A One-pot, Microwave-assisted Synthesis of Aryl Ureas and Carbamates Using HATU and HOSA

by

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ABSTRACT

The synthesis of ureas and carbamates has been accomplished using a wide variety of approaches over the past several decades. However, the development of such methods continues to be an important research topic as a result of advancing technology as well as efforts to reduce cost and environmental impact. Bao *et al.* (2018) previously reported a new synthetic method for aryl ureas and carbmates which is defined by the combination of benzoyl chloride with various nucleophilic starting materials. However, several disadvantages have been identified with the use of benzoyl chloride which can compromise product yield. Therefore, a revised method which replaced the role of benzoyl chloride with the combination of a carboxylic acid and HATU was developed. Once the parameters of the HATU method had been optimized, its versatility was tested through the synthesis of twenty aryl ureas and five aryl carbamates. In addition, ten of the twenty aryl ureas were synthesized a second time using a different combination of starting materials in order to better understand how reagent selection affects product yield. Although none of the aryl carbamate yields exceeded 70%, several aryl urea yields above 90% were obtained. After testing of the HATU method was completed, its alternative application as an approach to primary amine synthesis was briefly explored by using water as the nucleophilic starting material. However, all attempts to optimize the application resulted in negligible product formation. Afterwards, a total synthesis for the anticancer drug Sorafenib was designed using aspects of the HATU method. However, employment of the total synthesis revealed that only the Sorafenib precursors could be successfully prepared through this approach. It is possible that the effectiveness of the HATU method could be improved with additional refinements to both the synthetic and purification procedures. Also, its use in amine preparation and the total synthesis of drugs requires further investigation before such applications can be considered practical.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Geoff Tranmer. His patience and guidance have been central to the successful completion of my research. Additionally, I would also like to extend my gratitude to examination committee members, Dr. Ted Lakowski and Dr. John Sorensen. Their input and recommendations have helped me better understand the theoretical aspects of my project.

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LIST OF ABBREVIATIONS

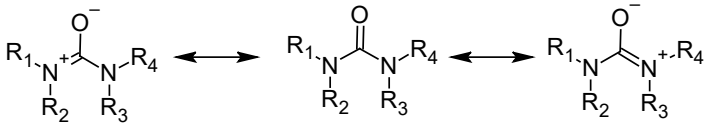
Boc	*t*-Butyloxycarbonyl
CBz	Benzyloxycarbonyl
^{13}C-NMR APT	Carbon-13 Nuclear Magnetic Resonance Attached Proton Test
CPMA	1-(Chlorophenylthiomethylene)dimethylammonium Chloride
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIC	*N,N'*-Diisopropylcarbodiimide
DIPEA	Disopropylethylamine
$DIPEAH^+$	Disopropylethylammonium Cation
DIU	*N,N'*-Diisopropylurea
DMMC	*N,N'*-Dimethyl Methylcarbamate
DMU	*N,N'*-Dimethylurea
DNA	Deoxyribonucleic Acid
DPPA	Diphenylphosphoryl azide
EDG	Electron Donating Group
EtOAc	Ethyl Acetate
EWG	Electron Withdrawing Group
FC	Flash Chromatography
Fmoc	Fluorenylmethyloxycarbonyl
HATU	Hexafluorophosphate *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetra-methyluronium
HBTU	Hexafluorophosphate *O*-(Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium
HOAt	1-Hydroxy-7-azabenzotriazole

HOBt	Hydroxybenzotriazole
HOSA	Hydroxylamine-*O*-sulfonic Acid
HOTU	Hexafluorophosphate *O*-[(Cyano(ethoxycarbonyl)methylidene)amino]-1,1,3,3-tetramethyluronium
^{1}H-NMR	Hydrogen-1 Nuclear Magnetic Resonance
MeCN	Acetonitrile
MeOH	Methanol
MMC	*N*-Methyl Methylcarbamate
OAt^{-}	1-Oxy-7-azabenzotriazole Anion
SOMP	5-(Succinimidyloxy)-3,4-dihydro-1-methyl-2H-pyrrolium Hexachloroantimonate
S_NAr	Nucleophilic Aromatic Substitution
TEA	Triethylamine
TLC	Thin Layer Chromatography
TMU	*N,N,N',N'*-Tetramethylurea

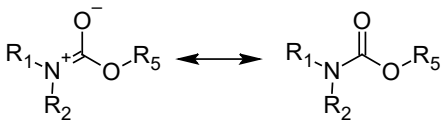
1. INTRODUCTION

1.1 Overview of Ureas and Carbamates

Ureas and carbamates are carbonyl functional groups in which both α-carbon atoms are replaced with heteroatoms. Although these functional groups are structurally similar, the nitrogen atoms that occur at both α-positions in ureas causes their physical and chemical properties to resemble those of amides. However, the presence of a second α-nitrogen atom causes ureas to have three main resonance structures instead of two, granting them higher stability under acidic and basic conditions as well as greater resistance to hydrolysis (**Figure 1.1**). In contrast, only one α-position is occupied by a nitrogen atom in carbamates while the other contains an oxygen atom. This results in carbamates having physical and chemical properties that are not unlike those of esters.[1] Since carbamates are restricted to having two main resonance structures, their stability under acidic and basic conditions is inferior to that of ureas and therefore, carbamates are more susceptible to hydrolysis. Furthermore, the absence of nitrogen atoms at the α-positions of esters prevents the existence of resonance structures, causing them to be hydrolyzed more readily than carbamates. However, the hydrolysis of ureas, carbamates, and esters can all readily occur through metabolic processes.[1]



Urea Resonance Structures



Carbamate Resonance Structures

R_1 = H, Alkyl or Aryl Group, Heterocycle with R_2 R_4 = H, Alkyl or Aryl Group, Heterocycle with R_3
R_2 = H, Alkyl or Aryl Group, Heterocycle with R_1 R_5 = Alkyl or Aryl Group
R_3 = H, Alkyl or Aryl Group, Heterocycle with R_4

Figure 1.1 *- Urea and carbamate resonance structures.*

In addition to providing higher stability, the greater electron delocalization in ureas allows them to engage in stronger dipole-dipole interactions than carbamates, especially hydrogen bonding. Along with the carbonyl oxygen atom, the α-nitrogen atoms in ureas are able to form hydrogen bonds if they are non- or mono-substituted.[1,2] Also, these ureas are able to self-associate in solution since they contain hydrogen bond donors and acceptors. This self-association is enhanced when one or both α-nitrogen atoms are aryl-substituted since the extensive conjugated π-electron system reduces electron density near the adjacent hydrogen atoms, allowing the formation of stronger hydrogen bonds as a result. However, self-association is limited in polar solvents since hydrogen bonding also occurs between urea and solvent molecules, causing the former to be dissolved.[3,4,5]

Unlike non- or mono-substituted α-nitrogen atoms in ureas, di-substituted α-nitrogen atoms cannot engage in hydrogen bonding since they do not share bonds with hydrogen atoms and are often too obstructed to interact with those in other molecules. Also, the absence of hydrogen bond acceptors in these ureas inhibits self-association. Finally, the higher lipophilicity of these ureas causes them to be more soluble in non-polar solvents, especially if the substituents are large in size or have branched molecular structures.[1,2,3] Although the hydrogen bonding capability of carbamates is similar to that of ureas, it is also more restricted since hydrogen atoms in adjacent molecules are unable to interact with the substituted α-oxygen atom that occurs in place of a second α-nitrogen atom (**Figure 1.2**). Therefore, ureas generally have higher boiling points and water solubility than carbamates.[1,2]

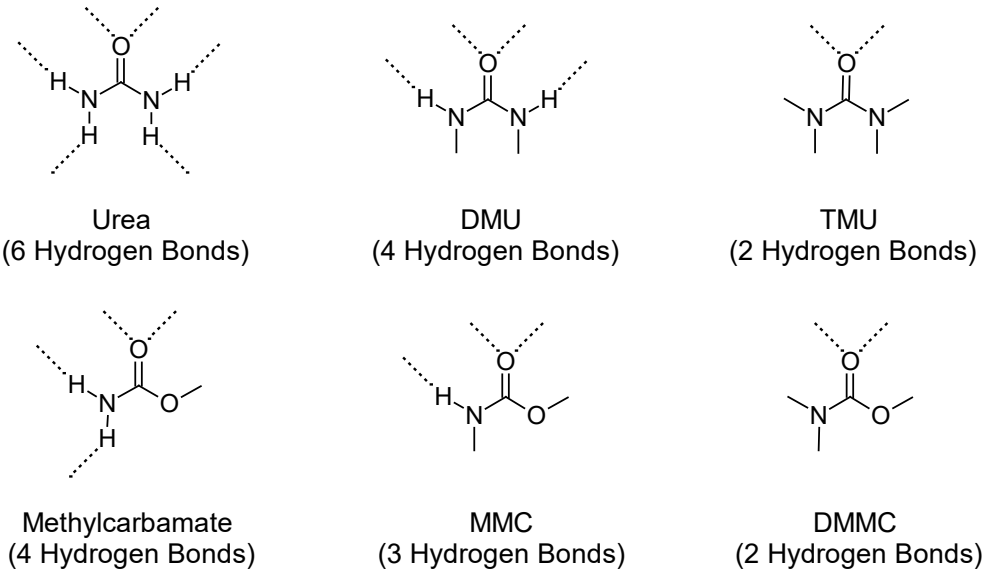


Figure 1.2 - *Influence of methyl group substitution on hydrogen bonding ability of α-nitrogen atoms in ureas and carbamates.*

The hydrogen bonding capabilities of ureas as well as carbamates have found countless applications in medical and related fields. For example, the presence of urea, carbamate, and amide monomers in foldamers allow these oligomers to take on secondary structures that are not unlike those adapted by proteins (**Figure 1.3**).[6,7] Therefore, foldamers are able to interact with various biomolecules in similar ways. In addition, the option to assemble a foldamer backbone using any combination of these carbonyl functional groups grants greater control over the conformations that comprise secondary structures.[6,7] This advantage has resulted in the development of foldamers which are specifically designed to alter the function of DNA, inhibit interaction between proteins, and mimic the molecular structure of antimicrobial peptides.[8]

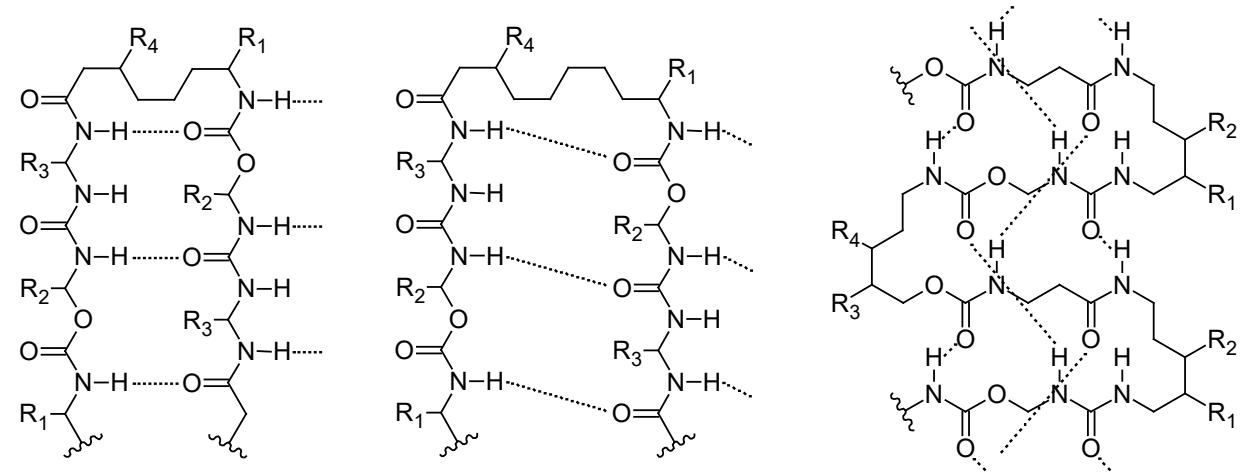


Figure 1.3 - *Secondary structures of foldamers containing ureas and carbamates.*

The self-association of ureas containing primary or secondary nitrogen atoms can occur through two main patterns of intermolecular hydrogen bonding (**Figure 1.4**). The chain pattern of hydrogen bonding results in a sequence of connected urea molecules that are oriented in the same direction. In contrast, the ribbon pattern of hydrogen bonding results in a sequence of connected urea molecules that are alternately oriented in opposing directions. Urea self-association through hydrogen bonding in a chain pattern has been employed as a method of physical cross-linking between gelators in various supramolecular gels.[9,10] As a result, the mechanical properties of supramolecular gels are highly responsive to changes in environmental conditions such as temperature, pressure, and acidity as well as the variation of sound intensity. This allows for a high amount of control over the incorporation and release of guest molecules, demonstrating the potential of these gels in drug delivery.[11,12,13,14,15]

In contrast, urea self-association through hydrogen bonding in a ribbon pattern has found use in the construction of host complexes which can contain guest molecules. Many of these complexes consist of ureas as well as ions and other functional groups.[16,17] However, guest

molecules can also be hosted within crystals of pure urea. Also, it must be noted that although pure urea adopts a tetragonal crystal structure, a hexagonal crystal structure is favoured when incorporating a guest molecule. The formation of this polymorph allows cylindrical tunnels to form within the crystal structure where the guest molecules can be hosted.[18,19] Also, the molecular framework surrounding the guest molecules has demonstrated the ability to protect them against moisture-induced degradation as well as improve their water solubility. However, these abilities are strongly affected by factors such as the size and shape of the guest molecule as well as its interaction with the molecular framework. Nevertheless, the potential application of this polymorph in drug preservation and transport is clearly evident.[20,21]

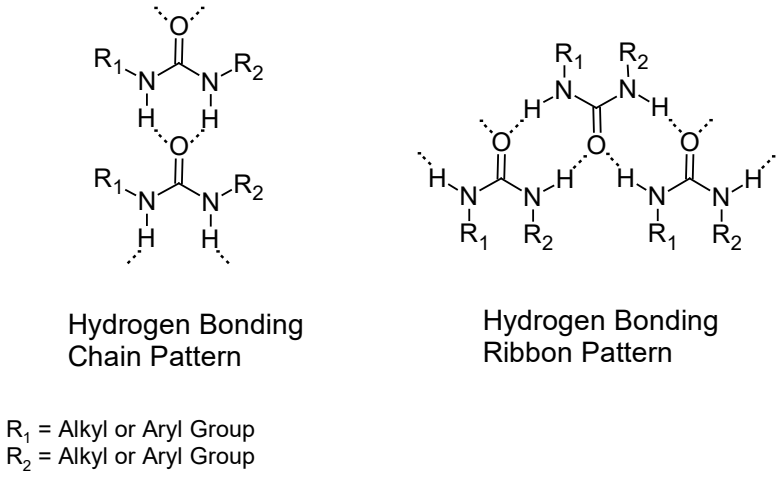


Figure 1.4 - *Hydrogen bonding patterns leading to self-association of ureas containing mono-substituted α-nitrogen atoms.*

The transformation of amino groups into carbamates has long been used in peptide synthesis to protect α-nitrogen atoms from side reactions. Many carbamates are particularly useful as protecting groups due to their reactivity and stability under specific conditions (**Figure 1.5**).[22] For example, N^{α}-Boc is stable under basic conditions while N^{α}-Fmoc is much less reactive under acidic conditions. However, both N^{α}-Fmoc and N^{α}-Boc are generally resistant to hydrogenolysis. In contrast, N^{α}-Cbz exhibits stability near neutral conditions, but is highly

susceptible to hydrogenolysis.[22] These variations in reactivity allow carbamates to be used orthogonally in peptides. Also, it should be noted that many preferred approaches to their removal involve cleavage of the bond shared by the α-oxygen atom and adjacent β-carbon atom. This is due to the formation of an unstable carbamic acid intermediate which conveniently decomposes into carbon dioxide and the unprotected amino group.[22]

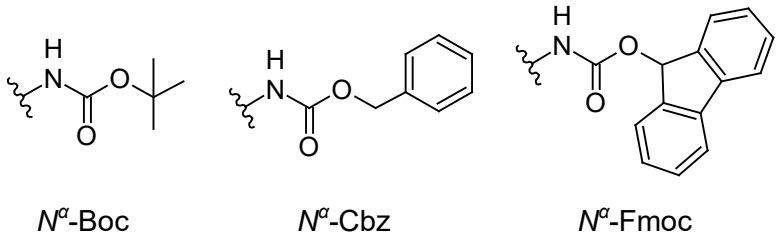


Figure 1.5 - *Carbamates used for amino group protection in peptides.*

Although the stability of ureas and carbamates has contributed to their importance in drug design, each functional group has also been found to be especially useful for certain applications. This can be illustrated by noting that carbamates often act as the site of metabolic activation in prodrugs due to their higher susceptibility to hydrolysis while the superior hydrogen bonding potential of ureas makes them suitable for enhancing interactions between drugs and receptors.[23,24,25,26,27] In addition to these applications, the molecular structures of ureas and carbamates can be designed to influence specific chemical properties of the drugs that they partially comprise. For example, the lipophilicity and stereochemistry of a drug which contains one or more of these functional groups can be modified by varying the degree of substitution at the α-positions as well as the size of the substituents. This has proven useful when adjustments to drug permeability and absorptivity in the human body are required.[23,25,28,29,30] As a result, both functional groups can be found in the molecular structures of drugs that treat a wide range of diseases and disorders. This includes drugs that are classified as anti-inflammatories, antiretrovirals, and antihypertensives (**Figure 1.6**).[23,25,31,32,33]

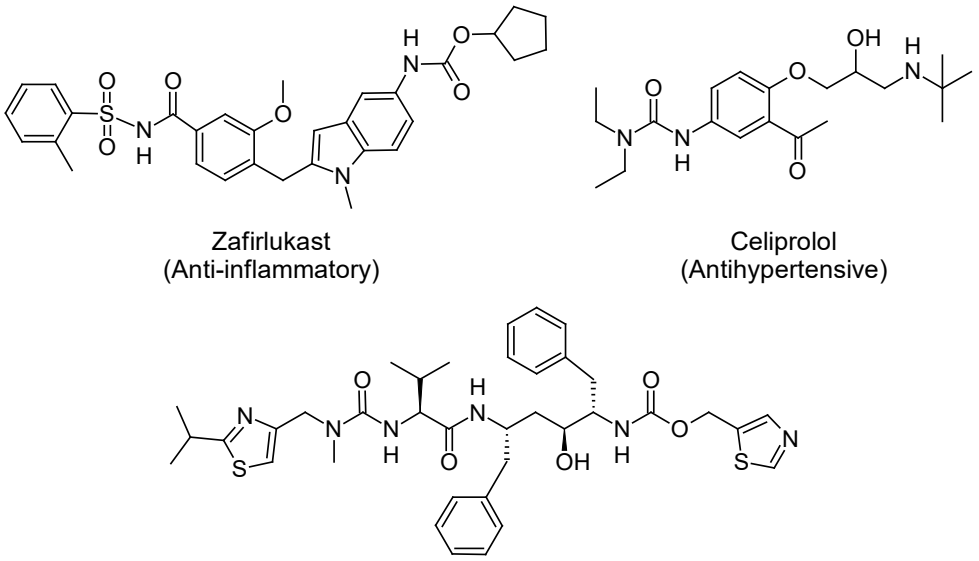
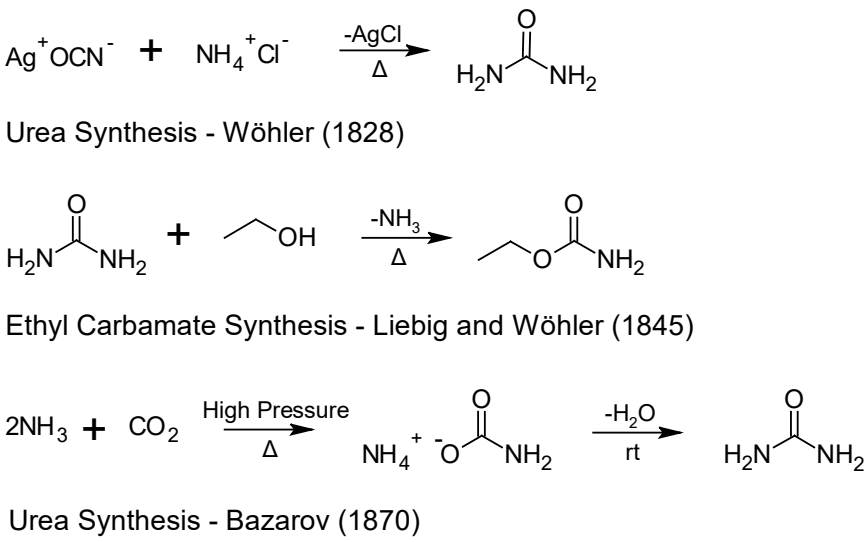


