20151005-25.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
167.69
166.38
147.74
140.91
140.54
139.89
135.44
134.85
132.68
130.49
123.97
123.22
124.94
122.38
113.30
111.55

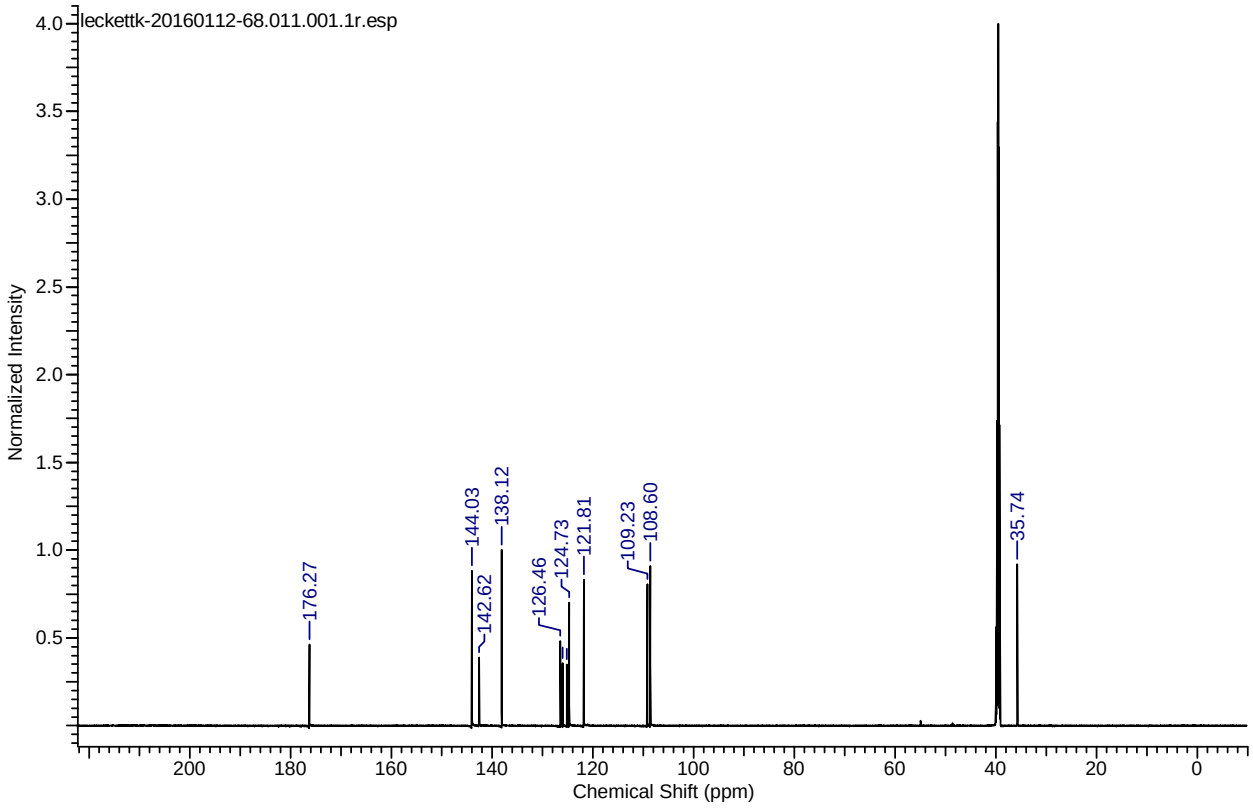

LL76_06Apr2016.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OMe
HO
O
N
H
1.16
1.19
0.20
0.15
2.04
0.19
1.00
1.16
2.19
0.40
2.39
3.86

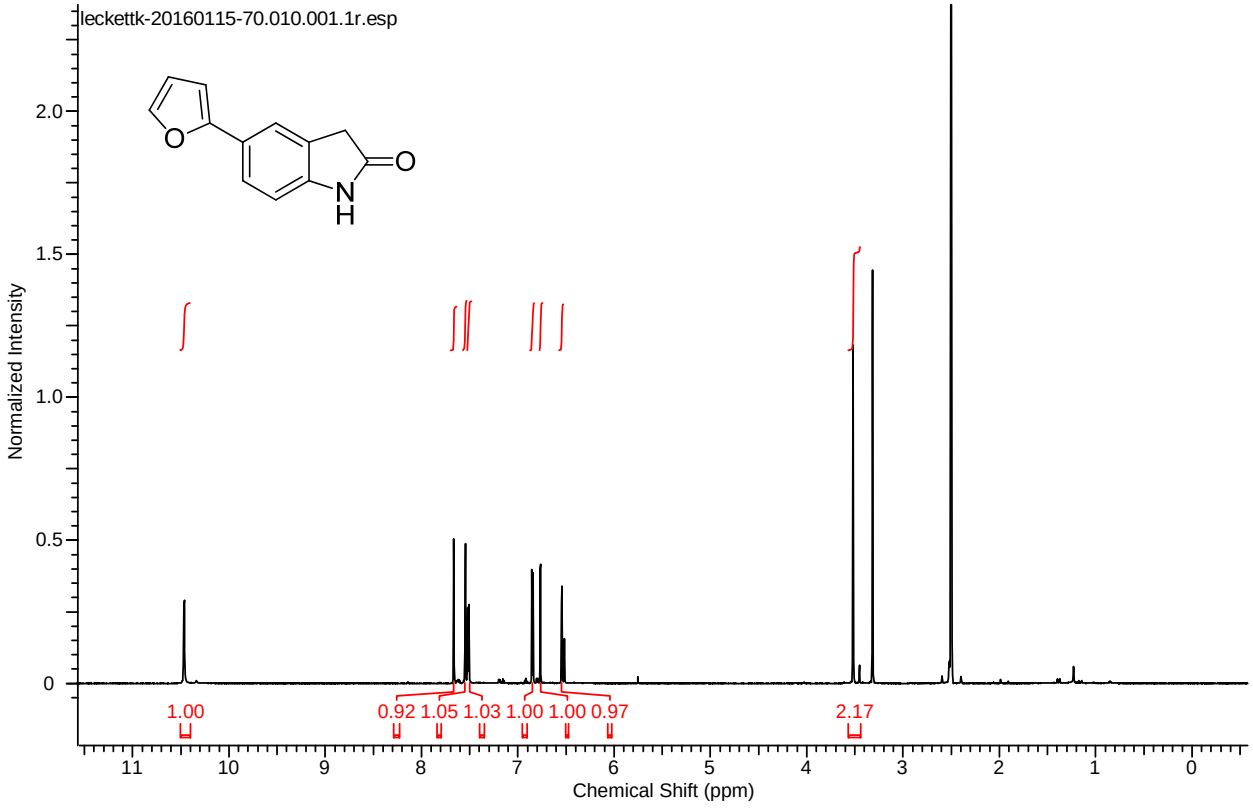

LL76_06Apr2016.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.92
160.38
151.78
161.05
152.17
136.40
135.60
131.34
126.66
126.51
121.84
114.22
116.25
110.34
109.67
106.71
55.37

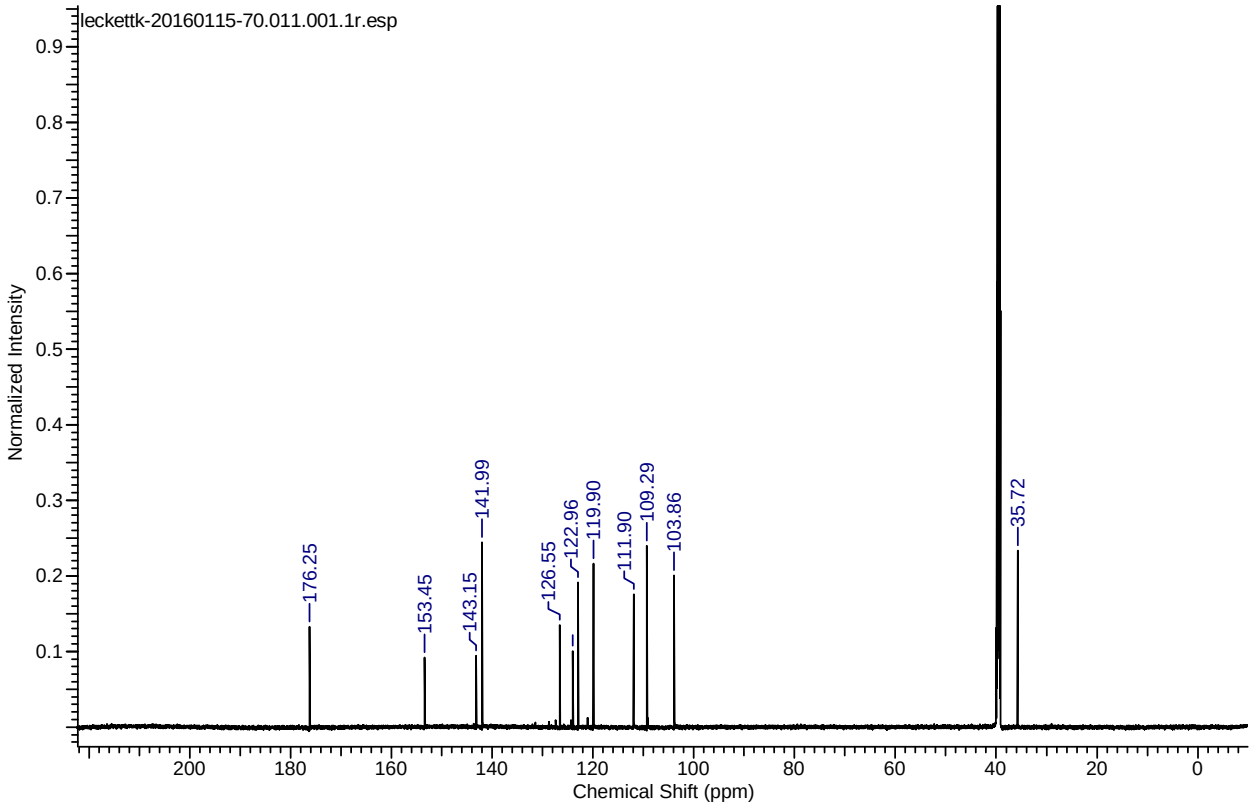

leckettk-20160411-105-column.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
Br
OH
HO
Br
O
N
H
0.78 0.95
1.00 0.14
1.90 0.08 0.95 0.07 0.95 2.07

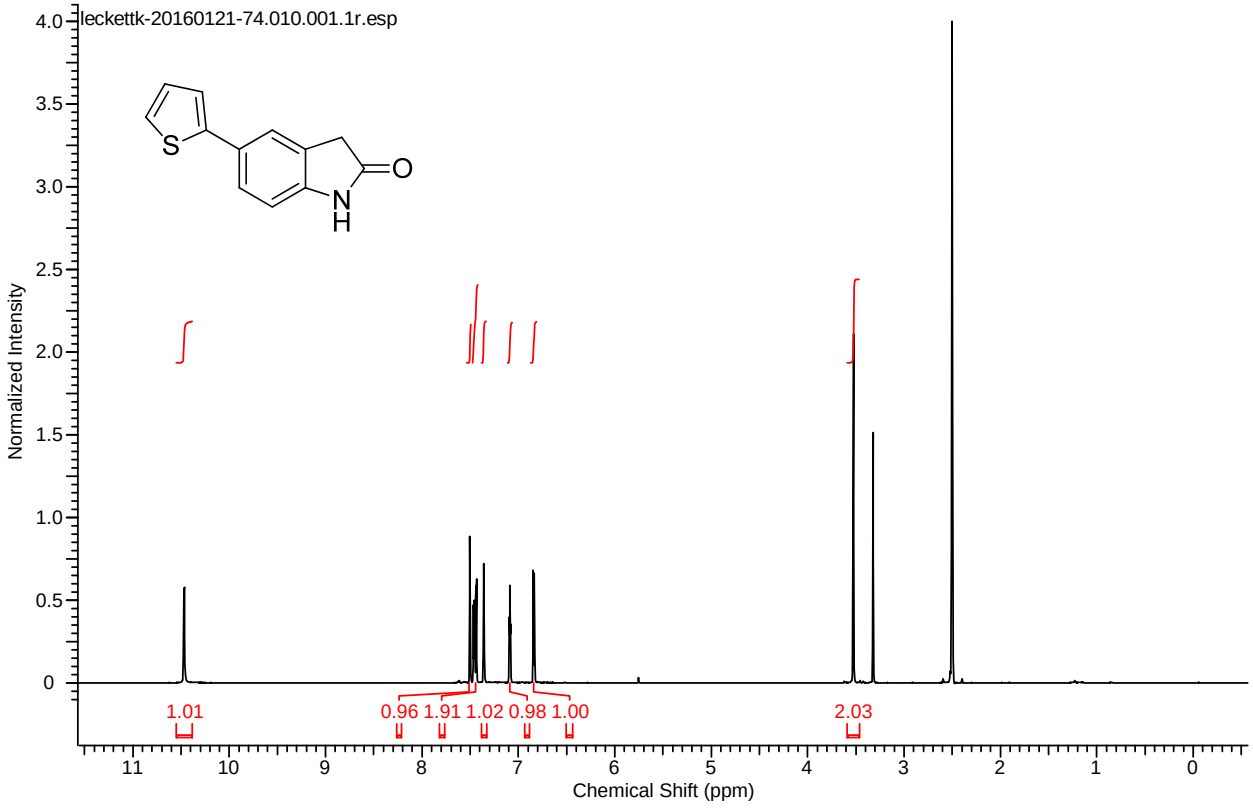

leckettk-20160411-105-column.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.42
151.87
151.74
133.05
132.93
135.39
128.74
128.47
121.37
116.83
111.82
110.60
109.70

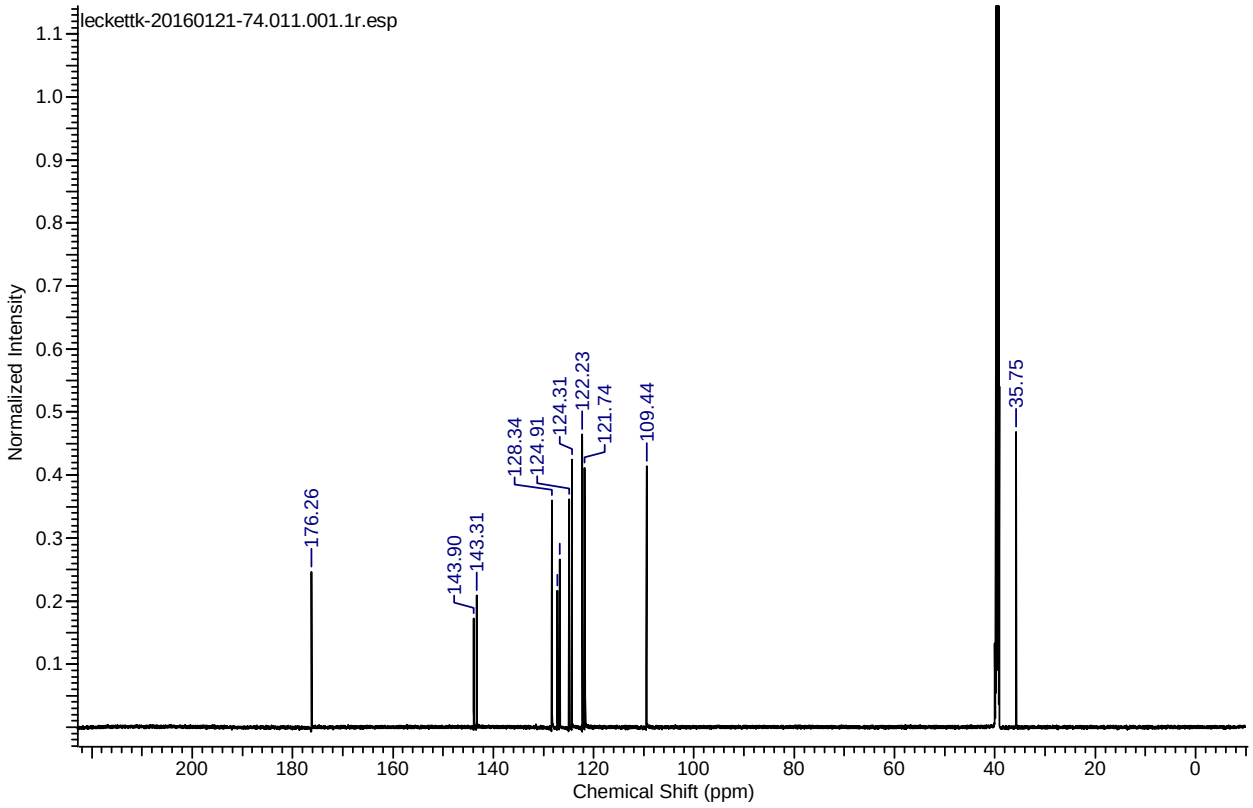

leckettk-20160112-68.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
N
H
1.00
0.94
0.91
1.99
2.00
2.03

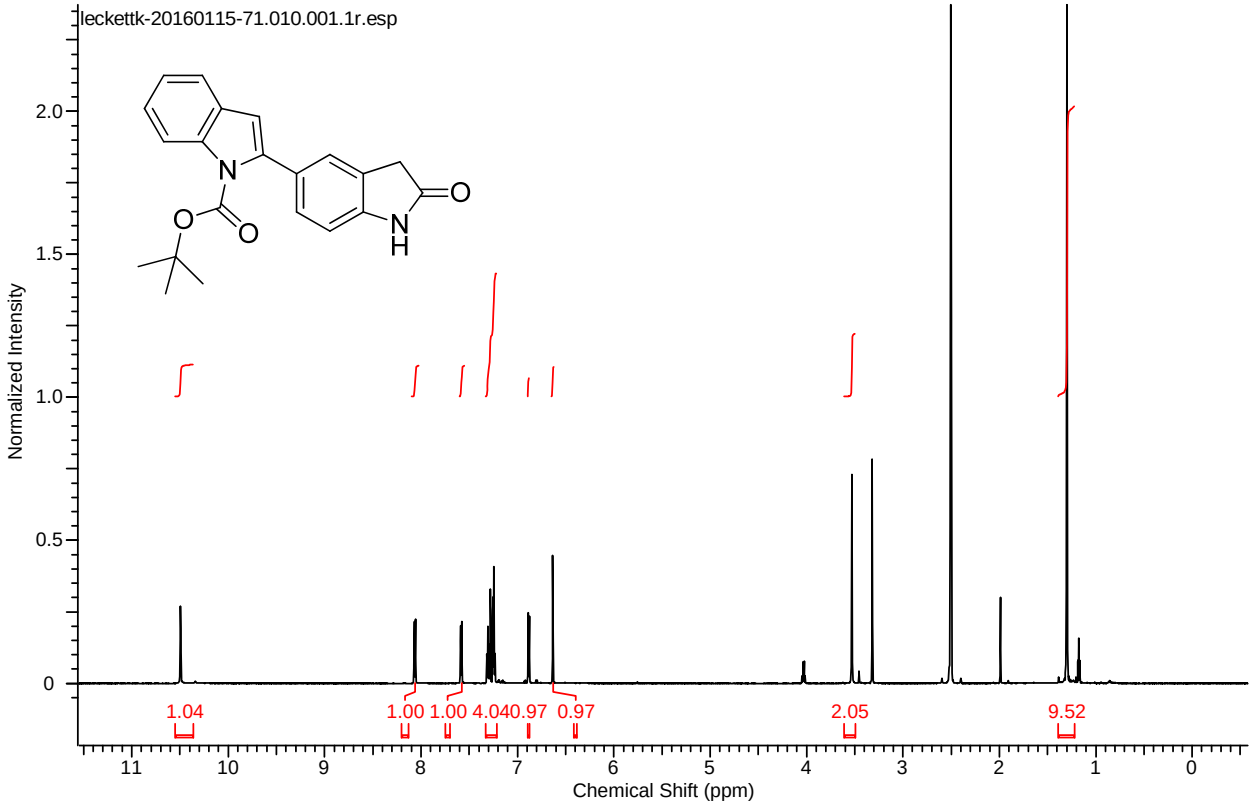

leckettk-20160112-68.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.27
144.03
142.62
138.12
126.46
124.73
121.81
109.23
108.60
35.74

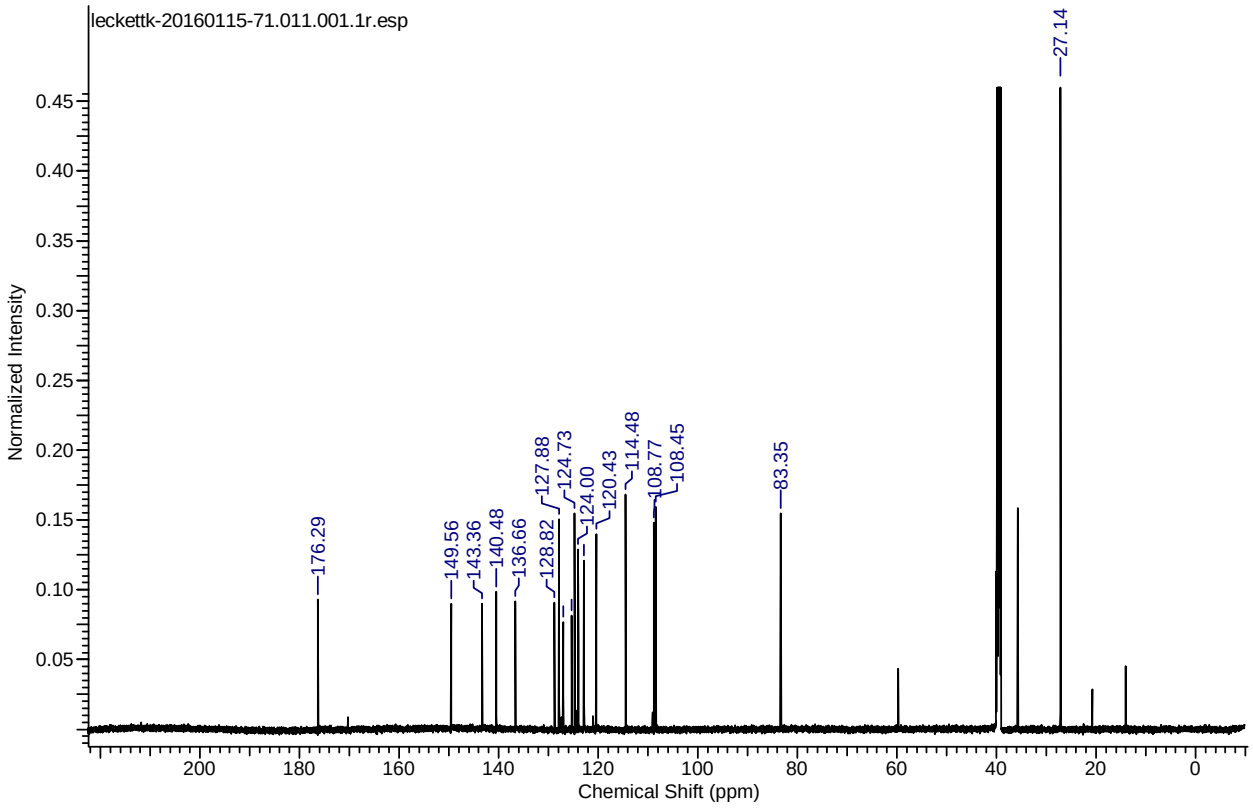

leckettk-20160115-70.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
N
H
1.00
0.92 1.05 1.03 1.00 1.00 0.97
2.17

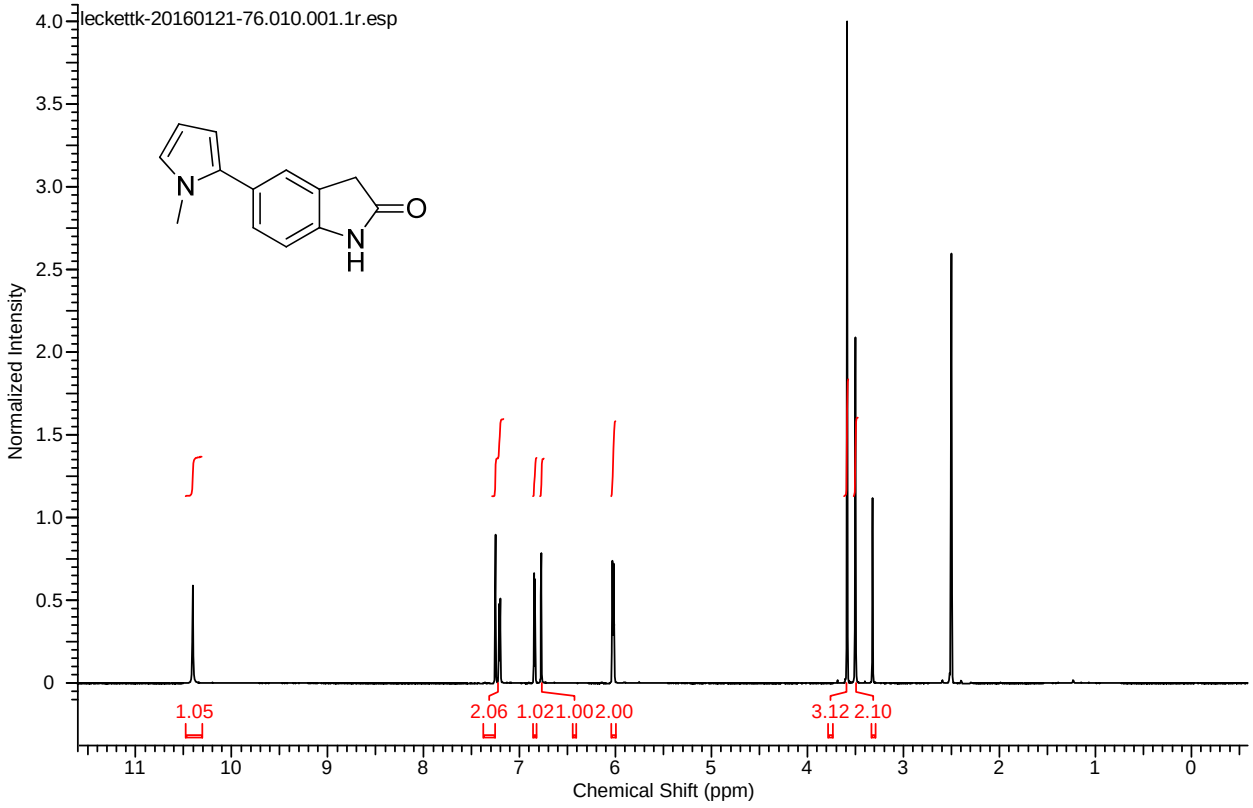

leckettk-20160115-70.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.25
153.45
143.15
141.99
126.55
122.96
119.90
111.90
109.29
103.86
35.72

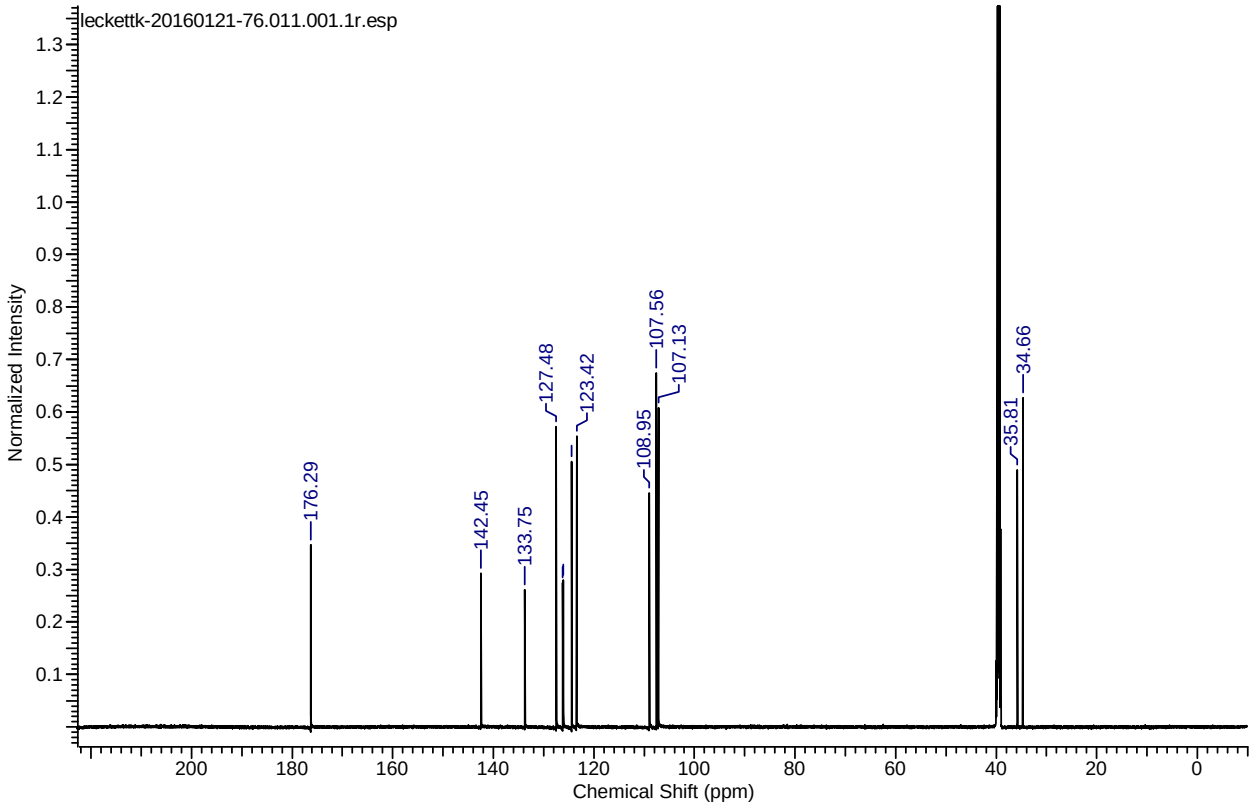

leckettk-20160121-74.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
O
N
H
1.01
0.96 1.91 1.02 0.98 1.00
2.03

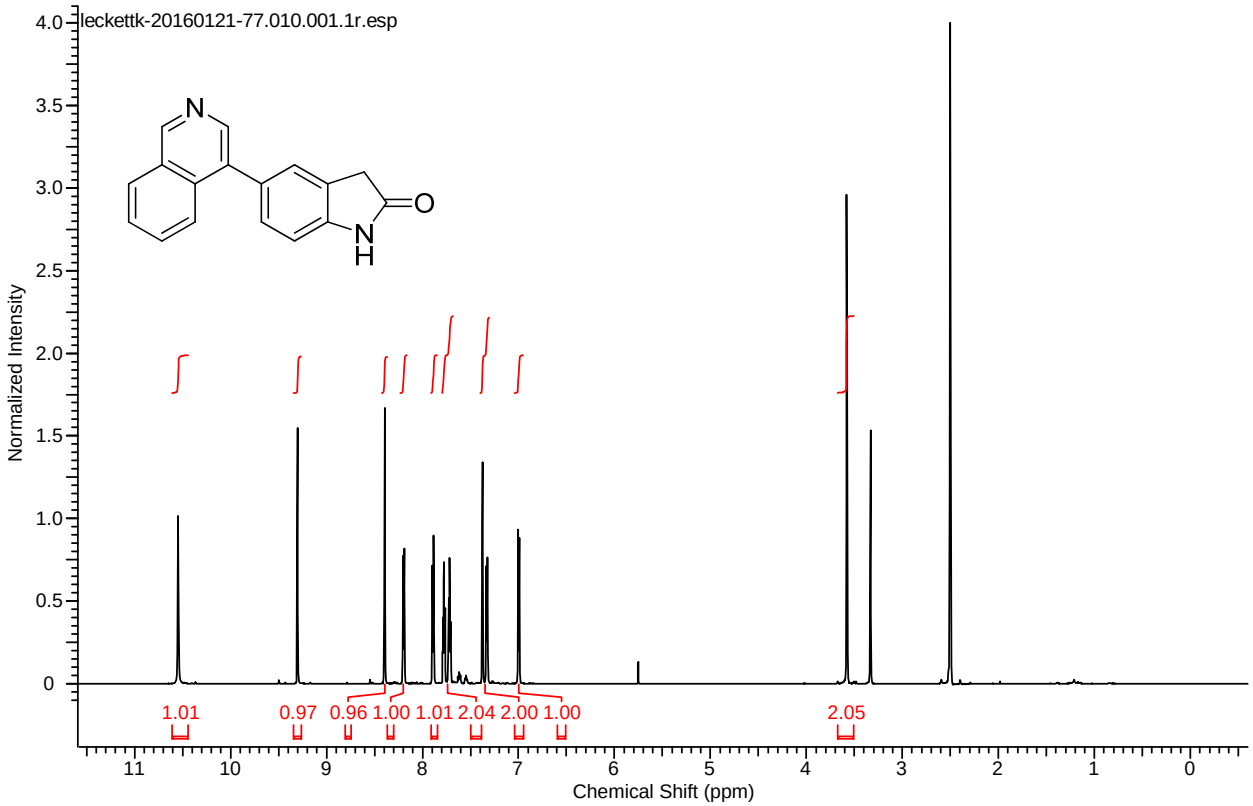

leckettk-20160121-74.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.26
143.90
143.31
128.34
124.91
124.31
122.23
121.74
109.44
35.75