Figure 1.6 *- Drugs containing ureas or carbamates.*

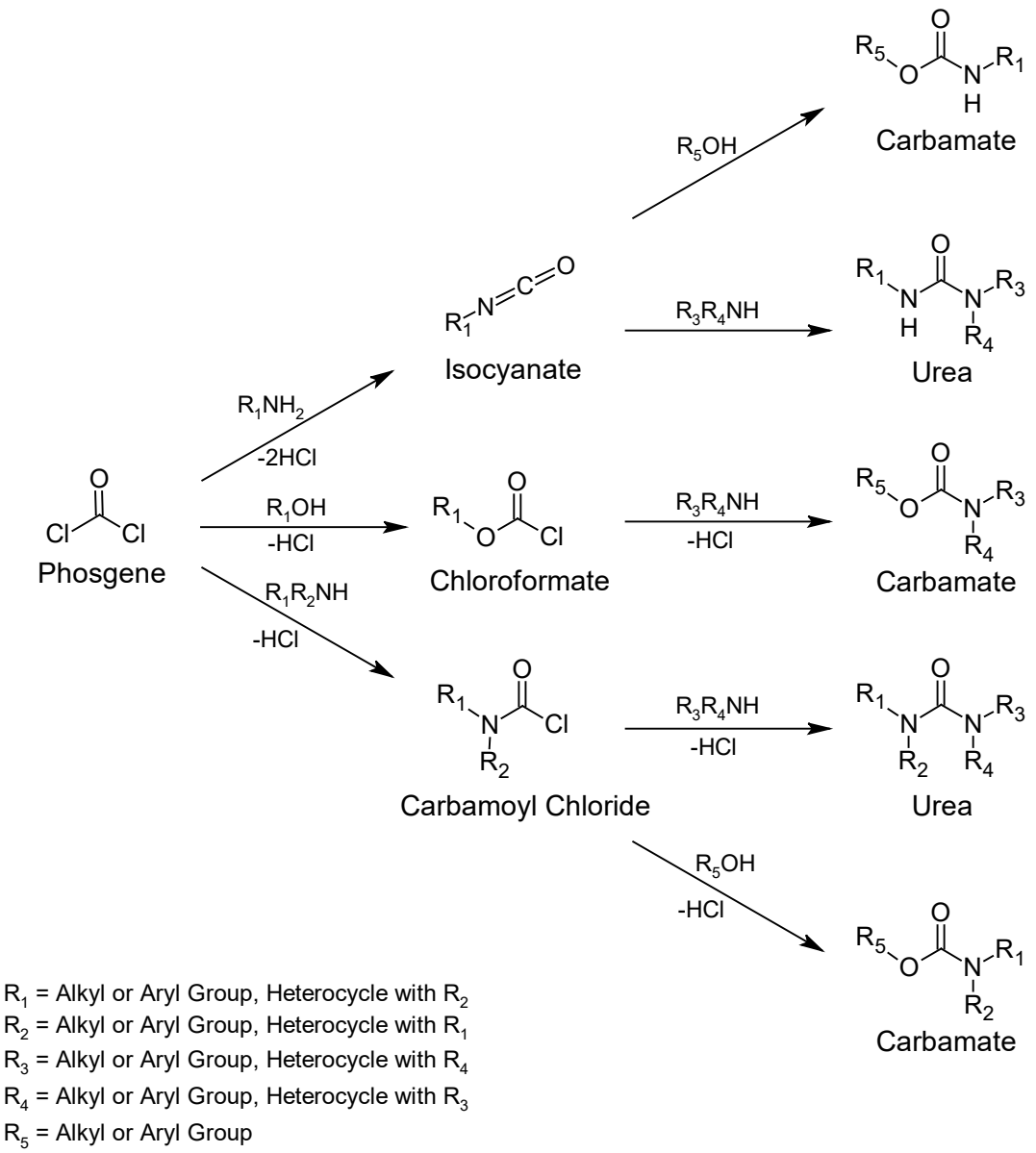
1.2 Synthetic Techniques for Ureas and Carbamates

The oldest synthetic techniques for ureas and carbamates were reported in the nineteenth century (**Scheme 1.1**).The earliest known synthesis of urea was achieved in 1828 by the German chemist Friedrich Wöhler. Wöhler discovered that the combination of silver cyanate and ammonium chloride in aqueous solution would generate urea when heated. In addition, the reaction was the first recorded synthesis of an organic product that was prepared using only inorganic starting materials.[34,35] Wöhler has also been credited with preparing ethyl carbamate in 1845 along with his colleague, Justus von Liebig. This was accomplished by dissolving urea in ethanol and heating the solution.[36,37] Approximately four decades later, Aleksandr Bazarov was able to prepare urea by heating ammonia and carbon dioxide gases under high pressure. This reaction initially results in the formation of ammonium carbamate as an intermediate which can then dissociate into urea and water through dehydration, following the removal of heat. The successful optimization of this reaction in subsequent years has caused it to be employed on a commercial scale.[34,38]



Scheme 1.1 - *Early synthetic techniques for preparation of ureas and carbamates.*

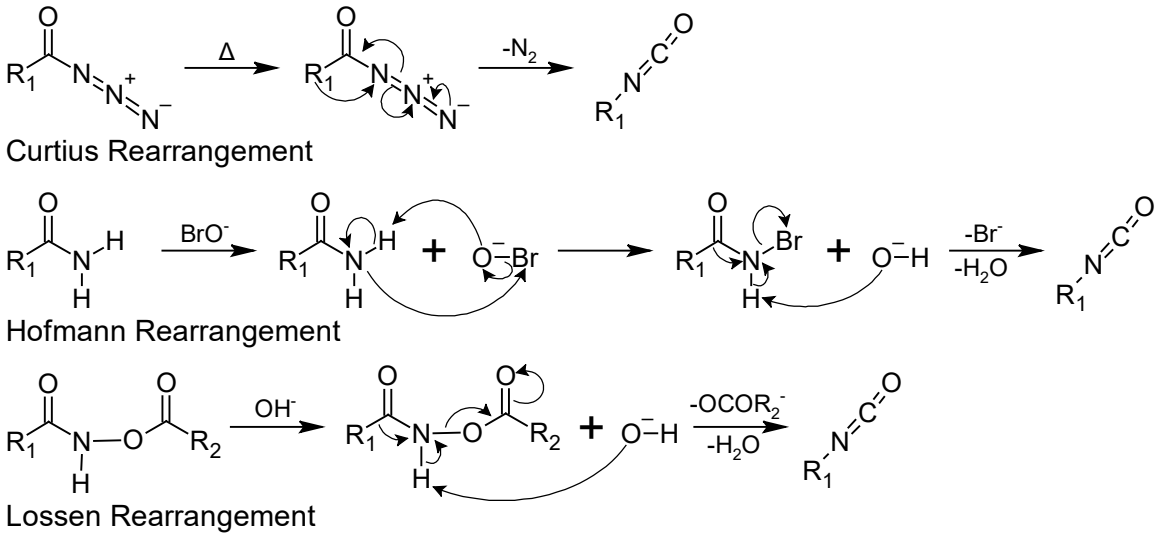
Phosgene is a gas discovered by John Davy in 1812 which has been commonly used to prepare ureas and carbamates on various scales.[39] This is achieved by first combining phosgene with a primary amine, secondary amine or alcohol. The intermediate which subsequently forms is dependent on the identity of the nucleophile (**Scheme 1.2**). For example, the addition of a primary amine to phosgene causes the formation of an isocyanate intermediate while the use of a secondary amine leads to a carbamoyl chloride intermediate instead. Similarly, the reaction between phosgene and an alcohol results in a chloroformate intermediate.[39] Afterwards, the formation of a urea can be achieved by combining a secondary amine with an isocyanate or carbamoyl chloride intermediate. In contrast, a reaction between an alcohol and either of these intermediates results in a carbamate. However, it is also possible to form a carbamate by combining a secondary amine with a chloroformate intermediate.[39] Although this demonstrates the versatility of phosgene as a starting material, the gas is highly toxic and difficult to handle. This problem has been partially solved by the use of liquid or solid derivatives, including di- and triphosgene.[39] Nevertheless, other methods of urea and carbamate preparation are continuously being developed for the purposes of safety as well as environmental sustainability.[40,41,42]



Scheme 1.2 - *Synthetic pathways for ureas and carbamates involving phosgene.*

The preparation of ureas and carbamates from isocyanate intermediates has been employed repeatedly for industrial as well as research purposes. However, the preparation of isocyanates can be hazardous even when phosgene is not among the starting materials. This is due to many isocyanates also exhibiting a high level of toxicity.[39] As a result, many modern synthetic techniques incorporate Curtius, Hofmann, or Lossen rearrangements since these reactions are also able to form isocyanates in solution, preventing their direct handling (**Scheme**

1.3).[43,44,45] However, all three reactions must be performed in the absence of moisture. This is due to the side reaction that can occur from the combination of water and isocyanate which results in the formation of a carbamic acid that subsequently dissociates into a primary amine and carbon dioxide through decarboxylation.[46]



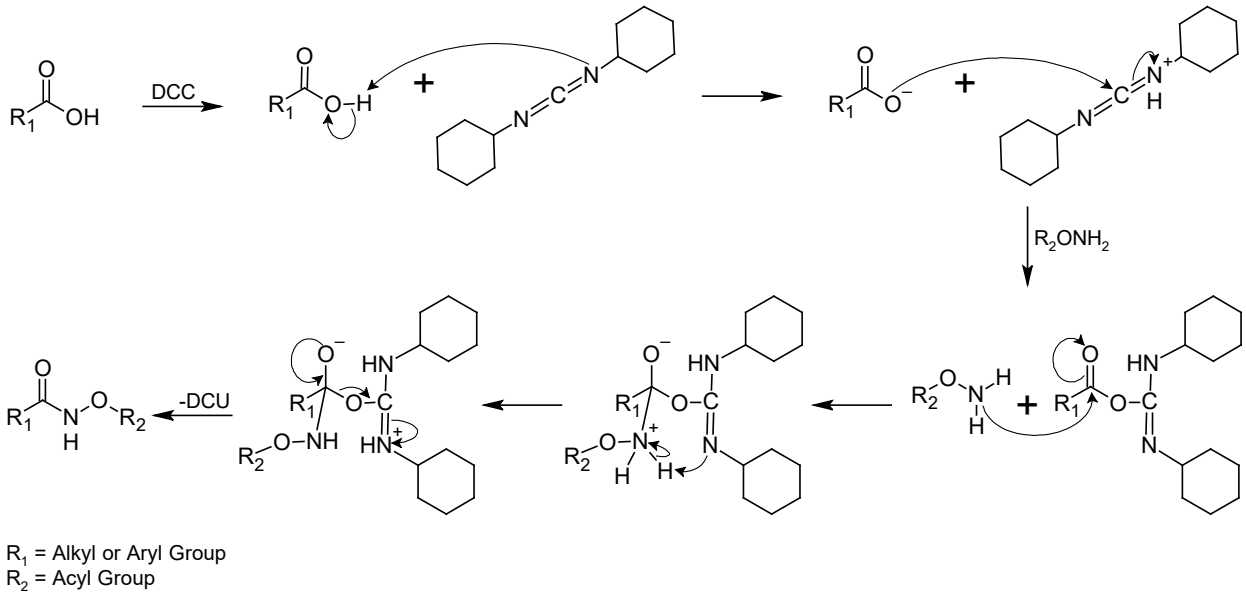
Scheme 1.3 - *Reaction mechanisms for Curtius, Hofmann, and Lossen rearrangements.*

The Curtius rearrangement is conducted by simply heating an acyl azide to a sufficient temperature which results in conversion to its isocyanate derivative and nitrogen gas as a by-product.[46] However, azides must be used with extreme caution since they are capable of exploding when exposed to rapid changes in temperature or pressure. In addition, azide salts can explode if disturbed by a strong impact.[47] Fortunately, the danger of explosion can be reduced by using liquid azides such as DPPA and maintaining mild reaction conditions.[48] Unlike the Curtius rearrangement, the Hofmann rearrangement is initiated by the addition of a hypobromite to a primary amide.[46] Although hypobromites are not explosive, their preparation requires the combination of a hydroxide salt with liquid bromine, the latter of which emits toxic vapour at

room temperature due to its high volatility.[49] In order to circumvent the use of liquid bromine, hypobromites can be substituted with similar reagents such as hypervalent iodobenzenes.[50] Alternatively, the Lossen rearrangement can be employed for isocyanate preparation instead since commencement of the reaction only requires deprotonation of the *O*-acyl hydroxamate starting material by a base such as a hydroxide.[46] Also, like primary amides, *O*-acyl hydroxamates do not share the risk of explosion that is associated with acyl azides. Unfortunately, the hydroxamic acid precursors from which *O*-acyl hydroxamates are traditionally prepared have low commercial availability. Therefore, the use of other hydroxamate analogues prepared from more accessible precursors such as a carboxylic acid is often preferred.[51,52,53]

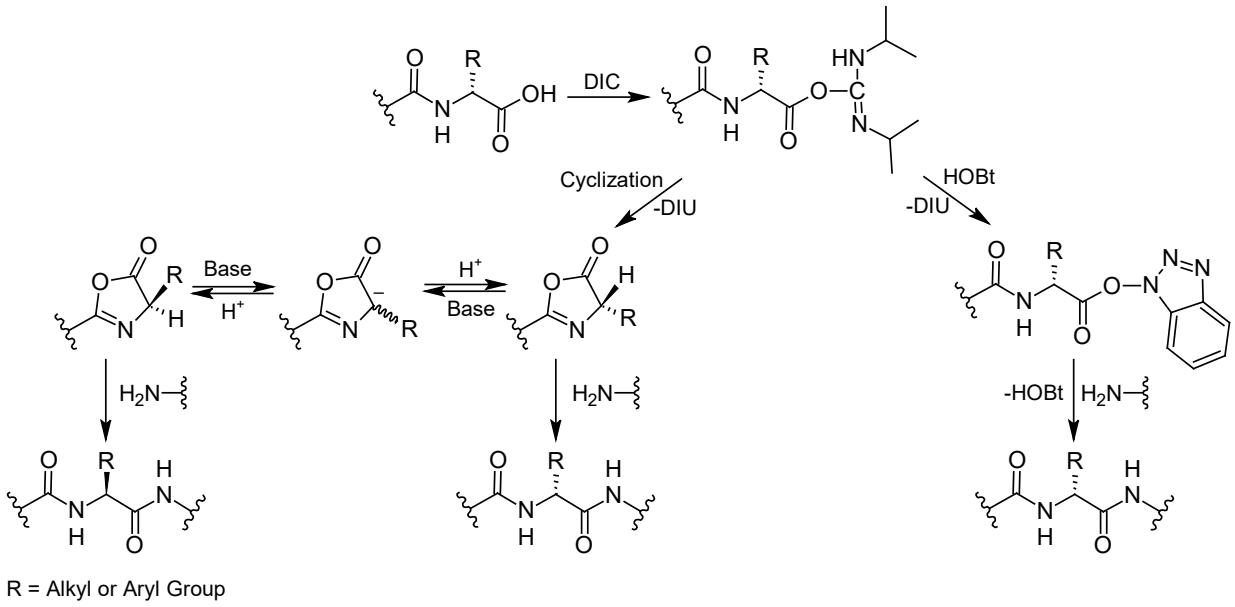
1.3 Coupling Reagents

The direct conversion of a carboxylic acid to a hydroxamate by combining it with a hydroxylamine derivative cannot be easily achieved under mild reaction conditions.[54,55] This is partly due to the low electrophilicity of the carbonyl carbon atom in the carboxylic acid which limits the rate of nucleophilic attack by the hydroxylamine acid derivative. In addition, the hydroxyl group which is released upon nucleophilic attack has low stability in anionic form and can form other reactive by-products such as water, making it a poor leaving group.[56,57,58,59,60] Therefore, the hydroxyl group must be converted into a moiety which is highly stable as an anion and capable of enhancing the electrophilicity of the carbonyl carbon atom through electron density removal. This can be achieved by combining the carboxylic acid with a coupling reagent prior to the addition of the hydroxylamine derivative, resulting in the formation of an activated derivative of the precursor (**Scheme 1.4**).[56,57,58,59,60]



Scheme 1.4 - *Reaction mechanism for conversion of carboxylic acid to O-acyl hydroxamate using hydroxylamine derivative and DCC coupling reagent.*

Coupling reagents were first developed in the middle of the twentieth century, beginning with carbodiimides such as DIC and DCC.[61,62,63] These particular coupling reagents were frequently employed in reactions that led to amide bond formation between peptides. However, their use was often found to cause product epimerization when the carboxyl group contained a chiral α-carbon atom. This was due to the frequent cyclization of the activated derivative into an oxazolone which can exist as one of two epimers under basic conditions, allowing a nucleophilic attack by the amino group to occur on either.[61,64] Product epimerization was later found to be minimized through the addition of a 1*H*-benzotriazole since this interfered with the formation of the oxazolone. Also, it was discovered that the 1*H*-benzotriazole stabilized the approach of the amino group toward the activated derivative of the carboxyl group through hydrogen bonding, resulting in a higher amount of product formation (**Scheme 1.5**).[61,63,65,66]



Scheme 1.5 - *Amide bond formation between peptides using DIC coupling reagent with and without HOBt additive.*

Although HOBt was initially the preferred 1*H*-benzotriazole additive for reactions that formed amide bonds using a carbodiimide coupling reagent, its popularity was later overtaken by HOAt which was found to reduce product epimerization even more efficiently. Also, the further improvement in product formation was attributed to the nitrogen atom in the pyridine moiety of HOAt since it allowed more hydrogen bonding to occur with the amine starting material than was possible with HOBt.[61,67] The effectiveness of these additives eventually led to the development of salt-based coupling reagents such as HATU and HBTU that each contain a 1*H*-benzotriazole moiety in their molecular structures. Therefore, the employment of these coupling reagents in reactions that result in amide bond formation eliminates the need to add a 1*H*-benzotriazole separately.[61,68] However, the early decades of the twenty-first century have revealed that many 1*H*-benzotriazoles are explosive under certain conditions, even when incorporated into coupling reagents.[61,69,70] Therefore, efforts to prepare other effective additives and coupling reagents without a 1*H*-benzotriazole moiety are ongoing (**Figure 1.7**).[71,72,73]

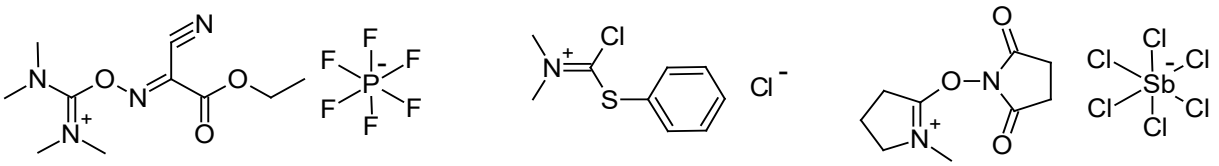


Figure 1.7 - *Coupling reagents not containing 1H-benzatriazole moiety.*

1.4 Carboxylic Acid Reactivity

The steric hindrance and electron density near the carbonyl carbon atom of a carboxylic acid heavily influence its reactivity since it often takes on the role of an electrophile. These factors also affect the nucleophilicity of the hydroxyl group once it is deprotonated. Furthermore, the electron density surrounding the hydroxyl group determines how readily it can be deprotonated.[1,74] When a carboxylic acid is transformed into *O*-acyl hydroxamate using a coupling reagent that contains a 1*H*-benzotriazole moiety, both the hydroxyl group and carbonyl carbon atom participate in the reaction.[61,68] Therefore, the use of various carboxylic acids in such a reaction in order to make a yield comparison requires an understanding of how differences in their molecular structures as well as the position and identity of substituents can affect product formation.[1,74]

As mentioned previously, a decrease in electron density near the carbonyl carbon atom in a carboxylic acid increases its electrophilicity. Similarly, the removal of electron density near the hydroxyl group enhances its acidity.[1,74] The distribution of electron density throughout a carboxylic acid is strongly influenced by substituents on the alkyl or aryl group which is connected to the carboxyl group. The presence of EDGs on the alkyl or aryl group causes more electron density to be exerted toward the carboxyl group while the presence of EWGs removes it. Furthermore, substituents can affect electron density distribution through the inductive or mesomeric effect (**Figure 1.8**).[1,74] However, the strength of each effect depends on the chemical

properties of the substituent from which it originates. For example, a methyl group primarily contributes electron density through the inductive effect while a cyano group mainly removes electron density through the mesomeric effect.[75,76]

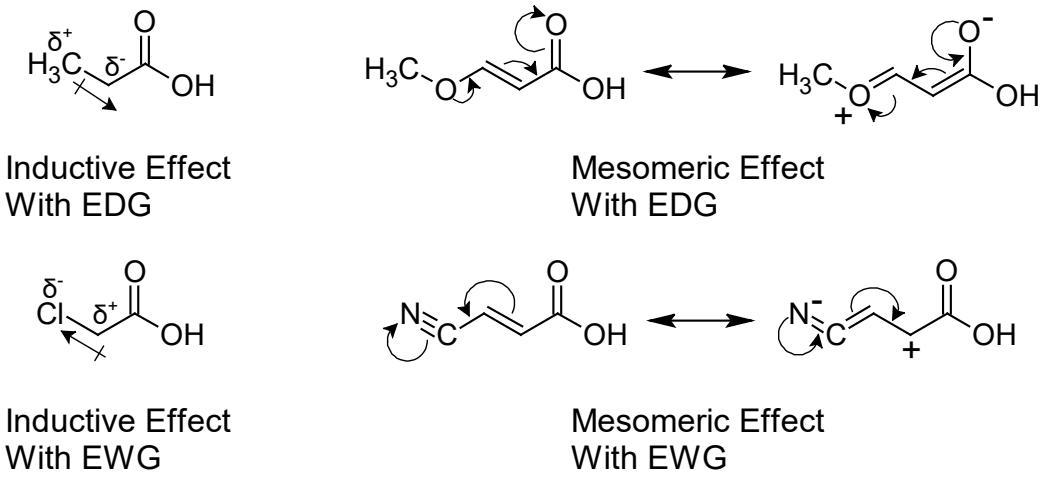


Figure 1.8 - *Inductive and mesomeric effects exerted in carboxylic acids by substituents with varying influences on electron density.*

When present on an aryl group, all EDGs act as *ortho,para*-directors of electron density and most EWGs act as *meta*-directors. However, halogen atoms also act as *ortho,para*-directors despite being classified as EWGs (**Figure 1.9**). This is due to halogen atoms weakly contributing electron density through the mesomeric effect while simultaneously removing it through the inductive effect that is slightly greater in strength.[75,76] Also, the positions on an aryl group to which a substituent directs electron density can be altered if other substituents are present on the group as well. In such cases, electron density becomes distributed based on the combined influenced of all the substituents on the aryl group.[77] Finally, it should also be noted that the influence of the inductive effect on electron density diminishes away from the permanent dipole moment that causes it while the impact of the mesomeric effect remains consistent throughout the conjugated π-electron systems over which it occurs.[74]

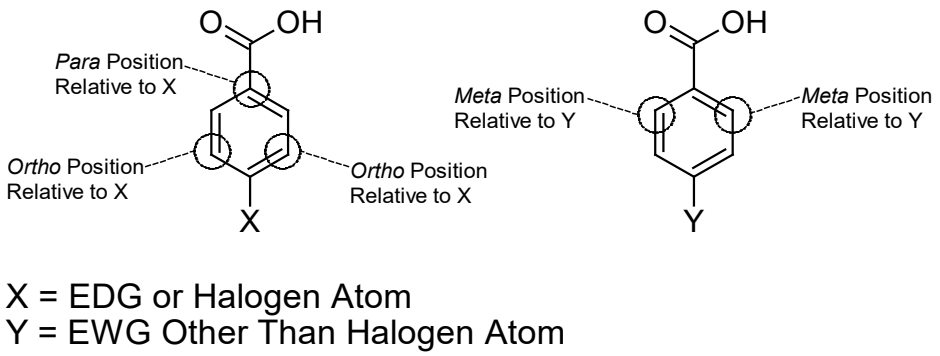


Figure 1.9 - *High electron density positions in aromatic carboxylic acids para-substituted with EDG, halogen atom, or EWG other than halogen atom.*