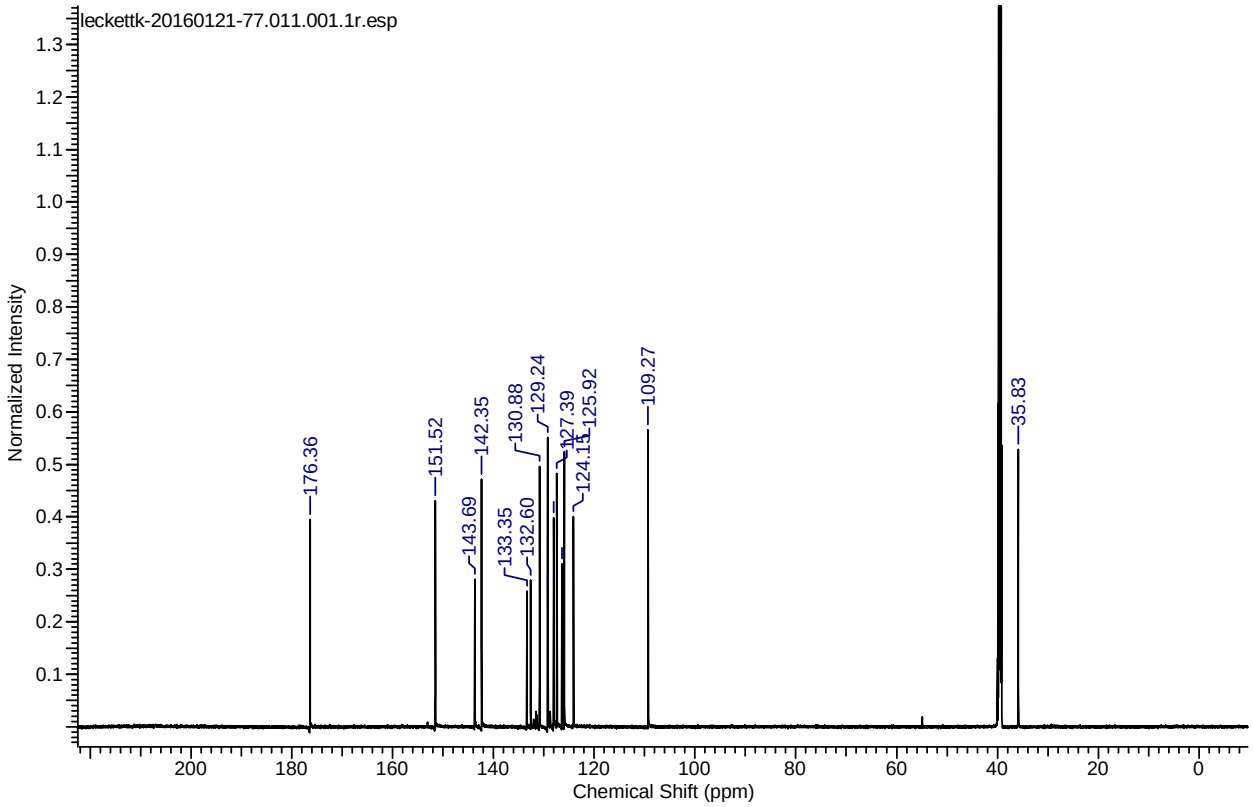

leckettk-20160115-71.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
1.04
1.00
1.00
4.04
0.97
0.97
2.05
9.52

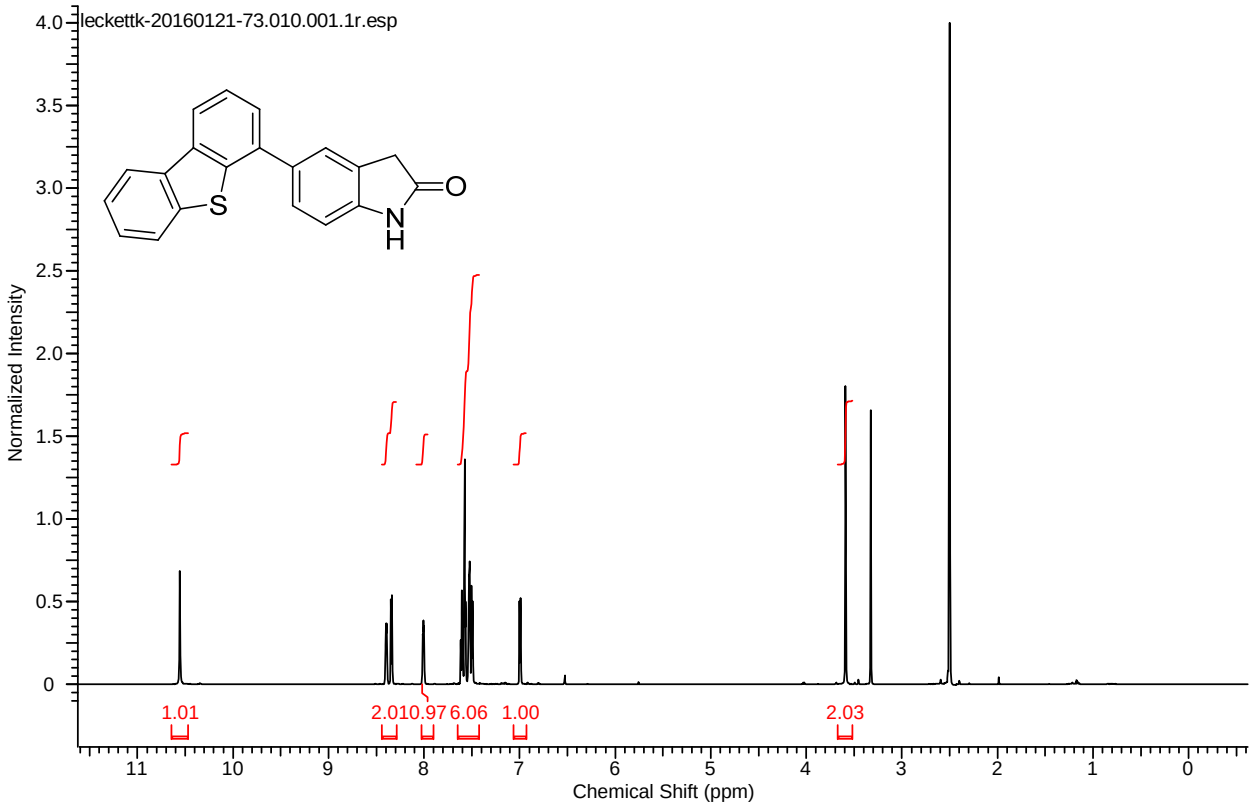

leckettk-20160115-71.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.29
149.56
143.36
140.48
136.66
128.82
127.88
124.73
124.00
120.43
114.48
108.77
108.45
83.35
27.14

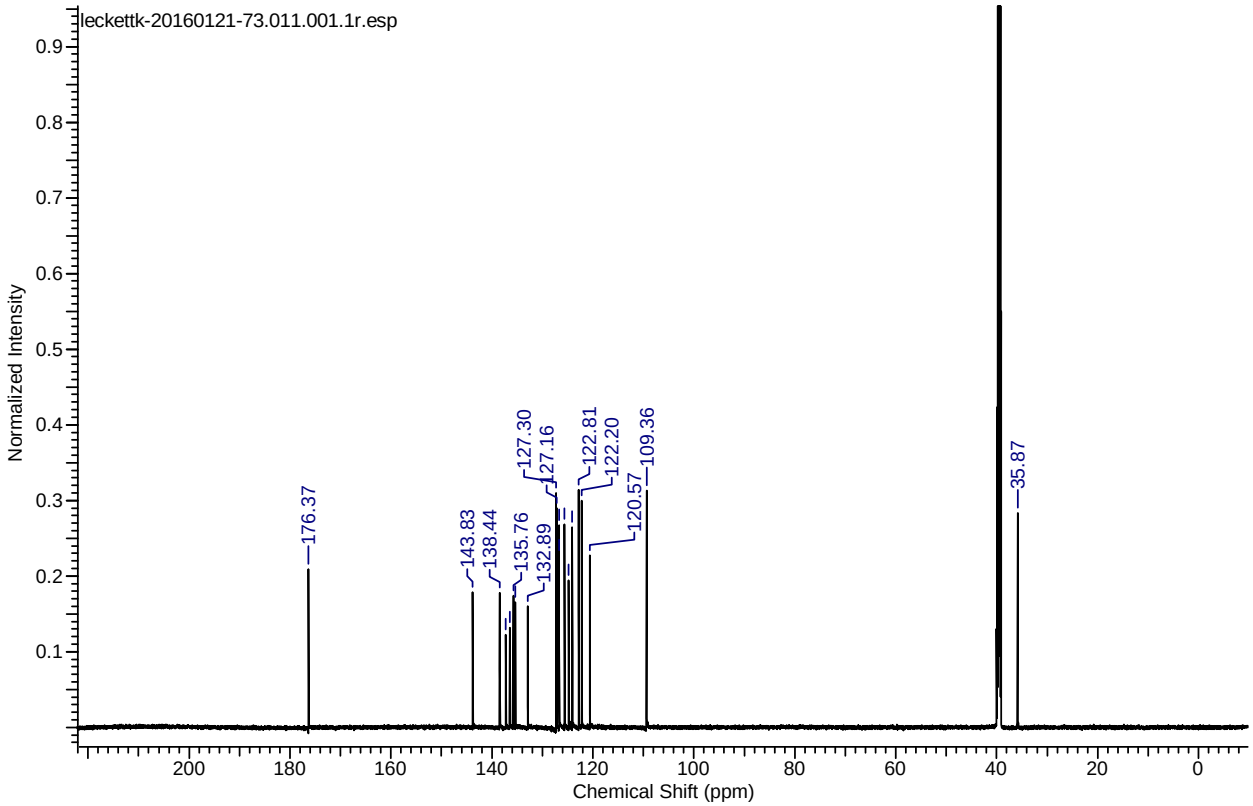

leckettk-20160121-76.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
N
O
N
H
1.05
2.06
1.02
1.00
2.00
3.12
2.10

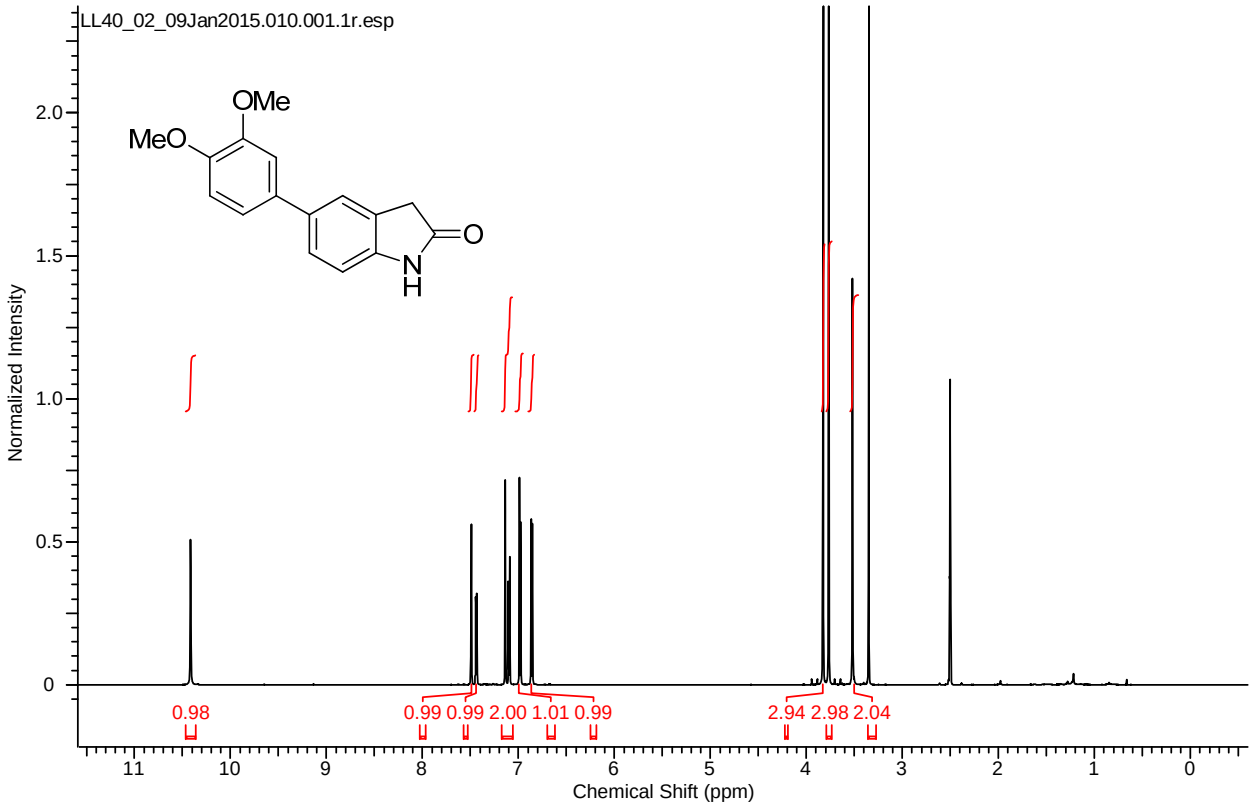

leckettk-20160121-76.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.29
142.45
133.75
127.48
123.42
108.95
107.56
107.13
35.81
34.66

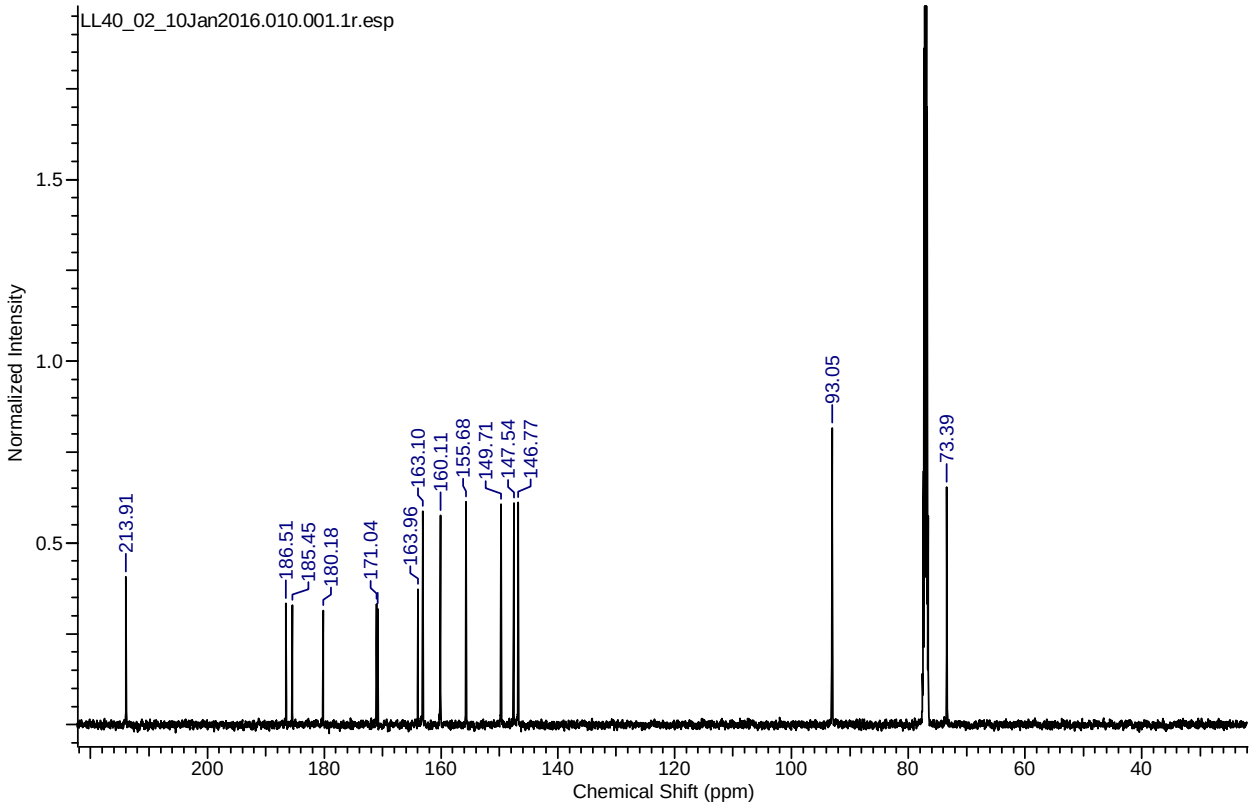

leckettk-20160121-77.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
N
O
N
H
1.01
0.97
0.96
1.00
1.01
2.04
2.00
1.00
2.05

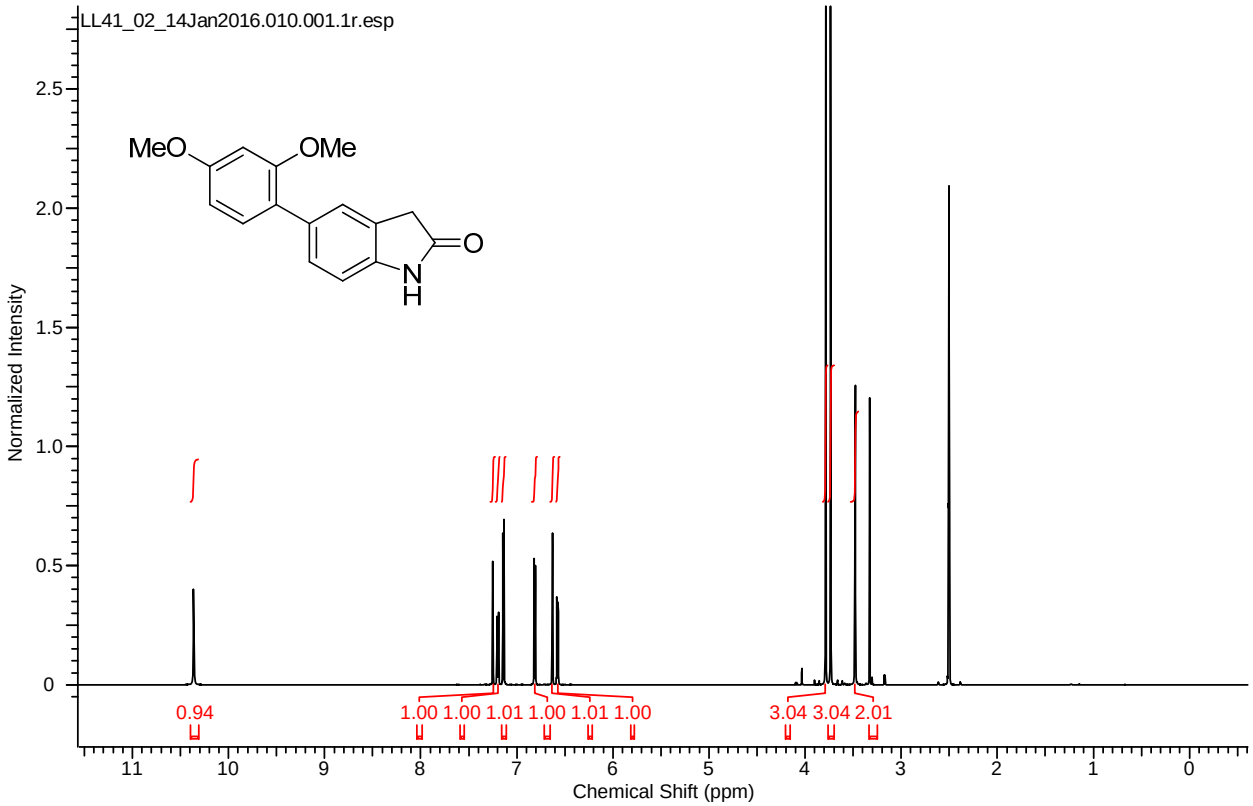

leckettk-20160121-77.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.36
151.52
143.69
142.35
133.35
132.60
130.88
129.24
127.39
125.92
124.15
109.27
35.83

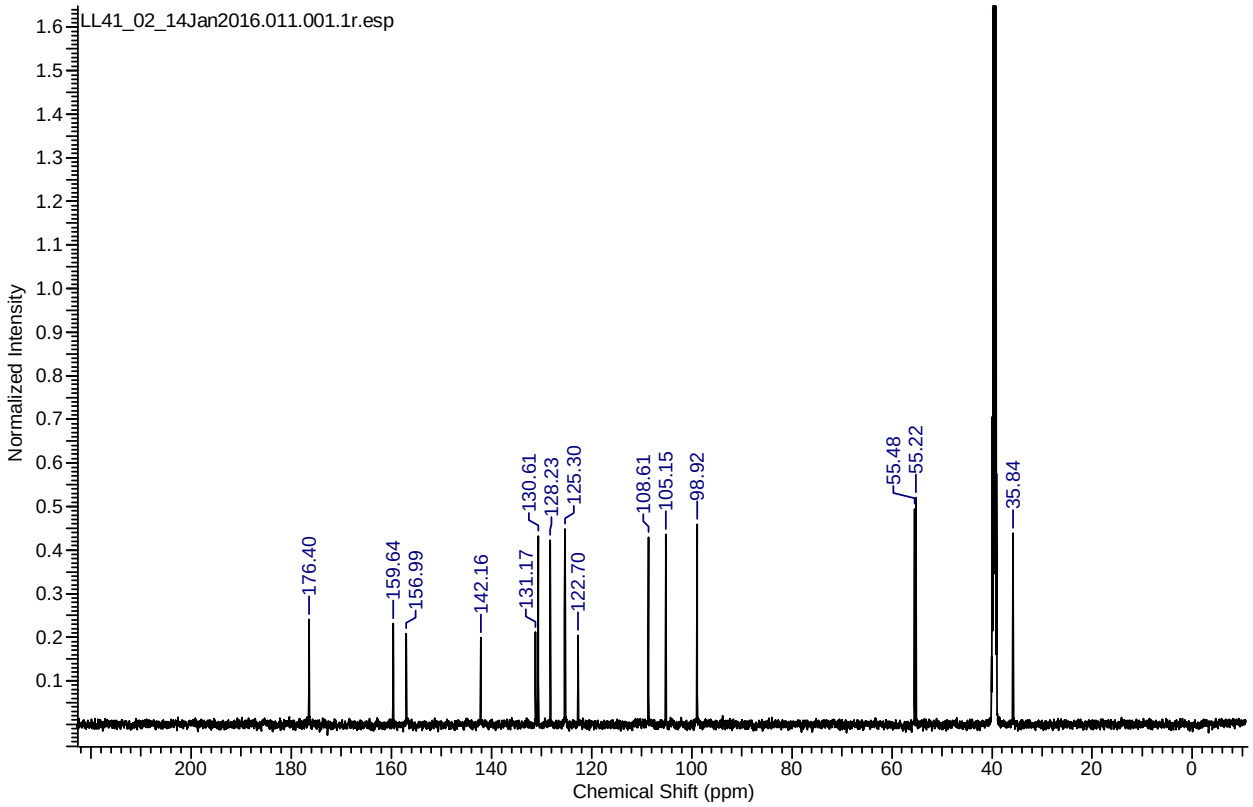

leckettk-20160121-73.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
N
H
O
1.01
2.01
0.97
6.06
1.00
2.03

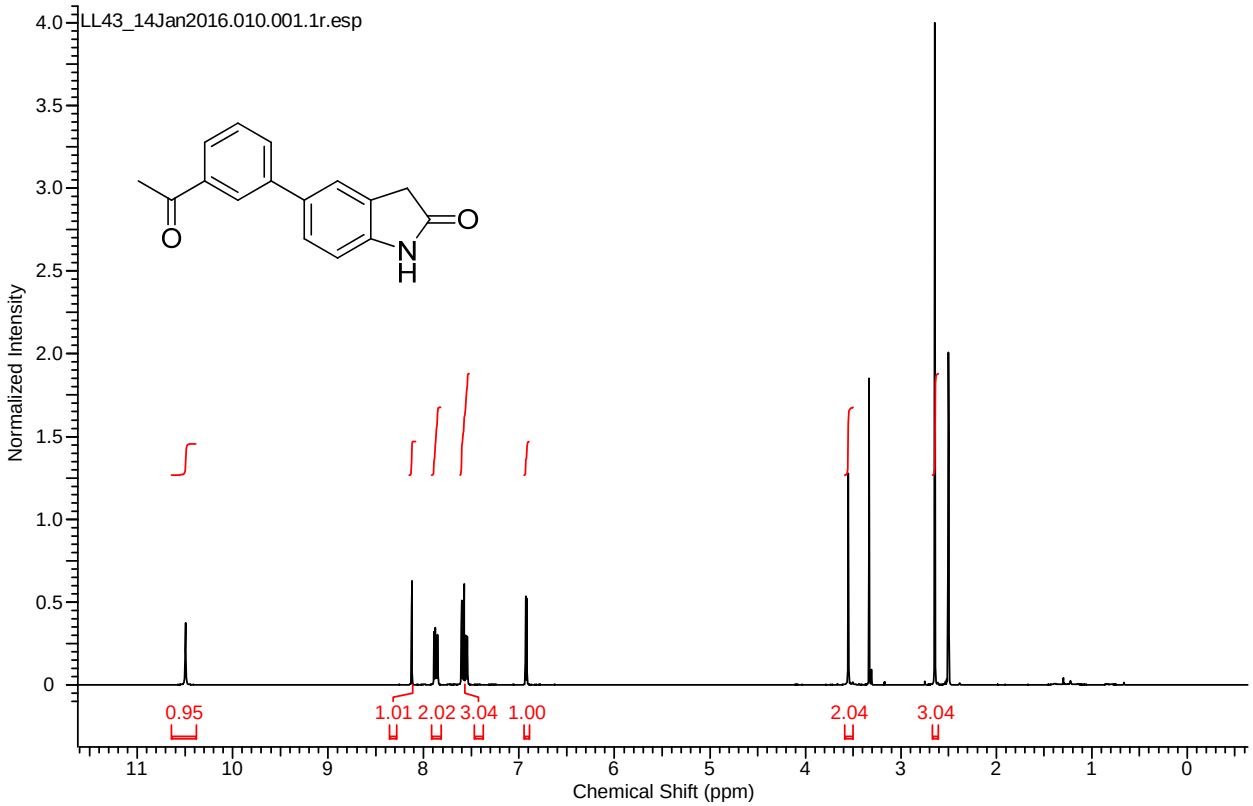

leckettk-20160121-73.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.37
143.83
138.44
135.76
132.89
127.30
127.16
122.81
122.20
120.57
109.36
35.87

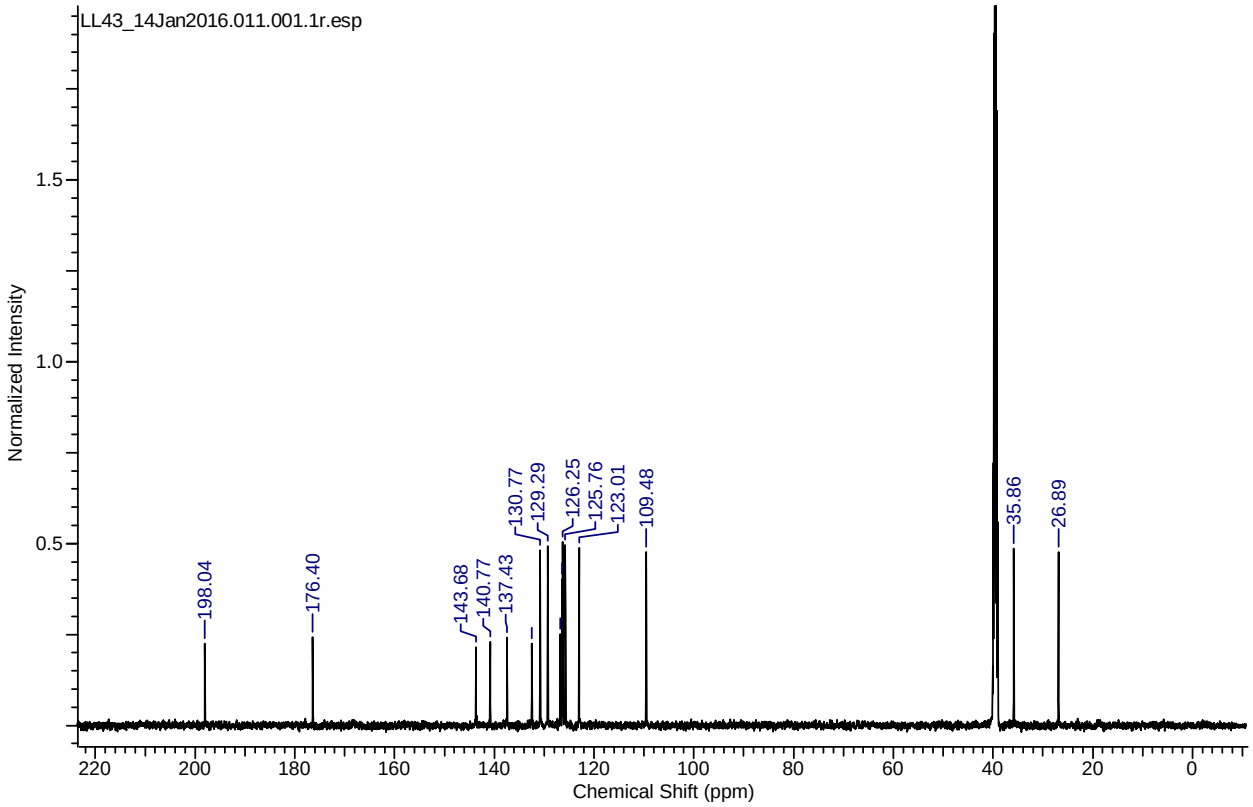

LL40_02_09Jan2015.010.001.1r.esp
OMe
MeO
O
N
H
Normalized Intensity
Chemical Shift (ppm)
0.98
0.99 0.99 2.00 1.01 0.99
2.94 2.98 2.04

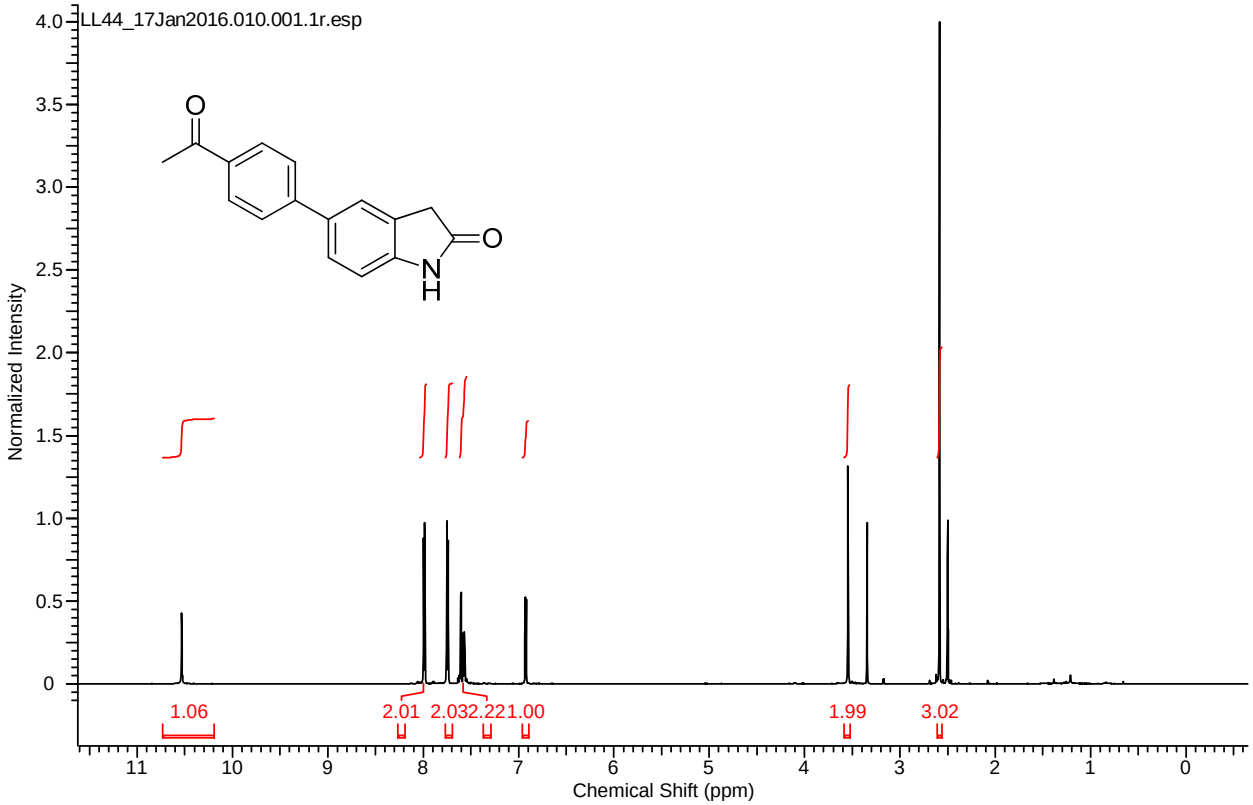

LL40_02_10Jan2016.010.001.1r.esp
Normalized Intensity
213.91
186.51
185.45
180.18
171.04
163.96
163.10
160.11
155.68
149.71
147.54
146.77
93.05
73.39
Chemical Shift (ppm)

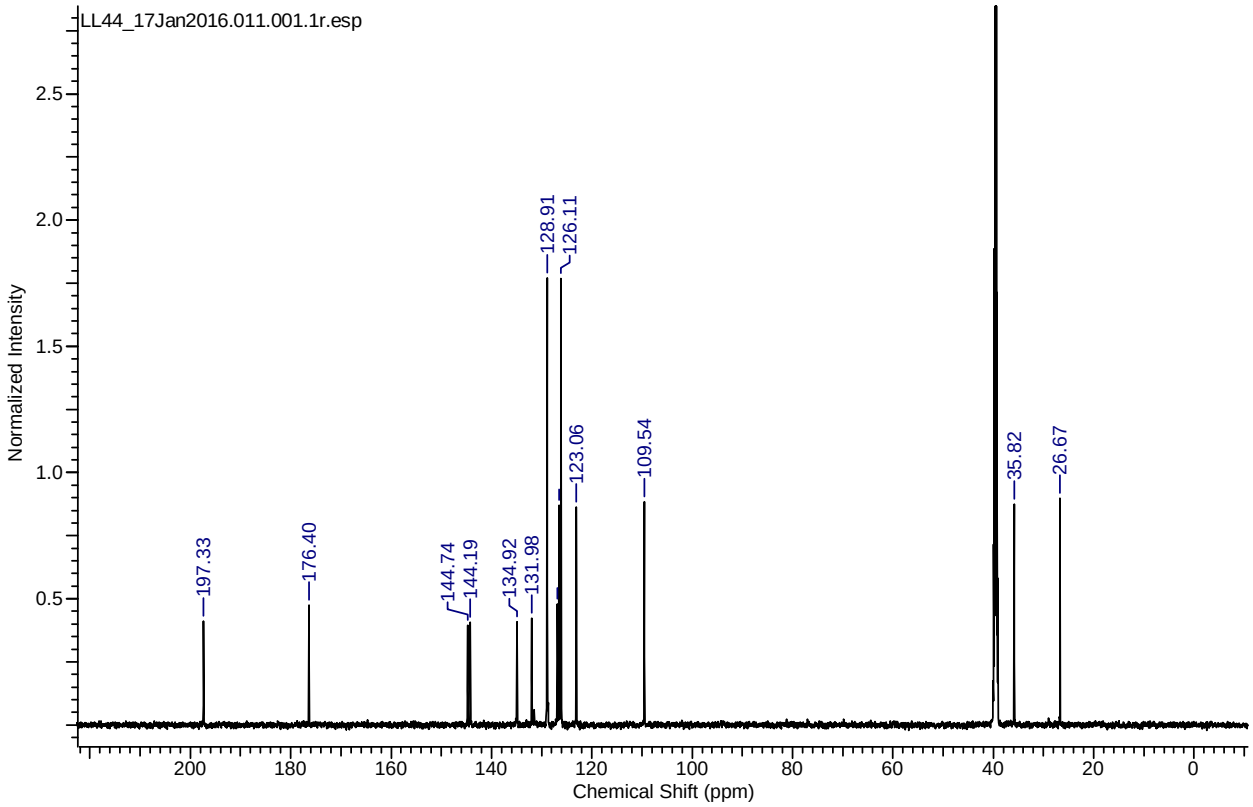

LL41_02_14Jan2016.010.001.1r.esp
MeO
OMe
O
N
H
Normalized Intensity
0.94
1.00 1.00 1.01 1.00 1.01 1.00
3.04 3.04 2.01
Chemical Shift (ppm)

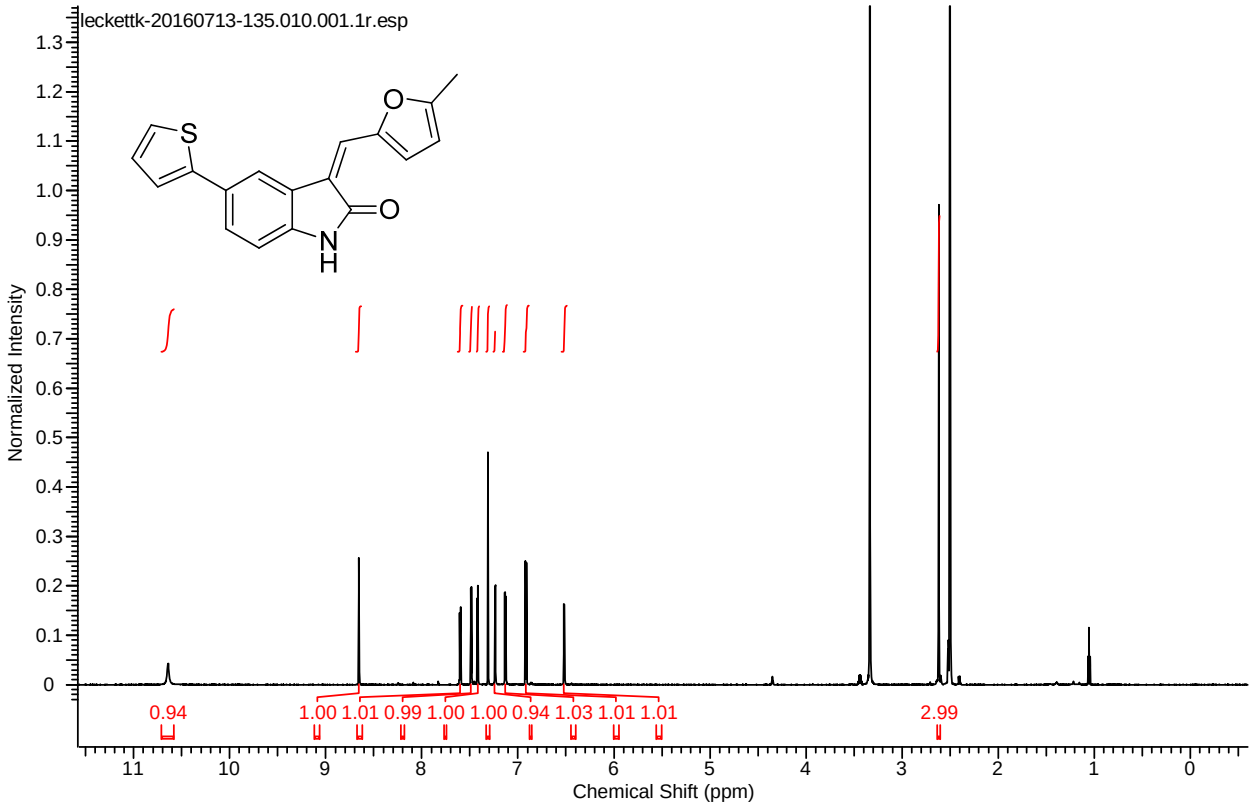

LL41_02_14Jan2016.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.40
159.64
156.99
142.16
131.17
130.61
128.23
125.30
122.70
108.61
105.15
98.92
55.48
55.22
35.84

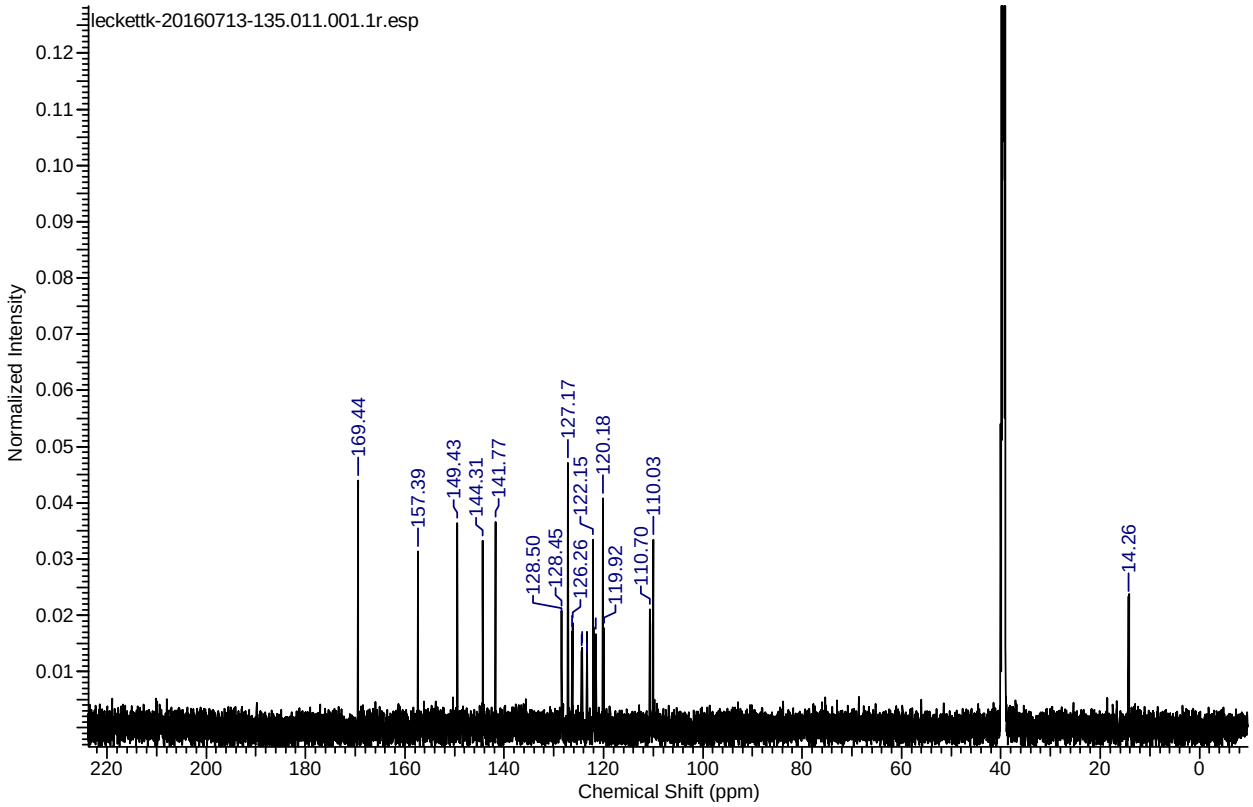

LL43_14Jan2016.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
N
H
0.95
1.01
2.02
3.04
1.00
2.04
3.04

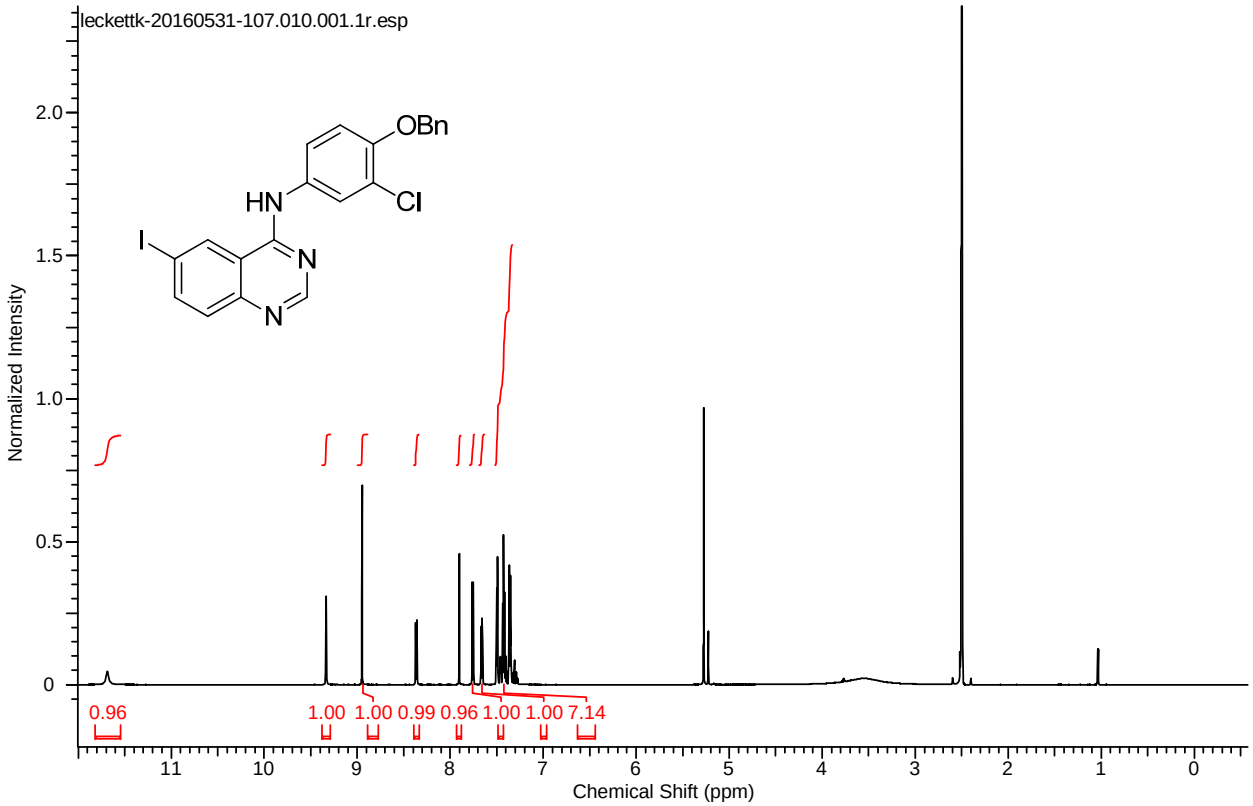

LL43_14Jan2016.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
198.04
176.40
143.68
140.77
137.43
130.77
129.29
126.25
125.76
123.01
109.48
35.86
26.89

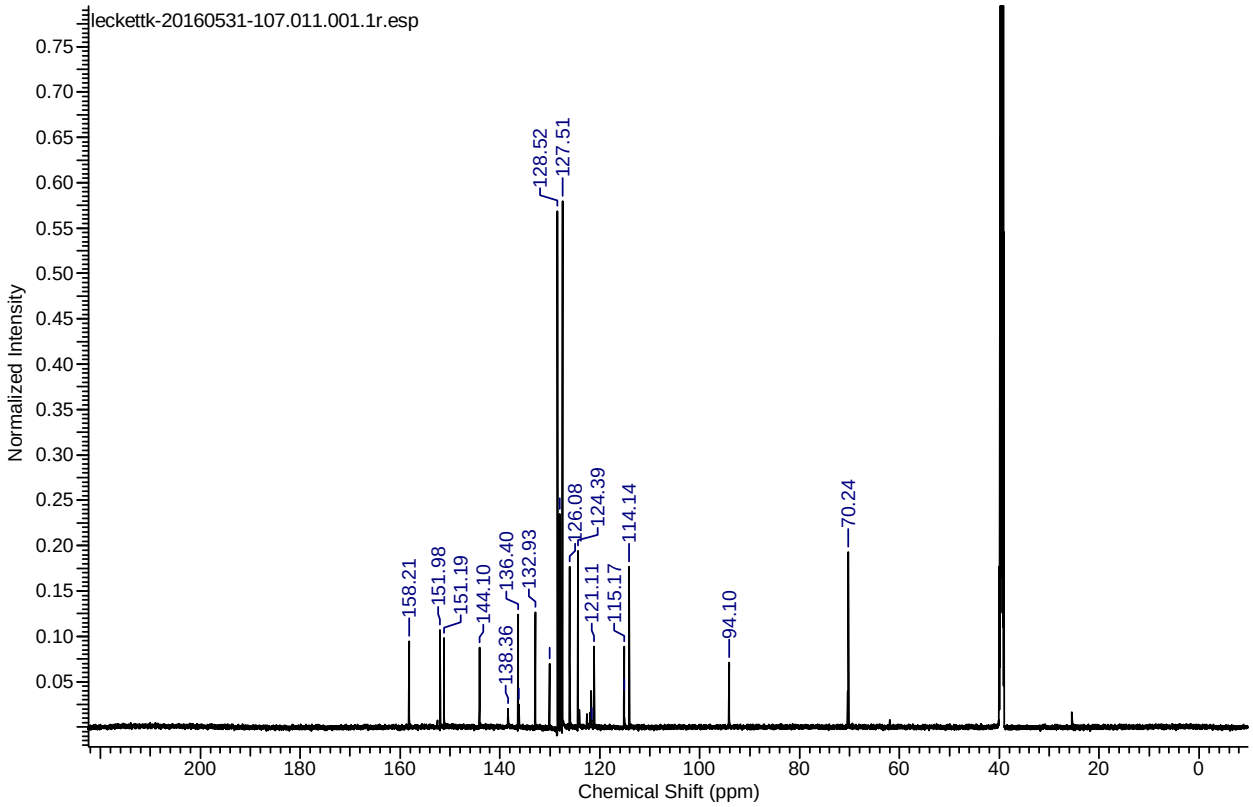

LL44_17Jan2016.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
1.06
2.01
2.03
2.22
1.00
1.99
3.02

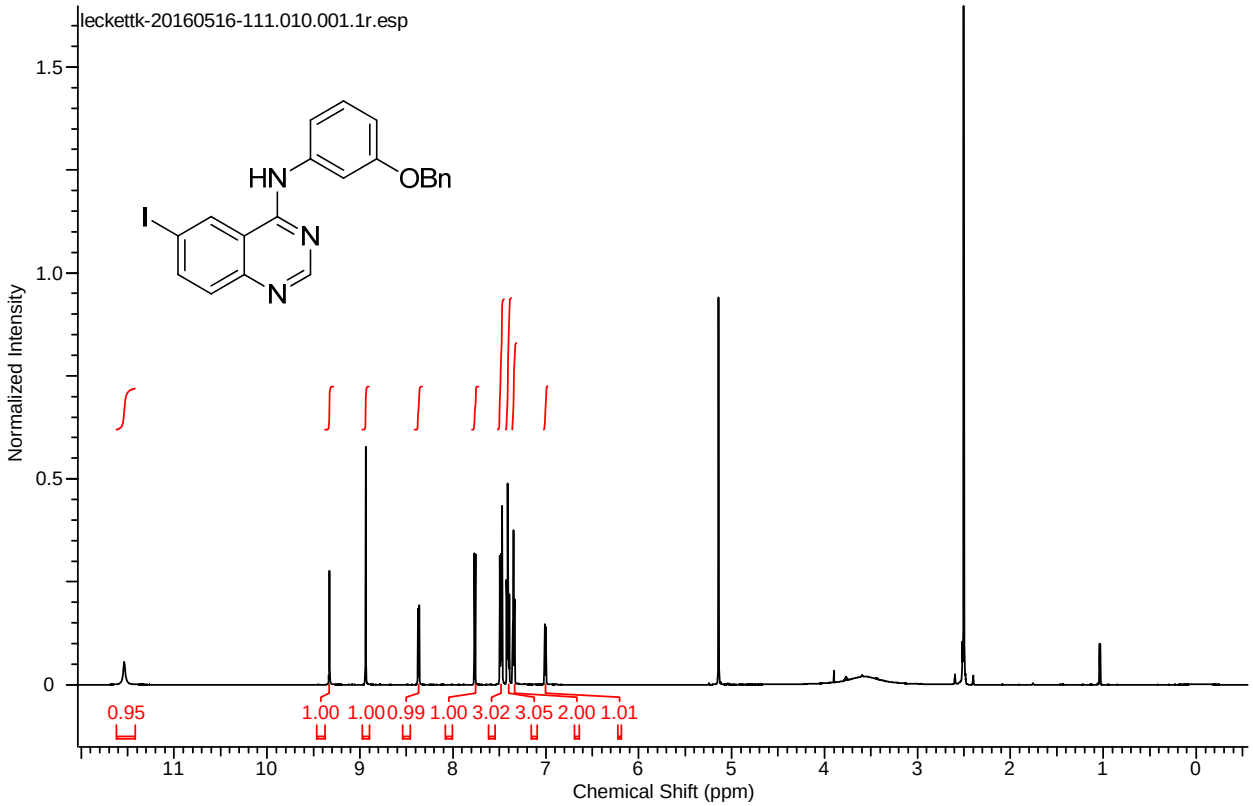

LL44_17Jan2016.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
197.33
176.40
144.74
144.19
134.92
131.98
128.91
126.11
123.06
109.54
35.82
26.67

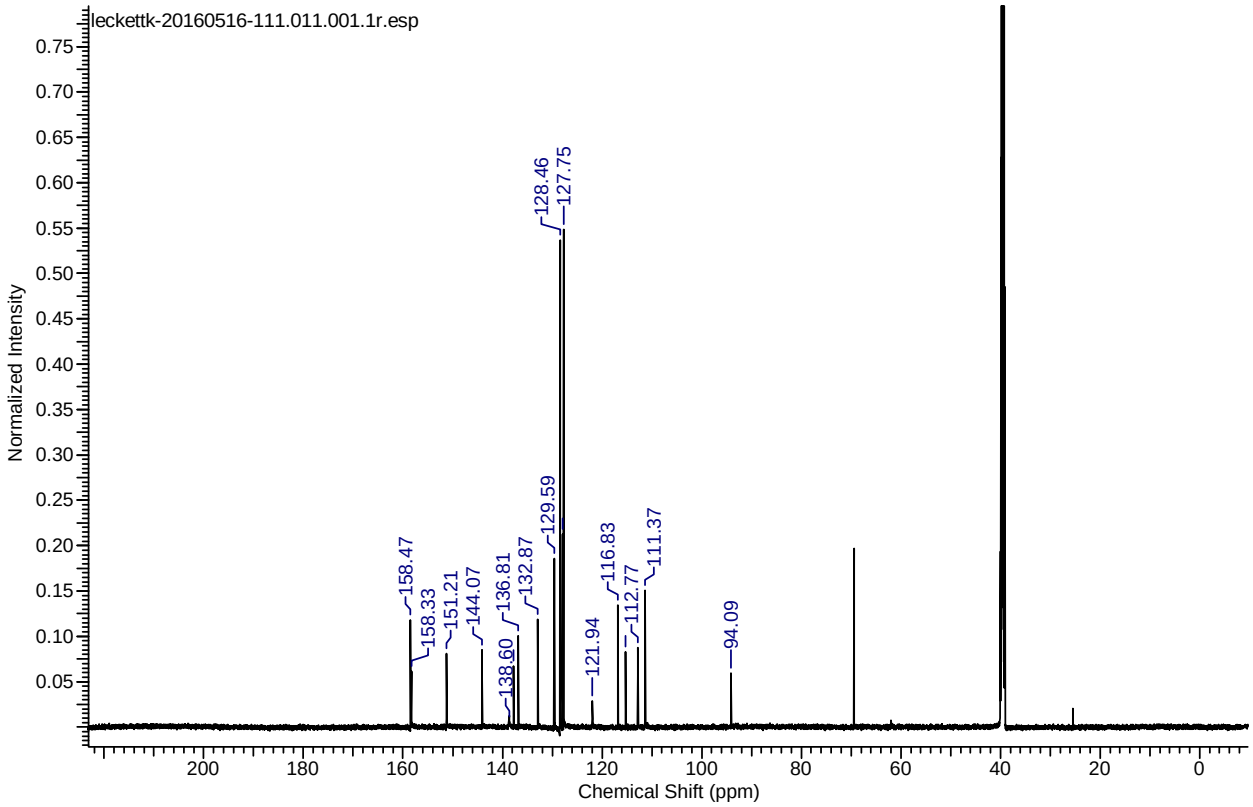

leckettk-20160713-135.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
O
O
N
H
0.94
1.00 1.01 0.99 1.00 1.00 0.94 1.03 1.01 1.01
2.99

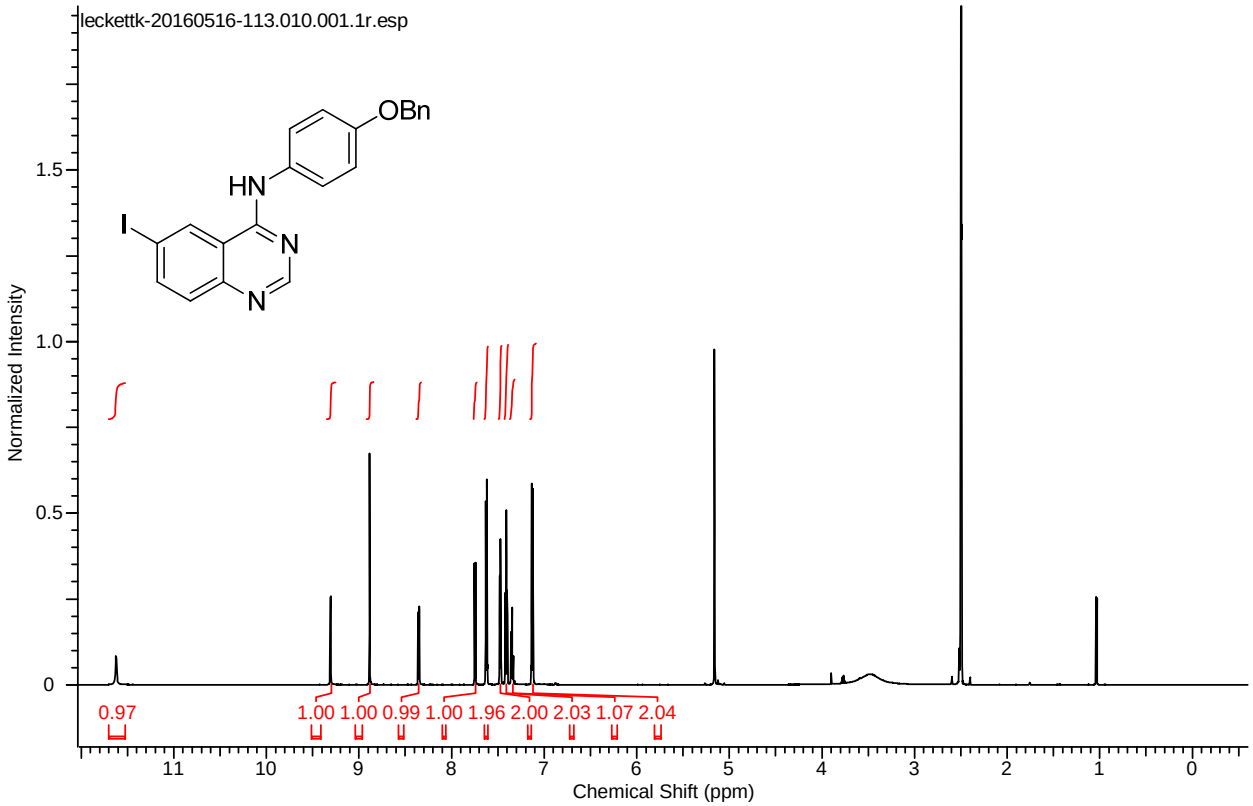

leckettk-20160713-135.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.44
157.39
149.43
144.31
141.77
128.50
128.45
127.17
126.26
122.15
120.18
119.92
110.70
110.03
14.26

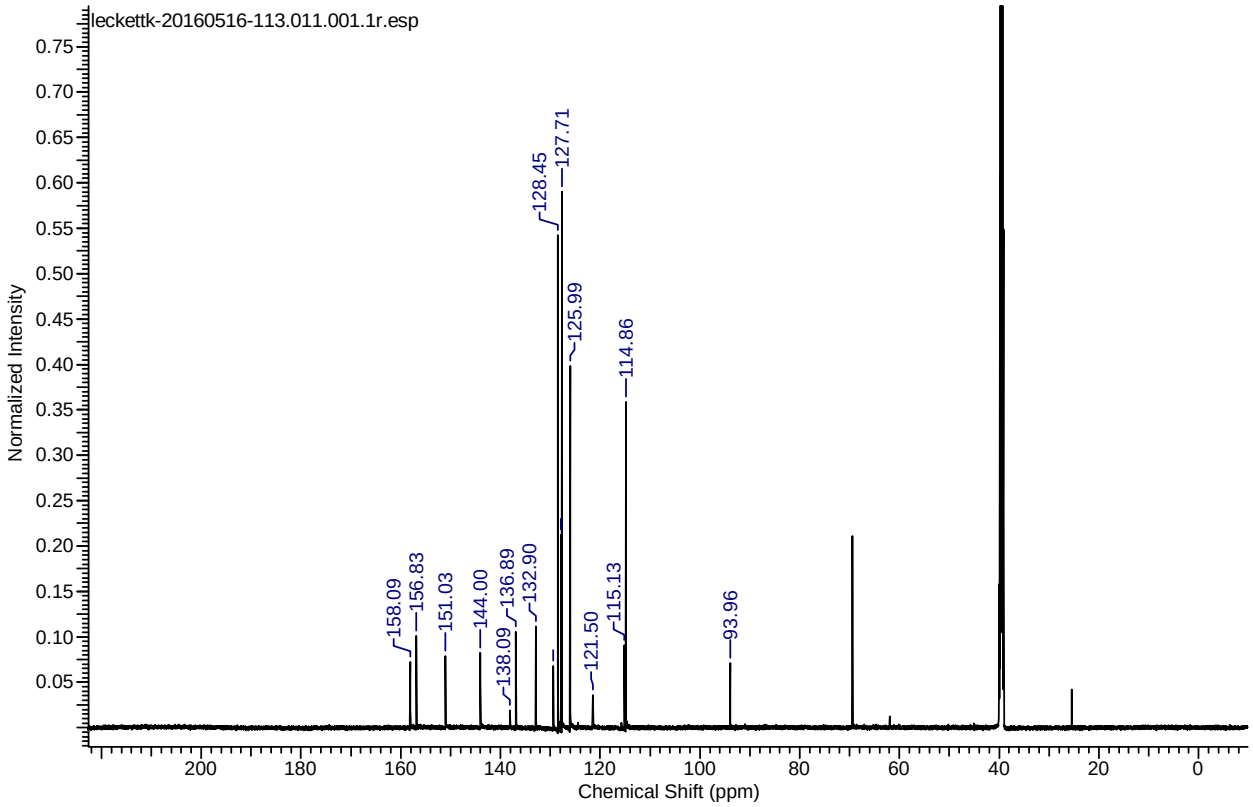

leckettk-20160531-107.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OBn
HN
Cl
I
N
N
0.96
1.00
1.00
0.99
0.96
1.00
1.00
7.14

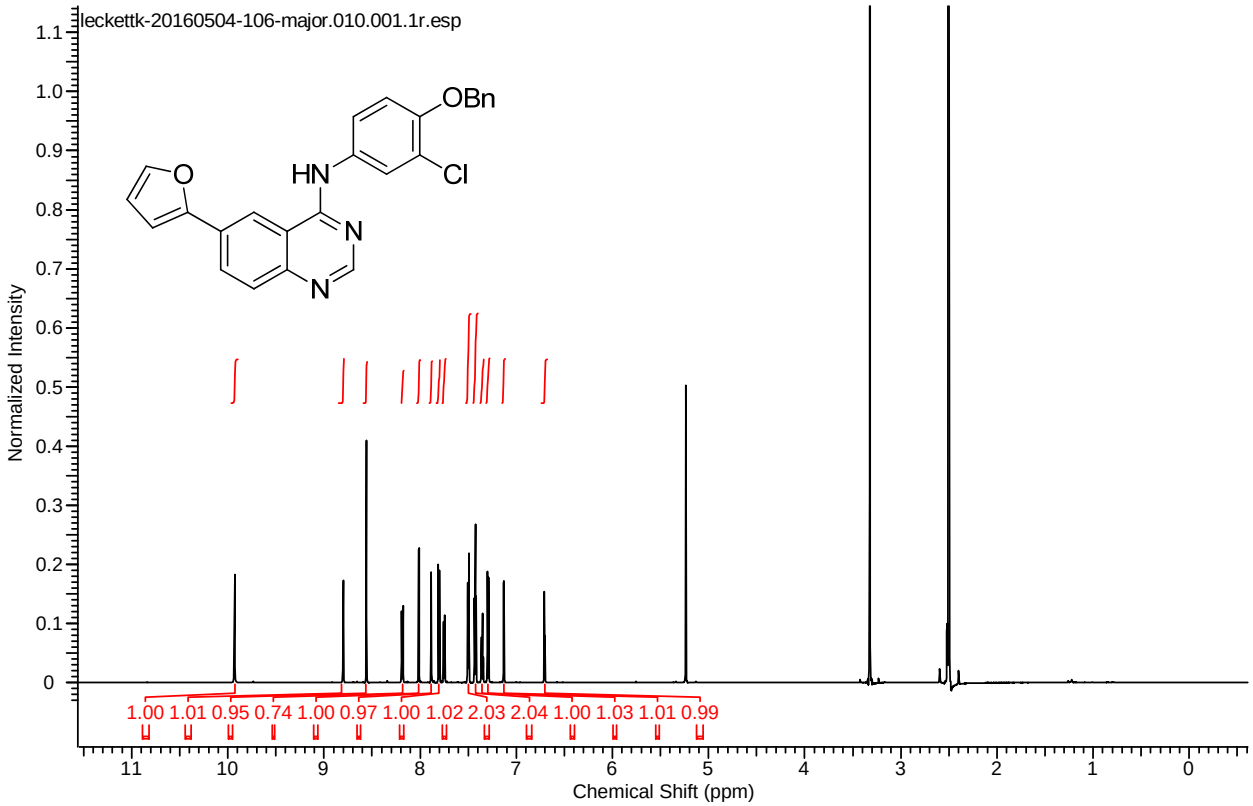

leckettk-20160531-107.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.21
151.98
151.19
144.10
138.36
136.40
132.93
128.52
127.51
126.08
124.39
121.11
115.17
114.14
94.10
70.24

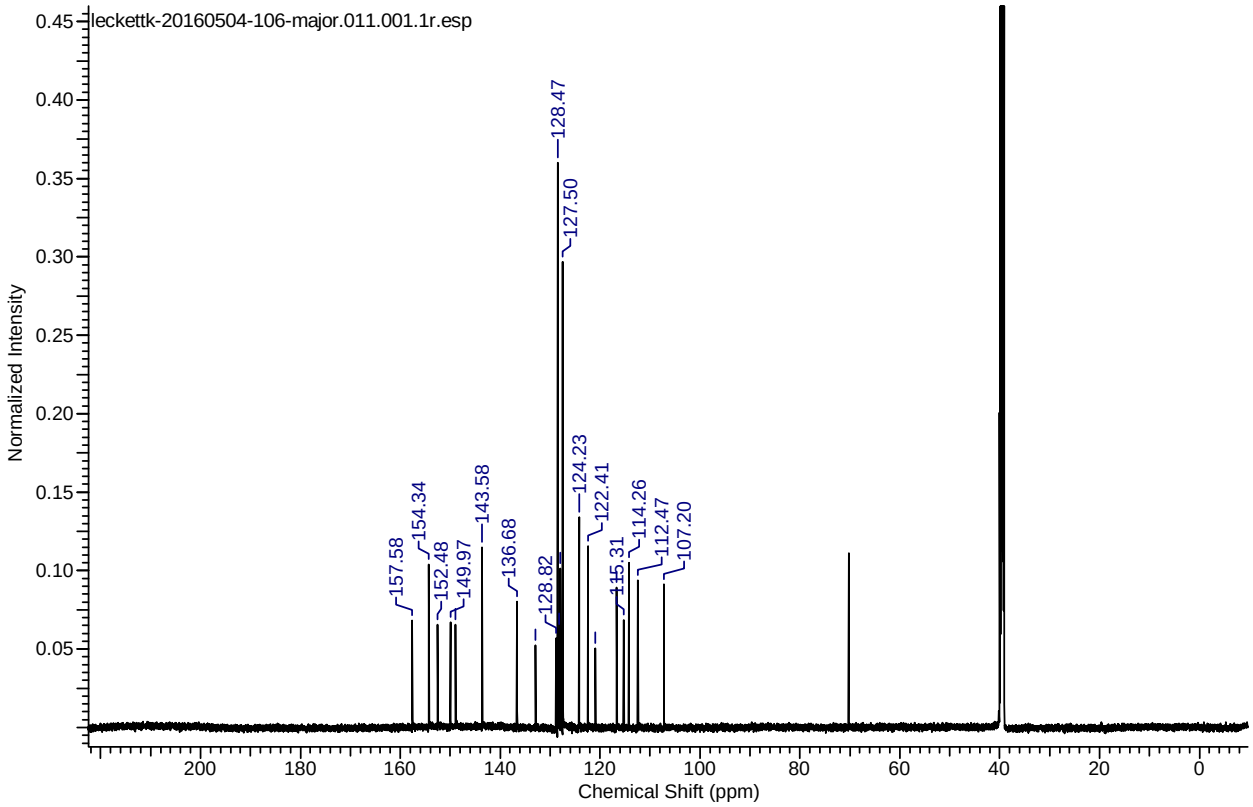

leckettk-20160516-111.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
HN
OBn
I
N
N
0.95
1.00
1.00
0.99
1.00
3.02
3.05
2.00
1.01