In addition to the influence of electron density distribution, the electrophilicity of the carbonyl carbon atom in a carboxylic acid can be affected by intermolecular steric hindrance.[74] This often results when the carboxyl group is connected to an alkyl group with a branched molecular structure that obstructs nucleophilic attack on the carbonyl carbon atom. However, intermolecular steric hindrance can also occur when the carboxyl group is connected to an aryl group if one or more substituents on the latter are directly adjacent to the former.[74] Furthermore, intramolecular steric hindrance exerted by these substituents can cause the bond which connects the carboxyl and aryl groups to rotate, disrupting the planarity of the carboxylic acid (**Figure 1.10**). As a result, the conjugated π-electron system that extends throughout the molecule is interrupted, inhibiting electron delocalization.[78]

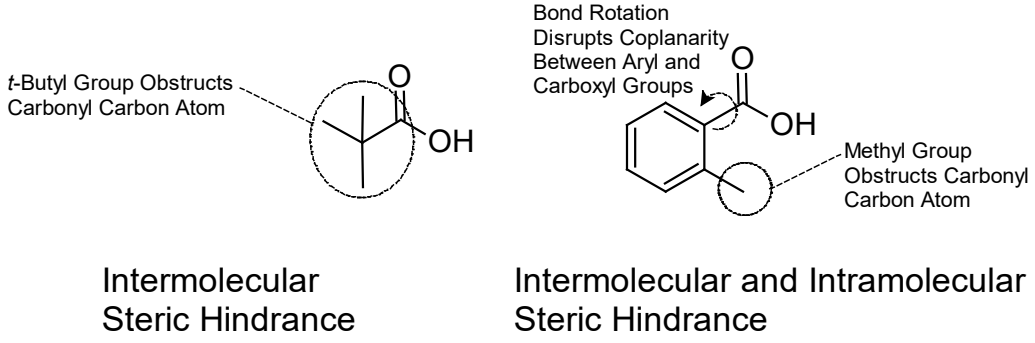


Figure 1.10 - *Carboxylic acids exhibiting steric hindrance caused by branched alkyl group or ortho-substituted aryl group.*

1.5 Amine and Alcohol Reactivity

The steric hindrance and electron density near the amino group of an amine as well as the hydroxyl group of an alcohol is an important factor in their reactivity since both often act as nucleophiles.[1,74] One frequently employed reaction which requires an amine or alcohol in this role is the conversion of isocyanates into ureas or carbamates respectively.[79,80,81] In such a reaction, the different yields achieved from a particular amine and its alcohol analogue are mainly a consequence of their atomic composition. However, the comparison of yields obtained from various amines or alcohols requires an understanding of how product formation is affected by their different molecular structures as well as the identity and position of substituents, as previously indicated for carboxylic acids.[1,74]

In general, amines exhibit a stronger nucleophilicity than their alcohol analogues due to oxygen atoms having a higher electronegativity than nitrogen atoms which results in the stronger retention of non-bonding electron pairs.[2,74] Aside from this difference, the nucleophilicity of amines as well as alcohols is otherwise similarly influenced by electron density distribution. For example, non-substituted aliphatic amines and alcohols often exhibit stronger nucleophilicity than those that are aromatic.[2,74] This is due to the concentration of electron density near the amino and hydroxyl groups since they are unable to act as EDGs through the mesomeric effect when not connected to a conjugated π-electron system. However, less electron density is retained near amino and hydroxyl groups which are connected to aryl groups due to electron delocalization (**Figure 1.11**).[74,75,76] This is in direct contrast to carboxyl groups which act as EWGs. Nevertheless, the presence of other EDGs and EWGs on the aryl group similarly influences the electron density distribution in aromatic amines, alcohols and carboxylic acids.[74,75,76]

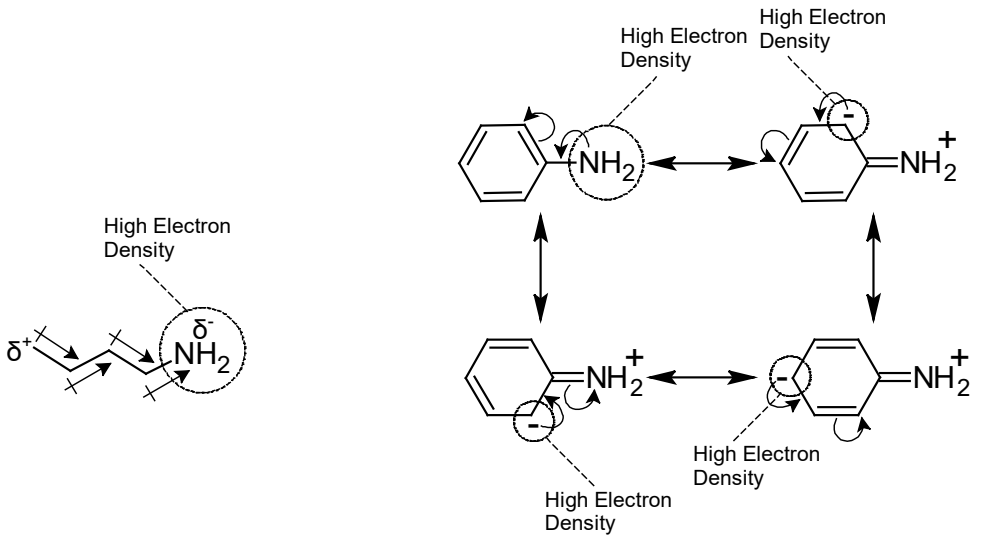


Figure 1.11 **-** *Electron density distribution in aliphatic and aromatic amines.*

The classification of primary, secondary, and tertiary amines is based on the number of alkyl or aryl groups that are connected to the nitrogen atom of the amino group. In contrast, the distinction between primary, secondary, and tertiary alcohols refers to the number of alkyl or aryl groups connected to the carbon atom which also shares a bond with the hydroxyl group (**Figure 1.12**).[2] As a result, secondary as well as tertiary amines often exhibit more intermolecular steric hindrance than secondary and tertiary alcohols. Furthermore, the high amount of intermolecular steric hindrance obscuring the nitrogen atom in tertiary amines generally causes their nucleophilicity to be weaker than that of primary and secondary amines.[2,74] However, the high electron density near nitrogen atoms which are connected to three alkyl groups greatly strengthens their basicity. In addition, the alkyl groups interfere with salt formation following protonation of the nitrogen atom. As a result, such tertiary amines are often effective base catalysts.[74,82,83]

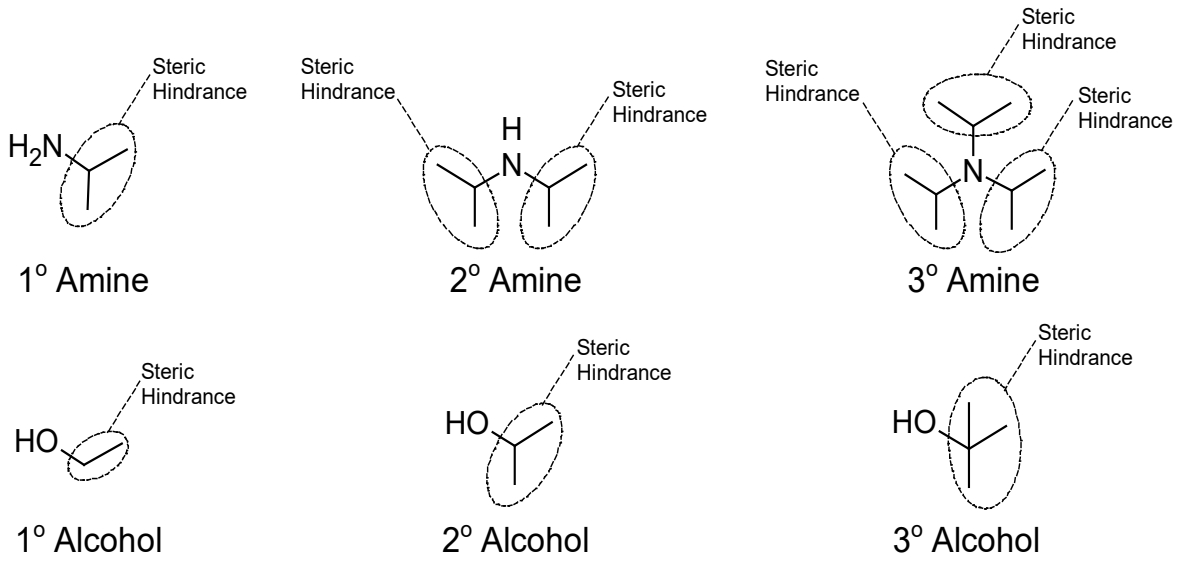
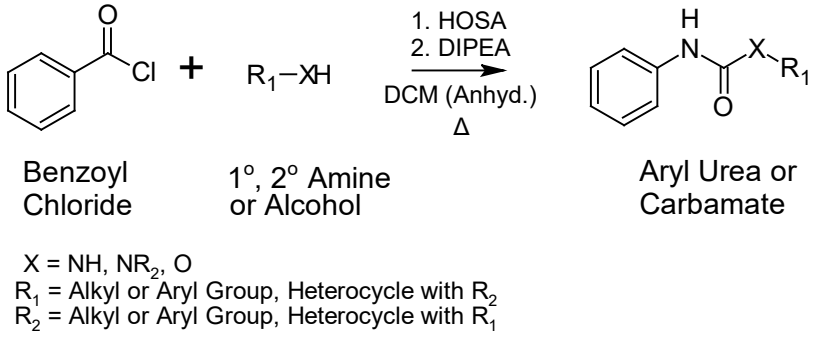


Figure 1.12 - *Influence of substitution on steric hindrance exhibited by amines and alcohols.*

The nucleophilicity of amines and alcohols is also affected by the solvent in which they are dissolved. For example, most amines and alcohols are able to form hydrogen bonds with the molecules that comprise a protic solvent.[84,85,86] Although this solvation aids in their solubility, it also weakens their nucleophilicity through stabilization. Therefore, nucleophilic addition and substitution reactions should be carried out in aprotic solvents instead.[84,85,86] Also, the use of a polar solvent is ideal when using microwave irradiation to heat the solution in order to increase the rate of nucleophilic attack. This is due to the ability of polar solvents to absorb microwave radiation more efficiently than non-polar solvents.[87] Finally, it is particularly important to minimize acidic conditions in solution when using alcohols as nucleophiles since their protonation can result in a dehydration side reaction. Furthermore, tertiary alcohols are more susceptible to dehydration reactions than primary and secondary alcohols due to their higher basicity.[88]

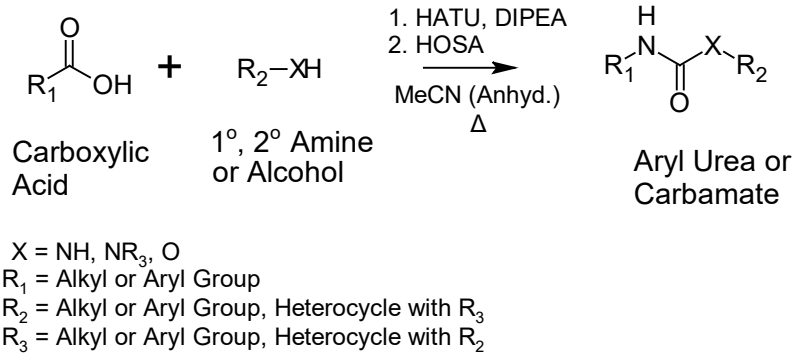
1.6 Project Hypothesis and Objectives

As mentioned previously, ureas as well as carbamates are frequently employed in the synthesis of drugs, foldamers, and other medically important molecules.[6,7,20,21,23,32] This has created a demand for their preparation using efficient methods that can be applied to a wide range of starting materials.[44,80,81] Previously, Bao *et al.* (2018) reported the synthesis of several aryl ureas and carbamates under an argon atmosphere by combining benzoyl chloride with various amine as well as alcohol starting materials. The reaction carried out in the synthetic procedure commenced with the dissolution of HOSA in anhydrous DCM with the aid of DIPEA which acted as a base catalyst. Benzoyl chloride was then added which caused the formation of a hydroxamate that was immediately converted to an isocyanate through a Lossen rearrangement. Finally, the isocyanate was transformed into an aryl urea or carbamate, depending on the identity of the nucleophile that was subsequently added (**Scheme 1.6**). In order to drive the reaction to completion, the reaction mixture was heated using a microwave synthesizer.[89] The product was then purified using FC and when necessary, triturated with chloroform. The yields achieved for many of the aryl ureas exceeded 70%, although several lower yields were also reported. In addition, all yields obtained for the aryl carbamates were below 50%.[89]



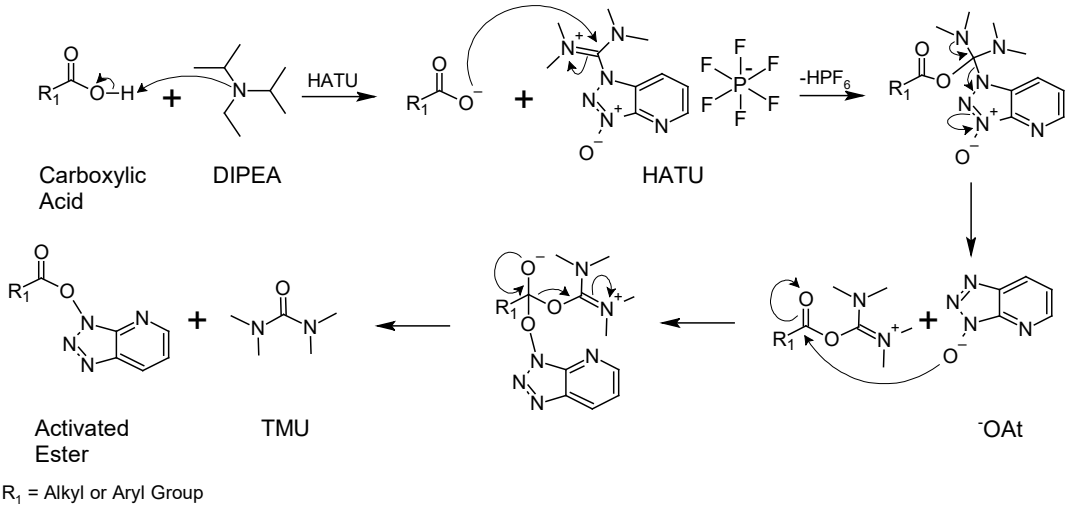
Scheme 1.6 - *Synthesis of aryl ureas and carbamates using synthetic procedure employed by Bao et al. (2018).*

Although these results demonstrate that this method is versatile, it was hypothesized that product yield could be improved by replacing the role benzoyl chloride with benzoic acid that is subsequently transformed into an activated ester using HATU (**Scheme 1.7**). This postulated improvement in product yield is based on several factors. First, benzoyl chloride is susceptible to hydrolysis while benzoic acid is not. Therefore, the presence of any water in the reaction mixture can inactivate a portion of the benzoyl chloride through this side reaction.[57,90] Secondly, the hydrochloric acid which forms as a by-product when benzoyl chloride is combined with HOSA can react with the amine or alcohol that is subsequently added to the reaction mixture, reducing its availability.[57,88,91] Finally, the -OAt moiety of the activated ester that is formed from benzoic acid and HATU is expected to reduce the energy that is required to form the hydroxamate by stabilizing HOSA during its nucleophilic attack through hydrogen bonding.[67,92] In addition to the substitution of benzoyl chloride, the solvent in which the reaction is conducted was switched from anhydrous DCM to anhydrous MeCN since the higher polarity of the latter absorbs radiation emitted by the microwave synthesizer more efficiently.[87,93] Along with these changes to the synthetic procedure, the product was extracted into a less polar solvent such as EtOAc or DCM and washed with water prior to the use of FC during purification. The purpose of this step was to pre-emptively separate the product from as many highly polar impurities as possible.[93,94]



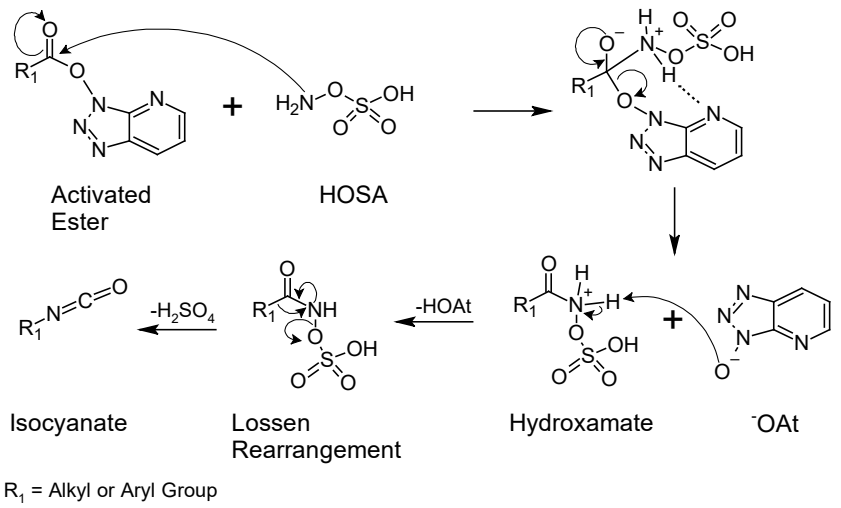
Scheme 1.7 - *Synthesis of aryl ureas and carbamates using synthetic procedure employed in HATU method.*

The first step of the proposed reaction mechanism begins with the consecutive addition of a carboxylic acid starting material, followed by HATU, and finally, DIPEA. The reaction is initiated by the deprotonation of the hydroxyl group in the carboxylic acid by DIPEA. The anionic oxygen atom then acts as a nucleophile, attacking the central carbon atom in the guanidinium moiety of HATU, causing the release of $^{-}$OAt. A nucleophilic attack on the carbonyl carbon atom by the anionic oxygen in $^{-}$OAt, immediately follows, resulting in the concurrent formation of an activated ester and TMU by-product (**Scheme 1.8**).



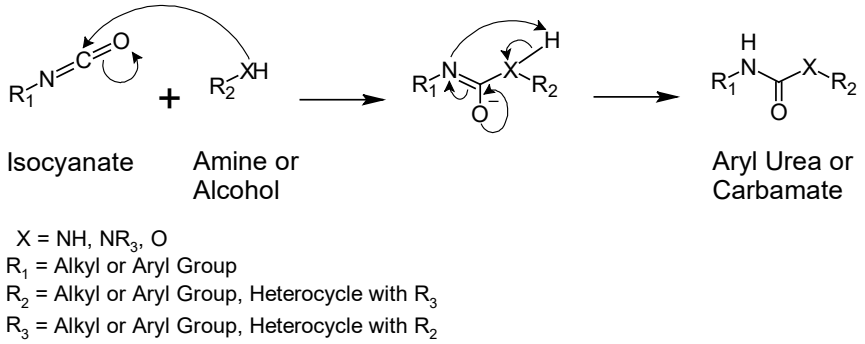
Scheme 1.8 - *First step of proposed reaction mechanism for synthetic procedure employed in HATU method.*

The second step of the reaction mechanism commences through the addition of HOSA. The amino group of HOSA acts as a nucleophile which attacks the carbonyl carbon atom of the activated ester, transforming it into a hydroxamate while $^{-}$OAt is once again released. A Lossen rearrangement is then promptly initiated through the deprotonation of the nitrogen atom in the hydroxamate by the anionic oxygen in $^{-}$OAt. This converts the hydroxamate to an isocyanate while simultaneously forming HOAt by-product. Upon formation of the isocyanate, the nitrogen atom is deprotonated by HSO_4^- which had been released from the hydroxamate during the Lossen rearrangement, resulting in sulfuric acid by-product (**Scheme 1.9**).



Scheme 1.9 - *Second step of proposed reaction mechanism for synthetic procedure employed in HATU method.*

The third step of the reaction mechanism begins when the amine or alcohol starting material is added. A nucleophilic attack by the amino or hydroxyl group occurs on the carbon atom of the isocyanato group in the isocyanate, forming a zwitterion of the aryl urea or carbamate product. The zwitterion is quickly converted to a neutral molecule through an intramolecular proton transfer from the cationic nitrogen or oxygen atom to the anionic nitrogen atom (**Scheme 1.10**).



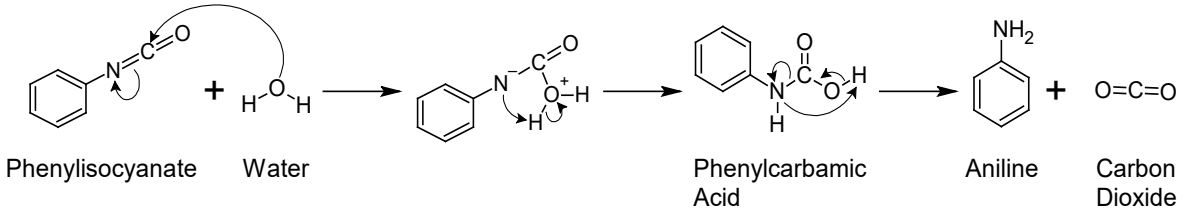
Scheme 1.10 - *Third step of proposed reaction mechanism for synthetic procedure employed in HATU method.*

The first objective of the project was the optimization of the HATU method in order to maximize product yield. This optimization was carried out through the repeated synthesis of

N,N'-diphenylurea from benzoic acid and aniline while varying parameters such as reagent proportions as well as reaction conditions. The parameters which resulted in the highest yield of *N,N'*-diphenylurea were then used for all subsequent reactions involving the HATU method, except where noted. The second objective of the project was the preparation of several aryl ureas using benzoic acid and various amines as starting materials. Similarly, the third objective of the project was the preparation of several aryl carbamates using benzoic acid and various alcohols as starting materials. The preparation of each aryl urea and carbamate was done in duplicate. Also, the yield reported herein for each product corresponds to the higher yield obtained from each pair of reactions. Among the aryl ureas and carbamates synthesized were those which had been previously prepared by Bao *et al.* (2018). Therefore, completion of these reactions not only provided insight into the versatility of the HATU method, but also allowed for direct comparisons to be made with the method employed by Bao *et al.* (2018).

Although many of the strengths and limitations of the HATU method were revealed through the variation of the amine as well as alcohol starting materials, it was determined that the use of different carboxylic starting materials was also necessary in order to gain a better understanding of how their chemical properties affect product yield. Therefore, the fourth objective of the project was the preparation of additional ureas using various carboxylic acids and aniline, many of which had already been synthesized from benzoic acid and certain amines. Once again, the preparation of each aryl urea was done in duplicate and only the higher yield obtained from each pair of reactions was reported herein. The preparation of several aryl ureas using two different combinations of starting materials provided an opportunity to determine which was more appropriate for the synthesis of each product based on comparisons between product yields.