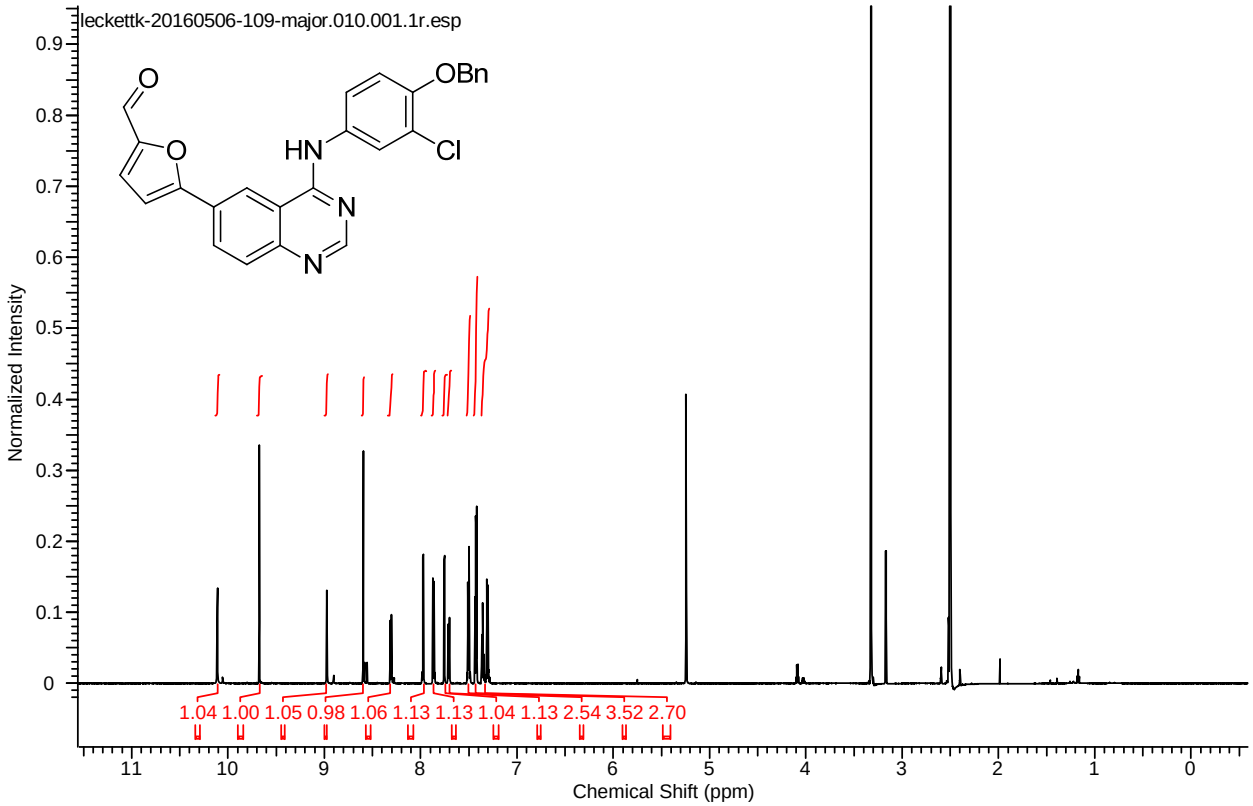

leckettk-20160516-111.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.47
158.33
151.21
144.07
136.81
138.60
132.87
129.59
128.46
127.75
121.94
116.83
112.77
111.37
94.09

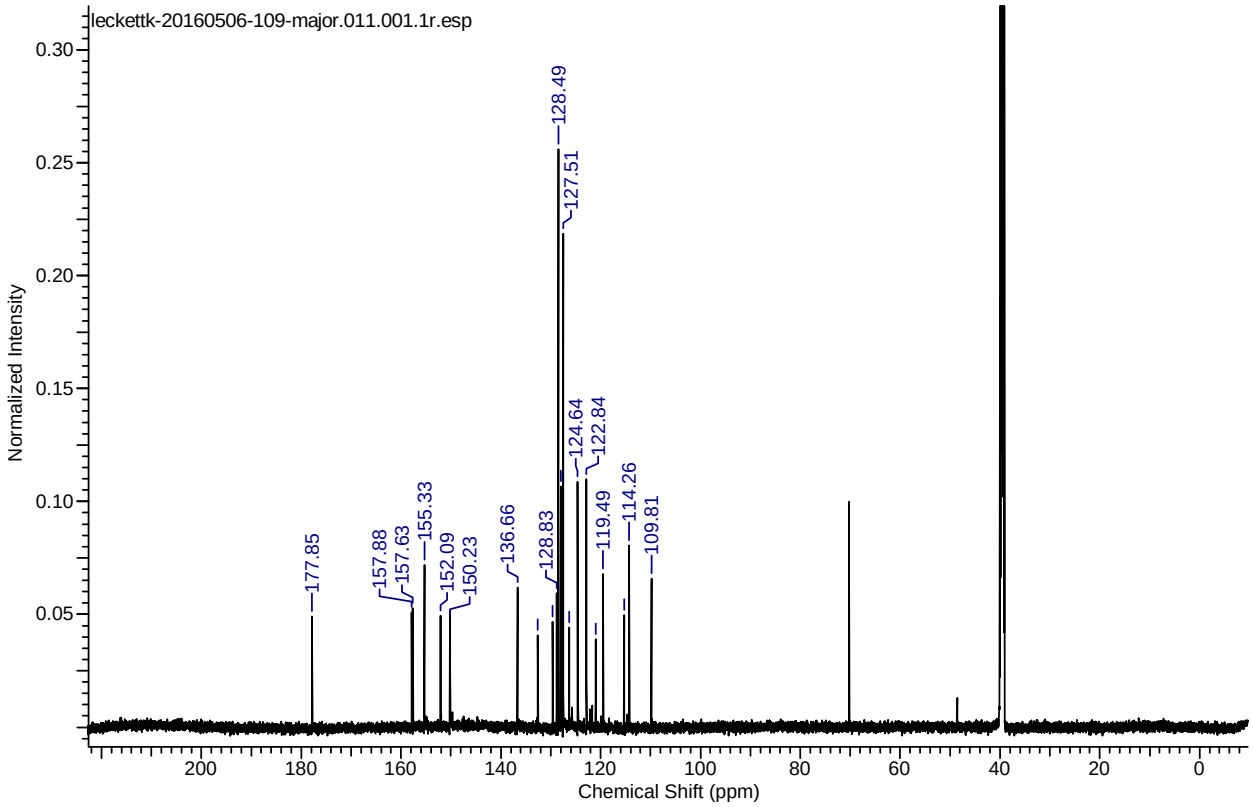

leckettk-20160516-113.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OBn
HN
I
N
N
0.97
1.00 1.00 0.99 1.00 1.96 2.00 2.03 1.07 2.04

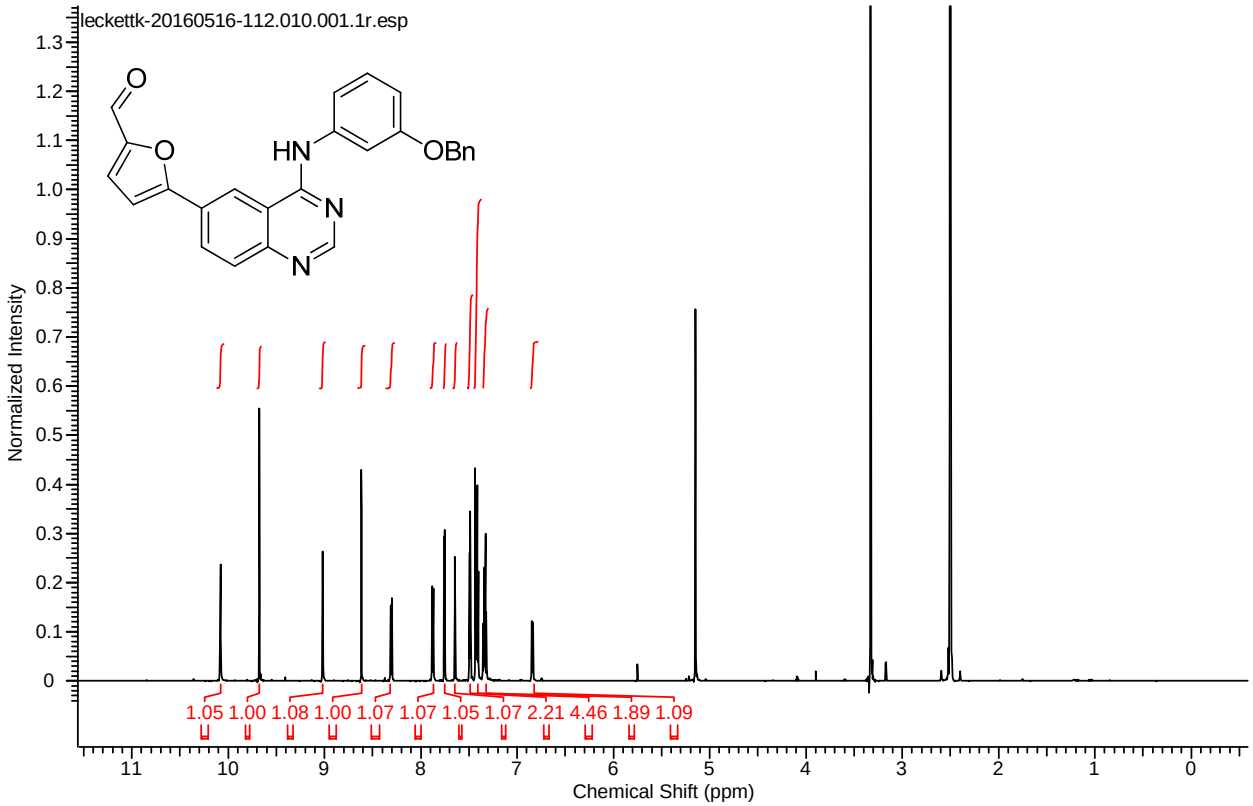

leckettk-20160516-113.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.09
156.83
151.03
144.00
138.09
136.89
132.90
128.45
127.71
125.99
121.50
115.13
114.86
93.96

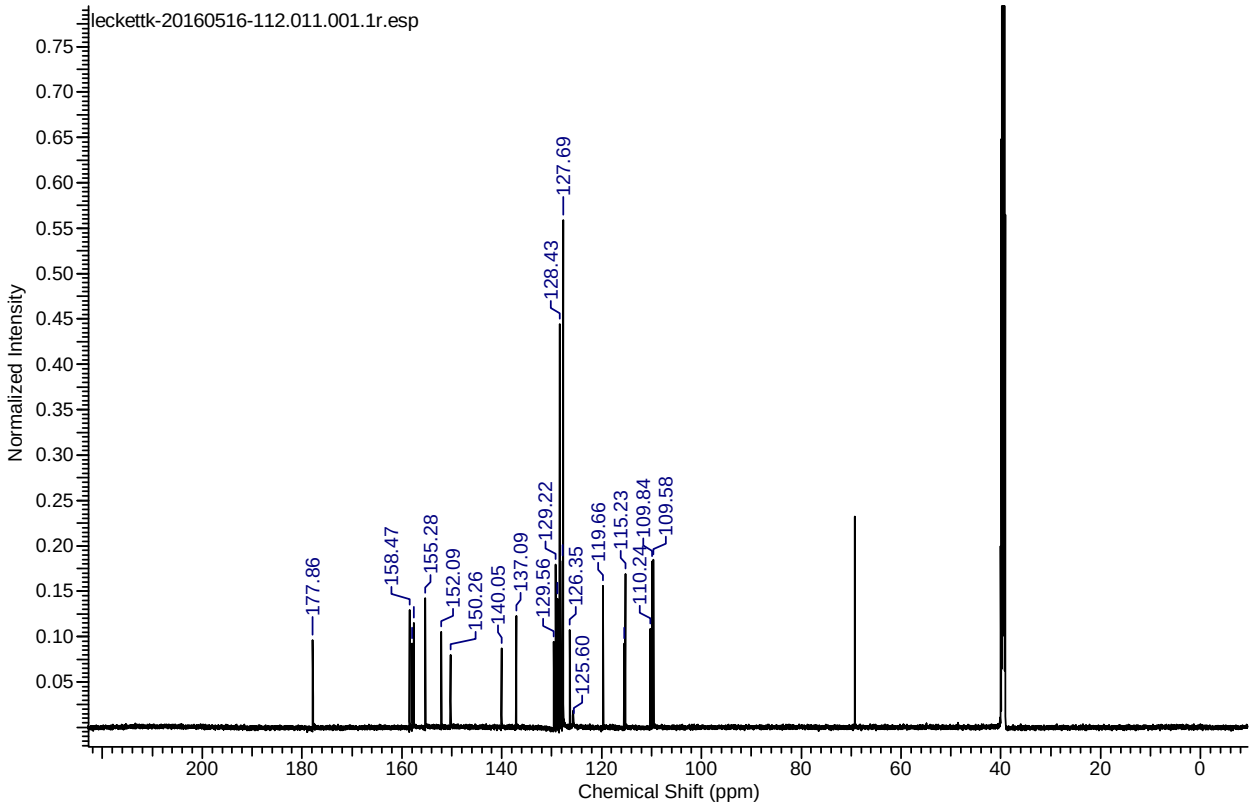

leckettk-20160504-106-major.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OBn
HN
Cl
O
N
N
1.00 1.01 0.95 0.74 1.00 0.97 1.00 1.02 2.03 2.04 1.00 1.03 1.01 0.99

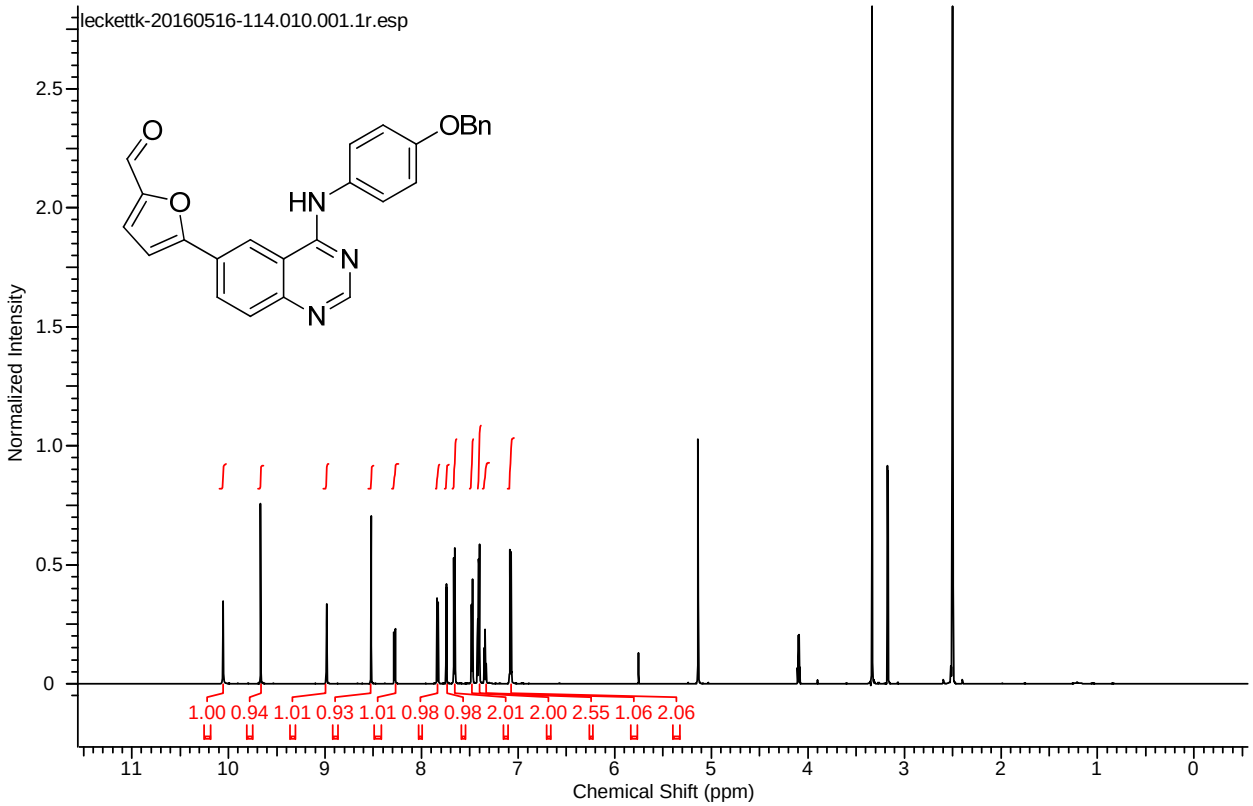

leckettk-20160504-106-major.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
157.58
154.34
152.48
149.97
143.58
136.68
128.82
128.47
127.50
124.23
122.41
115.31
114.26
112.47
107.20

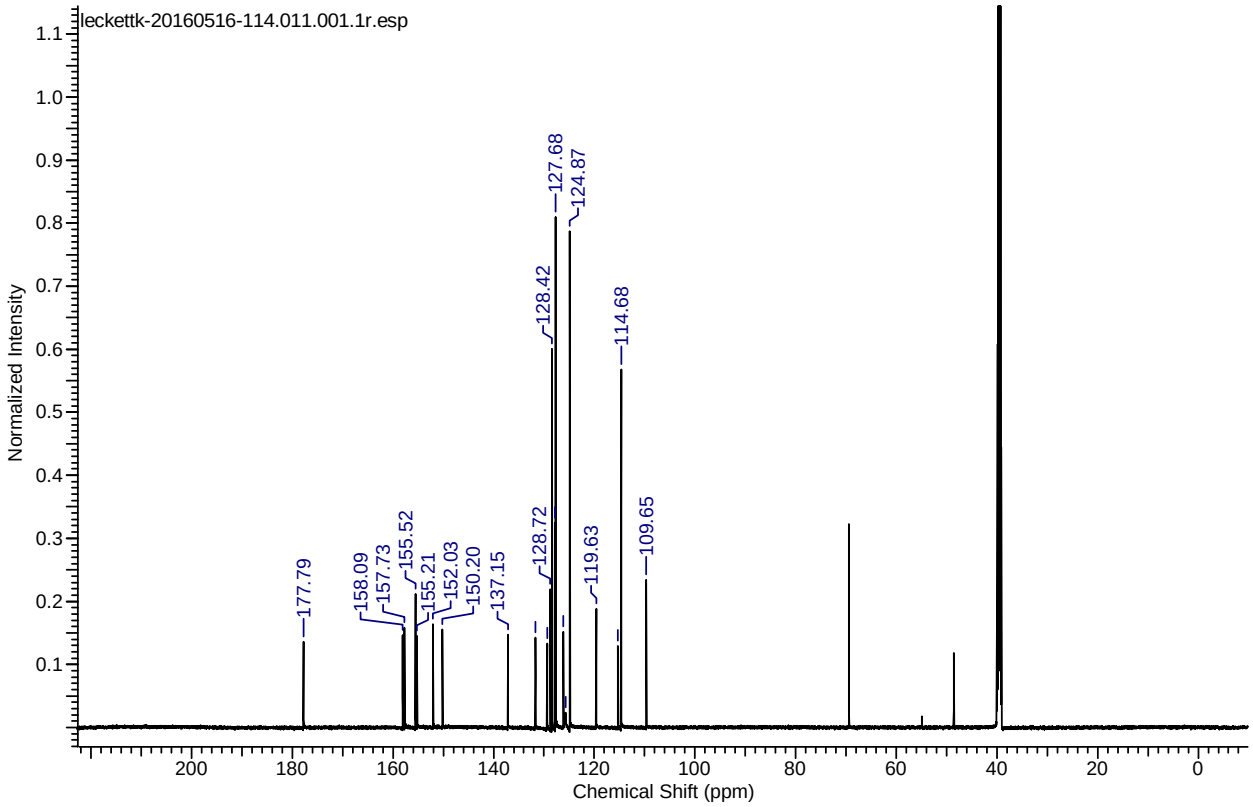

leckettk-20160506-109-major.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
HN
OBn
Cl
N
N
1.04 1.00 1.05 0.98 1.06 1.13 1.13 1.04 1.13 2.54 3.52 2.70

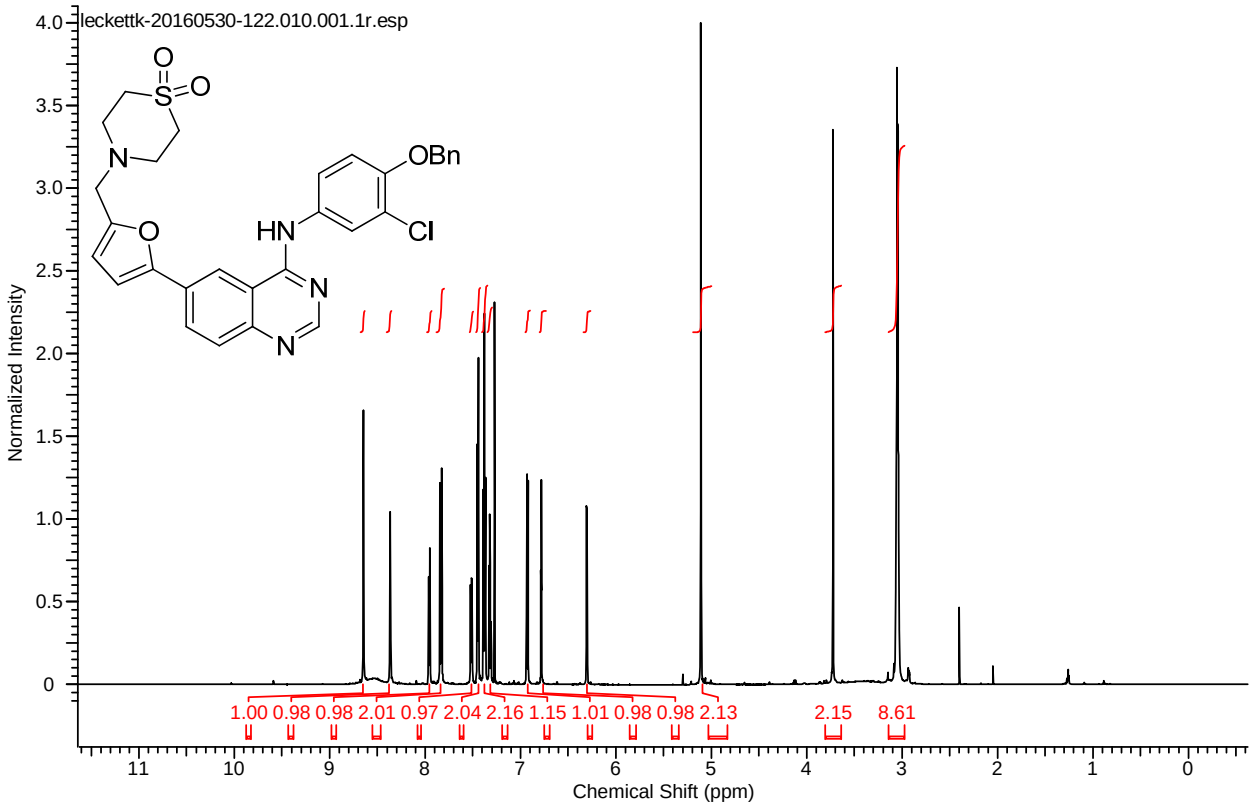

leckettk-20160506-109-major.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
177.85
157.88
157.63
155.33
152.09
150.23
136.66
128.83
128.49
127.51
124.64
122.84
119.49
114.26
109.81

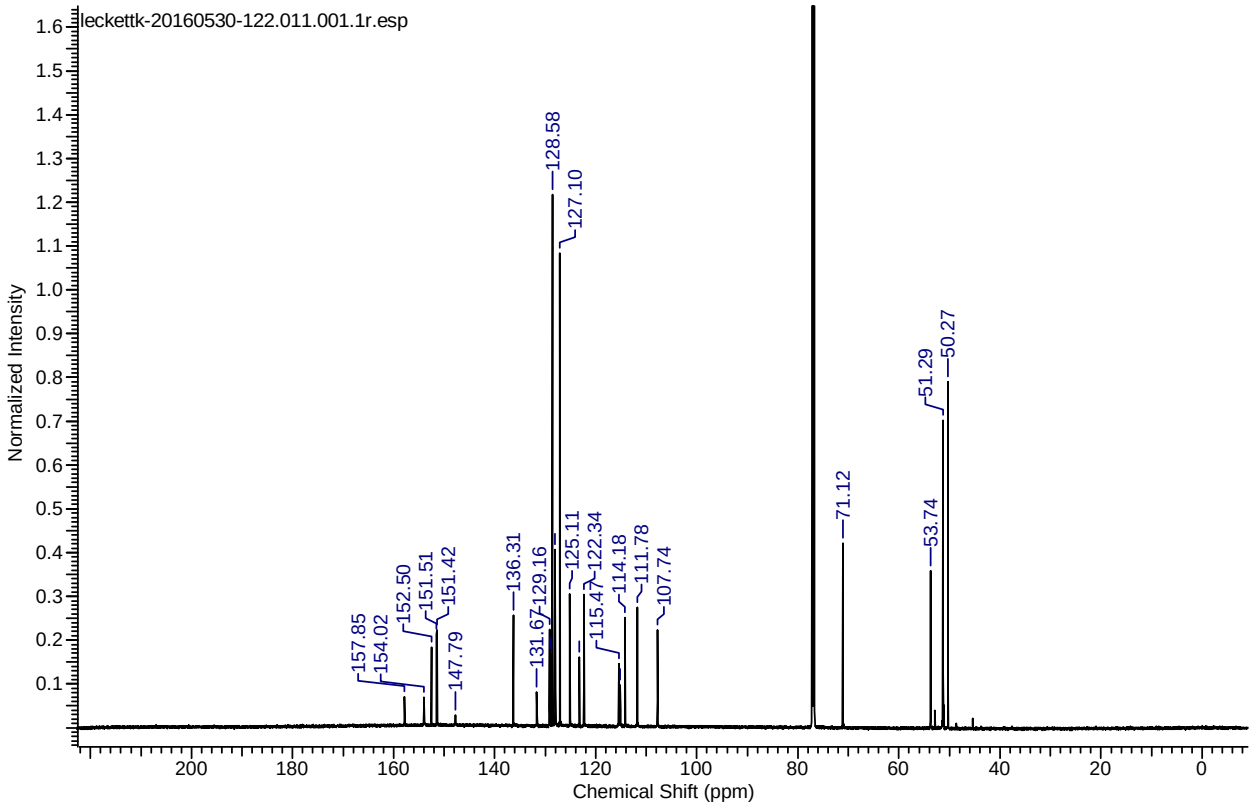

leckettk-20160516-112.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
HN
OBn
N
N
1.05 1.00 1.08 1.00 1.07 1.07 1.05 1.07 2.21 4.46 1.89 1.09

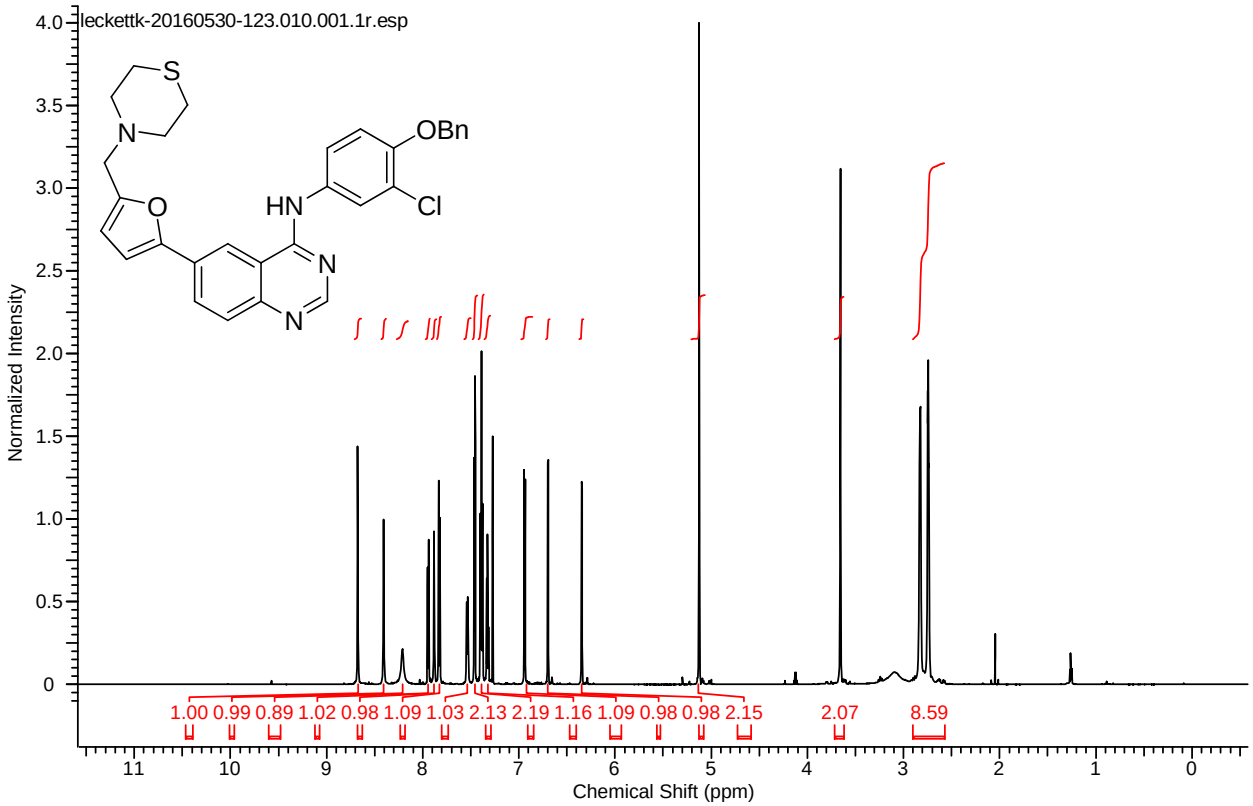

leckettk-20160516-112.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
177.86
158.47
155.28
152.09
150.26
140.05
137.09
129.56
129.22
128.43
127.69
126.35
125.60
119.66
115.23
110.24
109.84
109.58

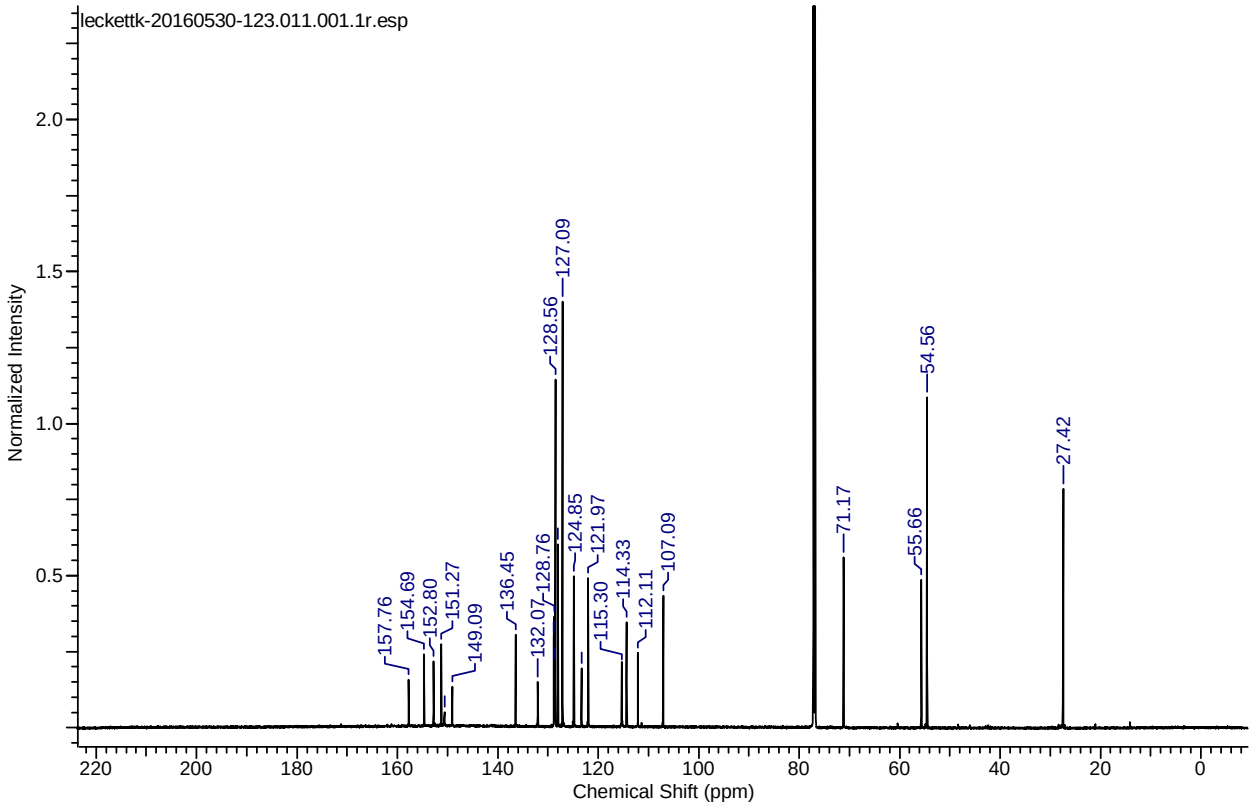

leckettk-20160516-114.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
HN
N
N
OBn
1.00 0.94 1.01 0.93 1.01 0.98 0.98 2.01 2.00 2.55 1.06 2.06

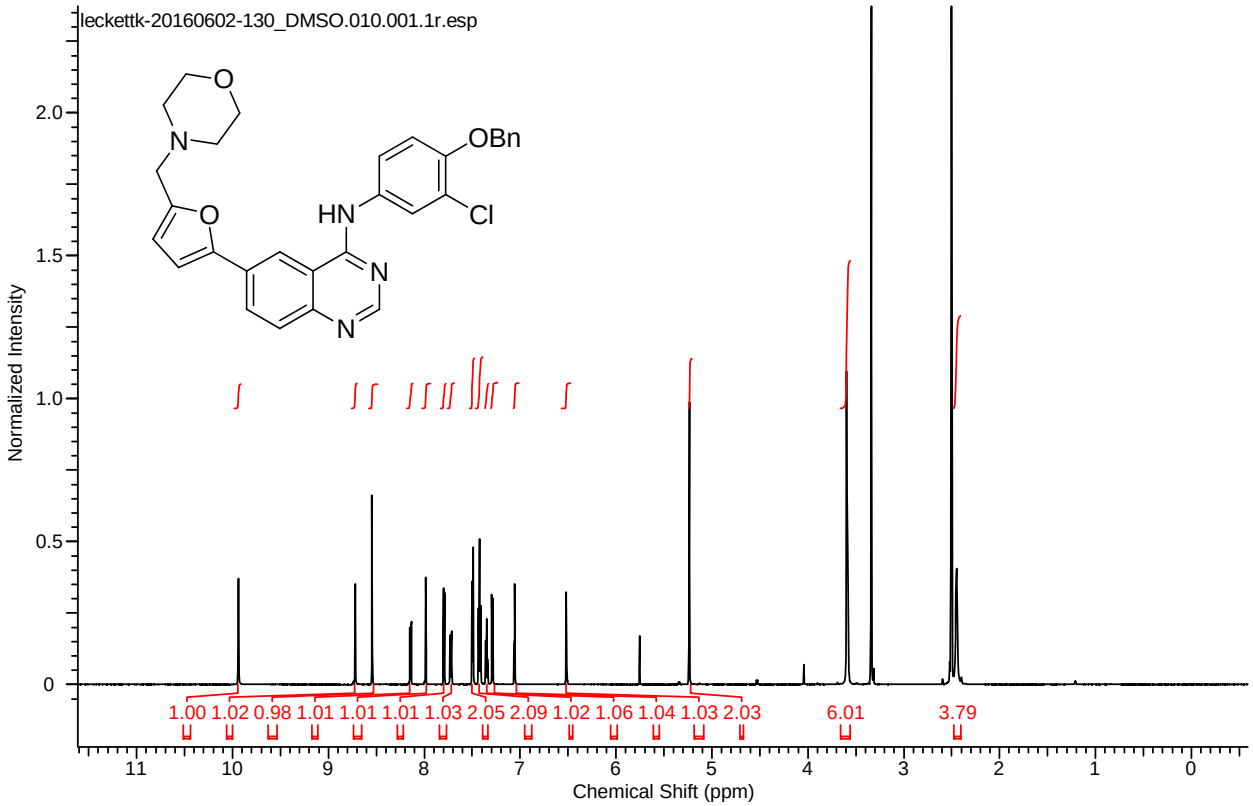

leckettk-20160516-114.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
177.79
158.09
157.73
155.52
155.21
152.03
150.20
137.15
128.72
128.42
127.68
124.87
119.63
114.68
109.65

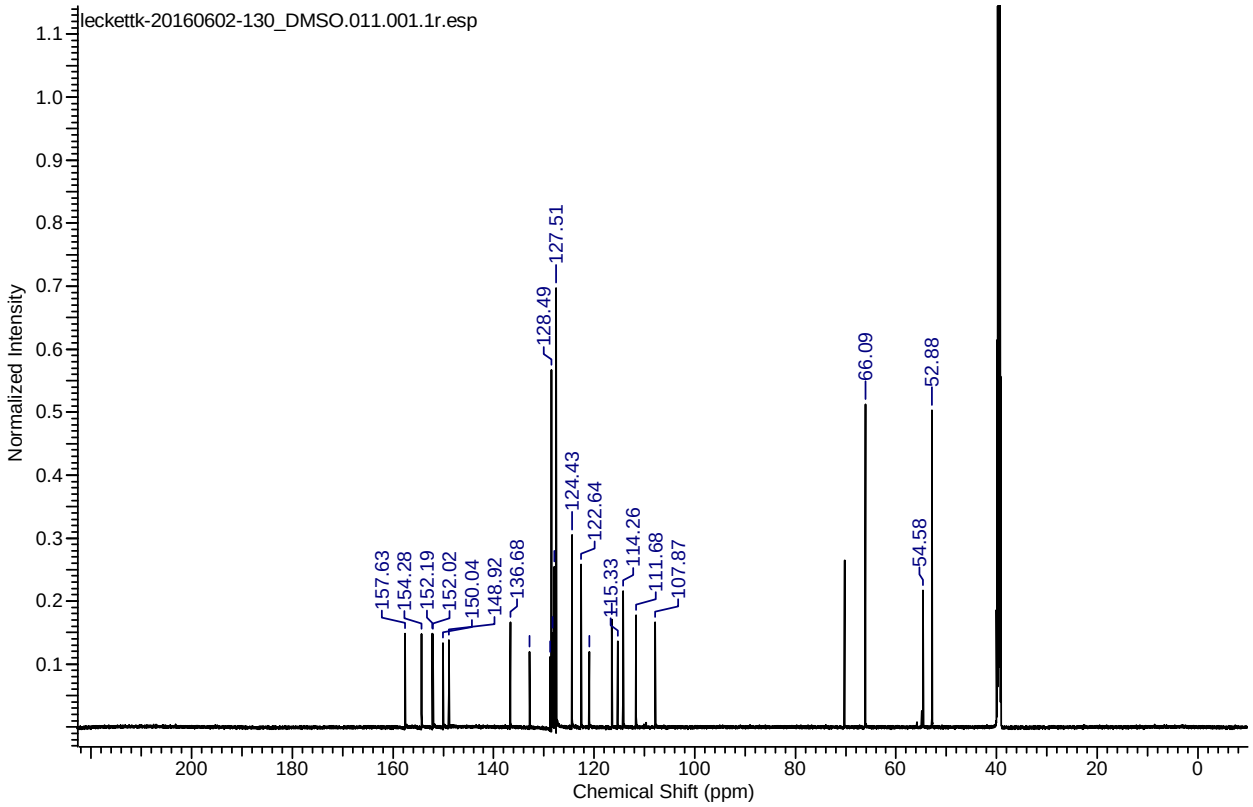

leckettk-20160530-122.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
O
N
O
HN
OBn
Cl
N
N
1.00 0.98 0.98 2.01 0.97 2.04 2.16 1.15 1.01 0.98 0.98 2.13
2.15
8.61

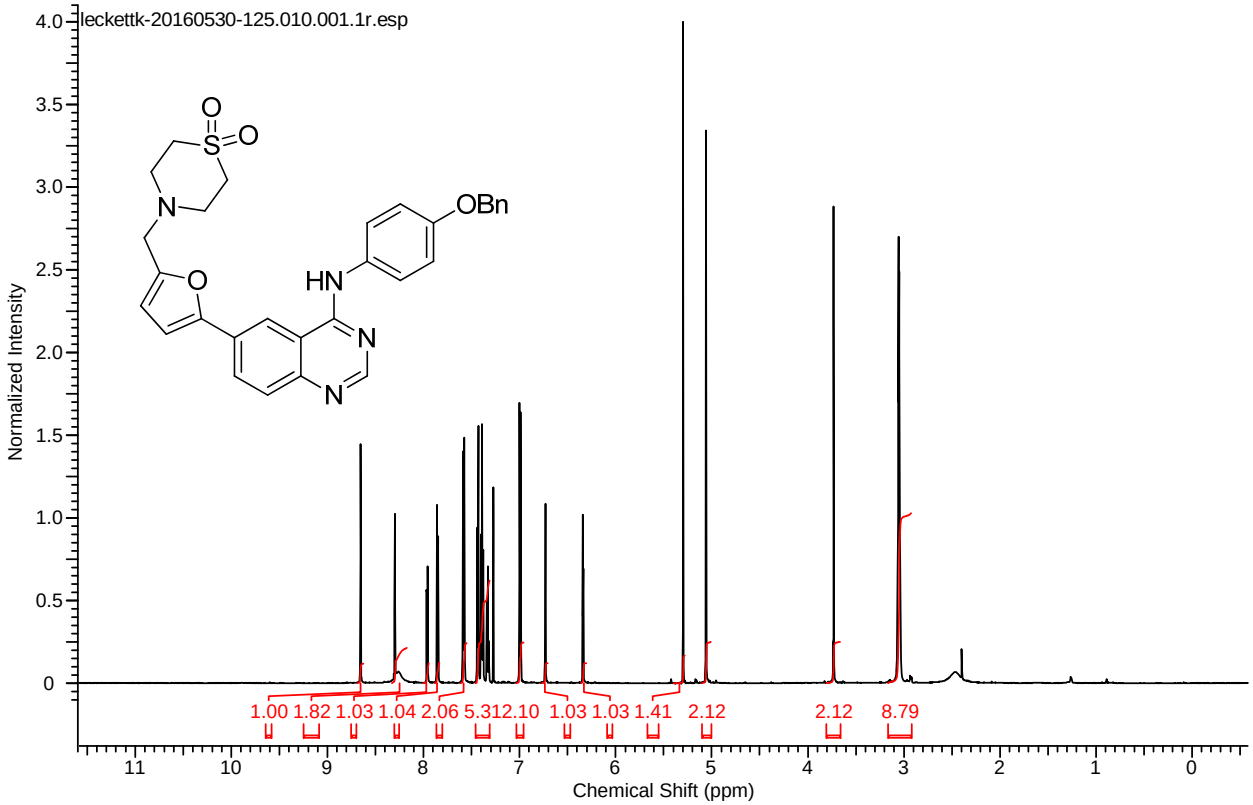

leckettk-20160530-122.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
157.85
154.02
152.50
151.51
151.42
147.79
136.31
131.67
129.16
128.58
127.10
125.11
122.34
115.47
114.18
111.78
107.74
71.12
53.74
51.29
50.27

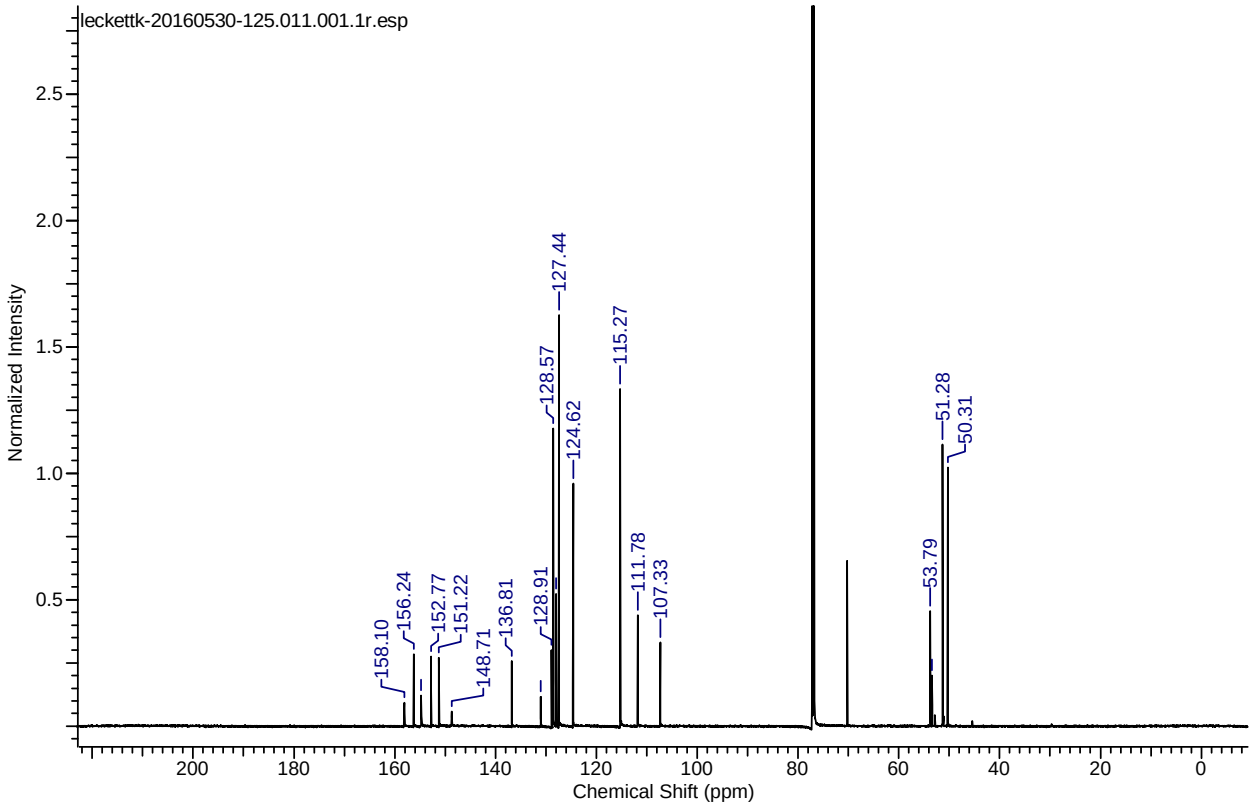

leckettk-20160530-123.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
N
O
HN
OBn
Cl
N
N
1.00 0.99 0.89 1.02 0.98 1.09 1.03 2.13 2.19 1.16 1.09 0.98 0.98 2.15
2.07
8.59

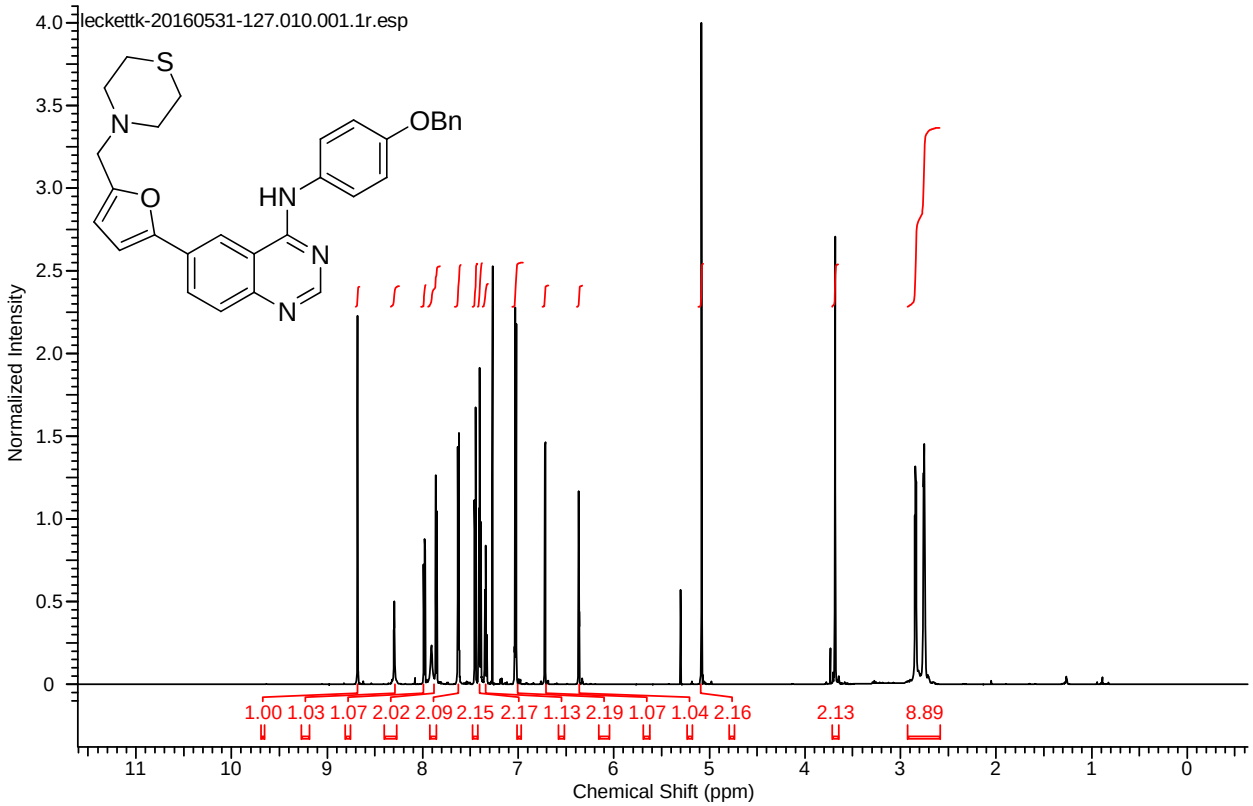

leckettk-20160530-123.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
157.76
154.69
152.80
151.27
149.09
136.45
132.07
128.76
128.56
127.09
124.85
121.97
115.30
114.33
112.11
107.09
71.17
55.66
54.56
27.42

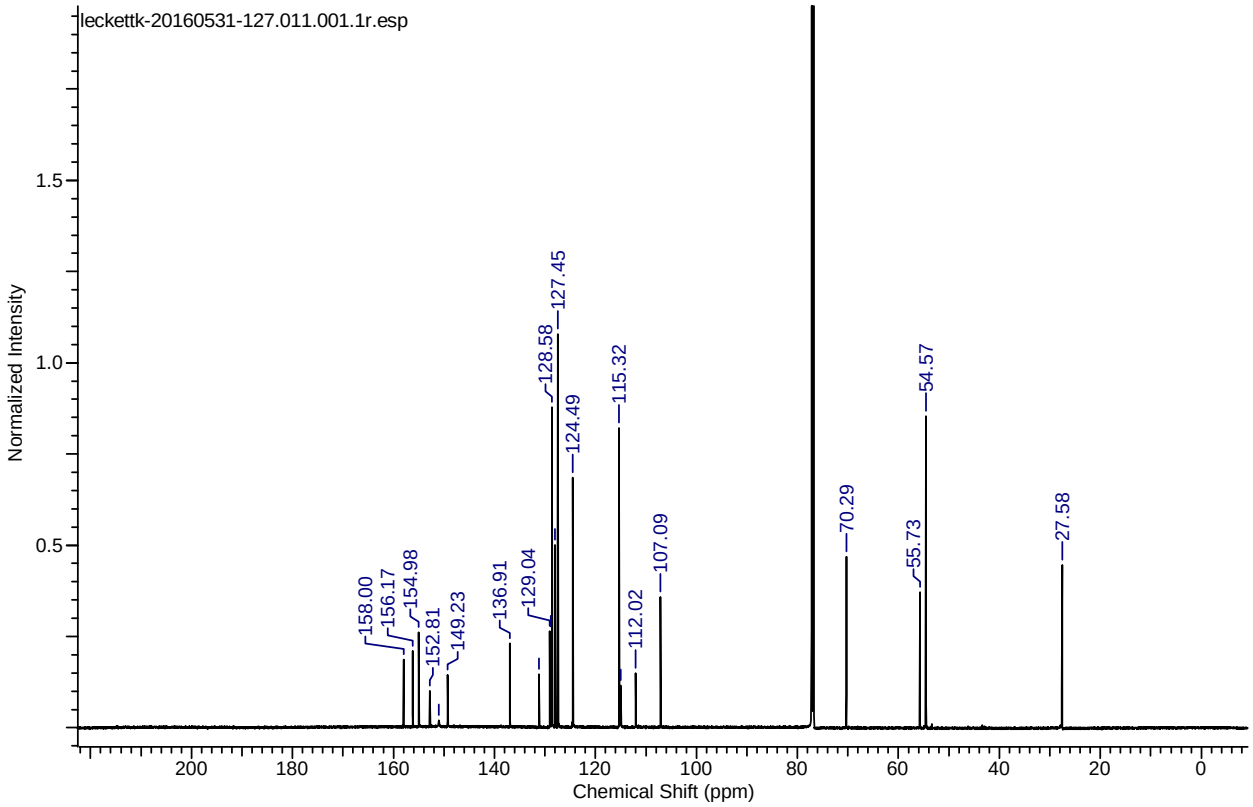

leckettk-20160602-130_DMSO.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
N
O
HN
OBn
Cl
N
N
1.00 1.02 0.98 1.01 1.01 1.01 1.03 2.05 2.09 1.02 1.06 1.04 1.03 2.03
6.01
3.79

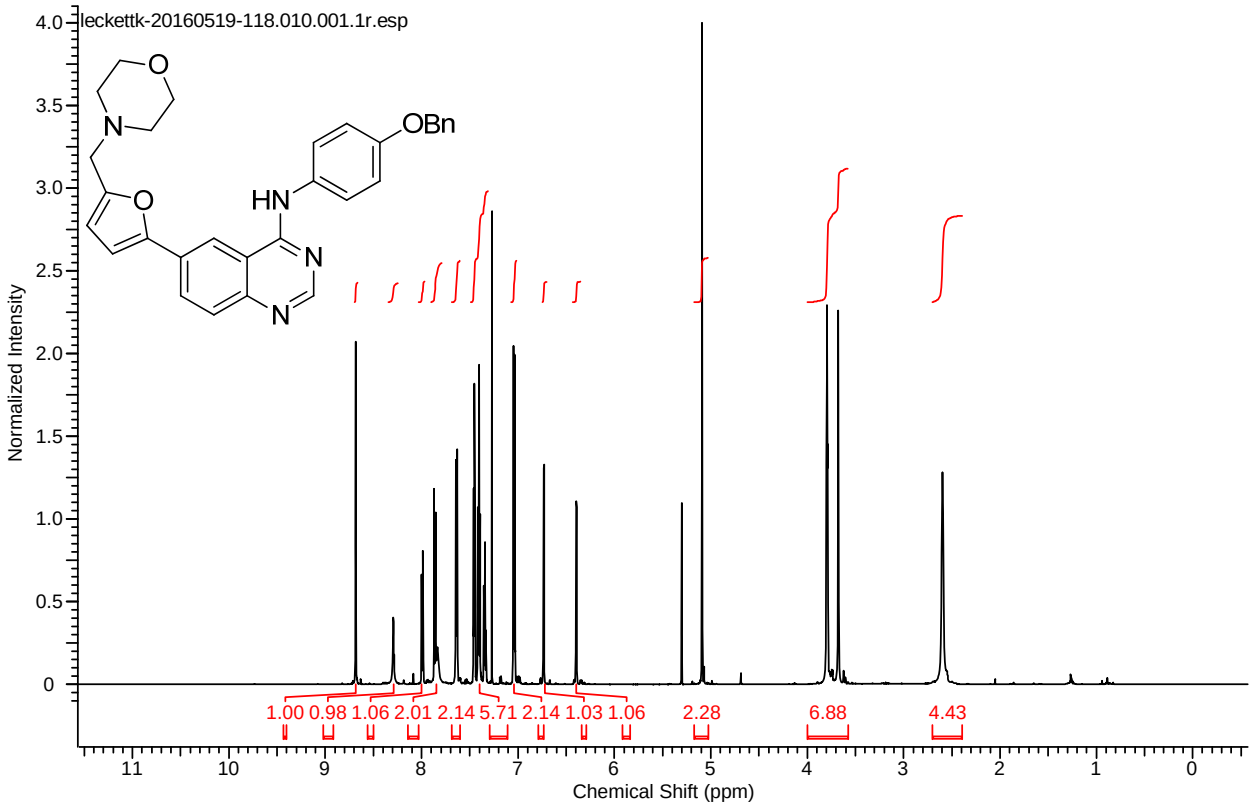

leckettk-20160602-130_DMSO.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
157.63
154.28
152.19
152.02
150.04
148.92
136.68
128.49
127.51
124.43
122.64
115.33
114.26
111.68
107.87
66.09
54.58
52.88

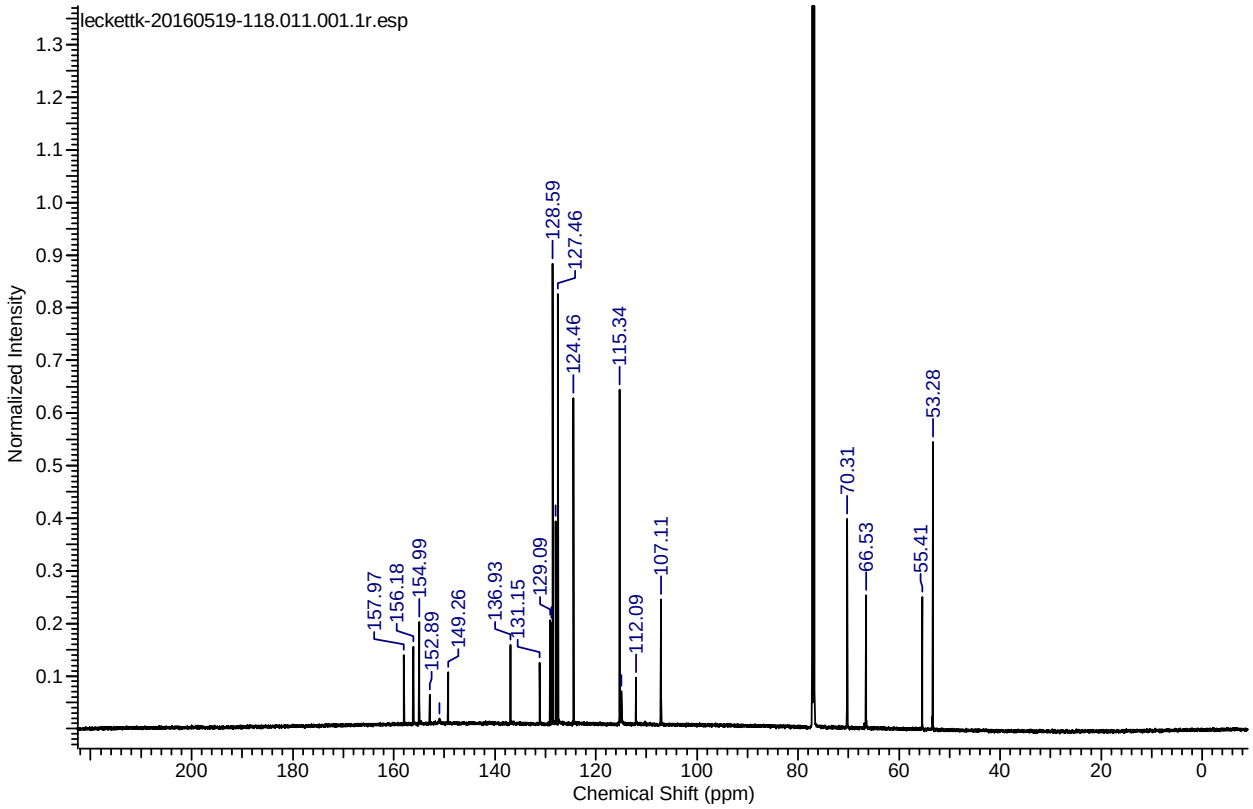

leckettk-20160530-125.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
O
N
O
HN
OBn
N
N
1.00 1.82 1.03 1.04 2.06 5.31 2.10 1.03 1.03 1.41 2.12 2.12 8.79

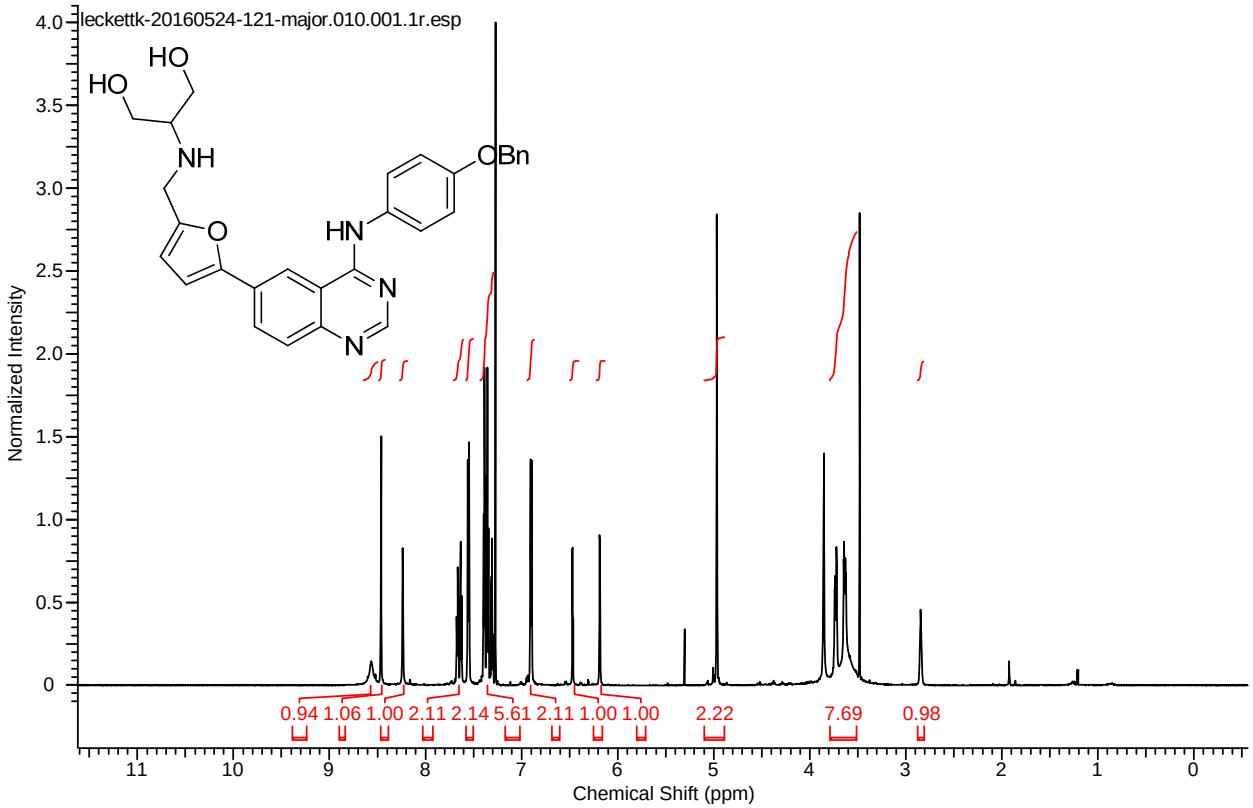

leckettk-20160530-125.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.10
156.24
152.77
151.22
148.71
136.81
128.91
128.57
127.44
124.62
115.27
111.78
107.33
53.79
51.28
50.31

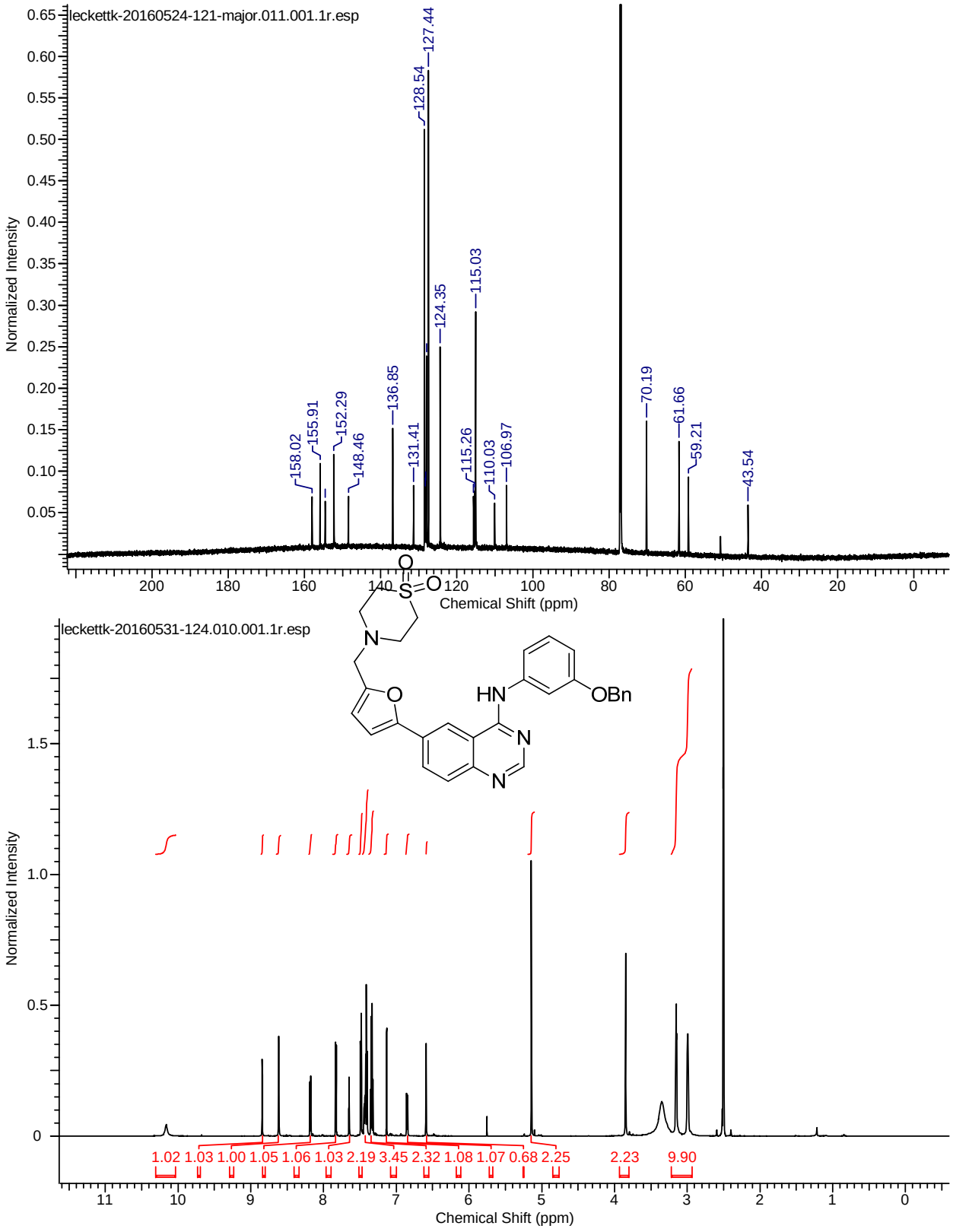

leckettk-20160531-127.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
N
O
HN
OBn
N
N
1.00 1.03 1.07 2.02 2.09 2.15 2.17 1.13 2.19 1.07 1.04 2.16
2.13
8.89