Once the preparation of the additional aryl ureas had been completed, the fifth objective of the project shifted focus to the evaluation of primary amine synthesis as an alternative application for the method. The potential for primary amine preparation through the HATU method exists since such products could be formed by using water as the nucleophilic starting material. Unlike the addition of an amine or alcohol, the addition of water results in the isocyanate being converted to a carbamic acid which subsequently dissociates into carbon dioxide and the primary amine (**Scheme 1.11**).[46] In order to determine the effectiveness of the HATU method as an approach to primary amine synthesis, a few attempts to prepare aniline from benzoic acid and water were carried out using slightly different parameters for the synthetic as well as purification procedures.

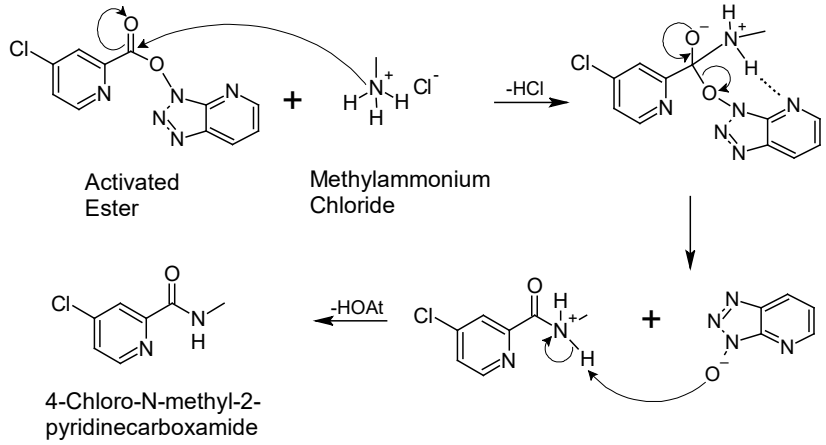


Scheme 1.11 - *Alternative third step of proposed reaction mechanism for synthetic procedure employed in HATU method when modified for synthesis of aniline.*

After the potential use of the HATU method for primary amine synthesis had been tested, the project was concluded with a sixth objective that explored the application of the method to drug synthesis by adapting it to an existing synthetic pathway for Sorafenib.[95] Sorafenib is marketed by Bayer and Onyx Pharmaceuticals in tosylate salt form under the brand name Nexavar. It is mainly used to treat kidney, liver, and thyroid cancer.[96,97] However, Sorafenib is expensive to manufacture and this results in a high cost of approximately $45 per 200mg tablet for patients. Furthermore, these tablets must be taken in 400mg doses twice each day.[97,98] As a result, a reduction in the manufacturing costs of this drug is extremely important in order to

make it an economically viable option for treatment. In addition, revisions to an existing synthetic pathway have the potential to lessen its environmental impact or expand its application to the preparation of other products with similar molecular structures.

Previously, Kumar *et al.* (2019) synthesized Sorafenib by first preparing *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea and 4-chloro-*N*-methyl-2-pyridinecarboxamide as precursors. The two precursors were then connected through an aryl ether group that forms following an SNAr reaction between the hydroxyl group of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea and the carbon atom that shares a bond with the chlorine atom in 4-chloro-*N*-methyl-2-pyridinecarboxamide.[95] Since one of the precursors used in this approach was an aryl urea, it was possible to synthesize it using the HATU method. Also, the aryl amide precursor could be prepared through the HATU method by simply excluding the addition of HOSA in the synthetic procedure (**Scheme 1.12**).

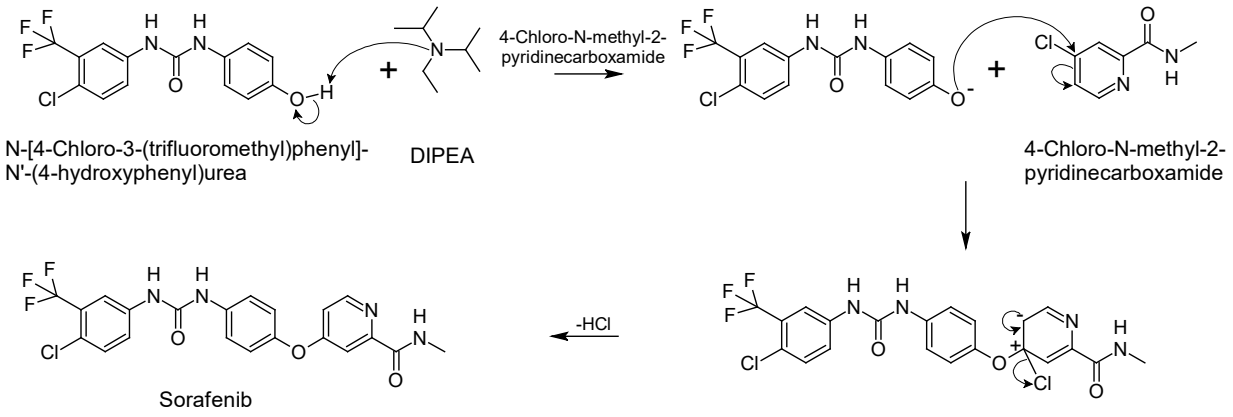


Scheme 1.12 - *Alternative second step of proposed reaction mechanism for synthetic procedure employed in HATU method when modified for synthesis of 4-chloro-N-methyl-2-pyridinecarboxamide.*

Finally, DIPEA was employed as the base catalyst for the SNAr reaction which connected the two precursors, despite such reactions often using alkoxide or amide bases instead due to their higher basicity (**Scheme 1.13**).[95,99,100] In order to compensate for the lower basicity of DIPEA,

the reaction mixture was heated in the microwave synthesizer for 30 minutes to maximize product formation.

All three steps involved in the total synthesis of Sorafenib were conducted in duplicate and only the higher yield achieved for each product was reported herein. The repeated use of a single base catalyst and certain reagents throughout this total synthesis of Sorafenib was done in an effort to make it more cost effective by eliminating the need to purchase an entirely different set of chemicals for each reaction. Also, it was expected that the one-pot design of the synthetic procedure in the HATU method would maximize the yields obtained for both precursors since there was no need to isolate any intermediates.[101,102,103] However, it must be emphasized that these reactions were designed to be performed on a laboratory scale and therefore, their employment on an industrial scale would likely present additional challenges.[104,105]



Scheme 1.13 - *Proposed S_NAr reaction mechanism for synthesis of Sorafenib from N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-hydroxyphenyl)urea and 4-chloro-N-methyl-2-pyridinecarboxamide.*

2. EXPERIMENTAL

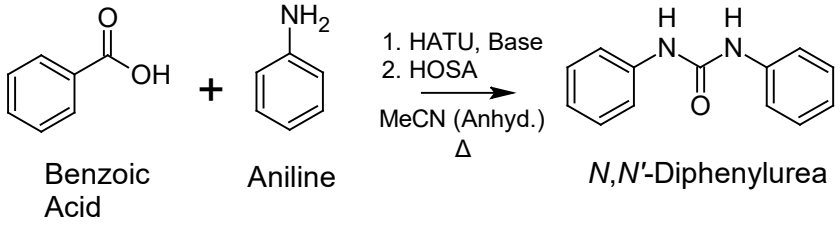
2.1 Synthesis of *N,N'*-Diphenyl Urea Under Various Conditions Using Benzoic Acid and Aniline

The optimization of the HATU method was conducted by repeatedly preparing N,N'diphenylurea under different conditions (**Scheme 2.1**). An oven-dried 10mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. Benzoic acid (1-1.25eq) was then added to the vial followed by anhydrous MeCN (5mL). The mixture was allowed to stir for a minute and HATU (1.05-1.25eq) was then added. Following another minute of stirring, an amine base (5eq) was added. Once a third minute had elapsed, HOSA (1.3-1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, aniline (1-1.3eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 5 minutes (50-100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with EtOAc or DCM (25mL) and washed with water (25mL). Any product which may have been extracted into the water was back-extracted with more of the EtOAc or DCM (25mL). The two portions of organic solvent were then combined and washed with brine (25mL) to remove any traces of water. The EtOAc or DCM was transferred to a 125mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The EtOAc or DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 10:90 EtOAc/Hexane, 1min. → 10:90 Ethyl Acetate/Hexane,

10min. → 10:90 to 80:20 EtOAc/Hexane, 1min. → 80:20 Ethyl Acetate/Hexane, 5min. → 80:20 to 100:0 EtOAc/Hexane, 1min. → 100:0 Ethyl Acetate/Hexane, 2min.). The product was then transferred to a 15mL sintered glass filter funnel and further purified by trituration with sufficient amounts of chloroform. As the trituration proceeded, the dissolved impurities were removed by vacuum filtration.



Scheme 2.1 *- Synthesis of N,N'-diphenylurea from benzoic acid and aniline using synthetic procedure employed in HATU method.*

2.1.1 Synthesis of *N,N'*Diphenylurea (Entry 1a)

N,N'-Diphenylurea was prepared from benzoic acid (114mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.1. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (155.5mg, 95%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89] Variations of the synthesis (**Table 3.1, Entries 1b-1j**) were also carried out using different proportions and conditions.

R_f = 0.74 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.66 (s, 2H), 7.45 (d, *J* = 7.8Hz, 4H), 7.27 (t, *J* = 7.6Hz, 4H), 6.96 (t, *J* = 7.3Hz, 2H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.5 (C), 139.7 (C), 128.8 (CH), 121.8 (CH), 118.2 (CH)

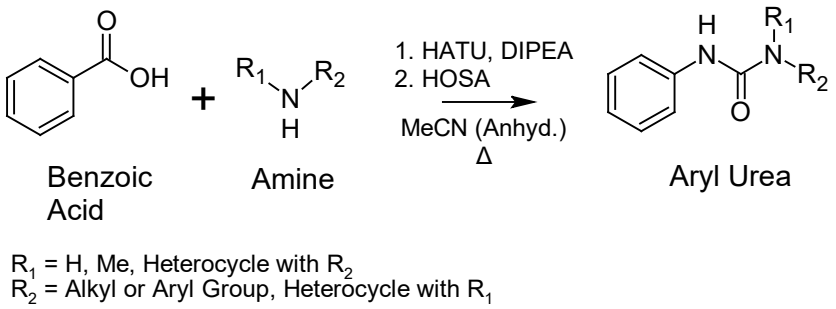
2.2 Synthesis of Aryl Ureas Using Benzoic Acid and Various Amines

The HATU method was used to prepare several aryl ureas by combining benzoic acid with different amines (**Scheme 2.2**). An oven-dried 10mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. Benzoic acid (1.25eq) was then added to the vial followed by anhydrous MeCN (5mL). The mixture was allowed to stir for a minute and HATU (1.25eq) was then added. Following another minute of stirring, DIPEA (5eq) was added. Once a third minute had elapsed, HOSA (1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, an amine (1eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 5 minutes (100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with EtOAc or DCM (25-50mL) and washed with water (25mL). Any product which may have been extracted into the water was back-extracted with more of the EtOAc or DCM (25-50mL). The two portions of EtOAc or DCM were then combined and washed with brine (25mL) to remove any traces of water. The EtOAc or DCM was transferred to a 125mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The organic solvent was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 10:90 EtOAc/Hexane, 1min. → 10:90 Ethyl Acetate/Hexane, 10min. → 10:90 to 80:20 EtOAc/Hexane, 1min. → 80:20 Ethyl Acetate/Hexane, 5min. → 80:20 to 100:0 EtOAc/Hexane, 1min. → 100:0 Ethyl Acetate/Hexane, 2min.). The product was then

transferred to a 15mL sintered glass filter funnel and further purified by trituration with sufficient amounts of chloroform or hexane-chloroform (90:10, v/v). As the trituration proceeded, the dissolved impurities were removed by vacuum filtration.



Scheme 2.2 - *Synthesis of aryl ureas from benzoic acid and various amines using synthetic procedure employed in HATU method.*

2.2.1 Synthesis of *N*-(2-Methylphenyl)-*N'*-phenylurea Using *o*-Toluidine (Entry 2a)

N-(2-Methylphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *o*-toluidine (0.08mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (124.7mg, 76%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.2Hz, 1H), 7.46 (d, *J* = 7.5Hz, 2H), 7.28 (t, *J* = 7.4Hz, 2H), 7.18-7.12 (m, 2H), 6.98-6.92 (m, 2H), 2.24 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.6 (C), 139.8 (C), 137.3 (C), 130.1 (CH), 128.7 (CH), 127.5 (C), 126.1 (CH), 122.6 (CH), 121.6 (CH), 121.0 (CH), 117.9 (CH), 17.8 (CH_3)

2.2.2 Synthesis of *N*-(4-Methylphenyl)-*N'*-phenylurea Using *p*-Toluidine (Entry 2b)

N-(4-Methylphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *p*-toluidine (80.4mg, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (137mg, 81%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.51 (s, 1H), 7.44 (d, *J* = 7.5Hz, 2H), 7.33 (d, *J* = 8.4Hz, 2H), 7.27 (t, *J* = 7.4Hz, 2H), 7.08 (d, *J* = 8.2Hz, 2H), 6.95 (t, *J* = 7.3Hz, 2H), 2.24 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.5 (C), 139.7 (C), 137.1 (C), 130.6 (C), 129.1 (CH), 128.7 (CH), 121.6 (CH), 118.2 (CH), 118.1 (CH), 20.3 (CH_3)

2.2.3 Synthesis of *N*-(3-Methylphenyl)-*N'*-phenylurea Using *m*-Toluidine (Entry 2c)

N-(3-Methylphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *m*-toluidine (0.08mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (106mg, 63%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[106]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.64 (s, 1H), δ 8.58 (s, 1H), δ 7.445 (d, *J* = 7.5Hz, 2H), δ 7.29-7.21 (m, 4H), δ 7.15 (t, *J* = 7.5Hz, 1H), δ 6.96 (t, *J* = 7.3Hz, 1H), δ 6.78 (d, *J* = 7.3Hz, 1H), δ 2.27 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 152.5 (C), δ 139.7 (C), δ 139.6 (C), δ 137.9 (C), δ 128.7 (CH), δ 128.6 (CH), δ 122.5 (CH), δ 121.7 (CH), δ 118.6 (CH), δ 118.1 (CH), δ 115.3 (CH), δ 21.2 (CH_3)

2.2.4 Synthesis of *N*-(2,4-Dimethylphenyl)-*N'*-phenylurea Using 2,4-Dimethylaniline (Entry 2d)

N-(2,4-Dimethylphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and 2,4-dimethylaniline (0.09mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (132mg, 76%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.79 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.90 (s, 1H), 7.81 (s, 1H), 7.65 (d, *J* = 8.1Hz, 1H), 7.45 (d, *J* = 7.5Hz, 2H), 7.27 (t, *J* = 7.4Hz, 2H), 6.98-6.93 (m, 3H), 2.22 (s, 3H), 2.20 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 153.2 (C), 140.5 (C), 135.2 (C), 132.1 (C), 131.2 (CH), 129.2 (CH), 128.3 (C), 127.0 (CH), 122.04 (CH), 121.98 (CH), 118.4 (CH), 20.8 (CH_3), 18.2 (CH_3)

2.2.5 Synthesis of *N*-(3,4-Dimethylphenyl)-*N'*-phenylurea Using 3,4-Dimethylaniline (Entry 2e)

N-(3,4-Dimethylphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and 3,4-dimethylaniline (91.3mg, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (127.8mg, 71%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[107]

R_f = 0.76 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.60 (s, 1H), δ 8.47 (s, 1H), δ 7.435 (d, *J* = 7.5Hz, 2H), δ 7.28-7.22 (m, 3H), δ 7.16 (dd, *J* = 8.1Hz, 2.2Hz, 1H), δ 7.02 (d, *J* = 8.2Hz, 1H), δ 6.95 (t, *J* = 7.3Hz, 1H), δ 2.18 (s, 3H), δ 2.15 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.5 (C), δ 139.8 (C), δ 137.3 (C), δ 136.3 (C), δ 129.6 (CH), δ 129.4 (C), δ 128.7 (CH), δ 121.6 (CH), δ 119.5 (CH), δ 118.0 (CH), δ 115.7 (CH), δ 19.6 (CH_3), δ 18.6 (CH_3)

2.2.6 Synthesis of *N*-(2,4,6-Trimethylphenyl)-*N'*-phenylurea Using 2,4,6-Trimethylaniline (Entry 2f)

N-(2,4,6-Trimethylphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and 2,4,6-trimethylaniline (0.1mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (101.9mg, 56%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.79 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.63 (s, 1H), 7.58 (s, 1H), 7.43 (d, *J* = 7.5Hz, 1H), 7.24 (t, *J* = 7.4Hz, 2H), 6.93-6.88 (m, 3H), 2.23 (s, 3H), 2.16 (s, 6H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 153.2 (C), 140.3 (C), 135.2 (C), 134.8 (C), 132.6 (C), 128.6 (CH), 128.2 (CH), 121.2 (CH), 117.8 (CH), 20.4 (CH_3), 18.1 (CH_3)

2.2.7 Synthesis of *N*-(4-Methoxyphenyl)-*N'*-phenylurea Using *p*-Anisidine (Entry 2g)

N-(4-Methoxyphenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *p*-anisidine (92.4mg, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (139.2mg, 76%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.46 (s, 1H), 7.43 (d, J = 7.5Hz, 2H), 7.35 (d, *J* = 9.0Hz, 2H), 7.26 (t, *J* = 7.3Hz, 2H), 6.94 (t, J = 7.5Hz, 1H), 6.86 (d, *J* = 9.0Hz, 2H), 3.71 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 154.4 (C), 152.7 (C), 139.9 (C), 132.7 (C), 128.7 (CH), 121.6 (CH), 120.0 (CH), 118.0 (CH), 114.0 (CH), 55.1 (CH_3)

2.2.8 Synthesis of *N*-(4-Chlorophenyl)-*N'*-phenylurea Using 4-Chloroaniline (Entry 2h)

N-(4-Chlorophenyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and 4-chloroaniline (95.7mg, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (149.9mg, 81%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.67 (s, 1H), 7.49-7.43 (m, 4H), 7.33-7.26 (m, 4H), 6.97 (t, *J* = 7.3Hz, 1H)

^{13}C NMR (101MHz, DMSO-d_6): δ 152.4 (C), 139.4 (C), 138.7 (C), 128.7 (CH), 128.5 (CH), 125.2 (C), 121.9 (CH), 119.6 (CH), 118.2 (CH)

2.2.9 Synthesis of *N*-Phenyl-4-morpholinecarboxamide Using Morpholine (Entry 2i)

N-Phenyl-4-morpholinecarboxamide was prepared from benzoic acid (114mg, 0.935mmol) and morpholine (0.06mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (82.1mg, 57%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.40 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.36-7.33 (m, 2H), 7.31-7.27 (m, 2H), 7.05 (t, J = 7.2Hz, 1H), 6.42 (bs, 1H), 3.72 (t, *J* = 4.8Hz, 4H), 3.46 (t, *J* = 5.0Hz, 4H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 155.2 (C), 138.7 (C), 129.0 (CH), 123.4 (CH), 120.1 (CH), 66.6 (CH_2), 44.3 (CH_2)

2.2.10 Synthesis of *N*-Methyl-*N,N'*-diphenylurea Using *N*-Methylaniline (Entry 2j)

N-Methyl-*N,N'*-diphenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *N*-methylaniline (0.08mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with a hexane-chloroform (90:10, v/v) solvent mixture, resulting in a white solid (76.9mg, 46%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR data with that reported in the literature.[89]

R_f = 0.74 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.49 (t, *J* = 7.3Hz, 2H), 7.40-7.27 (m, 5H), 7.23 (t, *J* = 7.1Hz, 2H), 6.99 (t, *J* = 7.1Hz, 1H), 6.23 (bs, 1H), 3.35 (s, 3H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 154.4 (C), 143.0 (C), 138.9 (C), 130.4 (CH), 128.9 (CH), 127.9 (CH), 127.5 (CH), 122.9 (CH), 119.3 (CH), 37.3 (CH_3)

2.2.11 Synthesis of *N*-Benzyl-*N'*-phenylurea Using Benzylamine (Entry 2k)

N-Benzyl-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and benzylamine (0.08mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (143mg, 86%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.54 (s, 1H), 7.40 (d, *J* = 7.5Hz, 2H), 7.35-7.29 (m, 4H), 7.25-7.20 (m, 3H), 6.89 (t, *J* = 7.3Hz, 1H), 6.60 (t, *J* = 5.9Hz, 1H), 4.29 (d, *J* = 5.9Hz, 2H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 155.2 (C), 140.4 (C), 140.3 (C), 128.6 (CH), 128.3 (CH), 127.1 (CH), 126.7 (CH), 121.1 (CH), 117.6 (CH), 42.7 (CH_2)

2.2.12 Synthesis of *N*-(*n*-Butyl)-*N'*-phenylurea Using *n*-Butylamine (Entry 2l)

N-(*n*-Butyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *n*-butylamine (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with a hexane-chloroform (90:10, v/v) solvent mixture, resulting in a white solid (128.2mg, 94%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.37 (d, *J* = 7.5Hz, 2H), 7.20 (t, *J* = 7.4Hz, 2H), 6.87 (t, *J* = 7.3Hz, 1H), 6.07 (t, *J* = 5.5Hz, 1H), 3.07 (q, *J* = 6.7Hz, 2H), 1.44-1.26 (m, 4H), 0.89 (t, *J* = 7.3Hz, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 155.1 (C), 140.5 (C), 128.5 (CH), 120.8 (CH), 117.5 (CH), 38.6 (CH_2), 31.8 (CH_2), 19.4 (CH_2), 13.6 (CH_3)

2.2.13 Synthesis of *N*-(*t*-Butyl)-*N'*-phenylurea Using *t*-Butylamine (Entry 2m)

N-(*t*-Butyl)-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and *t*-butylamine (0.08mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with a hexane-chloroform (90:10, v/v) solvent mixture, resulting in a white solid (110mg, 75%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[108]

R_f = 0.74 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.21 (s, 1H), δ 7.33 (d, *J* = 7.5Hz, 2H), δ 7.19 (t, *J* = 7.4Hz, 2H), δ 6.86 (t, *J* = 7.3Hz, 1H), δ 5.97 (s, 1H), δ 1.28 (s, 9H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 154.3 (C), δ 140.6 (C), δ 128.6 (CH), δ 120.7 (CH), δ 117.3 (CH), δ 49.3 (C), δ 29.0 (CH_3)