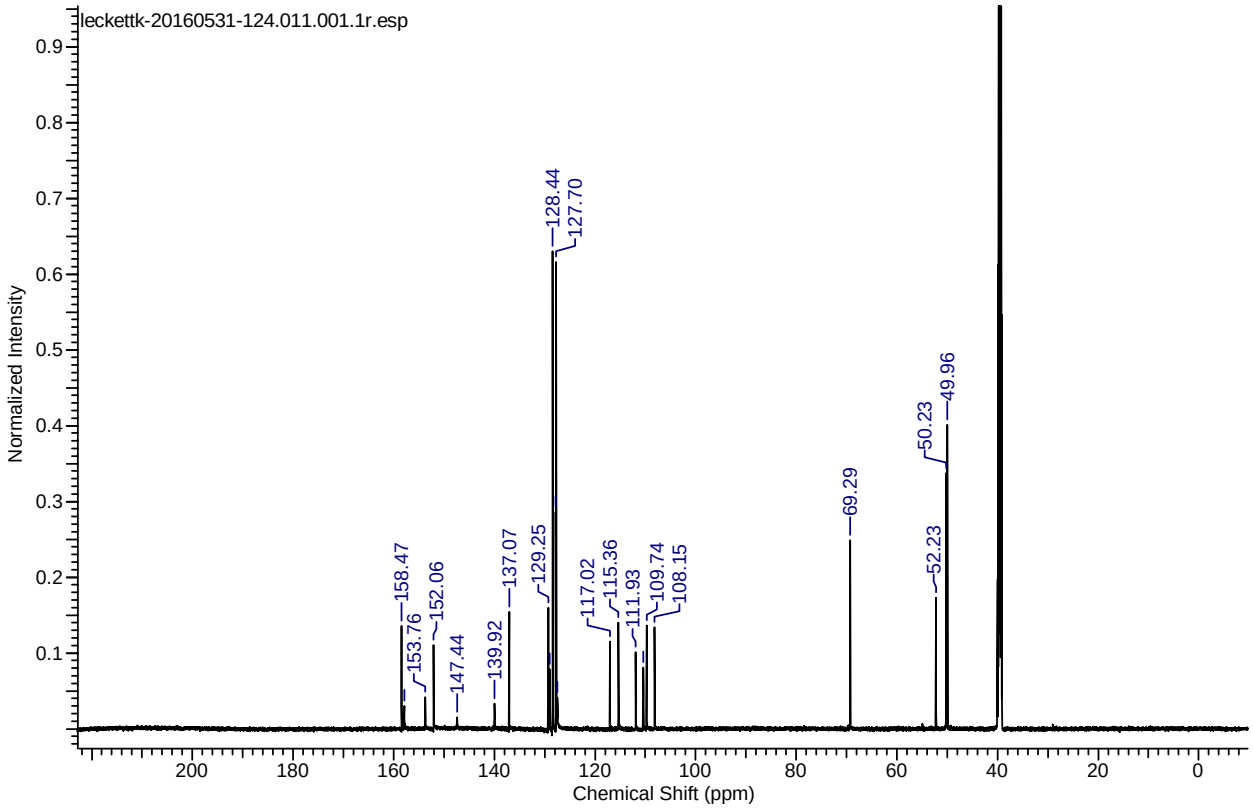

leckettk-20160531-127.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.00
156.17
154.98
152.81
149.23
136.91
129.04
128.58
127.45
124.49
115.32
112.02
107.09
70.29
55.73
54.57
27.58

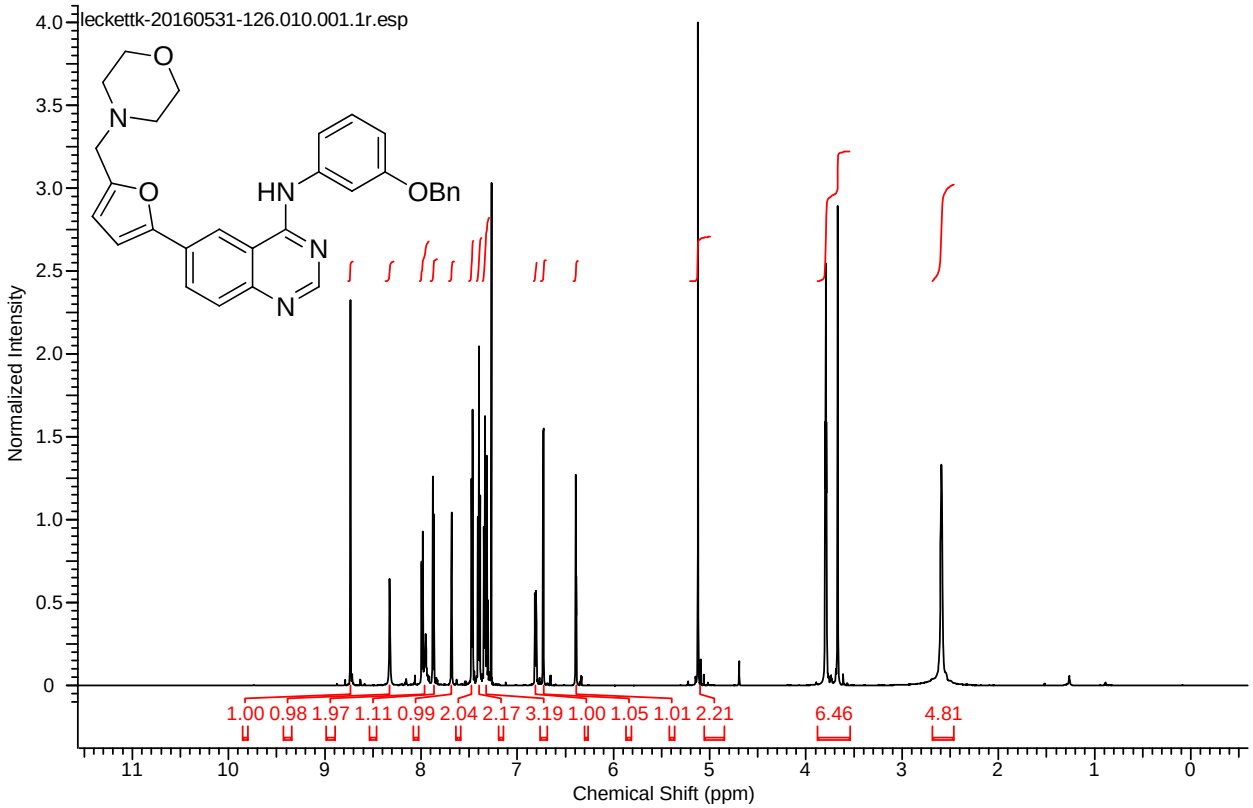

leckettk-20160519-118.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
N
O
HN
OBn
N
N
1.00 0.98 1.06 2.01 2.14 5.71 2.14 1.03 1.06
2.28
6.88
4.43

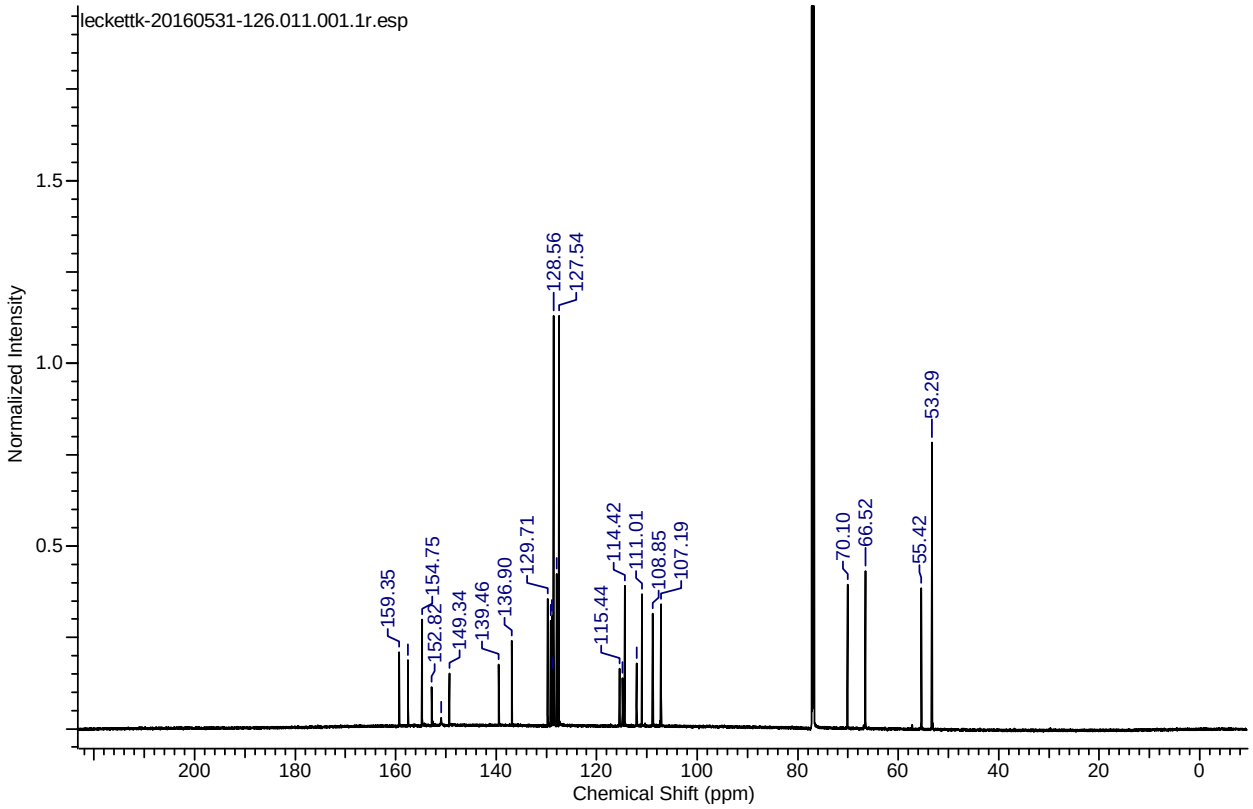

leckettk-20160519-118.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
157.97
156.18
154.99
152.89
149.26
136.93
131.15
129.09
128.59
127.46
124.46
115.34
112.09
107.11
70.31
66.53
55.41
53.28

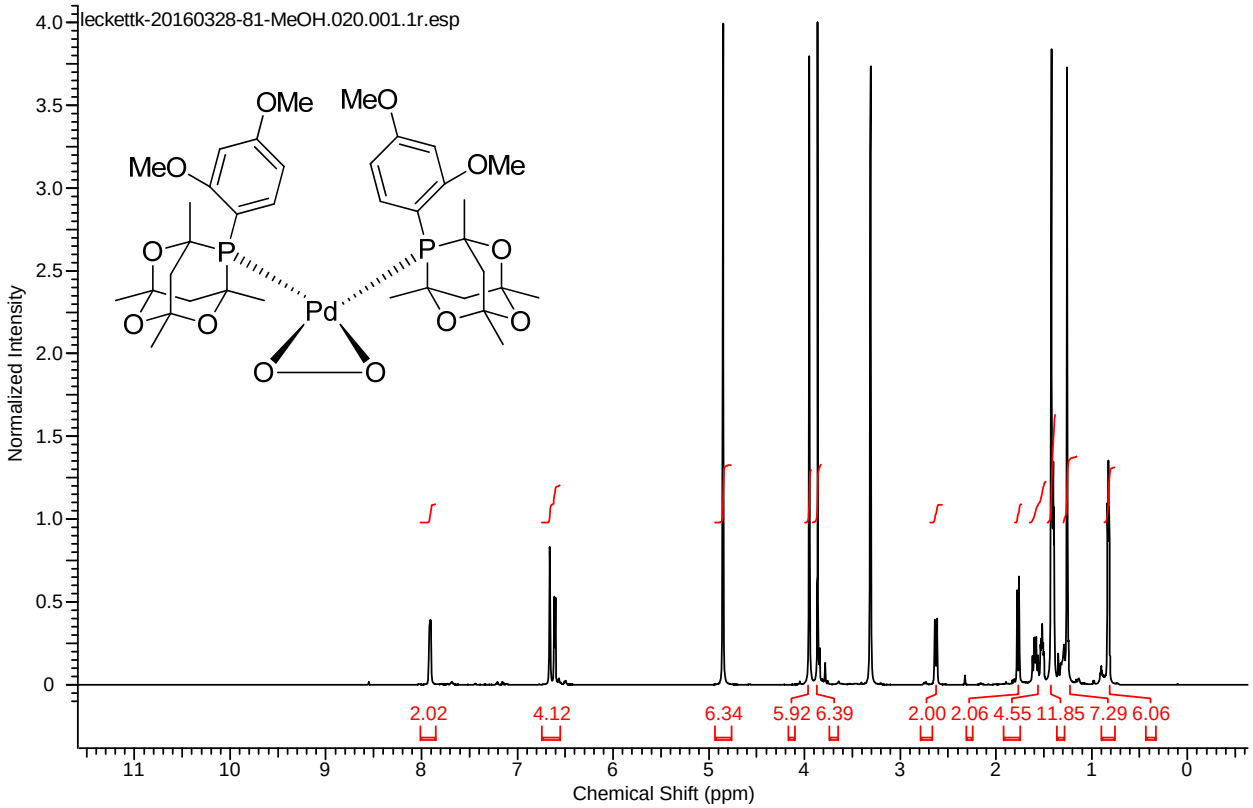

leckettk-20160524-121-major.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
HO
HO
NH
O
HN
CBn
N
N
0.94 1.06 1.00 2.11 2.14 5.61 2.11 1.00 1.00 2.22 7.69 0.98

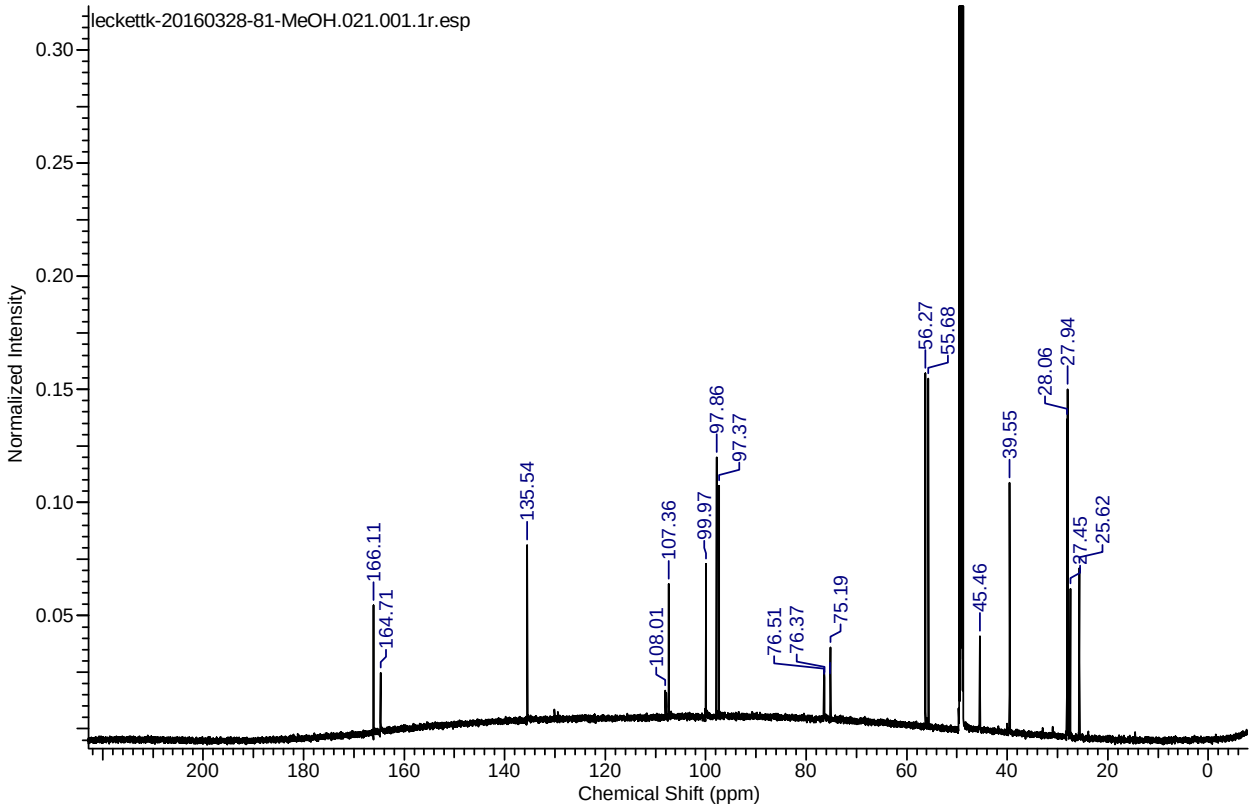

leckettk-20160524-121-major.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.02
155.91
152.29
148.46
136.85
131.41
128.54
127.44
124.35
115.26
115.03
110.03
106.97
70.19
61.66
59.21
43.54
leckettk-20160531-124.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
1.02 1.03 1.00 1.05 1.06 1.03 2.19 3.45 2.32 1.08 1.07 0.68 2.25
2.23
9.90
O
S
O
N
O
HN
OBn
N
N

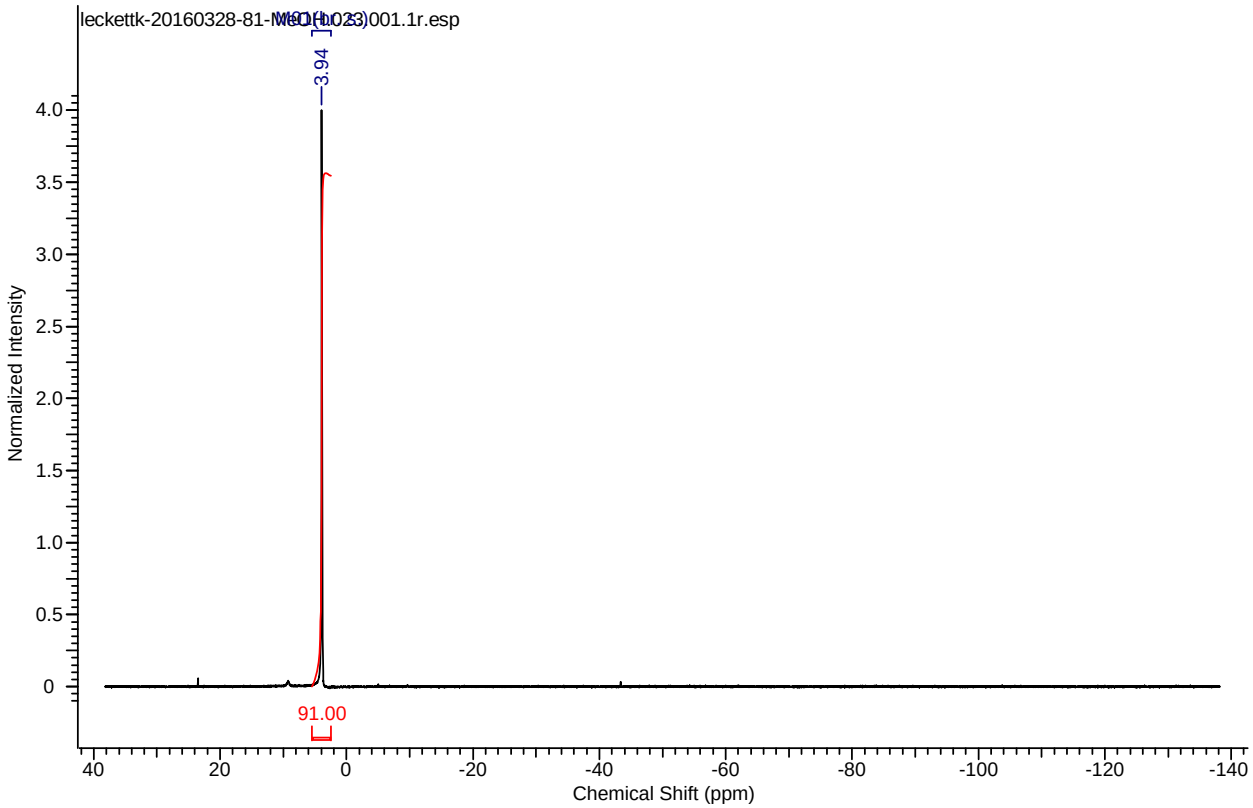

leckettk-20160531-124.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.47
153.76
152.06
147.44
139.92
137.07
129.25
128.44
127.70
117.02
115.36
111.93
109.74
108.15
69.29
52.23
50.23
49.96

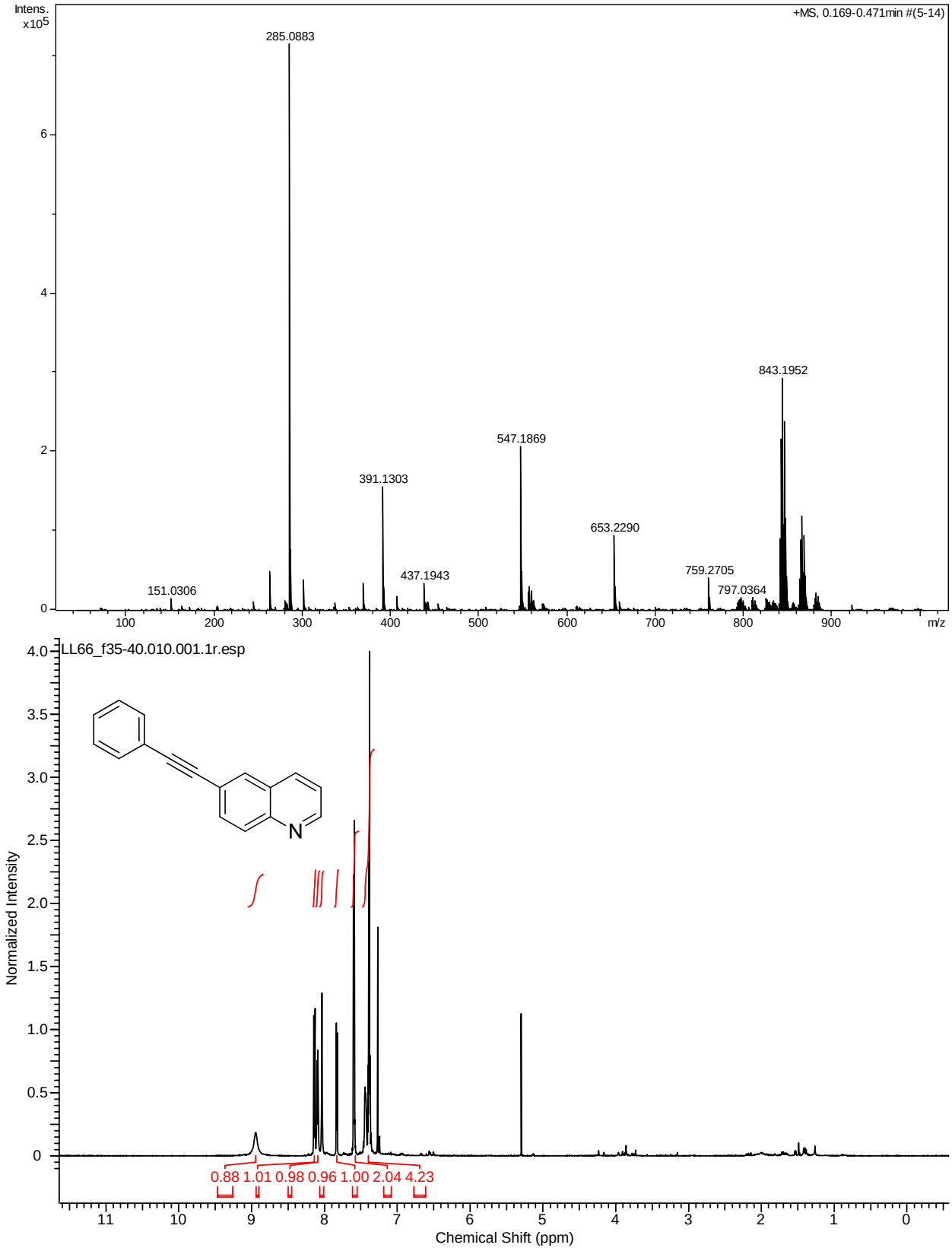

leckettk-20160531-126.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
N
O
HN
OBn
N
N
1.00 0.98 1.97 1.11 0.99 2.04 2.17 3.19 1.00 1.05 1.01 2.21
6.46
4.81

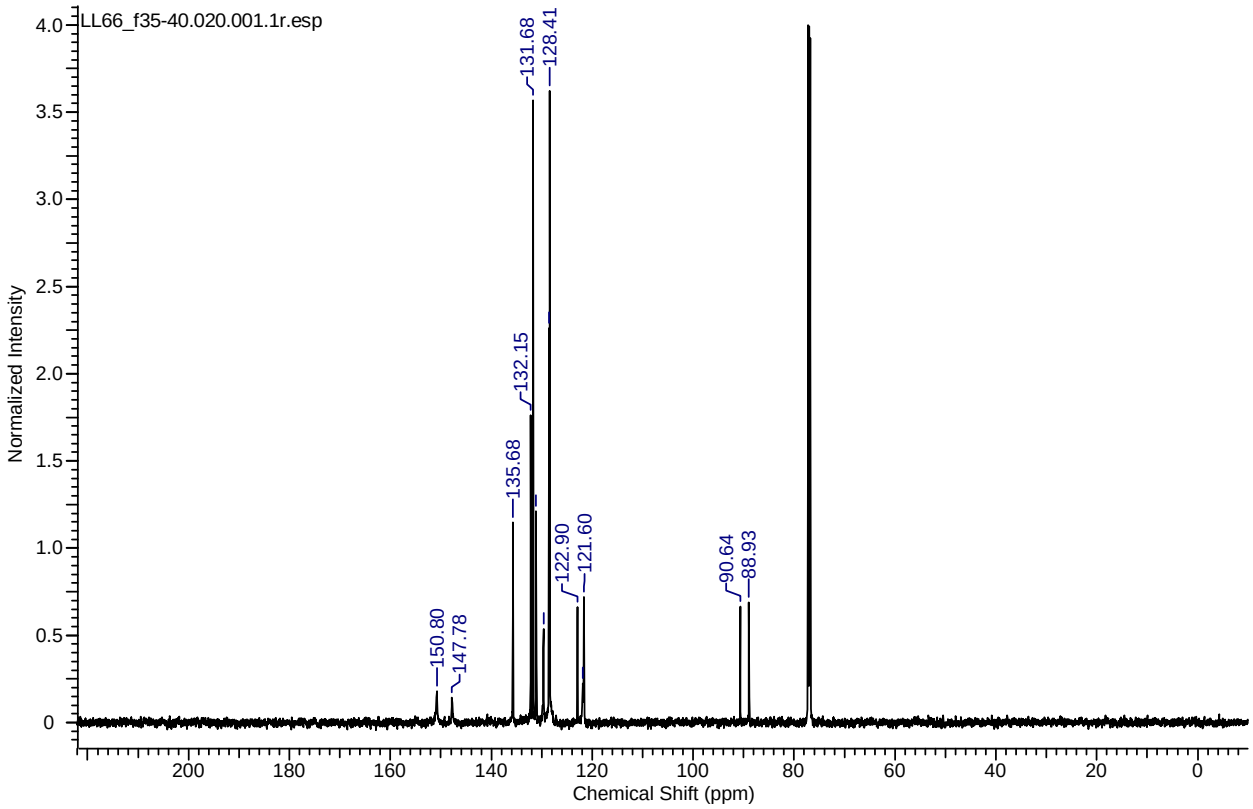

leckettk-20160531-126.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
159.35
154.75
152.82
149.34
139.46
136.90
129.71
128.56
127.54
115.44
114.42
111.01
108.85
107.19
70.10
66.52
55.42
53.29

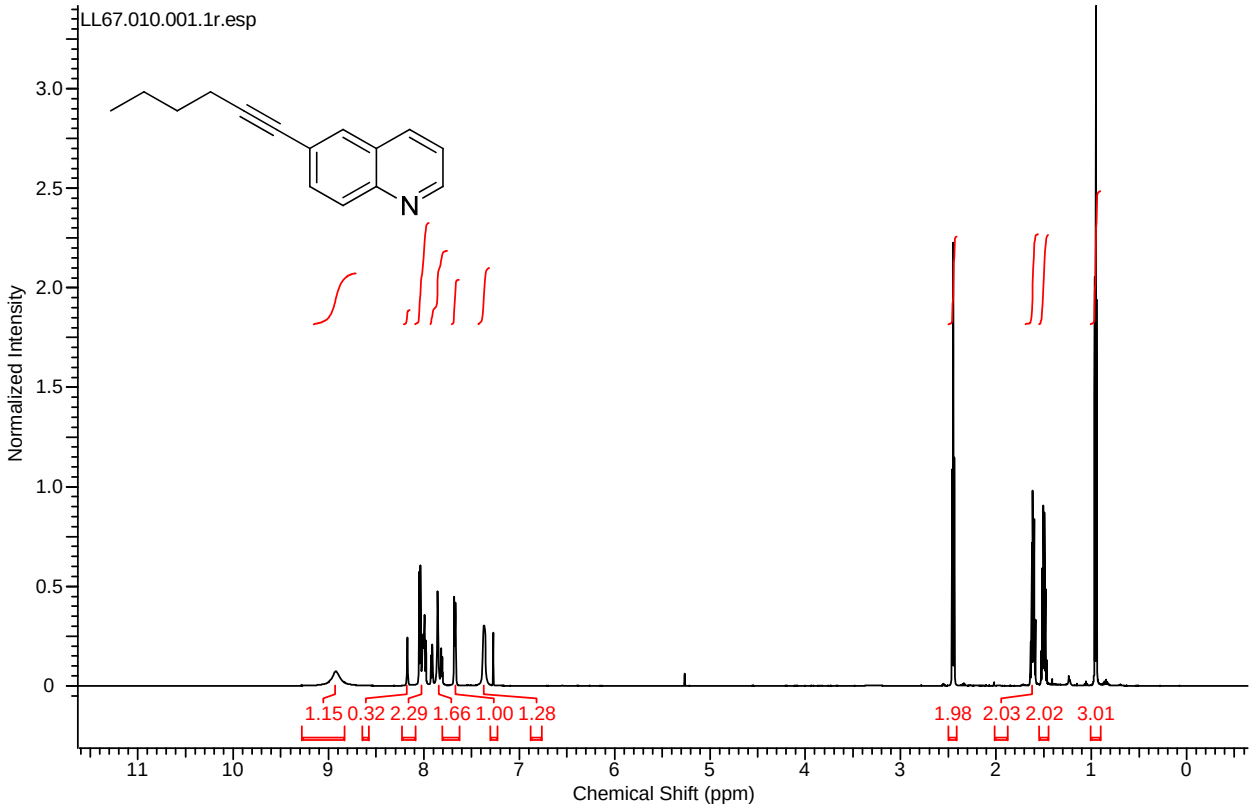

leckettk-20160328-81-MeOH.020.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
OMe
MeO
MeO
OMe
P
P
Pd
O
2.02
4.12
6.34
5.92
6.39
2.00
2.06
4.55
11.85
7.29
6.06

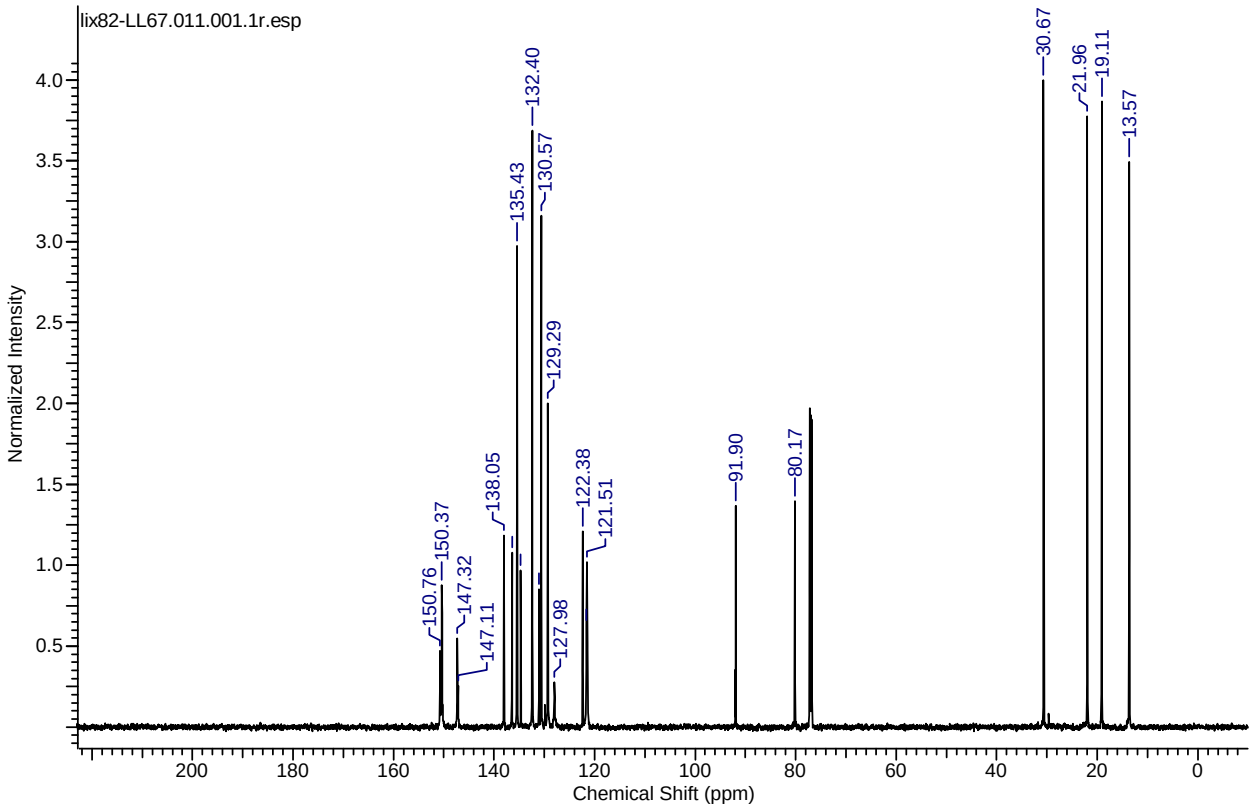

leckettk-20160328-81-MeOH.021.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
166.11
164.71
135.54
108.01
107.36
99.97
97.86
97.37
76.51
76.37
75.19
56.27
55.68
45.46
39.55
28.06
27.94
27.45
25.62