2.2.14 Synthesis of *N*-Cyclohexyl-*N'*-phenylurea Using Cyclohexylamine (Entry 2n)

N-Cyclohexyl-*N'*-phenylurea was prepared from benzoic acid (114mg, 0.935mmol) and cyclohexylamine (0.09mL, 0.75mmol) according to the synthetic procedure described in Section 2.2. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with a hexane-chloroform (90:10, v/v) solvent mixture, resulting in a white solid (139.2mg, 81%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[109]

R_f = 0.75 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.27 (s, 1H), δ 7.35 (d, *J* = 7.5 Hz, 2H), δ 7.20 (t, *J* = 7.4Hz, 2H), δ 6.86 (t, *J* = 7.3Hz, 1H), δ 6.05 (d, *J* = 7.8Hz, 1H), δ 3.49-3.42 (m, 1H), δ 1.81-1.77 (m, 2H), δ 1.67-1.63 (m, 2H), δ 1.55-1.51 (m, 1H), δ 1.34-1.26 (m, 2H), δ 1.21-1.11 (m, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 154.4 (C), δ 140.5 (C), δ 128.6 (CH), δ 120.8 (CH), δ 117.4 (CH), δ 47.5 (CH), δ 32.9 (CH_2), δ 25.2 (CH_2), δ 24.3 (CH_2)

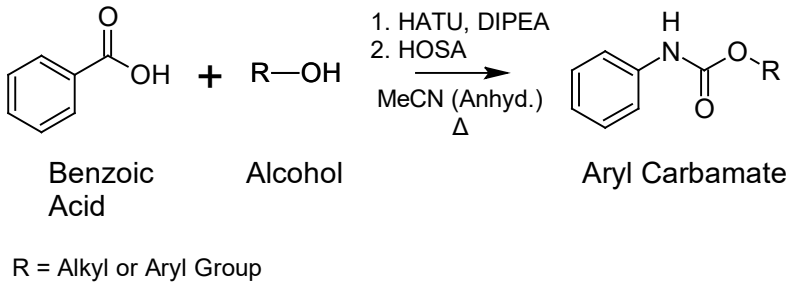
2.3 Synthesis of Aryl Carbamates Using Benzoic Acid and Various Alcohols

The HATU method was used to prepare several aryl carbamates by combining benzoic acid with different alcohols (**Scheme 2.3**). An oven-dried 10mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. Benzoic acid (1.25eq) was then added to the vial followed by anhydrous MeCN (5mL). The mixture was allowed to stir for a minute and HATU (1.25eq) was then added. Following another minute of stirring, DIPEA (5eq) was added. Once a third minute had elapsed, HOSA (1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, an alcohol (1eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 15 minutes (100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with DCM (50mL) and washed with water (25mL). Any product which may have been extracted into the water was back-extracted with more DCM (50mL). The two portions of DCM were then combined and washed with brine (25mL) to remove any traces of water. The DCM was transferred to a 125mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 10:90 EtOAc/Hexane, 1min. → 10:90 Ethyl Acetate/Hexane, 10min. → 10:90 to 80:20 EtOAc/Hexane, 1min. → 80:20 Ethyl Acetate/Hexane, 5min. → 80:20 to 100:0 EtOAc/Hexane, 1min. → 100:0 Ethyl Acetate/Hexane, 2min.). If the product was

recovered as a liquid, it was placed on ice for 1 hour to induce crystallization.



Scheme 2.3 - *Synthesis of aryl carbamates from benzoic acid and various alcohols using synthetic procedure employed in HATU method.*

2.3.1 Synthesis of Benzyl-*N*-phenylcarbamate Using Benzyl Alcohol (Entry 3a)

Benzyl-*N*-phenylcarbamate was prepared from benzoic acid (114mg, 0.935mmol) and benzyl alcohol (0.08mL, 0.75mmol) according to the synthetic procedure described in Section 2.3. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC, resulting in a clear liquid being isolated. The clear liquid was placed on ice for one hour, causing it to crystallize into a white solid (113mg, 65%). The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.86 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.42-7.29 (m, 9H), 7.07 (t, *J* = 7.3Hz, 1H), 6.66 (bs, 1H), 5.21 (s, 2H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 153.3 (C), 137.7 (C), 136.0 (C), 129.0 (CH), 128.6 (CH), 128.33 (CH), 128.29 (CH), 123.5 (CH), 118.7 (CH), 67.0 (CH_2)

2.3.2 Synthesis of Ethyl-*N*-phenylcarbamate Using Ethanol (Entry 3b)

Ethyl-*N*-phenylcarbamate was prepared from benzoic acid (114mg, 0.935mmol) and ethanol (0.04mL, 0.75mmol) according to the synthetic procedure described in Section 2.3. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC, resulting in a clear liquid being isolated. The clear liquid was placed on ice for one hour, causing it to crystallize into a white solid (75.7mg, 67%). The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.83 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.38 (d, *J* = 7.9Hz, 2H), 7.30 (t, *J* = 7.4Hz, 2H), 7.06 (t, J = 7.3Hz, 1H), 6.60 (bs, 1H), 4.23 (q, *J* = 7.1Hz, 2H), and 1.31 (t, *J* = 7.1Hz, 3H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 153.6 (C), 137.9 (C), 129.0 (CH), 123.3 (CH), 118.7 (CH), 61.2 (CH_2), 14.5 (CH_3)

2.3.3 Synthesis of *n*-Propyl-*N*-phenylcarbamate Using *n*-Propanol (Entry 3c)

n-Propyl-*N*-phenylcarbamate was prepared from benzoic acid (114mg, 0.935mmol) and *n*-propanol (0.06mL, 0.75mmol) according to the synthetic procedure described in Section 2.3. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC, resulting in a clear liquid being isolated. The clear liquid was placed on ice for one hour, causing it to crystallize into a white solid (92.9mg, 64%). The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.83 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.38 (d, *J* = 7.9Hz, 2H), 7.30 (t, *J* = 7.4Hz, 2H), 7.06 (t, J = 7.3Hz, 1H), 6.60 (bs, 1H), 4.13 (t, *J* = 6.7Hz, 2H), 1.75-1.66 (m, 2H), 0.98 (t, *J* = 7.4Hz, 3H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 153.7 (C), 138.0 (C), 129.0 (CH), 123.3 (CH), 118.6 (CH), 66.8 (CH_2), 22.3 (CH_2), 10.3 (CH_3)

2.3.4 Synthesis of *i*-Propyl-*N*-phenylcarbamate Using *i*-Propanol (Entry 3d)

i-Propyl-*N*-phenylcarbamate was prepared from benzoic acid (114mg, 0.935mmol) and *i*-propanol (0.06mL, 0.75mmol) according to the synthetic procedure described in Section 2.3. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC, resulting in a white solid (67.5mg, 48%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.85 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.38 (d, *J* = 7.9Hz, 2H), 7.30 (t, *J* = 7.4Hz, 2H), 7.05 (t, J = 7.3Hz, 1H), 6.54 (bs, 1H), 5.05-4.99 (m, 1H), 1.30 (d, *J* = 6.3Hz, 6H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 153.1 (C), 138.0 (C), 129.0 (CH), 123.2 (CH), 118.5 (CH), 68.7 (CH), 22.1 (CH_3)

2.3.5 Synthesis of *t*-Butyl-*N*-phenylcarbamate Using *t*-Butanol (Entry 3e)

t-Butyl-*N*-phenylcarbamate was prepared from benzoic acid (114mg, 0.935mmol) and *t*-butanol (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.3. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC, resulting in a white solid (13.3mg, 9%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.82 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, Chloroform-d$_1$): δ 7.35 (d, *J* = 7.9Hz, 2H), 7.29 (t, *J* = 7.4Hz, 2H), 7.03 (t, J = 7.3Hz, 1H), 6.47 (bs, 1H), 1.52 (s, 10H)

^{13}C NMR APT (101MHz, Chloroform-d$_1$): δ 152.6 (C), 138.3 (C), 128.9 (CH), 123.0 (CH), 118.5 (CH), 80.5 (C), 28.3 (CH_3)

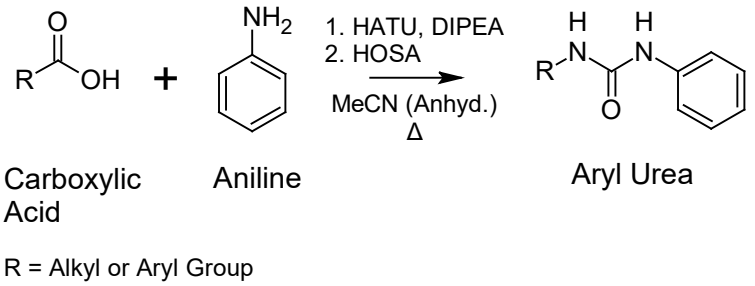
2.4 Synthesis of Aryl Ureas Using Various Carboxylic Acids and Aniline

The HATU method was used to prepare several aryl ureas by combining aniline with different carboxylic acids (**Scheme 2.4**). An oven-dried 10mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. A carboxylic acid (1.25eq) was then added to the vial followed by anhydrous MeCN (5mL). The mixture was allowed to stir for a minute and HATU (1.25eq) was then added. Following another minute of stirring, DIPEA (5eq) was added. Once a third minute had elapsed, HOSA (1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, aniline (1eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 5 minutes (100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with EtOAc or DCM (25-50mL) and washed with water (25mL). Any product which may have been extracted into the water was back-extracted with more EtOAc or DCM (25-50mL). The two portions of EtOAc or DCM were then combined and washed with brine (25mL) to remove any traces of water. The EtOAc or DCM was transferred to a 125mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The EtOAc or DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 10:90 EtOAc/Hexane, 1min. → 10:90 Ethyl Acetate/Hexane, 10min. → 10:90 to 80:20 EtOAc/Hexane, 1min. → 80:20 Ethyl Acetate/Hexane, 5min. → 80:20 to 100:0 EtOAc/Hexane, 1min. → 100:0 Ethyl Acetate/Hexane, 2min.). The product was then

transferred to a 15mL sintered glass filter funnel and further purified by trituration with sufficient amounts of chloroform, hexane-chloroform (90:10, v/v), or chloroform-EtOAc (90:10, v/v). As the trituration proceeded, the dissolved impurities were removed by vacuum filtration.



Scheme 2.4 - *Synthesis of aryl ureas from various carboxylic acids and aniline using synthetic procedure employed in HATU method.*

2.4.1 Synthesis of *N*-(2-Methylphenyl)-*N'*-phenylurea Using *o*-Toluic Acid (Entry 4a)

N-(2-Methylphenyl)-*N'*-phenylurea was prepared from *o*-toluic acid (127mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (70.3mg, 41%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 9.02 (s, 1H), δ 7.92 (s, 1H), δ 7.84 (d, *J* = 7.1Hz, 1H), δ 7.46 (d, *J* = 7.5Hz, 2H), δ 7.28 (t, *J* = 7.4Hz, 2H), δ 7.18-7.12 (m, 2H), δ 6.98-6.92 (m, 2H), δ 2.24 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 152.6 (C), δ 139.8 (C), δ 137.4 (C), δ 130.1 (CH), δ 128.8 (CH), δ 127.4 (C), δ 126.1 (CH), δ 122.6 (CH), δ 121.7 (CH), δ 121.0 (CH), δ 117.9 (CH), δ 17.9 (CH_3)

2.4.2 Synthesis of *N*-(4-Methylphenyl)-*N'*-phenylurea Using *p*-Toluic Acid (Entry 4b)

N-(4-Methylphenyl)-*N'*-phenylurea was prepared from *p*-toluic acid (127mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (92.3mg, 54%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.61 (s, 1H), δ 8.55 (s, 1H), δ 7.44 (d, *J* = 7.5Hz, 2H), δ 7.33 (d, *J* = 8.4Hz, 2H), δ 7.27 (t, *J* = 7.4Hz, 2H), δ 7.08 (d, *J* = 8.1Hz, 2H), δ 6.95 (t, *J* = 7.3Hz, 2H), δ 2.24 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 152.5 (C), δ 139.8 (C), δ 137.1 (C), δ 130.6 (C), δ 129.1 (CH), δ 128.7 (CH), δ 121.7 (CH), δ 118.2 (CH), δ 118.1 (CH), δ 20.3 (CH_3)

2.4.3 Synthesis of *N*-(2,4-Dimethylphenyl)-*N'*-phenylurea Using 2,4-Dimethylbenzoic Acid (Entry 4c)

N-(2,4-Dimethylphenyl)-*N'*-phenylurea was prepared from 2,4-dimethylbenzoic acid (140mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (112mg, 64%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.79 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.94 (s, 1H), δ 7.84 (s, 1H), δ 7.66 (d, *J* = 8.1Hz, 1H), δ 7.45 (d, *J* = 7.5Hz, 2H), δ 7.27 (t, *J* = 7.4Hz, 2H), δ 6.98-6.93 (m, 3H), δ 2.22 (s, 3H), δ 2.19 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.7 (C), δ 140.0 (C), δ 134.7 (C), δ 131.6 (C), δ 130.7 (CH), δ 128.8 (CH), δ 127.8 (C), δ 126.6 (CH), δ 121.6 (CH), δ 121.4 (CH), δ 117.9 (CH), δ 20.3 (CH_3), δ 17.8 (CH_3)

2.4.4 Synthesis of *N*-(2,4,6-Trimethylphenyl)-*N'*-phenylurea Using 2,4,6-Trimethylbenzoic Acid (Entry 4d)

N-(2,4,6-Trimethylphenyl)-*N'*-phenylurea was prepared from 2,4,6-trimethylbenzoic acid (153mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (2mg, 1%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.79 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.60 (s, 1H), 7.43 (d, *J* = 7.5Hz, 1H), 7.24 (t, *J* = 7.4Hz, 2H), 6.93-6.87 (m, 3H), 2.22 (s, 3H), 2.15 (s, 6H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 153.3 (C), 140.3 (C), 135.3 (C), 134.9 (C), 132.6 (C), 128.7 (CH), 128.3 (CH), 121.3 (CH), 117.8 (CH), 20.5 (CH_3), 18.1 (CH_3)

2.4.5 Synthesis of *N*-(4-Methoxyphenyl)-*N'*-phenylurea Using *p*-Anisic Acid (Entry 4e)

N-(4-Methoxyphenyl)-*N'*-phenylurea was prepared from *p*-anisic acid (142mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (41.7mg, 23%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.58 (s, 1H), δ 8.47 (s, 1H), δ 7.43 (d, *J* = 7.5Hz, 2H), δ 7.35 (d, *J* = 9.0Hz, 2H), δ 7.26 (t, *J* = 7.4Hz, 2H), δ 6.94 (t, *J* = 7.3Hz, 1H), δ 6.86 (d, *J* = 9.1Hz, 2H), δ 3.71 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 154.4 (C), δ 152.7 (C), δ 139.9 (C), δ 132.7 (C), δ 128.7 (CH), δ 121.6 (CH), δ 120.0 (CH), δ 118.0 (CH), δ 114.0 (CH), δ 55.1 (CH_3)

2.4.6 Synthesis of *N*-(4-Acetylphenyl)-*N'*-phenylurea Using 4-Acetylbenzoic Acid (Entry 4f)

N-(4-Acetylphenyl)-*N'*-phenylurea was prepared from 4-acetylbenzoic acid (153mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform-EtOAc (90:10, v/v), resulting in a light yellow solid (65.2mg, 34%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[110]

R_f = 0.61 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 9.14 (s, 1H), δ 8.84 (s, 1H), δ 7.905 (d, *J* = 8.8Hz, 2H), δ 7.58 (d, *J* = 8.8Hz, 2H), δ 7.465 (d, *J* = 7.5Hz, 2H), δ 7.30 (t, *J* = 7.5Hz, 2H), δ 6.99 (t, *J* = 7.3Hz, 1H), δ 2.51 (s, 3H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 196.3 (C), δ 152.2 (C), δ 144.4 (C), δ 139.3 (C), δ 130.4 (C), δ 129.6 (CH), δ 128.8 (CH), δ 122.2 (CH), δ 118.4 (CH), δ 117.1 (CH), δ 26.3 (CH_3)

2.4.7 Synthesis of *N*-(4-Cyanophenyl)-*N'*-phenylurea Using 4-Cyanobenzoic Acid (Entry 4g)

N-(4-Cyanophenyl)-*N'*-phenylurea was prepared from 4-cyanobenzoic acid (137mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (174.7mg, 98%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[109]

R_f = 0.63 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 9.21 (s, 1H), δ 8.87 (s, 1H), δ 7.73 (d, *J* = 8.8Hz, 2H), δ 7.63 (d, *J* = 8.9Hz, 2H), δ 7.46 (d, *J* = 7.5Hz, 2H), δ 7.30 (t, *J* = 7.4Hz, 2H), δ 7.0 (t, *J* = 7.4Hz, 1H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.1 (C), δ 144.2 (C), δ 139.1 (C), δ 133.3 (CH), δ 128.8 (CH), δ 122.3 (CH), δ 119.3 (C), δ 118.5 (CH), δ 118.0 (CH), δ 103.2 (C)

2.4.8 Synthesis of *N*-(4-Fluorophenyl)-*N'*-phenylurea Using 4-Fluorobenzoic Acid (Entry 4h)

N-(4-Fluorophenyl)-*N'*-phenylurea was prepared from 4-fluorobenzoic acid (131mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (150mg, 87%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[111]

R_f = 0.78 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.69 (s, 1H), δ 8.65 (s, 1H), δ 7.47-7.43 (m, 4H), δ 7.27 (t, *J* = 7.4Hz, 2H), δ 7.12 (t, *J* = 8.9Hz, 2H), δ 6.96 (t, *J* = 7.3Hz, 1H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 157.3 (d, *J* = 235.0Hz, C), δ 152.6 (C), δ 139.6 (C), δ 136.01 (d, *J* = 2.3Hz, C), δ 128.7 (CH), δ 121.8 (CH), δ 119.90 (d, *J* = 7.6Hz, CH), δ 118.2 (CH), δ 115.2 (d, *J* = 22.4Hz, CH)

2.4.9 Synthesis of *N*-(4-Bromophenyl)-*N'*-phenylurea Using 4-Bromobenzoic Acid (Entry 4i)

N-(4-Bromophenyl)-*N'*-phenylurea was prepared from 4-bromobenzoic acid (188mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (211.2mg, 97%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[106]

R_f = 0.76 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.81 (s, 1H), δ 8.70 (s, 1H), δ 7.455 (d, *J* = 6.1Hz, 6H), δ 7.28 (t, *J* = 7.4Hz, 2H), δ 6.97 (t, *J* = 7.3Hz, 1H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.4 (C), δ 139.5 (C), δ 139.1 (C), δ 131.5 (CH), δ 128.8 (CH), δ 122.0 (CH), δ 120.1 (CH), δ 118.3 (CH), δ 113.1 (C)

2.4.10 Synthesis of *N*-(2-Chlorophenyl)-*N'*-phenylurea Using 2-Chlorobenzoic Acid (Entry 4j)

N-(2-Chlorophenyl)-*N'*-phenylurea was prepared from 2-chlorobenzoic acid (146mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (3.9mg, 70%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[112]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 9.42 (s, 1H), δ 8.31 (s, 1H), δ 8.169 (dd, *J* = 8.3Hz, 1.5Hz, 1H), δ 7.479-7.444 (m, 3H), δ 7.318-7.279 (m, 3H), δ 7.047-6.971 (m, 2H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.1 (C), δ 139.4 (C), δ 135.9 (C), δ 129.2 (CH), δ 128.9 (CH), δ 127.5 (CH), δ 123.2 (CH), δ 122.1 (CH), δ 121.9 (C), δ 121.3 (CH), δ 118.2 (CH)

2.4.11 Synthesis of *N*-(4-Chlorophenyl)-*N'*-phenylurea Using 4-Chlorobenzoic Acid (Entry 4k)

N-(4-Chlorophenyl)-*N'*-phenylurea was prepared from 4-chlorobenzoic acid (146mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (173.6mg, 94%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.81 (s, 1H), δ 8.70 (s, 1H), δ 7.49-7.43 (m, 4H), δ 7.33-7.26 (m, 4H), δ 6.97 (t, *J* = 7.4Hz, 1H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 152.4 (C), δ 139.5 (C), δ 138.7 (C), δ 128.8 (CH), δ 128.6 (CH), δ 125.3 (C), δ 121.9 (CH), δ 119.7 (CH), δ 118.3 (CH)

2.4.12 Synthesis of *N*-(2,4-Dichlorophenyl)-*N'*-phenylurea Using 2,4-Dichlorobenzoic Acid (Entry 4l)

N-(2,4-Dichlorophenyl)-*N'*-phenylurea was prepared from 2,4-dichlorobenzoic acid (178mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with a chloroform-EtOAc (90:10, v/v) solvent mixture, resulting in a white solid (45.2mg, 20%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[113]

R_f = 0.76 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): 9.45 (s, 1H), δ 8.40 (s, 1H), δ 8.20 (d, *J* = 9.0Hz, 1H), δ 7.629 (d, *J* = 2.5Hz, 1H), δ 7.455 (d, *J* = 7.5Hz, 2H), δ 7.385 (dd, *J* = 9.0Hz, 2.5Hz, 1H), δ 7.30 (t, *J* = 7.4Hz, 2H), δ 7.0 (t, *J* = 7.3Hz, 1H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 151.9 (C), δ 139.2 (C), δ 135.2 (C), δ 128.9 (CH), δ 128.5 (CH), δ 127.6 (CH), δ 126.0 (C), δ 122.6 (C), δ 122.2 (CH), δ 122.1 (CH), δ 118.2 (CH)

2.4.13 Synthesis of *N*-Benzyl-*N'*-phenylurea Using Phenylacetic Acid (Entry 4m)

N-Benzyl-*N'*-phenylurea was prepared from phenylacetic acid (127mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (10.7mg, 18%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.56 (s, 1H), δ 7.40 (d, *J* = 7.5Hz, 2H), δ 7.35-7.29 (m, 4H), δ 7.25-7.20 (m, 3H), δ 6.89 (t, *J* = 7.3Hz, 1H), δ 6.61 (t, *J* = 5.9Hz, 1H), δ 4.295 (d, *J* = 5.9Hz, 2H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 155.2 (C), δ 140.4 (C), δ 140.3 (C), δ 128.6 (CH), δ 128.3 (CH), δ 127.1 (CH), δ 126.7 (CH), δ 121.0 (CH), δ 117.6 (CH), δ 42.7 (CH_2)