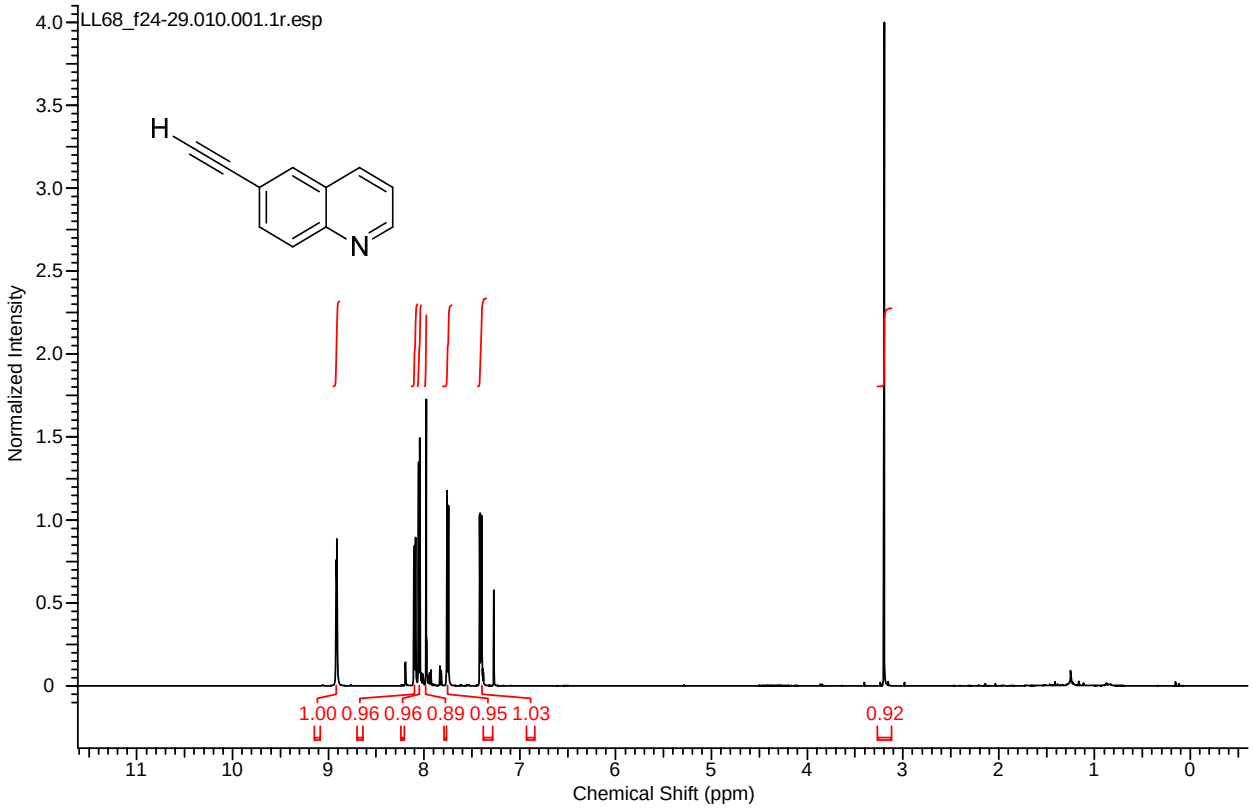

leckettk-20160328-81-MeOH.023.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
3.94
91.00

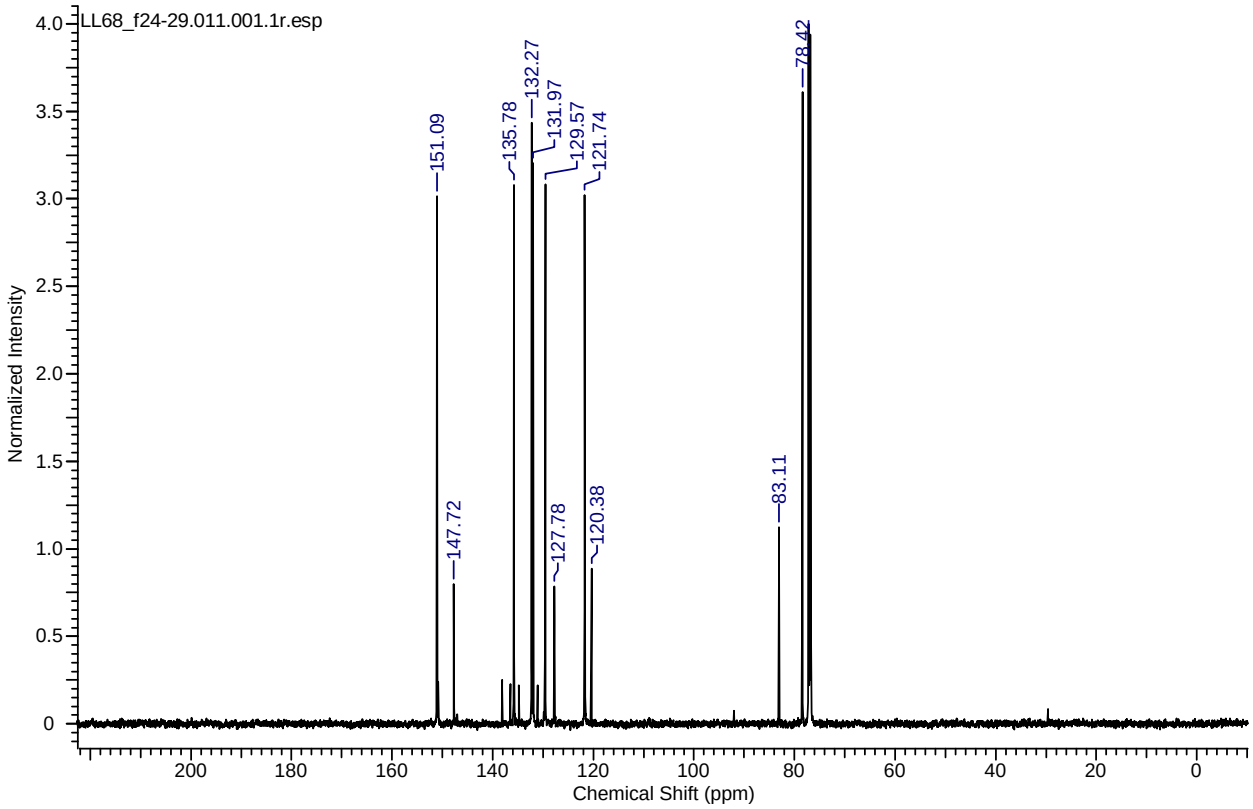

Intens.
x10^5
+MS, 0.169-0.471min #(5-14)
285.0883
843.1952
547.1869
391.1303
653.2290
759.2705
797.0364
437.1943
151.0306
m/z
LL66_f35-40.010.001.1r.esp
Normalized Intensity
0.88 1.01 0.98 0.96 1.00 2.04 4.23
Chemical Shift (ppm)

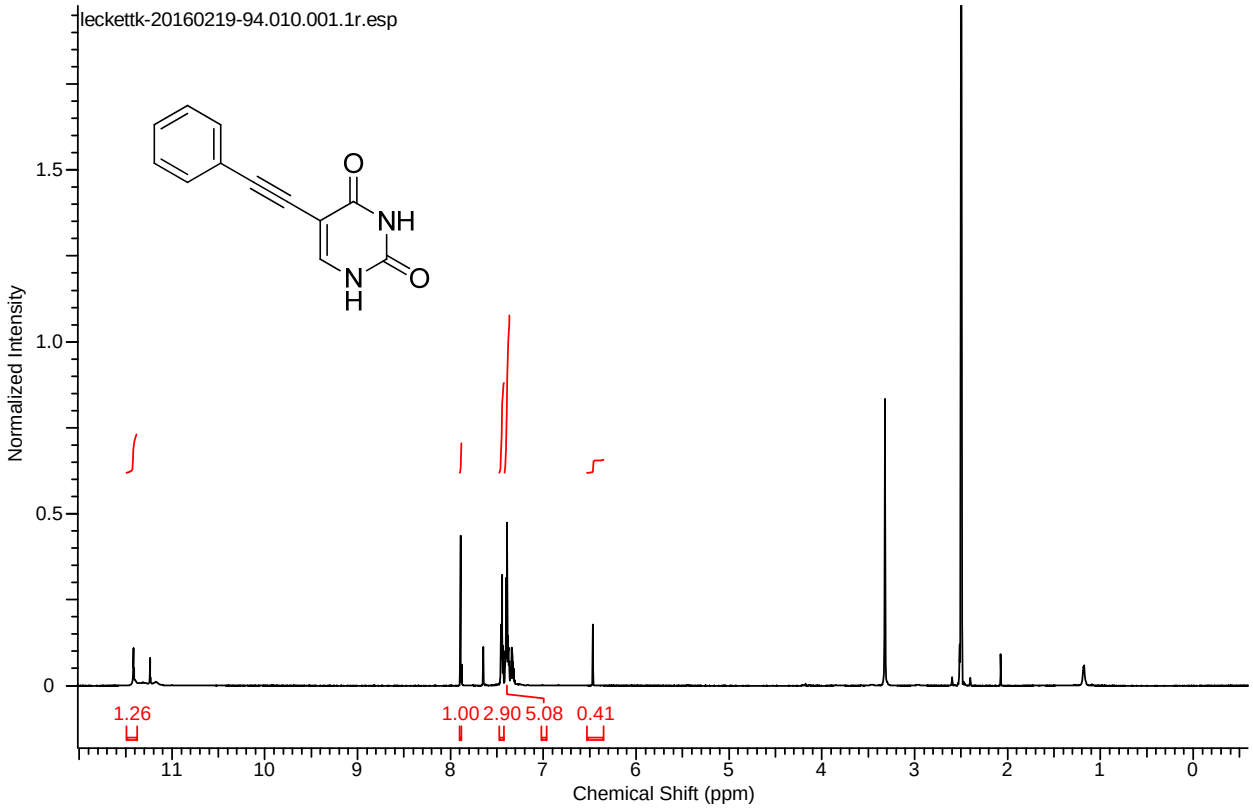

LL66_f35-40.020.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
131.68
128.41
132.15
135.68
122.90
121.60
90.64
88.93
150.80
147.78

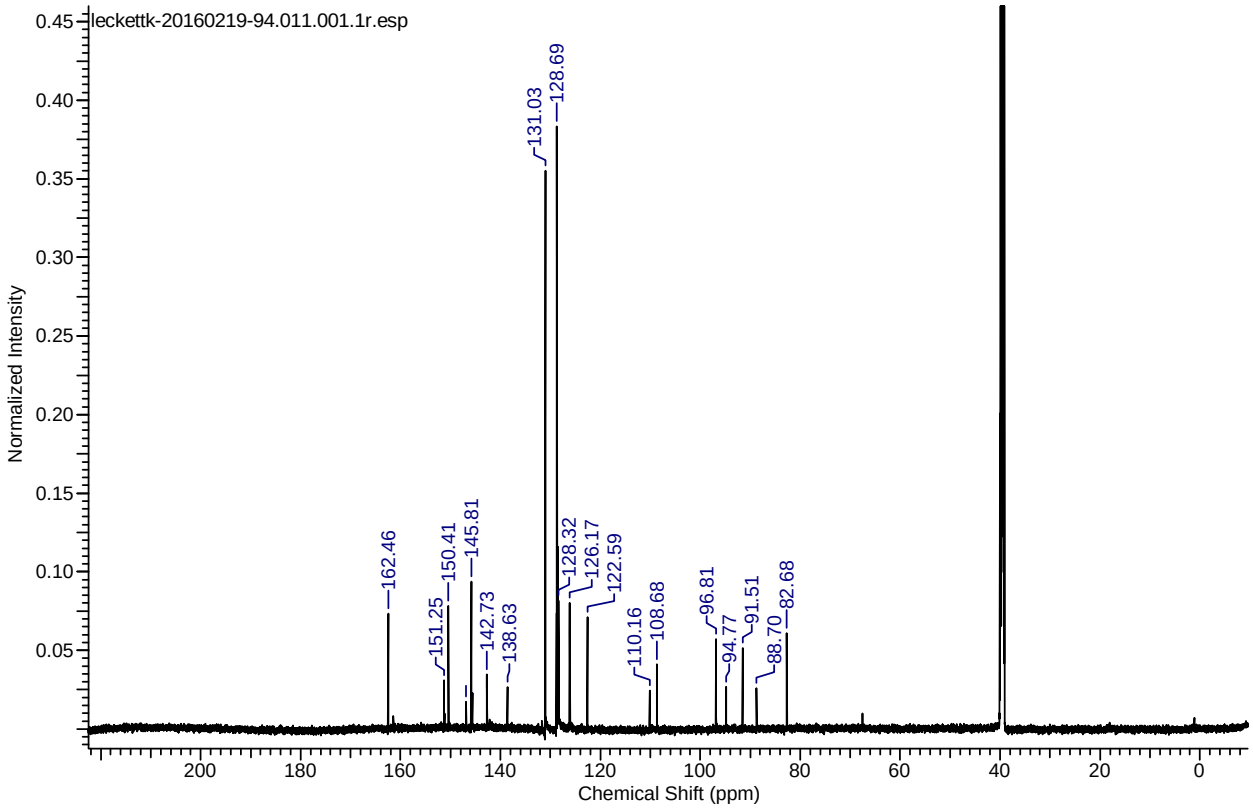

LL67.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
N
1.15 0.32 2.29 1.66 1.00 1.28
1.98 2.03 2.02 3.01

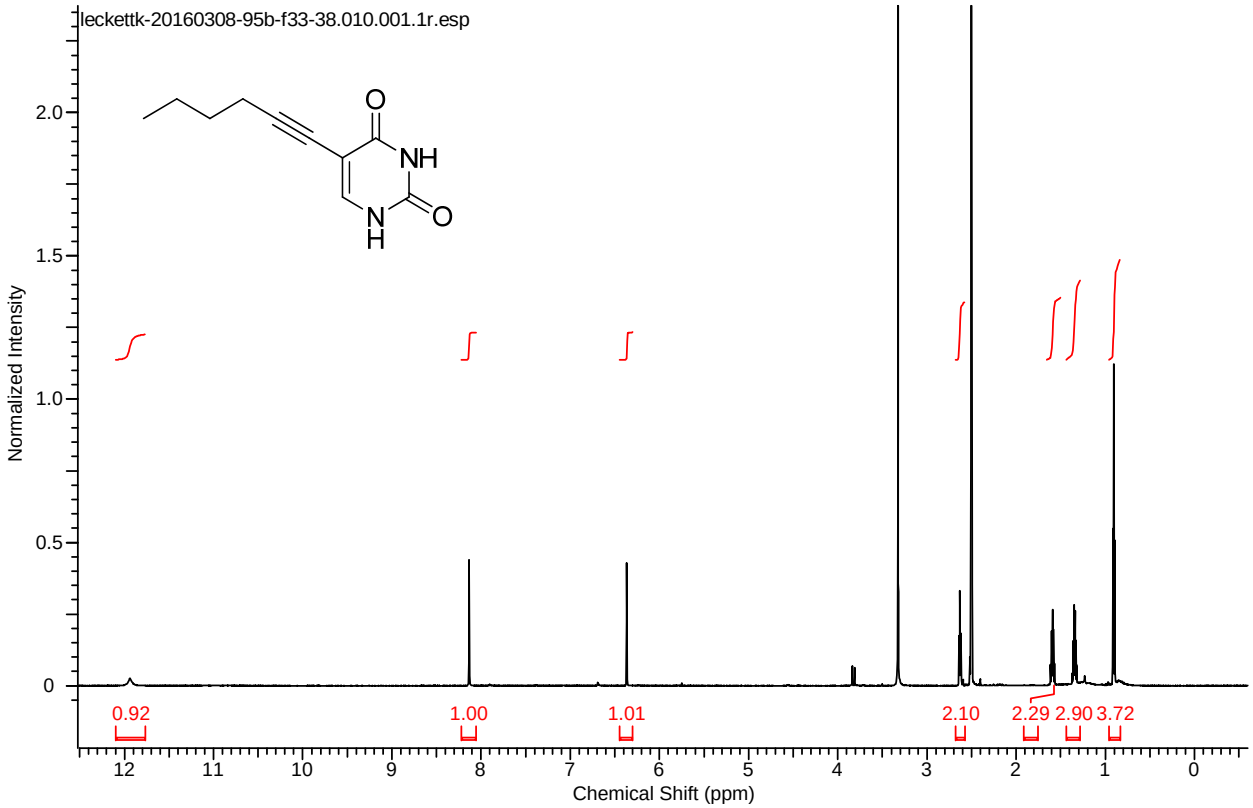

lix82-LL67.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
150.76
150.37
147.32
147.11
138.05
135.43
132.40
130.57
129.29
127.98
122.38
121.51
91.90
80.17
30.67
21.96
19.11
13.57

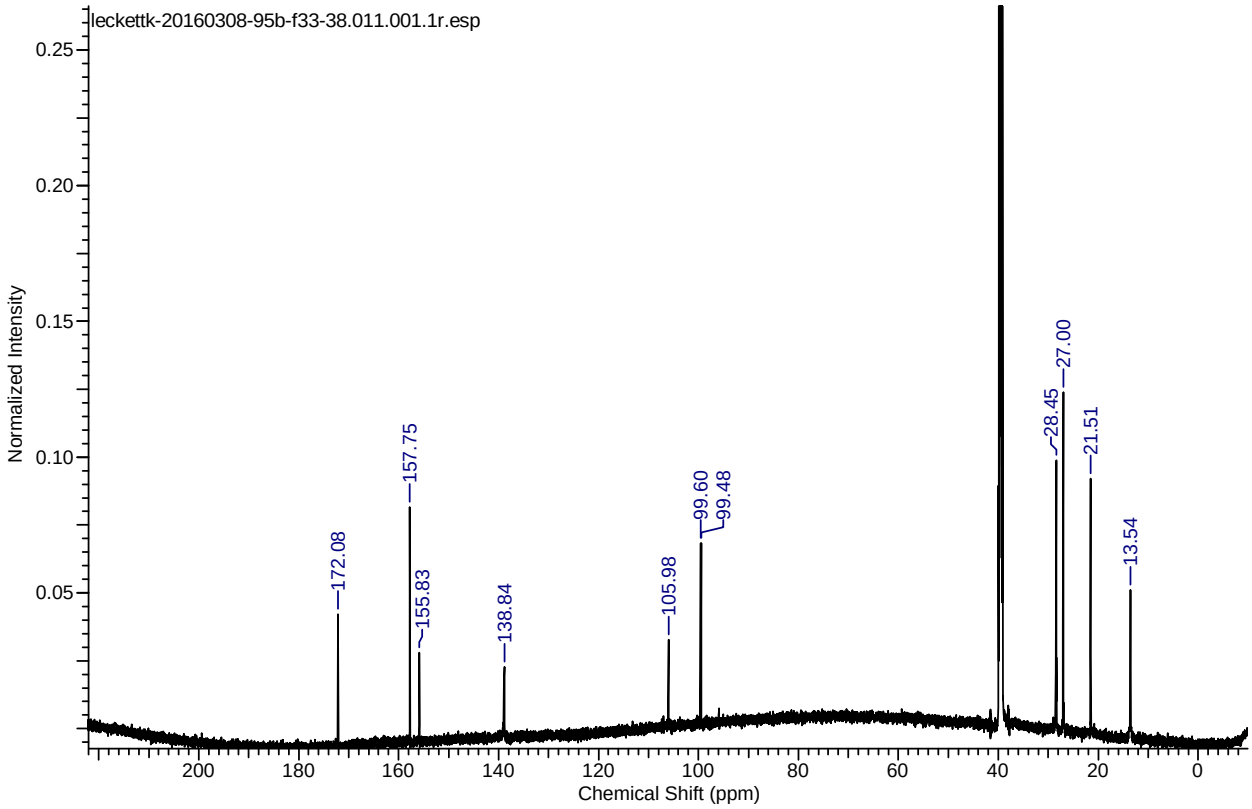

LL68_f24-29.010.001.1r.esp
H
N
Normalized Intensity
Chemical Shift (ppm)
1.00 0.96 0.96 0.89 0.95 1.03
0.92

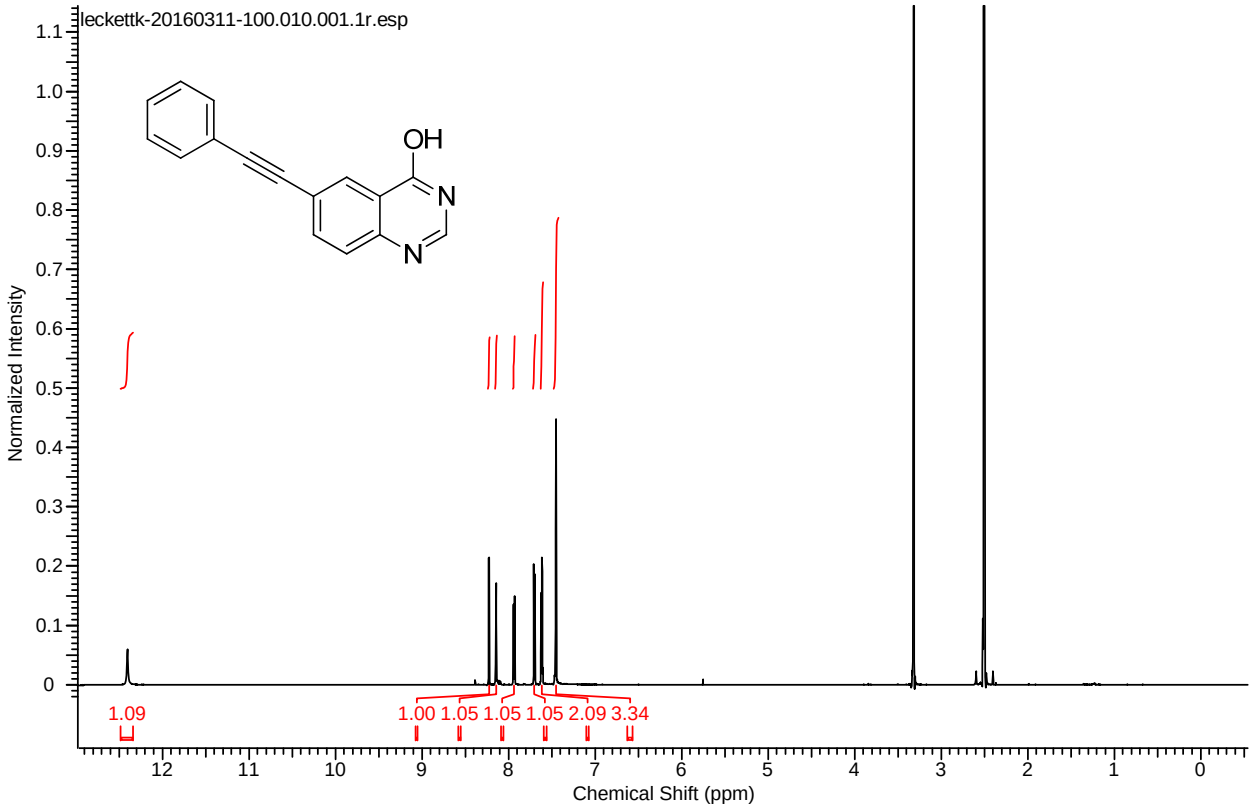

LL68_f24-29.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
151.09
147.72
135.78
132.27
131.97
129.57
127.78
121.74
120.38
83.11
78.42

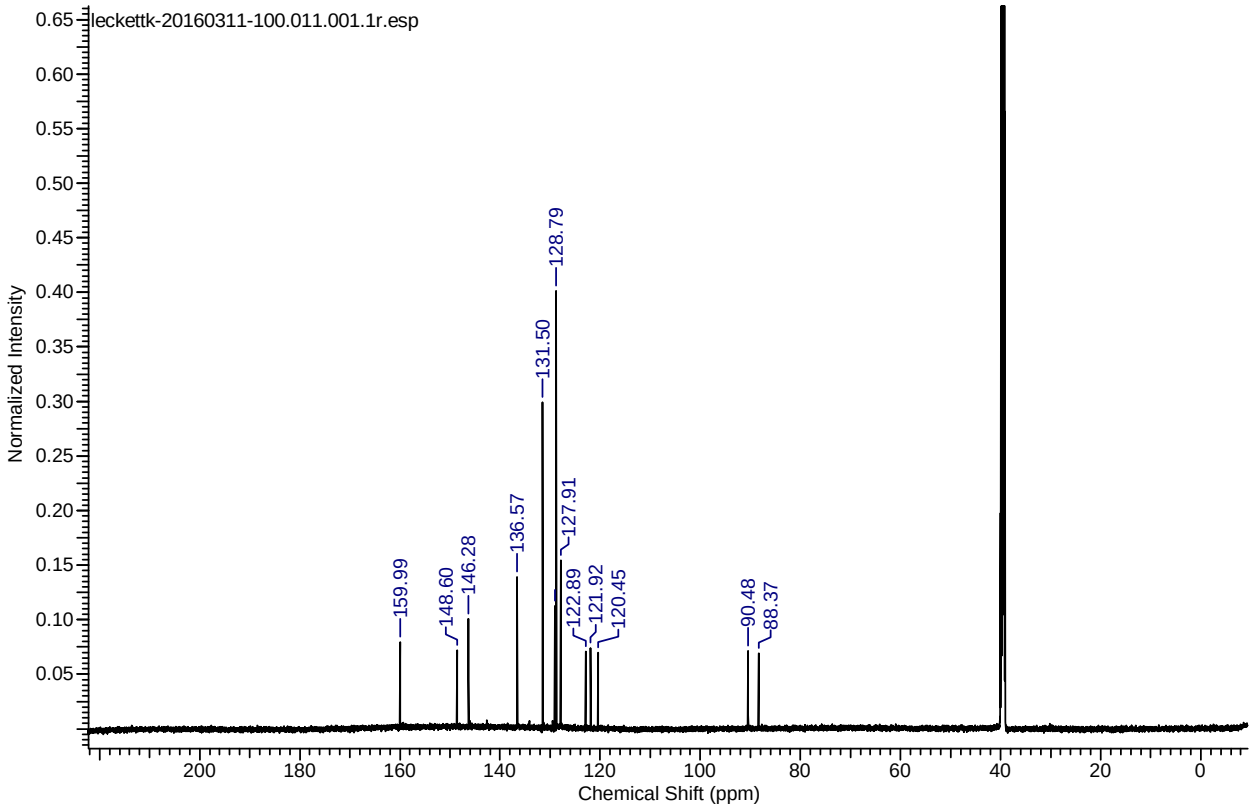

leckettk-20160219-94.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
NH
N
H
O
1.26
1.00
2.90
5.08
0.41

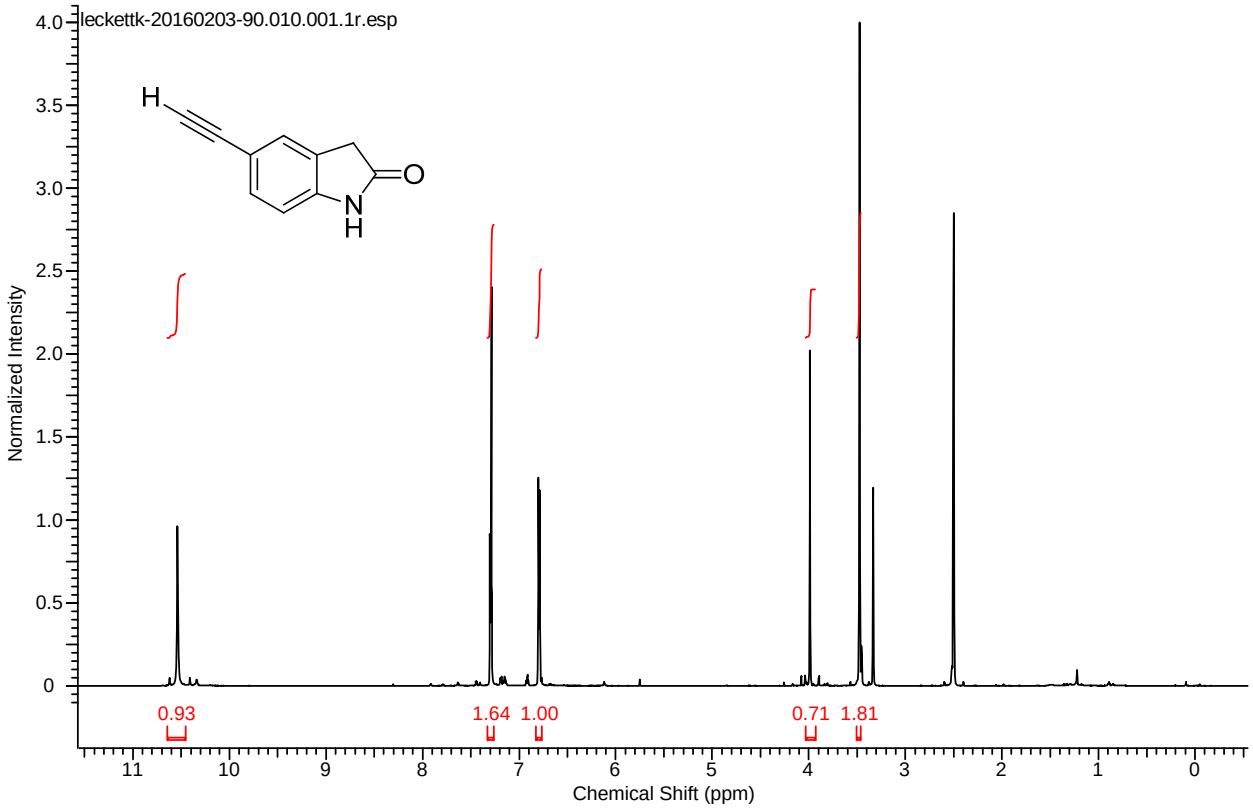

leckettk-20160219-94.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
162.46
151.25
150.41
145.81
142.73
138.63
131.03
128.69
128.32
126.17
122.59
110.16
108.68
96.81
94.77
91.51
88.70
82.68

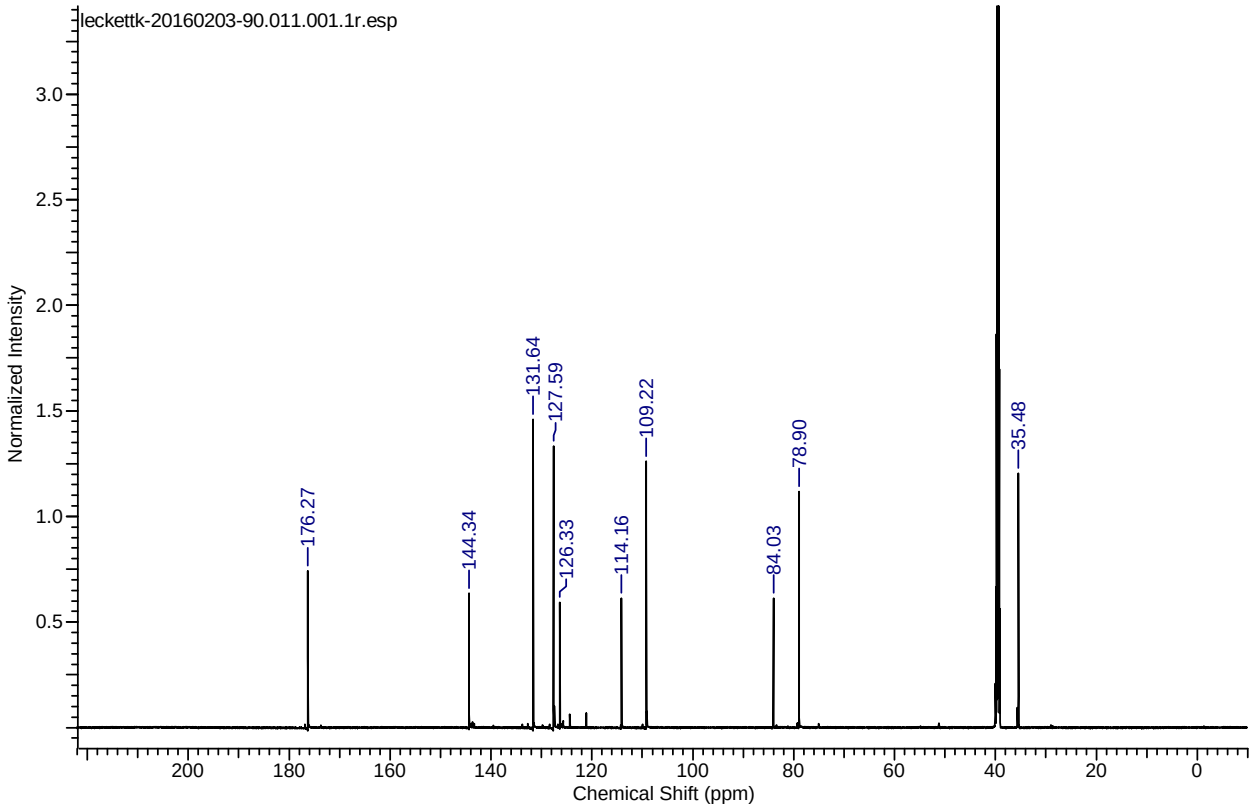

leckettk-20160308-95b-f33-38.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
NH
N
H
O
0.92
1.00
1.01
2.10
2.29
2.90
3.72