2.4.14 Synthesis of *N*-(*n*-Butyl)-*N'*-phenylurea Using Valeric Acid (Entry 4n)

N-(*n*-Butyl)-*N'*-phenylurea was prepared from valeric acid (0.1mL, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (26.8mg, 20%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[89]

R_f = 0.77 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.38 (s, 1H), δ 7.37 (d, *J* = 7.5Hz, 2H), δ 7.20 (t, *J* = 7.4Hz, 2H), δ 6.87 (t, *J* = 7.3Hz, 1H), δ 6.10 (t, *J* = 5.5Hz, 1H), δ 3.065 (q, *J* = 6.7Hz, 2H), δ 1.44-1.25 (m, 4H), δ 0.89 (t, *J* = 7.3Hz, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 155.2 (C), δ 140.6 (C), δ 128.6 (CH), δ 120.8 (CH), δ 117.5 (CH), δ 38.6 (CH_2), δ 31.9 (CH_2), δ 19.5 (CH_2), δ 13.7 (CH_3)

2.4.15 Synthesis of *N*-(*t*-Butyl)-*N'*-phenylurea Using Pivalic Acid (Entry 4o)

N-(*t*-Butyl)-*N'*-phenylurea was prepared from pivalic acid (95.5mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (7.4mg, 5%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[108]

R_f = 0.74 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 8.20 (s, 1H), δ 7.32 (d, *J* = 7.5Hz, 2H), δ 7.19 (t, *J* = 7.4Hz, 2H), δ 6.85 (t, *J* = 7.3Hz, 1H), δ 5.96 (s, 1H), δ 1.27 (s, 9H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 154.3 (C), δ 140.6 (C), δ 128.6 (CH), δ 120.7 (CH), δ 117.3 (CH), δ 49.3 (C), δ 29.0 (CH_3)

2.4.16 Synthesis of *N*-Cyclohexyl-*N'*-phenylurea Using Cyclohexanoic Acid (Entry 4p)

N-Cyclohexyl-*N'*-phenylurea was prepared from cyclohexanoic acid (120mg, 0.935mmol) and aniline (0.07mL, 0.75mmol) according to the synthetic procedure described in Section 2.4. The product was extracted from the reaction mixture using two 50mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC followed by trituration with chloroform, resulting in a white solid (53.3mg, 32%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[109]

R_f = 0.75 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d$_6$): δ 8.28 (s, 1H), δ 7.35 (d, *J* = 7.5 Hz, 2H), δ 7.20 (t, *J* = 7.4Hz, 2H), δ 6.86 (t, *J* = 7.3Hz, 1H), δ 6.05 (d, *J* = 7.8Hz, 1H), δ 3.48-3.41 (m, 1H), δ 1.81-1.77 (m, 2H), δ 1.67-1.63 (m, 2H), δ 1.55-1.51 (m, 1H), δ 1.34-1.25 (m, 2H), δ 1.21-1.10 (m, 3H)

^{13}C NMR APT (101MHz, DMSO-d$_6$): δ 154.4 (C), δ 140.5 (C), δ 128.6 (CH), δ 120.8 (CH), δ 117.4 (CH), δ 47.5 (CH), δ 32.9 (CH_2), δ 25.2 (CH_2), δ 24.3 (CH_2)

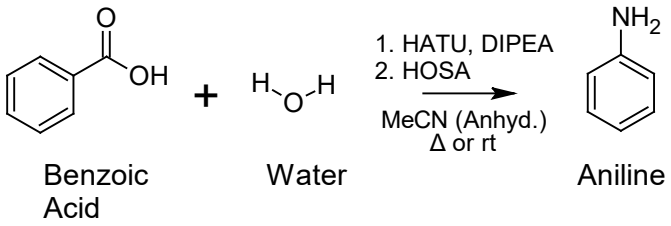
2.5 Synthesis of Aniline Using Benzoic Acid and Water

An attempt to modify the HATU method for the purpose of preparing aniline was conducted by repeatedly combining benzoic acid with water under different conditions (**Scheme 2.5**). An oven-dried 10mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. Benzoic acid (1-1.25eq) was then added to the vial followed by anhydrous MeCN (5mL). The mixture was allowed to stir for a minute and HATU (1.05-1.25eq) was then added. Following another minute of stirring, DIPEA (5eq) was added. Once a third minute had elapsed, HOSA (1.3-1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, water (1-1.3eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and the mixture was poured into a 250mL separatory flask immediately, or, after the vial had been heated in a microwave synthesizer for 5 minutes (100°C). If the vial was heated, it was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with EtOAc or DCM (25-50mL) and washed with water (25mL). Any product which may have been extracted into the water was back-extracted with more of the EtOAc or DCM (25-50mL). The two portions of EtOAc or DCM were then combined and washed with brine (25mL) to remove any traces of water. The EtOAc or DCM was transferred to a 125mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The EtOAc or DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 10:90 EtOAc/Hexane, 1min. → 10:90 Ethyl Acetate/Hexane,

10min. → 10:90 to 80:20 EtOAc/Hexane, 1min. → 80:20 Ethyl Acetate/Hexane, 5min. → 80:20 to 100:0 EtOAc/Hexane, 1min. → 100:0 Ethyl Acetate/Hexane, 2min.).



Scheme 2.5 - *Synthesis of aniline from benzoic acid and water using synthetic procedure employed in HATU method.*

2.5.1 Synthesis of Aniline (Entry 5a)

Aniline was prepared from benzoic acid (114mg, 0.935mmol) and water (0.01mL, 0.75mmol) according to the synthetic procedure described in Section 2.5. The product was extracted from the reaction mixture using two 25mL quantities of EtOAc which were subsequently combined. Purification of the product was attempted using FC, but none was recovered from the solvent fractions selected by the instrument software. Variations of the synthesis (**Table 3.4, Entries 5b-5d**) were also carried out using different proportions and conditions.

R_f = 0.69 (70% EtOAc/Hexane)

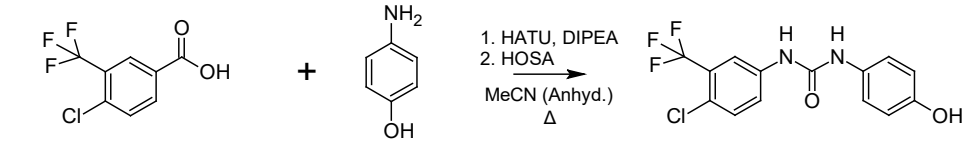
2.6 Synthesis of Sorafenib Using *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea and 4-Chloro-*N*-methyl-2-pyridinecarboxamide

Sorafenib preparation was attempted over three steps which each employed all or some conditions from the HATU method. In the first step, the HATU method was used to prepare *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea by combining 4-chloro-3-(trifluoromethyl)benzoic acid with 4-aminophenol (**Scheme 2.6**). An oven-dried 35mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. 4-Chloro-3-(trifluoromethyl)benzoic acid (1.25eq) was then added to the vial followed by anhydrous MeCN (15mL). The mixture was allowed to stir for a minute and HATU (1.25eq) was then added. Following another minute of stirring, DIPEA (5eq) was added. Once a third minute had elapsed, HOSA (1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, 4-aminophenol (1eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 5 minutes (100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with EtOAc (75mL) and washed with water (75mL). Any product which may have been extracted into the water was back-extracted with more of EtOAc (75mL). The two portions of EtOAc or DCM were then combined and washed with brine (75mL) to remove any traces of water. The EtOAc or DCM was transferred to a 250mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The EtOAc or DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100

EtOAc/Hexane, 2min. → 0:100 to 30:70 EtOAc/Hexane, 60min. → 30:70 Ethyl Acetate/Hexane, 30min. → 30:70 to 100:0 EtOAc/Hexane, 25min. → 100:0 Ethyl Acetate/Hexane, 2min.). The product was then transferred to a 15mL sintered glass filter funnel and further purified by trituration with sufficient amounts of chloroform-MeOH (90:10, v/v). As the trituration proceeded, the dissolved impurities were removed by vacuum filtration.



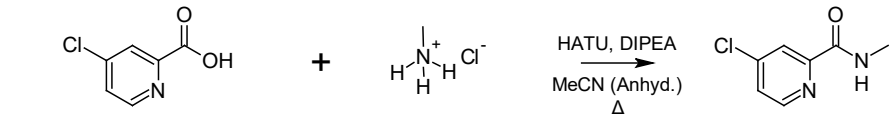
4-Chloro-3-(trifluoromethyl)-benzoic Acid | 4-Aminophenol | *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea

Scheme 2.6 - *Synthesis of N-[4-chloro-3-(trifluoromethyl)phenyl]-N′-(4-hydroxyphenyl)urea from 4-chloro-3-(trifluoromethyl)benzoic acid and 4-aminophenol using synthetic procedure employed in HATU method.*

Once *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea had been isolated, a modified version of the HATU method which excluded the addition of HOSA was used to prepare 4-chloro-*N*-methyl-2-pyridinecarboxamide by combining 4-chloro-2-pyridinecarboxylic acid with methylammonium chloride (**Scheme 2.7**). An oven-dried 35mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. 4-Chloro-2-pyridinecarboxylic acid (1.25eq) was then added to the vial followed by anhydrous MeCN (10mL). The mixture was allowed to stir for a minute and HATU (1.25eq) was then added. Following another minute of stirring, DIPEA (5eq) was added. Once a third minute had elapsed, HOSA (1.5eq) was added to the mixture and it was left to stir for 5 minutes. Finally, methylammonium chloride (1eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 5 minutes (100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The product was extracted with with DCM (100mL) and washed with water (50mL). Any product which may have been extracted into the water was back-extracted with more of DCM (100mL). The two portions of EtOAc or DCM were then combined and washed with brine (50mL) to remove any traces of water. The EtOAc or DCM was transferred to a 250mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The EtOAc or DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the crude product.

The crude product was loaded onto silica gel (40-60μm) and purified using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 10:90 EtOAc/Hexane, 5min. → 10:90 Ethyl Acetate/Hexane, 40min. → 10:90 to 100:0 EtOAc/Hexane, 10min. → 100:0 Ethyl Acetate/Hexane, 2min.). The product was recovered as a liquid and placed on ice for 1 hour to induce crystallization.



4-Chloro-2-pyridinecarboxylic Acid | Methylammonium Chloride | 4-Chloro-*N*-methyl-2-pyridinecarboxamide

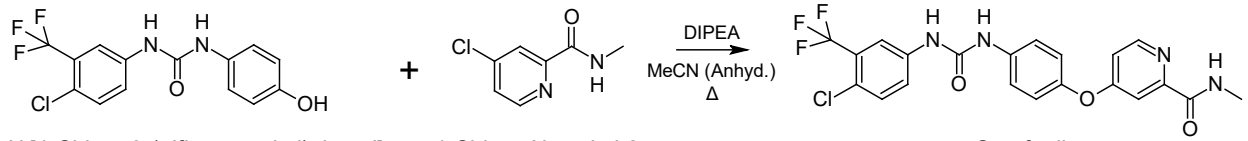
Scheme 2.7 **-** *Synthesis of 4-chloro-N-methyl-2-pyridinecarboxamide from 4-chloro-2-pyridinecarboxylic acid and methylammonium chloride using modified version of synthetic procedure employed in HATU method that excludes addition of HOSA.*

Following the isolation of 4-chloro-*N*-methyl-2-pyridinecarboxamide, it was then combined with *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea in an attempt to prepare Sorafenib using a S_NAr reaction (**Scheme 2.8**). An oven-dried 10mL microwave vial containing a magnetic stir bar was closed off by a septum cap and placed under an argon atmosphere. *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea (1.25eq) was then added to the vial followed by anhydrous MeCN (5mL). The mixture was allowed to stir for

a minute and DIPEA (5eq) was then added. Following another minute, 4-chloro-*N*-methyl-2-pyridinecarboxamide (1eq) was added to the vial and the mixture was given another five minutes to stir. The vial was then removed from the argon atmosphere and heated in a microwave synthesizer for 30 minutes (100°C). The vial was allowed to reach room temperature upon removal from the microwave synthesizer.

The reaction mixture was poured into a 250mL separatory funnel. The less polar components of the reaction mixture were extracted with EtOAc (25mL) and washed with water (25mL). Any of the less polar components which may have been extracted into the water were back-extracted with more EtOAc (25mL). The two portions of EtOAc or DCM were then combined and washed with brine (25mL) to remove any traces of water. The EtOAc or DCM was transferred to a 125mL flask and the presence of residual water was further minimized by the addition of a sufficient amount of sodium sulfate. The EtOAc or DCM was then gravity filtered to remove the sodium sulfate and rotoevaporated, leaving the less polar components of the reaction mixture.

The less polar reaction mixture components were loaded onto silica gel (40-60μm) and separated using FC (0:100 EtOAc/Hexane, 2min. → 0:100 to 100:0 Ethyl Acetate/Hexane, 60min. → 100:0 EtOAc/Hexane, 2min.). However, none of the solid components were identified as the product.



N-[4-Chloro-3-(trifluoromethyl)phenyl]-*N*′-(4-hydroxyphenyl)urea + 4-Chloro-*N*-methyl-2-pyridinecarboxamide → Sorafenib

Scheme 2.8 - *Synthesis of Sorafenib from N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-hydroxyphenyl)urea and 4-chloro-N-methyl-2-pyridinecarboxamide using S_NAr reaction.*

2.6.1 Synthesis of *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-hydroxyphenyl)urea (Entry 6a)

N-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-hydroxyphenyl)urea was prepared from 4-Chloro-3-(trifluoromethyl)benzoic acid (629mg, 2.8mmol) and 4-aminophenol (245mg, 2.25mmol) according to the synthetic procedure described in Section 2.6. The product was extracted from the reaction mixture using two 75mL quantities of EtOAc which were subsequently combined. Purification of the product was conducted using FC followed by trituration with a chloroform-MeOH (90:10, v/v) solvent mixture, resulting in a beige solid (332.3mg, 45%) being isolated. The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[114]

R_f = 0.65 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, DMSO-d_6): δ 9.15 (s, 1H), δ 9.04 (s, 1H), δ 8.50 (s, 1H), δ 8.095 (d, *J* = 2.1Hz, 1H), δ 7.62-7.57 (m, 2H), δ 7.22 (d, *J* = 8.8Hz, 2H), δ 6.69 (d, *J* = 8.9Hz, 2H)

^{13}C NMR APT (101MHz, DMSO-d_6): δ 153.0 (C), δ 152.6 (C), δ 139.7 (C), δ 131.9 (CH), δ 130.5 (C), δ 126.8 (q, *J* = 26.5Hz, C), δ 122.8 (CH), δ 121.8 (C), δ 121.0 (CH), δ 116.5 (q, *J* = 5.5Hz, CH), δ 115.2 (CH)

2.6.2 Synthesis of 4-Chloro-*N*-methyl-2-pyridinecarboxamide (Entry 6b)

4-Chloro-*N*-methyl-2-pyridinecarboxamide was prepared from 4-Chloro-2-pyridinecarboxylic acid (295mg, 1.87mmol) and methylammonium chloride (101mg, 1.5mmol) according to the synthetic procedure described in Section 2.6. The product was extracted from the reaction mixture using two 100mL quantities of DCM which were subsequently combined. Purification of the product was conducted using FC, resulting in a clear liquid being isolated. The clear liquid was placed on ice for one hour, causing it to crystallize into a white solid (188.1mg, 73%). The identity of the product was verified by comparing recorded ^{1}H NMR and ^{13}C NMR APT data with that reported in the literature.[115]

R_f = 0.67 (70% EtOAc/Hexane)

^{1}H NMR (400MHz, $CDCl_3$-d_1): δ 8.43 (d, *J* = 5.2Hz, 1H), δ 8.199 (d, *J* = 2.1Hz, 1H), δ 7.96 (br, 1H), δ 7.421 (dd, *J* = 5.2Hz, 2.1Hz, 1H), δ 3.03 (d, *J* = 5.1Hz, 3H)

^{13}C NMR APT (101MHz, $CDCl_3$-d_1): δ 163.7 (C), δ 151.4 (C), δ 148.9 (CH), δ 145.9 (C), δ 126.2 (CH), δ 122.8 (CH), δ 26.2 (CH_3)

2.6.3 Synthesis of Sorafenib (Entry 6c)

Sorafenib preparation was attempted from *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-hydroxyphenyl)urea (309mg, 0.935mmol) and 4-Chloro-*N*-methyl-2-pyridinecarboxamide (128mg, 0.75mmol) according to the synthetic procedure described in Section 2.6. The less polar components of the reaction mixture were extracted using two 25mL quantities of EtOAc which were subsequently combined. Separation of the components was effectively achieved by FC, but the product was not recovered from the solvent fractions selected by the instrument software.

3. RESULTS AND DISCUSSION

3.1 Optimization of HATU Method

The optimization of the HATU method was necessary to ensure that product yield was mostly influenced by the properties of the starting materials, rather than controllable factors such as reagent proportion or order of addition (**Table 3.1**). A 95% yield of *N,N'*-diphenylurea (**Entry 1a**) was achieved by replacing benzoyl chloride in the corresponding synthetic procedure with the combination of benzoic acid and HATU, along with substitution of DCM with MeCN as the reaction solvent. When compared to the 80% yield obtained by Bao *et al.* (2018), the potential for the HATU method to be the superior approach for the preparation of aryl ureas and carbamates became evident. There are two factors which are suggested to have contributed to this improved yield. First, the use of a more polar solvent likely improved the heat absorption of the reaction mixture in the microwave synthesizer.[87] Secondly, the use of benzoic acid and HATU resulted in the formation of an activated ester that was able to be converted to phenyl isocyanate more efficiently than benzoyl chloride upon nucleophilic attack by HOSA. This increased efficiency is likely due to hydrogen bond formation between the nitrogen atom of the pyridine moiety in the activated ester and one of the hydrogen atoms that are connected to the nitrogen atom in HOSA, stabilizing the interaction between the two molecules.[67,92]

Despite obtaining a higher yield for N'*N*-Diphenylurea than that reported by Bao *et al.* (2018), alterations to the HATU method were still attempted for the purpose of further optimization. One such alteration was the immersion of the reaction mixture in an ice bath during the addition of HOSA (**Entry 1b**). This was done to reduce any side reactions which may occur following its addition. Unfortunately, this did not cause a noticeable reduction in by-products and slightly decreased product yield to 86%. Another attempt to reduce by-product formation

was made by reducing the maximum temperature setting of the microwave synthesizer from 100°C to 50°C while heating the reaction mixture for 5 minutes (**Entry 1c**). Once again, by-product formation did not seem to be affected by this alteration. Furthermore, the lower maximum temperature setting resulted in only a minimal amount of *N,N'*-diphenylurea being formed, resulting in a yield of 10%. This demonstrated the necessity of heating the reaction mixture to an appropriate temperature in order to drive the conversion of phenyl isocyanate into N,N'diphenylurea, following the addition of aniline.

Since neither of these alterations to the synthetic procedure appeared to decrease by-product formation, focus was shifted to by-product removal during purification instead. It was postulated that the efficiency of polar by-product removal could be improved during product extraction from the reaction mixture by switching EtOAc with DCM, an organic solvent with slightly lower polarity (**Entry 1d**).[93] However, by-products with higher polarity appeared to still persist following product extraction with DCM, suggesting that their solubility does not greatly differ from that of *N,N'*-diphenylurea or their concentration in the reaction mixture was too high to be completely removed. Also, the reduction in yield to 70% indicated that the solubility of *N,N'*-diphenylurea in DCM was lower in comparison to its solubility in EtOAc.

Although DIPEA appeared to be an effective catalyst for the synthetic procedure, it was questioned whether the yield of *N,N'*-Diphenylurea could still be slightly improved by adding DIPEA before HATU, substituting DIPEA with a similar catalyst, or a combination of both. By adding DIPEA before HATU, it was anticipated that the rate of interaction between benzoic acid and DIPEA would increase, allowing for more deprotonation to occur (**Entry 1e**). This would result in a higher concentration of benzoate anion being available to interact with HATU which would likely increase the formation of the activated ester and subsequently, *N,N'*-diphenylurea.

However, this alteration to the synthetic procedure resulted in a slightly lower product yield of 86%. This observation prompted another approach at improving the rate of deprotonation by replacing DIPEA with TEA, another tertiary amine catalyst with similar molecular structure, but with less steric hindrance surrounding the central nitrogen atom (**Entry 1f**).[82] Unfortunately, this alteration to the synthetic procedure once again led to a minor decrease in product formation that caused a yield of 87% to be obtained. This indicated that steric hindrance was not a large factor in the rate of deprotonation.[74] It also suggested that the basicity of TEA was slightly lower than that of DIPEA in anhydrous MeCN.[82] Therefore, it was expected that the product yield would be further hindered if TEA was substituted for DIPEA and added prior to HATU as well (**Entry 1g**). Surprisingly, a product yield of 97% was achieved when these two alterations were made to the synthetic procedure. However, the ^{1}H-NMR spectrum of the product revealed that it consisted of HOAt in addition to N,N'diphenylurea. Therefore, it is possible that much of the product mass was contributed by the impurity. This observation suggested that while the addition of the catalyst before HATU does increase the rate of benzoic acid deprotonation, it also increases the rate of ionic interaction between $DIPEAH^{+}$ or $TEAH^{+}$ and OAt^{-} as well as other anions in the reaction mixture.[82,83] Consequently, less OAt^{-} is available to participate in the formation of the activated ester and subsequently, hinders formation of phenyl isocyanate.

The repeatedly inferior product yields obtained through the previously mentioned alterations to the HATU method indicated that such changes were unnecessary. Therefore, efforts were redirected to minimizing excess reagent quantities in the synthetic procedure in order to reduce material cost. Three different alterations to the reagent quantities were tested to evaluate how changes in their amounts affected product yield. The first alteration to reagent quantities included reducing the amount of benzoic acid to 1eq as well as decreasing the amounts

of HATU to 1.05eq and HOSA to 1.3eq. The amount of aniline was also increased to 1.15eq, making benzoic acid the new limiting reagent (**Entry 1h**). This was done to determine if a high product yield could be maintained by slightly increasing the amount of aniline to compensate for the reduced amounts of benzoic acid, HATU, and HOSA. Unfortunately, this combination of reagent quantities led to a product yield of only 58%. However, when the amount of aniline was raised to 1.3eq, product yield was found to increase to 78% (**Entry 1i**). This indicated that the amount of *N,N'*-diphenylurea formed from the reaction partly relies on the rate of interaction between phenyl isocyanate and aniline. In spite of this observation, it became clear that reducing the added amounts of the other three reagents was highly detrimental to product yield. Therefore, the third alteration to reagent quantities included raising the amounts of benzoic acid and HATU to 1.1eq while keeping the amount of HOSA at 1.3eq. Also, the amount of aniline was reduced back to 1eq, making it the limiting reagent once again (**Entry 1j**). As a result of these changes, a slighter greater product yield of 85% was achieved. This strongly suggested that *N,N'*-diphenylurea formation heavily depends on the addition of sufficient amounts of benzoic acid, HATU, and HOSA to the reaction mixture. Based on this observation, it did not seem justifiable to alter the required amount of any particular reagent in the synthetic procedure. Following the completion of this final optimization reaction, the HATU method was determined to be ready for testing with various carboxylic acid, amine, and alcohol starting materials.