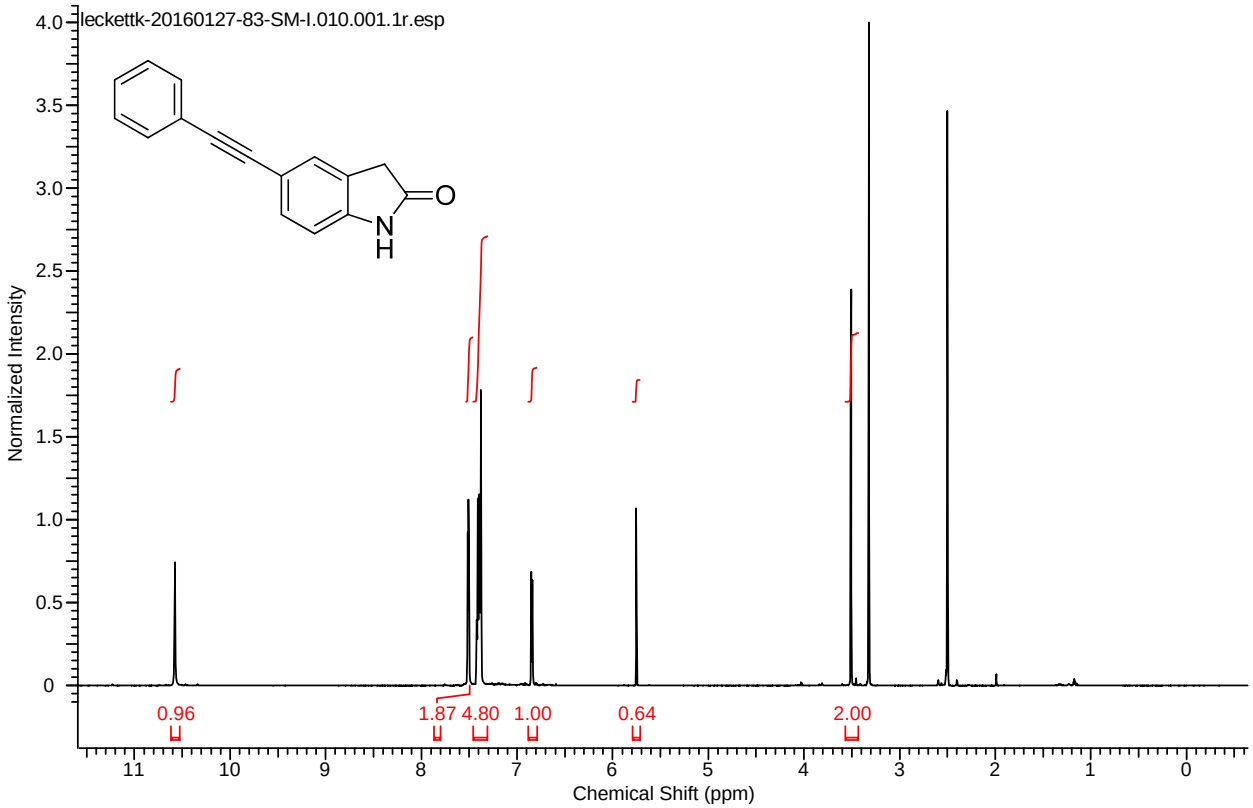

leckettk-20160308-95b-f33-38.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
172.08
157.75
155.83
138.84
105.98
99.60
99.48
28.45
27.00
21.51
13.54

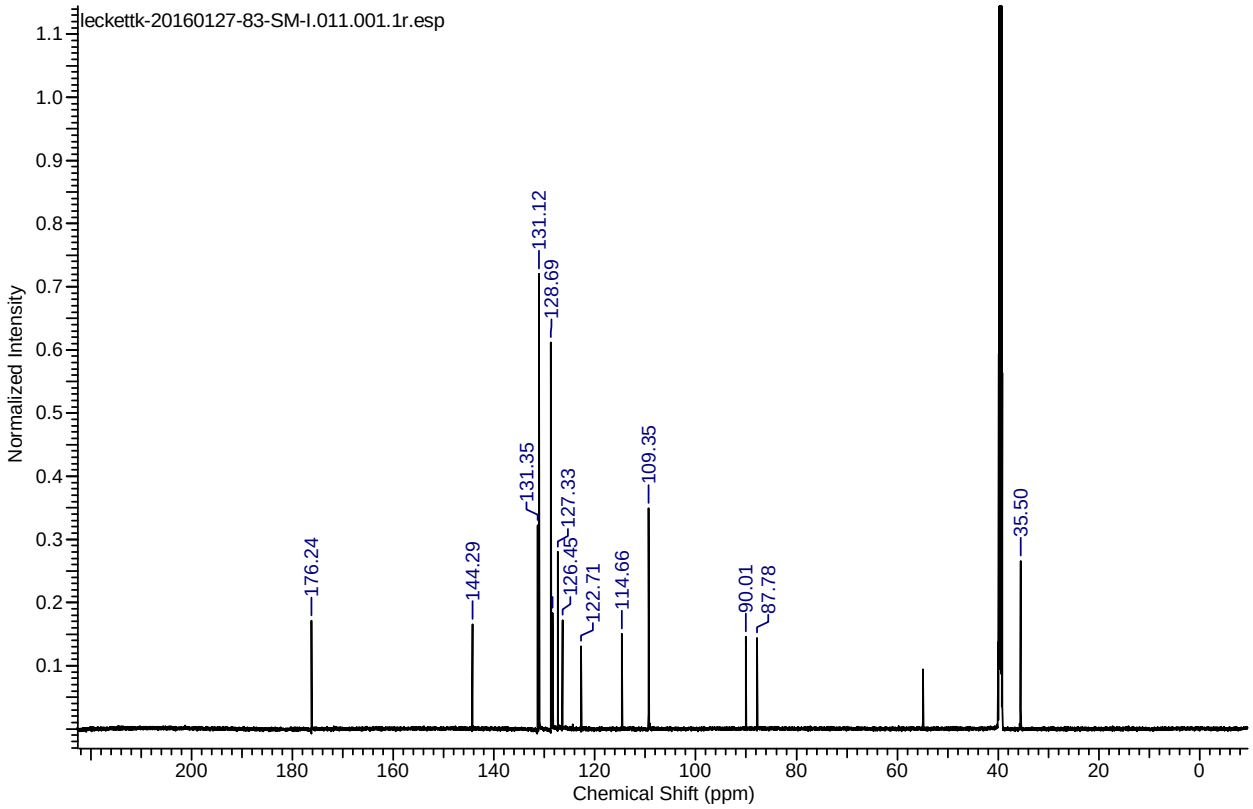

leckettk-20160311-100.010.001.1r.esp
OH
N
N
Normalized Intensity
Chemical Shift (ppm)
1.09
1.00 1.05 1.05 1.05 2.09 3.34

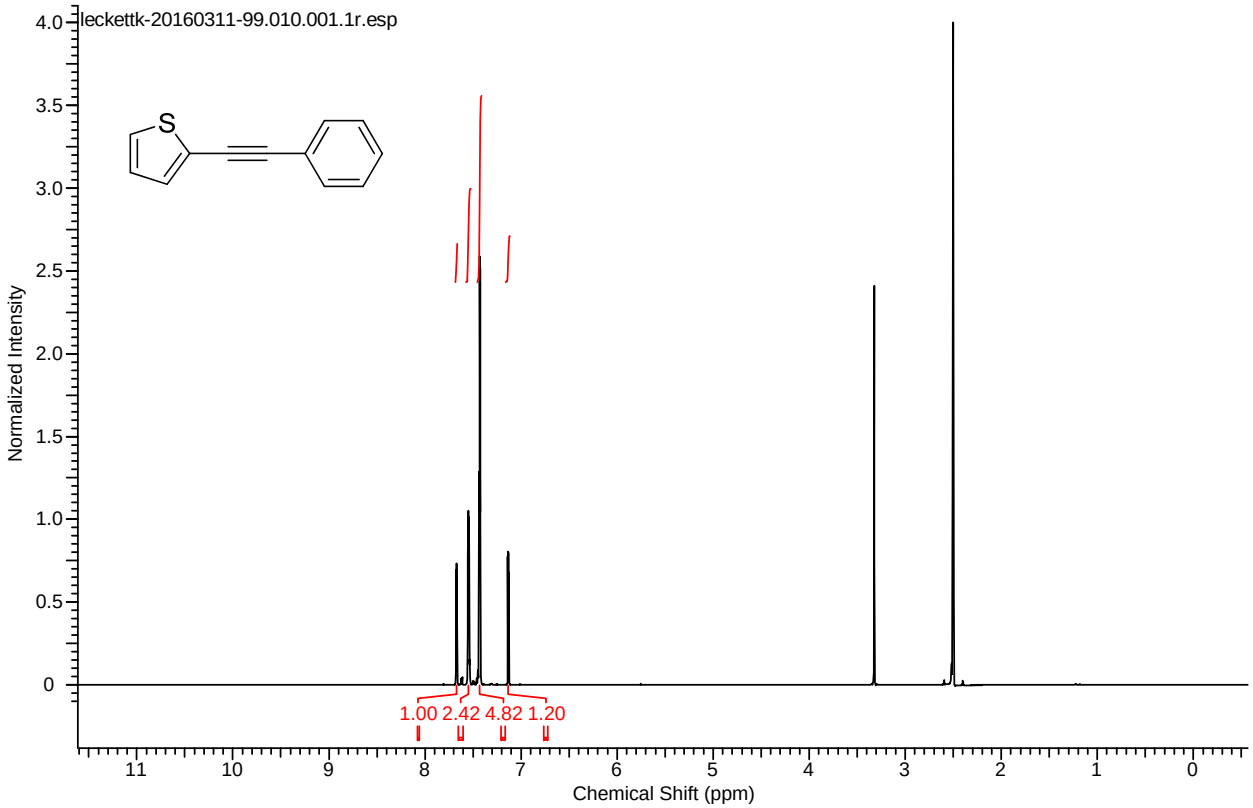

leckettk-20160311-100.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
159.99
148.60
146.28
136.57
131.50
128.79
127.91
122.89
121.92
120.45
90.48
88.37

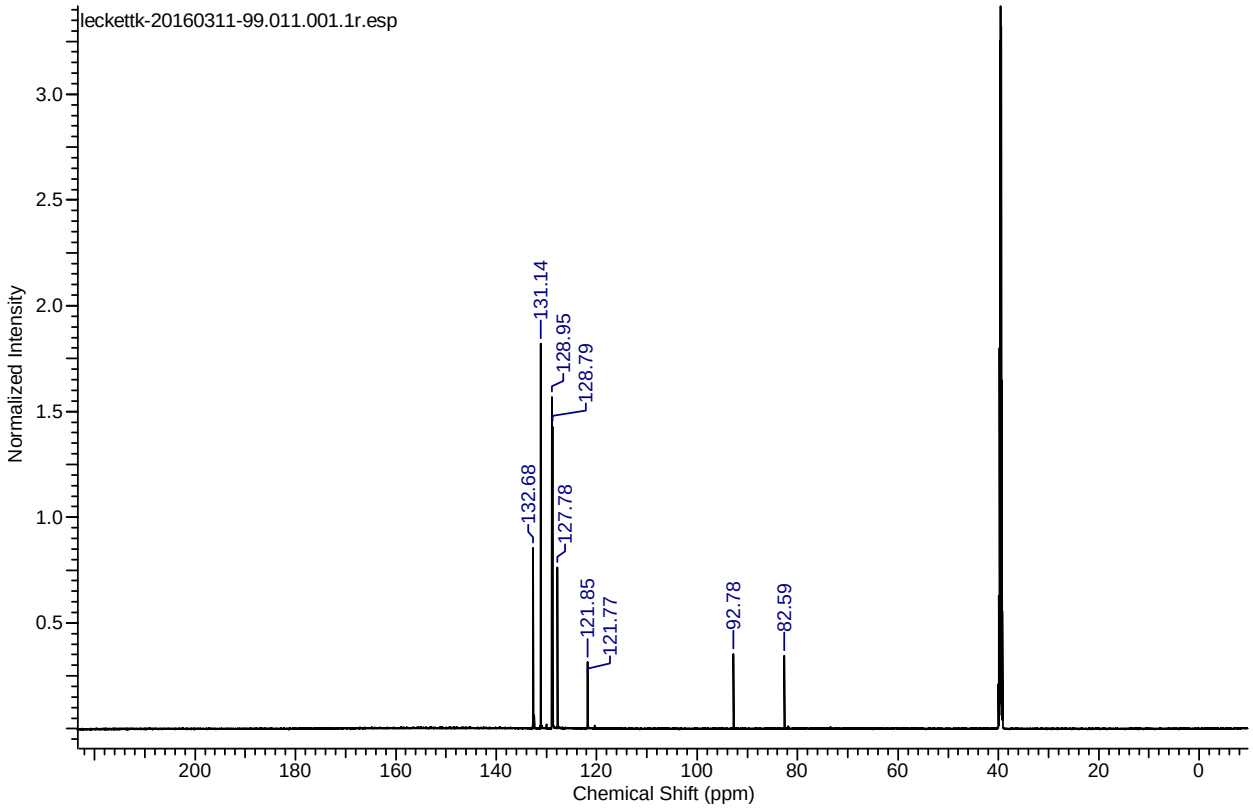

leckettk-20160203-90.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
H
O
N
H
0.93
1.64
1.00
0.71
1.81

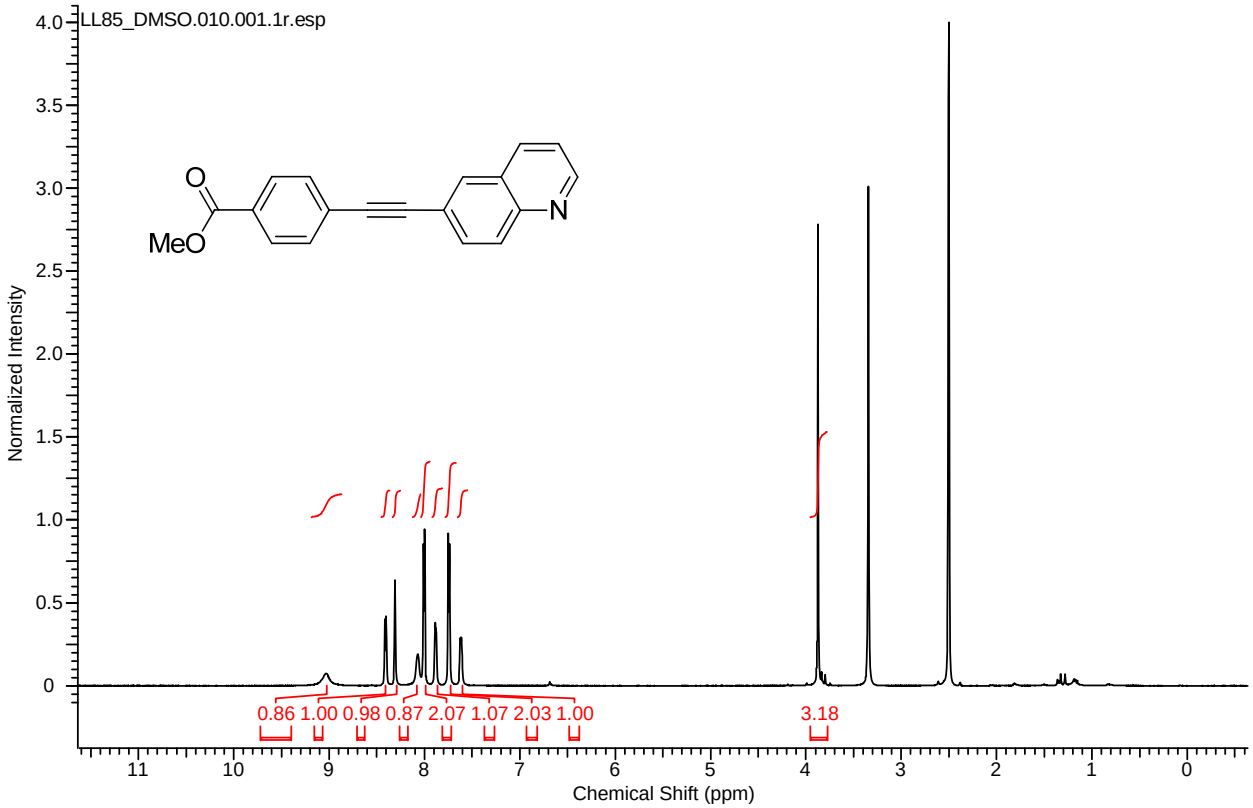

leckettk-20160203-90.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.27
144.34
131.64
127.59
126.33
114.16
109.22
84.03
78.90
35.48

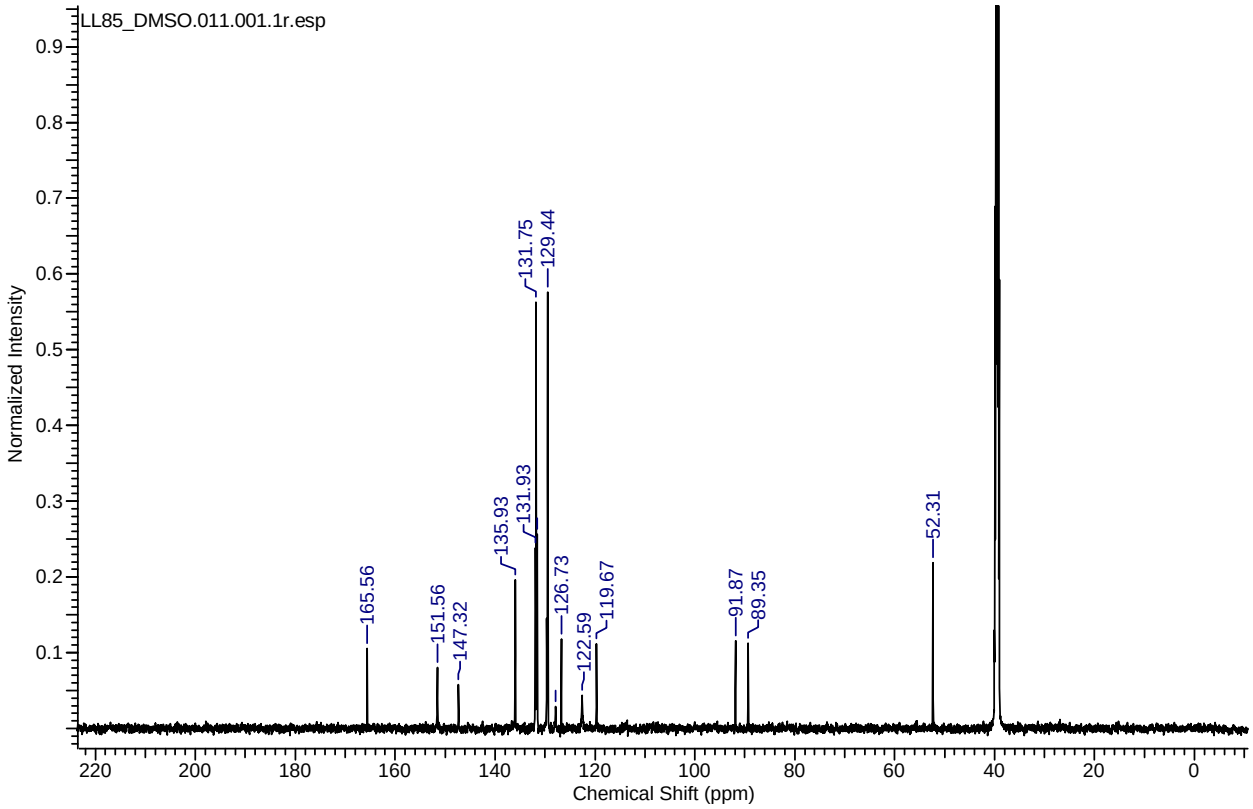

leckettk-20160127-83-SM-I.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
N
H
0.96
1.87
4.80
1.00
0.64
2.00

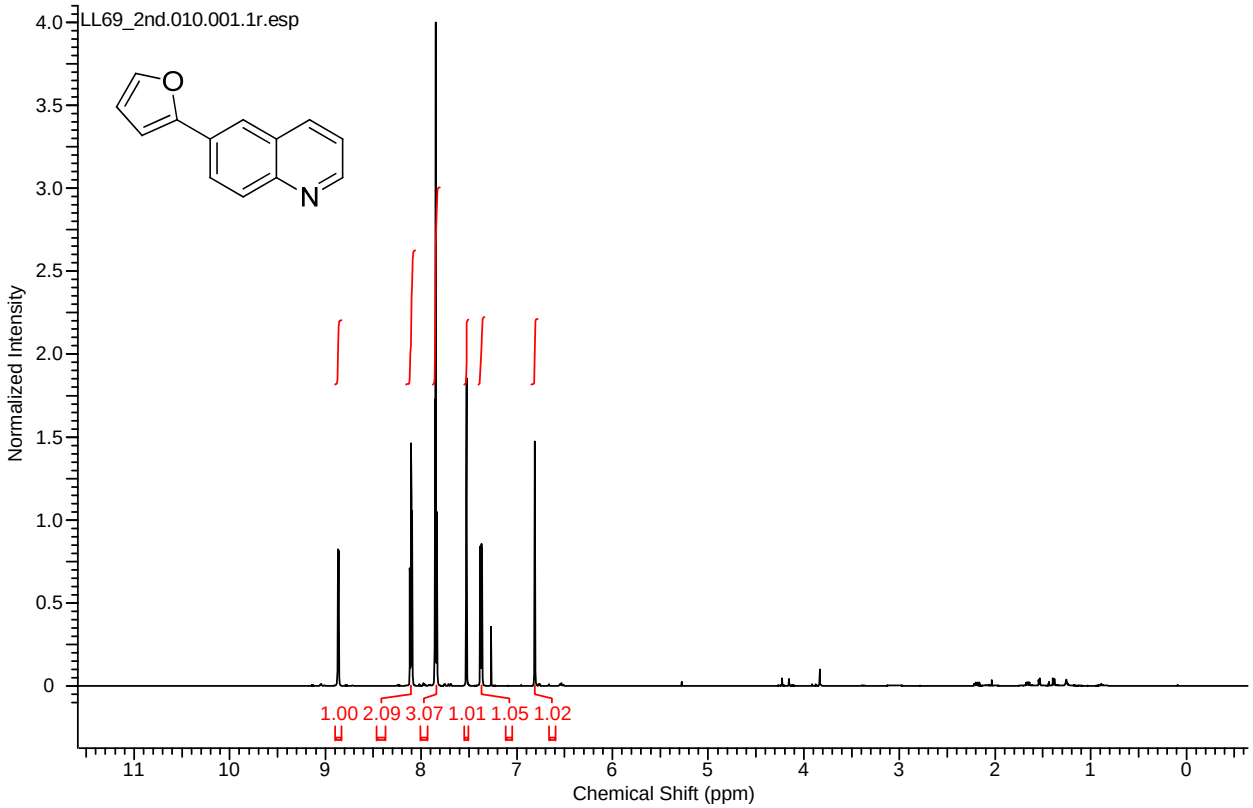

leckettk-20160127-83-SM-I.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
176.24
144.29
131.35
131.12
128.69
127.33
126.45
122.71
114.66
109.35
90.01
87.78
35.50

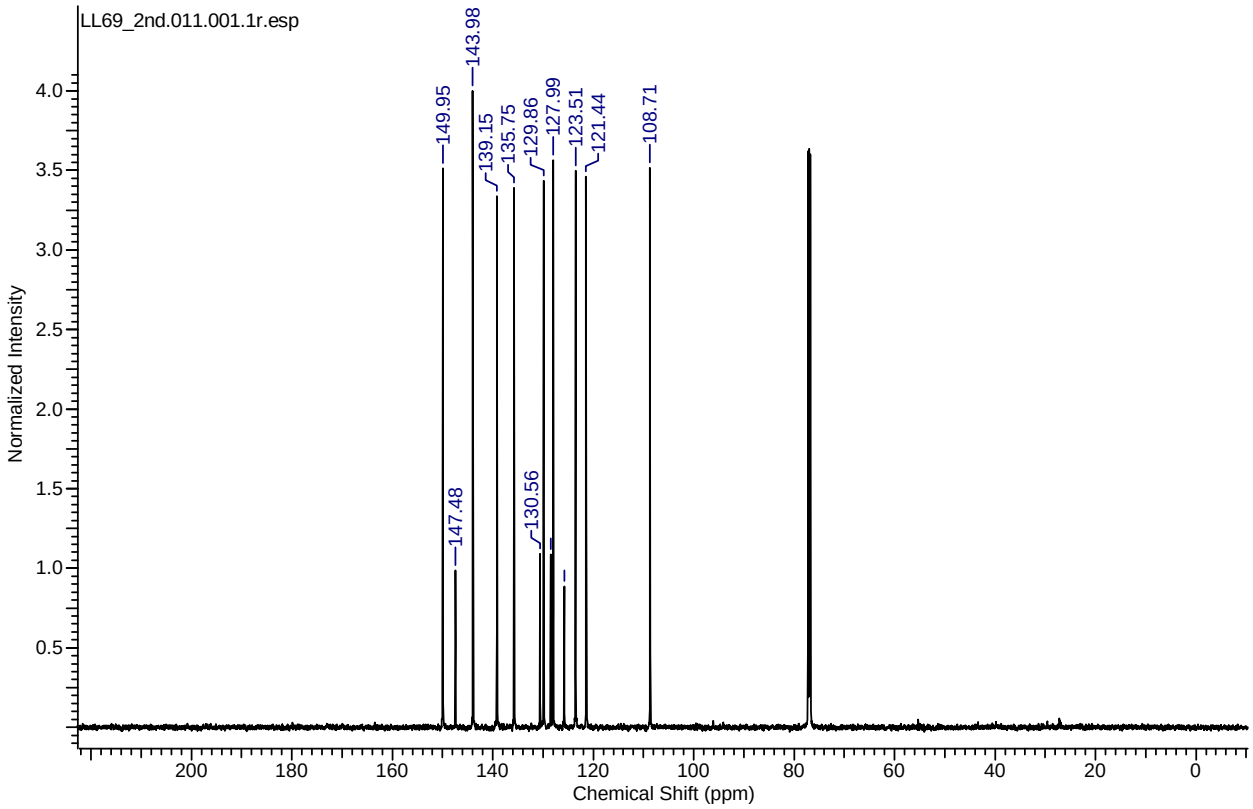

leckettk-20160311-99.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
S
1.00 2.42 4.82 1.20

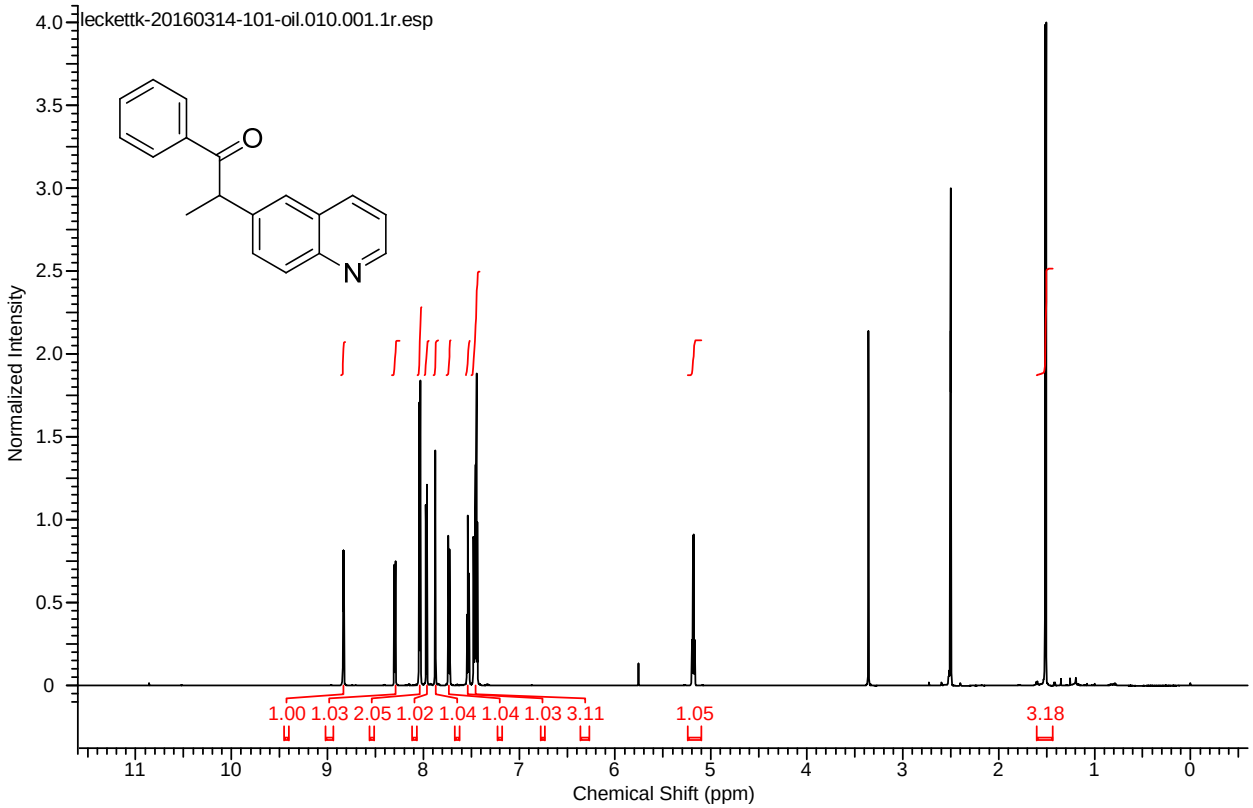

leckettk-20160311-99.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
131.14
128.95
128.79
132.68
127.78
121.85
121.77
92.78
82.59

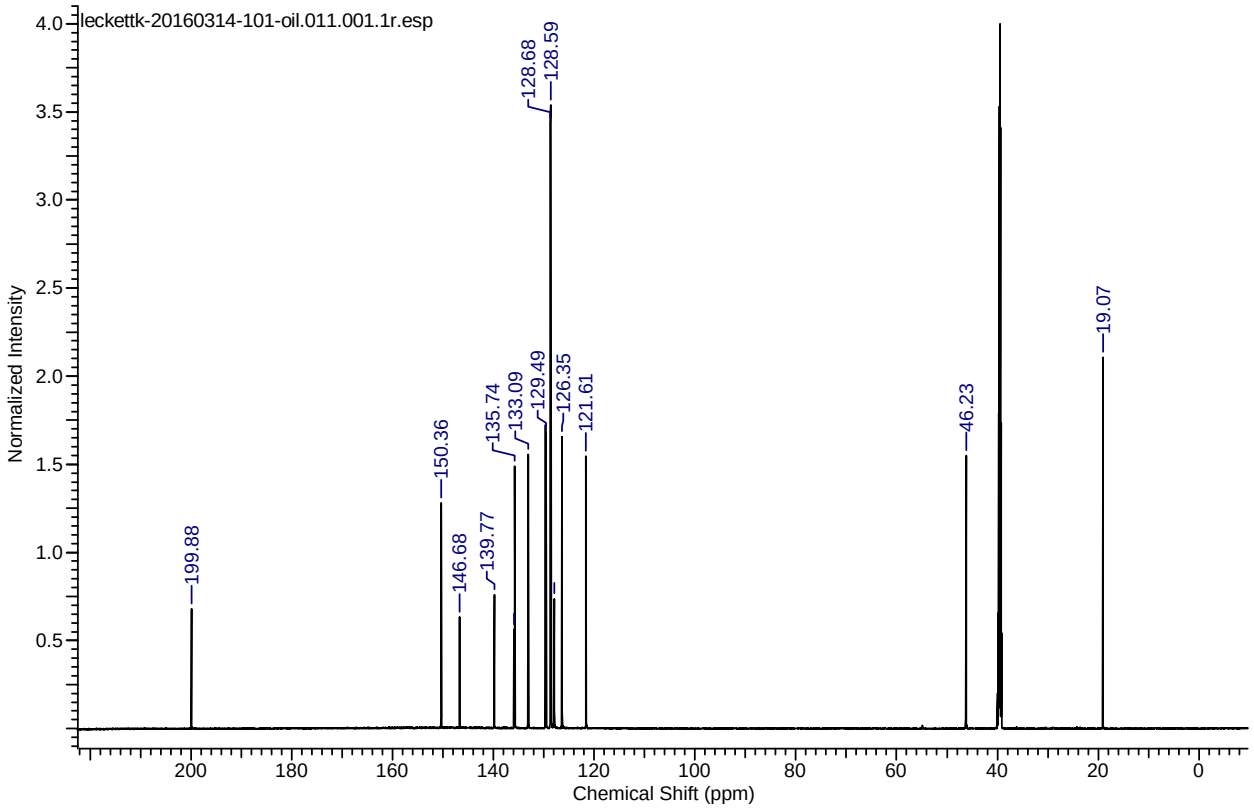

LL85_DMSO.010.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
MeO
N
0.86 1.00 0.98 0.87 2.07 1.07 2.03 1.00
3.18


LL85_DMSO.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
165.56
151.56
147.32
135.93
131.93
131.75
129.44
126.73
122.59
119.67
91.87
89.35
52.31


LL69_2nd.010.001.1r.esp
O
N
Normalized Intensity
Chemical Shift (ppm)
1.00 2.09 3.07 1.01 1.05 1.02


LL69_2nd.011.001.1r.esp
149.95
143.98
139.15
135.75
129.86
127.99
123.51
121.44
108.71
147.48
130.56
Normalized Intensity
Chemical Shift (ppm)


leckettk-20160314-101-oil.010.001.1r.esp
O
N
1.00 1.03 2.05 1.02 1.04 1.04 1.03 3.11
1.05
3.18
Normalized Intensity
Chemical Shift (ppm)


leckettk-20160314-101-oil.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
199.88
150.36
146.68
139.77
135.74
133.09
129.49
128.68
128.59
126.35
121.61
46.23
19.07