Table 3.1 - *Summary of yields obtained for N,N'-diphenylurea under various conditions using benzoic acid and aniline as starting materials.*

Entry	Benzoic Acid (eq)	HATU (eq)	HOSA (eq)	Aniline (eq)	Microwave Conditions	Yield (%)	Additional Conditions
1a	1.25	1.25	1.5	1	100°C, 5min.	(127) 95	N/A
1b	1.25	1.25	1.5	1	100°C, 5min.	(155) 86	Ice bath used during addition of HOSA
1c	1.25	1.25	1.5	1	50°C, 5min.	(56) 10	N/A
1d	1	1.25	1.5	1	100°C, 5min	(80) 70	DCM substituted for EtOAc during extraction
1e	1.25	1.25	1.5	1	100°C, 5min.	(129) 85.9	DIPEA added before HATU
1f	1.25	1.25	1.5	1	100°C, 5min.	(125) 87	Et_3N substituted for DIPEA
1g	1.25	1.25	1.5	1	100°C, 5min.	(155) 97*	Et_3N substituted for DIPEA and added before HATU
1h	1	1.05	1.3	1.15	100°C, 5min.	(88) 58	N/A
1i	1	1.05	1.3	1.3	100°C, 5min.	(100) 78	N/A
1j	1.1	1.1	1.3	1	100°C, 5min.	(98) 85	N/A

( ) Product yield prior to trituration.
* Product contained minor amount of HOAt.

3.2 Application of HATU Method to Aryl Urea Preparation Using Benzoic Acid and Various Amines as Starting Materials

The versatility of the HATU method was first tested using fourteen different amine starting materials in place of aniline (**Table 3.2**). The majority of the selected reagents were aniline analogues containing one or more substituents on the aryl group. This allowed the effects of different EWGs and EDGs on the nucleophilicity of the amino group to be explored. Also, the inclusion of *p*-toluidine, *o*-toluidine, 2,4-dimethylaniline, and 2,4,6-trimethylaniline among the chosen amine starting materials allowed for comparative evaluation of how quantity and positioning of a particular substituent on the aryl group can influence product yield. For example, it was anticipated that the yield obtained for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 2b**) when it was prepared using *p*-toluidine would be slightly higher than the 95% yield obtained for *N,N'*-diphenylurea (**Entry 1a**) that was prepared using aniline. This expectation was based on the amino group of *p*-toluidine having a higher electron density in its proximity than the amino group of aniline, enhancing the nucleophilicity of this starting material.[74,116] This higher electron density results from the methyl group acting as an *ortho,para*-directing EDG through the inductive effect.[75,76] However, only an 81% yield was obtained for *N*-(4-methylphenyl)-*N'*-phenylurea and this likely resulted from the product being more soluble in chloroform than *N,N'*-diphenylurea, causing a portion to be lost during trituration. It is also possible that a greater portion of *N*-(4-methylphenyl)-*N'*-phenylurea was not retained during its extraction from the reaction mixture due to it having a more limited solubility in ethyl acetate.

Although *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 2b**) and *N*-(2-methylphenyl)-*N'*-phenylurea (**Entry 2a**) are related through structural isomerism, preparation of the latter product when using *o*-toluidine only resulted in a 73% yield as opposed to the 81% yield obtained for the former which was prepared using *p*-toluidine. Although this difference in yield is minor, it is

possible that the closer proximity of the methyl group to the amino group in *o*-toluidine caused steric hindrance to interfere with the formation of *N*-(2-methylphenyl)-*N'*-phenylurea.[74] Additional support for this postulate was provided by the 76% yield obtained for *N*-(2,4-dimethylphenyl)-*N'*-phenylurea (**Entry 2d**) when it was prepared using 2,4-dimethylaniline. Furthermore, the yield obtained for *N*-(2,4-dimethylphenyl)-*N'*-phenylurea demonstrated that even when two methyl groups contribute electron density to the amino group, the associated enhancement in nucleophilicity is still negligible in comparison to the detrimental effect of steric hindrance.[74] Therefore, the presence of two methyl groups near the amino group in 2,4,6-trimethylaniline was expected to cause even more steric hindrance and consequently, a greater reduction in product yield. Indeed, the yield obtained for *N*-(2,4,6-trimethylphenyl)-*N'*-phenylurea (**Entry 2f**) when it was prepared using 2,4,6-trimethylaniline was found to be only 56%.

Since a methyl group is an *ortho,para*-directing EDG through the inductive effect, the position of the methyl group in *m*-toluidine prevents the contribution of electron density toward the amino group.[75,76] However, this position also does not introduce any steric hindrance since the methyl group is sufficiently distant from the amino group.[74] Therefore, the nucleophilicity of *m*-toluidine was expected to be similar to that of aniline. Accordingly, the yield obtained for *N*-(3-methylphenyl)-*N'*-phenylurea (**Entry 2c**) when it was prepared using *m*-toluidine had been anticipated to be similar to the 95% yield obtained for *N,N'*-diphenylurea (**Entry 1a**) that was prepared using aniline. However, only a 63% yield was achieved for *N*-(3-methylphenyl)-*N'*-phenylurea. This indicated that product recovery was possibly limited during purification due to greater solubility in chloroform than in EtOAc, as had been suggested for *N*-(4-methylphenyl)-*N'*-phenylurea. Therefore, it is likely that the other methyl-substituted analogues of *N,N'*-

diphenylurea also shared similar limitations during purification. Based on this postulate, the slightly higher yield of 71% that was achieved for *N*-(3,4-dimethylphenyl)-*N'*-phenylurea (**Entry 2e**) when it was prepared with 3,4-dimethylaniline had likely been a direct result of 3,4-dimethylaniline being a slightly stronger nucleophile than *m*-toluidine due to more electron density being exerted toward the amino group by the additional methyl group in the former reagent.[74]

Unlike a methyl group, a halogen atom acts as a weak *ortho,para*-directing EDG through the mesomeric effect while simultaneously acting as a slightly stronger EWG through the inductive effect.[75,76] Therefore, the nucleophilicity of 4-chloroaniline is expected to be slightly lower than that of aniline. This postulate is supported by the 81% yield obtained for *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 2h**) when it was prepared using 4-chloroaniline since it is comparatively lower than the 95% yield obtained for *N,N'*-diphenylurea (**Entry 1a**) that was prepared using aniline. Furthermore, this indicates that *N*-(4-chlorophenyl)-*N'*-phenylurea has a slightly higher solubility in polar solvents such as EtOAc than *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 2b**) since a similar yield of 81% was obtained for the latter product when it was prepared using *p*-toluidine.[93,116,117]

The yield of 76% obtained for *N*-(4-methoxyphenyl)-*N'*-phenylurea (**Entry 2g**) when it was prepared using *p*-anisidine was only slightly lower than 81% achieved for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 2b**) that was prepared using *p*-toluidine. Although the difference between these yields is minimal, a slightly superior yield was expected for *N*-(4-methoxyphenyl)-*N'*-phenylurea since the nucleophilicity of *p*-anisidine is strengthened by the strong *ortho,para*-directing mesomeric effect of a methoxy group, rather than the weak *ortho,para*-directing of a methyl group. However, the methoxy group also acts as a weak EWG

through the inductive effect. Therefore, the nucleophilicity of *p*-anisidine is likely similar to that of *p*-toluidine.[74,75,76,116]

Unlike aniline and its analogues, the addition of *n*-butylamine to the reaction mixture resulted in the instantaneous precipitation of a large amount of product. Therefore, it was evident that not only was *n*-butylamine a strong nucleophile, but the resulting product had low solubility in MeCN.[118] The second of these two observations suggested that *N*-(*n*-butyl)-*N'*-phenylurea would also have low solubility in other solvents of similar polarity.[2] Therefore, it was postulated that extraction of the product from the reaction mixture using DCM instead of EtOAc would be more suitable due to the slightly lower polarity of the former solvent.[93] In addition, the volume of solvent used in the extraction was doubled in an attempt to further enhance product retention. Although a yield of 63% was obtained for *N*-(*n*-butyl)-*N'*-phenylurea when it was prepared using *n*-butylamine, it was anticipated that product retention could be further improved during trituration. Although chloroform is more polar than DCM, it was anticipated that trituration with this solvent could still greatly contribute to product loss.[93] Based on this expectation, trituration of the product was attempted using a much lower concentration of chloroform. Hexane was selected as a diluent since the extremely low polarity of this solvent in comparison to chloroform was expected to limit product dissolution.[93] Fortunately, trituration with a solvent mixture of 80% hexane and 20% chloroform was found to increase the yield obtained for *N*-(*n*-butyl)-*N'*-phenylurea to 87% without compromising purity. The success of this alteration prompted an effort to once again improve product yield by reducing the chloroform concentration in the mixture by an additional 10%. Indeed, a yield of 94% was achieved for *N*-(*n*-butyl)-*N'*-phenylurea (**Entry 2l**) with the continued absence of impurities when trituration was conducted using a 90% hexane and 10% chloroform solvent mixture.

The immediate formation of product followed by its precipitation was also observed when benzylamine, *t*-butylamine, and cyclohexylamine were used as nucleophiles in the synthetic procedure. Therefore, it was postulated that *N*-benzyl-*N'*-phenylurea, *N*-(*t*-butyl)-*N'*-phenylurea, and *N*-cyclohexyl-*N*'phenylurea had a low polarity that was similar to that of *N*-(*n*-butyl)-*N'*-phenylurea. This postulate was supported by the observation that the retention factors of these four products ranged from only 0.74 to 0.77 when determined through TLC analysis using an EtOAc-hexane (70:30, v/v) solvent mixture.[119] As a result, these products were also extracted from the reaction mixture using DCM and triturated with a hexane-chloroform (90:10, v/v) solvent mixture. This resulted in a 91% yield being obtained for *N*-benzyl-*N'*-phenylurea when it was prepared using benzylamine. In contrast, a yield of 81% was achieved for *N*-cyclohexyl-*N'*-phenylurea (**Entry 2n**) when it was prepared using cyclohexylamine while a slightly lower yield of 75% was obtained for *N*-(*t*-butyl)-*N'*-phenylurea (**Entry 2m**) when it was prepared using *t*-butylamine. Initially, these high yields appeared to justify the continued use of the alterations made during the purification of *N*-(*n*-butyl)-*N'*-phenylurea. However, the ^{1}H NMR spectrum of *N*-benzyl-*N'*-phenylurea revealed that *N*-benzylbenzamide was present as an impurity. This aryl amide was likely formed from a side reaction that occurred between benzylamine and activated ester that had not been converted into benzyl isocyanate.[61,68] Therefore, it appeared necessary to triturate the product with pure chloroform in an attempt to eliminate the impurity. Fortunately, the use of pure chloroform effectively removed *N*-benzylbenzamide while only reducing the yield obtained for *N*-benzyl-*N'*-phenylurea (**Entry 2k**) to 86%.

The high amount of product formation that occurred when benzylamine, *n*-butylamine, *t*-butylamine, and cyclohexylamine were used as starting materials was likely a result of the

strong nucleophilicity that primary alkyl amines generally exhibit.[116,118] This strong nucleophilicity is due to the high electron density near the amino group which partially results from the inductive effect exerted by the alkyl group. In addition, electron delocalization does not occur in any of the four primary alkyl amines that were used as starting materials since each does not contain a conjugated π-electron system that is directly connected to the amino group.[74] However, minor variations in nucleophilicity still exist between these reagents due to factors such as steric hindrance. A clear example of the influence of steric hindrance on nucleophilicity can be observed when comparing the 91% yield obtained for *N*-(*n*-butyl)-*N'*-phenylurea (**Entry 2l**) that was prepared using *n*-butylamine to the 75% yield achieved for *N*-(*t*-butyl)-*N'*-phenylurea (**Entry 2m**) which was prepared using *t*-butylamine. The inferior yield obtained for the latter product can likely be attributed to the branched molecular structure of the alkyl group in *t*-butylamine which exerts much more steric hindrance near the amino group than the linear molecular structure of the alkyl group in *n*-butylamine.[116,118]

In addition to steric hindrance, the nucleophilicity of primary alkyl amines can be compromised by the removal of electron density near the amino group through the inductive effect of an EWG in the molecular structure, especially if the EWG contains one or more atoms with high electronegativity.[74] For example, the electron density near the nitrogen atom in morpholine is likely drawn towards the oxygen atom at the opposite end of the ring. However, this shift in electron density is suggested to be minimal due to the decreasing influence of the inductive effect as the distance from its origin increases. Therefore, the nucleophilicity of morpholine is expected to be greater than that of benzylamine, *n*-butylamine, *t*-butylamine, and cyclohexylamine since it is a secondary amine while the other four starting materials are primary amines.[74,118] Despite this expectation, only a yield of 57% was achieved for *N*-phenyl-4-

morpholinecarboxamide (**Entry 2i**) when it was prepared with morpholine. In contrast, yields of 75% or higher were obtained for the four products that were prepared using the primary alkyl amine starting materials. Therefore, the yield obtained for *N*-phenyl-4-morpholinecarboxamide was likely a consequence of this product having a higher polarity than the other four, limiting its solubility in the weakly polar DCM that was used to extract it from the reaction mixture.[2,93] Evidence for this suggestion was obtained when TLC analysis revealed that *N*-phenyl-4-morpholinecarboxamide had a retention factor of 0.40 while those noted for the other four products ranged from 0.74 to 0.77.[119]

Among the yields achieved for the aryl ureas that were prepared using different amine starting materials, the lowest was found to be a yield of 46% which had been obtained for *N*-methyl-*N,N'*-diphenylurea (**Entry 2j**) that was prepared using *N*-methylaniline. This poor yield was likely due to the steric hindrance exerted by the methyl group adjacent to the nitrogen atom in *N*-methylaniline which greatly weakened its nucleophilicity.[74] Furthermore, the close proximity of the methyl group to the nitrogen atom would likely overshadow the strengthening of nucleophilicity that is caused by its simultaneous contribution of electron density through the inductive effect.[74]

Following the successful preparation of fourteen other aryl ureas in addition to *N,N'*-diphenylurea, a product yield comparison was carried out for those which were also reported by Bao *et al.* (2018). It should be noted that the method used by Bao *et al.* (2018) did not include product extraction following heating of the reaction mixture in the microwave synthesizer. The purpose of including an extraction step in the HATU method was to remove by-products such as tetramethylurea which result from HATU being used in the synthetic procedure. Unfortunately, certain by-products such as HOAt were not completely removed by extraction or FC. Therefore,

all aryl urea products additionally required trituration with pure chloroform or a hexane-chloroform (90:10, v/v) solvent mixture. In contrast, trituration with chloroform was only used by Bao *et al.* (2018) during the purification of *N*-(2-methylphenyl)-*N'*-phenylurea, *N*-(4-methylphenyl)-*N'*-phenylurea, *N*-(4-methoxyphenyl)-*N'*-phenylurea, and *N*-(4-chlorophenyl)-*N'*-phenylurea. The HATU method achieved a slightly greater yield of 76% for *N*-(4-methoxyphenyl)-*N'*-phenylurea (**Entry 2b**) in comparison to the 68% yield obtained by Bao *et al.* (2018). Also, the 81% yield obtained for *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 2h**) using the HATU method was found to be far superior to the 52% yield achieved by Bao *et al.* (2018).

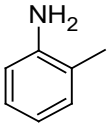
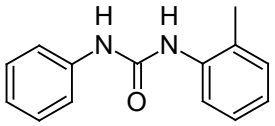
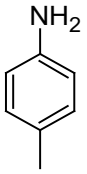
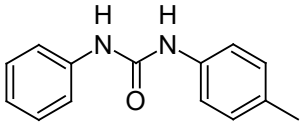
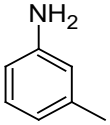
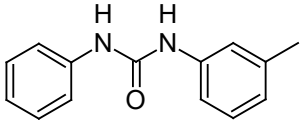
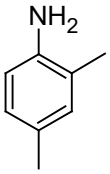
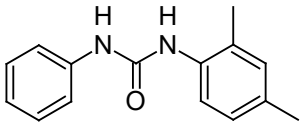
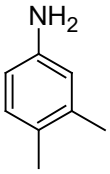
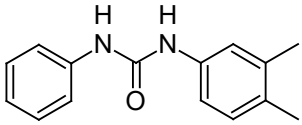
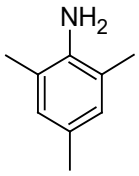
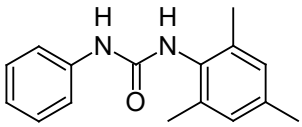
The yields obtained for *N*-(2-methylphenyl)-*N'*-phenylurea and *N*-(4-methylphenyl)-*N'*-phenylurea using the HATU method were quite similar to those reported by Bao *et al.* (2018). However, the HATU method achieved a slightly lower yield of 73% for *N*-(2-methylphenyl)-*N'*-phenylurea (**Entry 2a**) when compared to the 80% yield reported by Bao *et al.* (2018). In contrast, the 80% yield obtained for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 2b**) using the HATU method was slightly higher than the 71% yield obtained by Bao *et al.* (2018). As mentioned previously, the lower nucleophilicity of *o*-toluidine in comparison to *p*-toluidine suggests that the latter reagent would react with phenyl isocyanate more readily.[74] However, it is possible that *o*-toluidine is slightly more soluble than *p*-toluidine in DCM, allowing *o*-toluidine to react more frequently with phenyl isocyanate in this solvent. Therefore, a slightly higher yield for *N*-(2-methylphenyl)-*N'*-phenylurea would be possible when using the method developed by Bao *et al.* (2018).

The difference between the 76% yield obtained for *N*-(2,4-dimethylphenyl)-*N'*-phenylurea (**Entry 2d**) using the HATU method and the 78% yield obtained by Bao *et al.*

(2018) was minimal. However, a noticeably lower yield of 56% was obtained for *N*-(2,4,6-trimethylphenyl)-*N'*-phenylurea (**Entry 2f**) using the HATU method in comparison to the 69% yield reported by Bao *et al.* (2018). This likely suggests that the extraction and trituration steps included in the HATU method were especially detrimental to this product. Furthermore, it is possible that these additional purification steps had a similar impact on the yields of other aryl ureas that were prepared by the HATU method. For example, the yield achieved for *N*-phenyl-4-morpholinecarboxamide (**Entry 2i**) using the HATU method was only 57% while a much higher yield of 78% was reported by Bao *et al.* (2018). Similarly, a 46% yield was obtained for *N*-methyl-*N,N'*-diphenylurea (**Entry 2j**) using the HATU method while a far superior yield of 66% was achieved by Bao *et al.* (2018).

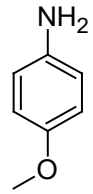
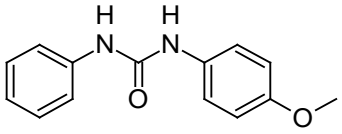
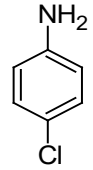
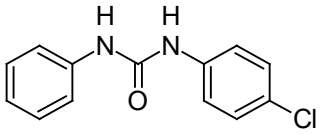
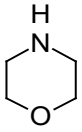
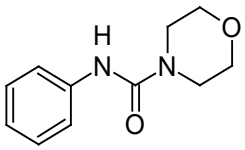
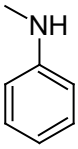
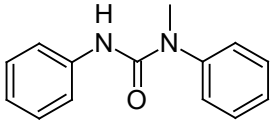
The yield of 94% obtained for *N*-(*n*-butyl)-*N'*-phenylurea (**Entry 2l**) using the HATU method was extremely similar to the 95% yield achieved by Bao *et al.* (2018). However, the 86% yield obtained for *N*-benzyl-*N'*-phenylurea (**Entry 2k**) using the HATU method was slightly lower than the 93% yield reported by Bao *et al.* (2018). It is possible that the slightly greater difference between the two yields obtained for *N*-benzyl-*N'*-phenylurea resulted from the product being triturated with pure chloroform when prepared through the HATU method instead of the hexane-chloroform (90:10, v/v) solvent mixture that was used to triturate *N*-(*n*-butyl)-*N'*-phenylurea.

Table 3.2 - *Summary of yields obtained for aryl ureas under optimized conditions using benzoic acid and various amines as starting materials.*

Entry	Amine Reagent	Urea Product	Yield (%)
2a			(125) 73
	o-Toluidine	*N*-(2-Methylphenyl)-*N'*-phenylurea	
2b			(98) 81
	p-Toluidine	*N*-(4-Methylphenyl)-*N'*-phenylurea	
2c			(76) 63
	m-Toluidine	*N*-(3-Methylphenyl)-*N'*-phenylurea	
2d			(94) 76
	2,4-Dimethylaniline	*N*-(2,4-Dimethylphenyl)-*N'*-phenylurea	
2e			(91) 71
	3,4-Dimethylaniline	*N*-(3,4-Dimethylphenyl)-*N'*-phenylurea	
2f			(80) 56
	2,4,6-Trimethylaniline	*N*-(2,4,6-Trimethylphenyl)-*N'*-phenylurea	

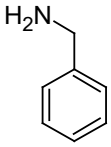
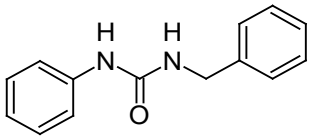
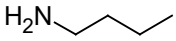
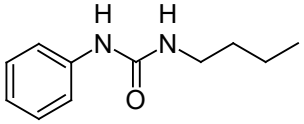
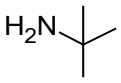
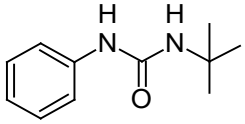
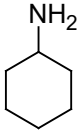
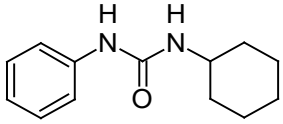
( ) Product yield prior to trituration.

Table 3.2 (Cont.) - *Summary of yields obtained for aryl ureas under optimized conditions using benzoic acid and various amines as starting materials.*

Entry	Amine Reagent	Urea Product	Yield (%)
2g			(122) 76
	p-Anisidine	*N*-(4-Methoxyphenyl)-*N'*-phenylurea	
2h			(98) 81
	4-Chloroaniline	*N*-(4-Chlorophenyl)-*N'*-phenylurea	
2i			(125) 57
	Morpholine	*N*-Phenyl-4-morpholinecarboxamide	
2j			(69) 46*
	N-Methylaniline	*N*-Methyl-*N,N'*-diphenylurea	

( ) Product yield prior to trituration.
* Product triturated with hexane-chloroform (90:10, v/v) instead of pure chloroform.

Table 3.2 (Cont.) - *Summary of yields obtained for aryl ureas under optimized conditions using benzoic acid and various amines as starting materials.*

Entry	Amine Reagent	Urea Product	Yield (%)
2k			(114) 86
	Benzylamine	*N*-Benzyl-*N'*-phenylurea	
2l			(112) 94*
	n-Butylamine	*N*-(*n*-Butyl)-*N'*-phenylurea	
2m			(81) 75*
	t-Butylamine	*N*-(*t*-Butyl)-*N'*-phenylurea	
2n			(93) 81*
	Cyclohexylamine	*N*-Cyclohexyl-*N'*-phenylurea	

( ) Product yield prior to trituration.
* Product triturated with hexane-chloroform (90:10, v/v) instead of pure chloroform.

3.3 Application of HATU Method to Aryl Carbamate Preparation Using Benzoic Acid and Various Alcohols as Starting Materials

Following the comparison of yields obtained for aryl ureas prepared by both the HATU method and Bao *et al.* (2018), the HATU method was further tested by preparing aryl carbamates using five different alcohol starting materials (**Table 3.3**). Although the successful isolation of several aryl ureas provided confidence that the HATU method could also be used to prepare aryl carbamates, the generally lower nucleophilicity of alcohols in comparison to amines was expected to limit product formation. This lower nucleophilicity is due to the oxygen atom of a hydroxyl group exerting higher electronegativity than the nitrogen atom of an amino group.[74,2] As a result, it was anticipated that the yields obtained for the aryl carbamates would not be as high as those obtained for many of the aryl ureas. However, unlike the aryl ureas, each aryl carbamate was effectively purified by FC due to the greater polarity of impurities which were also retained following product extraction and washing. Therefore, subsequent trituration of the aryl carbamates with chloroform was unnecessary, avoiding any product loss that could have resulted from this purification step.

A 57% yield obtained for benzyl-*N*-phenylcarbamate when it was prepared using benzyl alcohol was found to be much lower than the 86% yield achieved for *N*-benzyl-*N'*-phenylurea (**Entry 2k**) that was prepared using benzylamine, despite only the latter product being triturated with chloroform during purification. Since benzylamine and benzyl alcohol are structurally similar, the inferior yield obtained for benzyl-*N*-phenylcarbamate was likely due to the weaker nucleophilicity of benzyl alcohol.[74,2] Therefore, an attempt to increase the formation of benzyl-*N*-phenylcarbamate was made by heating the reaction mixture in the microwave synthesizer for 15 minutes instead of 5 minutes. Although the extended heating duration only caused the yield obtained for benzyl-*N*-phenylcarbamate (**Entry 3a**) to increase to

65%, this alteration was considered to be a minor benefit to product formation and therefore, applied to the synthetic procedure for the preparation of the other four aryl carbamates.

The 67% yield obtained for ethyl-*N*-phenylcarbamate (**Entry 3b**) when it was prepared using ethanol was quite similar to the yield of 65% achieved for benzyl-*N*-phenylcarbamate (**Entry 3a**) that was prepared using benzylamine. This was also found to be the case for the 64% yield obtained for *n*-propyl-*N*-phenylcarbamate (**Entry 3c**) when it was prepared using *n*-propanol. In contrast, a noticeably lower yield of 48% was obtained for *i*-propyl-*N*-phenylcarbamate (**Entry 3d**) when it was prepared using *i*-propanol. However, the 9% yield obtained for *t*-butyl-*N*-phenylcarbamate (**Entry 3e**) when it was prepared using *t*-butanol was the lowest among those obtained for the aryl carbamates which were isolated using the HATU method. Initially, the low yields obtained for *i*-propyl-*N*-phenylcarbamate and *t*-butyl-*N*-phenylcarbamate were primarily attributed to steric hindrance exerted by methyl groups adjacent to the hydroxyl group in each alcohol starting material.[117] However, the preparation of all five aryl carbamates were found to generate *N,N'*-diphenylurea as a by-product according to TLC analysis that was conducted following the extraction of each product from the reaction mixture. This suggested that upon addition of HOSA during the synthetic procedure, a portion of the resulting phenyl isocyanate had reacted with water in the reaction mixture and subsequently, the aniline reacted with more phenyl isocyanate to generate *N,N'*-diphenylurea. As a consequence, the formation of each aryl carbamate was limited.[89]

The repeated presence of water in the reaction mixture could be attributed to the alcohol starting materials being highly hygroscopic although it should be noted that these reagents were of anhydrous grade and each bottle of reagent was septum-sealed.[120] Alternatively, it is possible that a portion of each alcohol starting material reacted with sulfuric acid, a by-product that forms

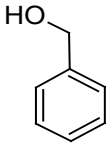
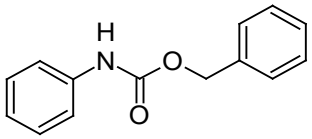
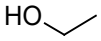
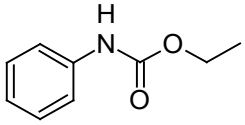
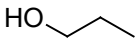
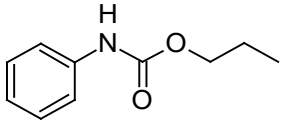
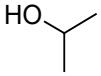
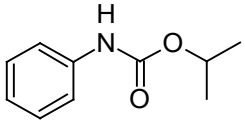
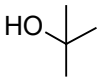
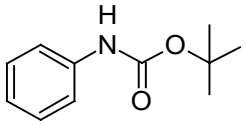
upon the addition of HOSA, causing the formation of water through dehydration. Also, this side reaction occurs more readily with secondary and tertiary alcohols due to the higher stability of their corresponding carbocation intermediates that result following the formation of water.[88] Therefore, it is unsurprising that the yield obtained for *i*-propyl-*N*-phenylcarbamate was much lower than that obtained for benzyl-*N*-phenylcarbamate, ethyl-*N*-phenylcarbamate, and *n*-propyl-*N*-phenylcarbamate. Furthermore, the additional decrease in yield between *i*-propyl-*N*-phenylcarbamate and *t*-butyl-*N*-phenylcarbamate reflects the greater susceptibility of *t*-butanol to dehydration.[88]

Once preparation of the five aryl carbamates had been completed, a comparison was made once again between the yields obtained with the HATU method and those reported by Bao *et al.* (2018). It was found that 65% yield obtained for-*N*-phenylcarbamate (**Entry 3a**) using the HATU method was superior to the 45% yield achieved by Bao *et al.* (2018). Similarly, the yield of 67% that was obtained for ethyl-*N*-phenylcarbamate (**Entry 3b**) using the HATU method was much higher than the 48% yield reported by Bao *et al.* (2018). In addition, the 64% yield achieved for *n*-propyl-*N*-phenylcarbamate (**Entry 3c**) through the HATU method greatly exceeded the 49% yield obtained by Bao *et al.* (2018). These three yield comparisons strongly suggest that the HATU method is more suitable for the preparation of aryl carbamates, despite fewer purification steps being required in the method employed by Bao *et al.* (2018). In particular, the yield improvements associated with the use of the HATU method are likely the result of HATU enhancing the formation of the hydroxamic acid derivative as described earlier in the proposed mechanism.[67,92] Also, it should be noted that the benzoyl chloride starting material which is used in the method developed by Bao *et al.* (2018) can exhibit susceptibility to hydrolysis and as a result, the availability of this starting material is likely reduced when water is

present in the reaction mixture.[121] Consequently, water that forms though the dehydration of the alcohol reagents could subsequently react with this starting material, limiting product formation.

Although the HATU method clearly appeared to be the preferential approach for the preparation of aryl carbamates when using primary alcohols as starting materials, this did not appear to be the case when secondary or tertiary alcohols were employed. For example, the 48% yield obtained for *i*-propyl-*N*-phenylcarbamate (**Entry 3d**) using the HATU method was nearly identical to the 48% yield achieved by Bao *et al.* (2018). Furthermore, the yield of 9% obtained for *t*-butyl-*N*-phenylcarbamate (**Entry 3e**) through the HATU method was noticeably lower than the 27% yield reported by Bao *et al.* (2018). Based on these two observations, it is possible that when secondary and tertiary alcohols are used as starting materials in the HATU method, their greater vulnerability to hydrolysis results in rapid dehydration due to the higher concentration of sulfuric acid that accompanies an increased formation of hydroxamic acid derivative.[88]

Table 3.3 - *Summary of yields obtained for aryl carbamates under optimized conditions using benzoic acid and various alcohols as starting materials.*

Entry	Alcohol Reagent	Carbamate Product	Yield (%)
3a			65
	Benzyl Alcohol	Benzyl-*N*-phenylcarbamate	
3b			67
	Ethanol	Ethyl-*N*-phenylcarbamate	
3c			64
	n-Propanol	*n*-Propyl-*N*-phenylcarbamate	
3d			48
	i-Propanol	*i*-Propyl-*N*-phenylcarbamate	
3e			9
	t-Butanol	*t*-Butyl-*N*-phenylcarbamate	

3.4 Application of HATU Method to Aryl Urea Preparation Using Various Carboxylic Acids and Aniline as Starting Materials

Following the comparison of the product yields achieved for the five aryl carbamates through the HATU method with those reported by Bao *et al.* (2018), the preparation of aryl ureas using the HATU method was revisited. However, the focus of the testing was shifted to varying the identity of the carboxylic acid while using aniline as the nucleophile. Many of the chosen reagents were analogues of benzoic acid containing one ormore substituents on the aryl group, allowing the influence of different EDGs and EWGs on reactivity to be compared (**Table 3.4**). Also, ten of the sixteen carboxylic acid starting materials were purposely selected in order to prepare several aryl ureas which were previously prepared through the HATU method using another combination of starting materials. This provided the additional opportunity to determine which combination of reagents was more suitable for the preparation of each product and the factors that contribute to variations in yield between each approach.

The 54% yield achieved for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 4b**) when it was prepared using *p*-toluic acid was much lower than the 80% yield achieved when *p*-toluidine was used (**Entry 2b**). There are several factors which likely contributed to this reduction in product formation. For example, the role of the methyl group in *p*-toluic acid as an *ortho,para*-directing EDG causes it to increase electron density near the carbonyl carbon atom through the inductive effect, resulting in it becoming slightly less electrophilic.[74] Therefore it possible that this additional electron density hindered the rate of nucleophilic attack by the $^{-}$OAt anion prior to the formation of the activated ester in the proposed mechanism. Furthermore, this reduced electrophilicity was also likely detrimental to the nucleophilic attack rate of HOSA at the same position before the hydroxamic acid derivative was formed.[74] Along with its negative influence on the electrophilicity of the carbonyl carbon atom, the inductive effect exerted by the methyl

group in *p*-toluic acid was suggested to interfere with product formation once again following conversion to 4-methylphenyl isocyanate due to the increased electron density near the isocyanate carbon atom.[122]

Aside from hindering nucleophilic attack rates, the contribution of electron density toward the carboxyl group by the methyl group in *p*-toluic acid also destabilizes its conjugate base, causing it to be less acidic than benzoic acid.[1] An indication of this difference in acidity can be seen by comparing the 4.37 pK_a value of *p*-toluic acid in water to the lower 4.20 pK_a value of benzoic acid.[77] As a result of this lower acidity, less conjugate base is available to react with HATU, further contributing to the overall decline in product formation. In contrast, the acidity of *o*-toluic acid is much higher than that of *p*-toluic acid, as is indicated by the 3.91 pK_a value of the former reagent in water in comparison to the 4.37 pK_a value of the latter.[77] The lower acidity of *o*-toluic acid is due to a permanent disruption in the conjugated π-electron system of the former reagent which restricts the contribution of electron density toward the carboxyl group through the mesomeric effect.[74] This interference in electron delocalization results from distortion in the molecular structure which is driven by steric hindrance that occurs between the carboxyl group and the adjacent methyl group.[78] However, the 41% yield obtained for *N*-(2-methylphenyl)-*N'*-phenylurea (**Entry 4a**) when it was prepared using *o*-toluic acid was found to be slightly lower than the 54% yield achieved for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 4b**), despite the conjugate base of *o*-toluic acid being more abundant in the reaction mixture. This is likely another consequence of the methyl group position as it partially obstructs nucleophilic attack on the carbonyl carbon atom, further limiting the formation of the activated ester as well as the hydroxamic acid derivative.[74]

Although the molecular structures of *o*-toluic acid and 2,4-dimethylbenzoic acid are

similar, the latter contains a second methyl group which would be expected to exert additional electron density toward the carboxyl group, further limiting product formation.[77] However, the 64% yield obtained for *N*-(2,4-dimethylphenyl)-*N'*-phenylurea (**Entry 4c**) when it was prepared using 2,4-dimethylbenzoic acid was higher than the 41% yield obtained for *N*-(2-methylphenyl)-*N'*-phenylurea (**Entry 4a**) that was prepared using *o*-toluic acid. Furthermore, the 64% yield obtained for *N*-(2,4-dimethylphenyl)-*N'*-phenylurea also exceeded the 54% yield achieved for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 4b**) which was prepared using *p*-toluic acid. This indicated that the additional electron density provided by the second methyl group in 2,4-dimethylbenzoic acid simultaneously enhanced product formation at a position outside of the carboxyl group. This position likely corresponded to the tertiary carbon atom in the aryl group since this atom is directly involved with the Lossen rearrangement in the proposed mechanism. Furthermore, the contribution of electron density toward the atom from both methyl groups would greatly increase its rate of nucleophilic attack on the deprotonated nitrogen atom, allowing the Lossen rearrangement to proceed more rapidly.[74,77] Although the contribution of electron density from a third methyl group in 2,4,6-trimethylbenzoic acid likely increases the rate of the Lossen rearrangement even further, only a minimal yield of 1% was obtained for *N*-(2,4,6-dimethylphenyl)-*N'*-phenylurea (**Entry 4d**) when it was prepared using this starting material. This was attributed to additional distortion in molecular structure and further obstruction of the carbonyl carbon atom in 2,4,6-trimethylbenzoic acid that results from the carboxyl group being directly adjacent to two methyl groups instead of one.[77]

The preparation of *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 4k**) when using 4-chlorobenzoic acid resulted in a 94% yield. This was slightly greater than the 81% yield achieved when 4-chloroaniline was used as the amine starting material. This minor improvement

in yield was likely due in large part to the chlorine atom in 4-chlorobenzoic acid acting as an EWG through the inductive effect since the simultaneous influence of the substituent as an *ortho,para*-directing EDG through the mesomeric effect is slightly lower in strength.[10,75] In particular, the resulting increase in the electrophilicity of the carbonyl carbon atom was suggested to enhance the formation of the activated ester and subsequently, the hydroxamic acid derivative in the proposed mechanism. In addition, similar enhancement to the electrophilicity of the isocyanate carbon atom was postulated following conversion to 4-chorophenylisocyanate.[122] Finally, the reduction of electron density around the carboxyl group in 4-chlorobenzoic acid enhances the stabilization of its conjugate base, causing it to have a higher acidity than benzoic acid. This would benefit product formation since there is a higher amount of conjugate base available to react with HATU in the reaction mixture.[1] In comparison to the 94% yield achieved for *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 4k**) when it was prepared using 4-chorobenzoicacid, a noticeably lower yield of 70% was obtained for *N*-(2-chlorophenyl)-*N'*-phenylurea (**Entry 4j**) that was prepared using 2-chlorobenzoic acid. However, this was not surprising since 2-chlorobenzoic acid is a structural analogue of *o*-toluic acid. Therefore, the molecular structure of the former reagent is also distorted by intramolecular steric hindrance and the chlorine atom on the aryl group of 2-chlorobenzoic acid similarly obstructs accessibility to the carbonyl carbon atom.[74,78] As a result, the formation of *N*-(2-chlorophenyl)-*N'*-phenylurea is more limited than that of *N*-(4-chlorophenyl)-*N'*-phenylurea when using the synthetic procedure employed in the HATU method.

A low yield of 20% was obtained for *N*-(2,4-dichlorophenyl)-*N'*-phenylurea (**Entry 4l**) when it was prepared using 2,4-dichlorobenzoic acid. This was far inferior to the 70% achieved for *N*-(2-chlorophenyl)-*N'*-phenylurea (**Entry 4j**) that was prepared using 2-chlorobenzoic acid

as well as the 94% yield obtained for *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 4k**) which was prepared using 4-chlorobenzoic acid despite the second chlorine atom acting as an additional EWG in 2,4-dichlorobenzoic acid and subsequently, 2,4-dichlorophenyl isocyanate.[1,74,77,122] Therefore, it was postulated that the solubility of *N*-(2,4-dichlorophenyl)-*N'*-phenylurea in EtOAc is lower than that of *N*-(2-chlorophenyl)-*N'*-phenylurea and *N*-(4-chlorophenyl)-*N'*-phenylurea since this would result in a lower amount of product being retained during extraction from the reaction mixture. However, it is also important to note that unlike *N*-(2-chlorophenyl)-*N'*-phenylurea and *N*-(4-chlorophenyl)-*N'*-phenylurea, *N*-(2,4-dichlorophenyl)-*N'*-phenylurea required trituration with a chloroform-EtOAc (90:10, v/v) solvent mixture instead of pure chloroform following FC. Although the use of this solvent mixture caused a reduction in product retention based on the 33% yield that was obtained when using pure chloroform for trituration, the alteration was necessary since the polarity of pure chloroform was not high enough to effectively dissolve all impurities which co-eluted with *N*-(2,4-dichlorophenyl)-*N'*-phenylurea during FC.[93]

The preparation of *N*-(4-bromophenyl)-*N'*-phenylurea (**Entry 4i**) using 4-bromobenzoic acid resulted in a yield of 97%. This was very similar to the 94% yield obtained for *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 4k**) that was prepared using 4-chlorobenzoic acid, despite the chlorine atom acting as a stronger EWG through the inductive effect than the bromine atom. However, it is important to note that the chlorine atom also exerts a stronger mesomeric effect than the bromine atom.[123] This difference in strength is based on the efficiency with which a valence *p* orbital of the halogen atom overlaps a valence *2p* orbital of the adjacent carbon atom in the aryl group. Furthermore, the overlap efficiency is dependent on the difference in size between the two *p* orbitals.[123] Since the *3p* orbital of the chlorine atom overlaps the *2p* orbital of

the adjacent carbon atom more efficiently than the *4p* orbital of the bromine atom, the contribution of π electrons toward the aryl group occurs more readily in 4-chlorobenzoic acid than in 4-bromobenzoic acid. Therefore, it is likely that the overall reduction in electron density around the carbonyl group is greater in the latter reagent. It is also possible that upon addition of aniline to the reaction mixture, the stronger mesomeric effect exerted by the chlorine atom would cause 4-chloroisocyanate to react less rapidly with the reagent than 4-bromoisocyanate.[122,123] In contrast, the highly efficient overlap that occurs between the *2p* orbital of the fluorine atom and *2p* orbital of the adjacent carbon atom in 4-fluorobenzoic acid results in a mesomeric effect that is even stronger than that exerted by the chlorine atom in 4-chlorobenzoic acid. Therefore, the 87% yield achieved for *N*-(4-fluorophenyl)-*N'*-phenylurea (**Entry 4h**) when it was prepared using 4-fluorobenzoic acid was unsurprisingly lower than the 94% yield obtained for *N*-(4-chlorophenyl)-*N'*-phenylurea (**Entry 4k**) that was prepared using 4-chlorobenzoic acid.[123]

Although a halogen atom and methoxy group both act as *ortho,para*-directing EDGs through the mesomeric effect as well as EWGs through the inductive effect, a methoxy group exerts a stronger mesomeric effect than a halogen atom while displaying a weaker inductive effect.[75,76] This results in *p*-anisic acid exhibiting lower acidity due to its weaker conjugate base.[1] In addition, the decreased electrophilicity of the carbonyl carbon atom greatly hinders its reactivity towards the $^{-}$OAt anion and subsequently, HOSA.[74] Finally, product formation is expected to be further hindered following conversion of the hydroxamic acid derivative to 4-methoxyphenyl isocyanate since the methoxy group weakens the electrophilicity of the isocyanate carbon atom, reducing the rate of nucleophilic attack by aniline.[122] These influences on electron density are not unlike those exerted by the methyl group in *p*-toluic acid and 4-methylisocyanate. However, it is important to remember that a methyl functional group

contributes electron density through the inductive effect. In addition, it is important to recall that the strength with which the inductive effect influences electron density distribution is generally weaker than that of the mesomeric effect over the distance of several bonds. This is likely the main reason that the 23% yield obtained for *N*-(4-methoxyphenyl)-*N'*-phenylurea (**Entry 4e**) when it was prepared using *p*-anisic acid was much lower than the 54% yield achieved for *N*-(4-methylphenyl)-*N'*-phenylurea (**Entry 4b**) that was prepared using *p*-toluic acid.[74]

Unlike the other functional groups present in the benzoic acid analogues which have been used as starting materials, the cyano group in 4-cyanobenzoic acid and acetyl group in 4-acetylbenzoic acid each act as a strong *meta*-directing EWG through the mesomeric effect. Therefore, they influence electron density distribution similarly to halogen atoms, but with much greater strength.[75,76] This causes electron density to be quite low near the tertiary atom in the aryl group of 4-cyanobenzoic acid and 4-acetylbenzoic acid. As a result, the subsequent formation of 4-cyanophenyl isocyanate or 4-acetylbenzoic acid in the proposed mechanism likely proceeds more slowly.[122] However, the 98% yield achieved for *N*-(4-cyanophenyl)-*N'*-phenylurea (**Entry 4g**) when it was prepared using 4-cyanobenzoic acid was found to be very similar to the 97% yield obtained for *N*-(4-bromophenyl)-*N'*-phenylurea (**Entry 4i**) that was prepared using 4-bromobenzoic acid, indicating that the Lossen rearrangement was not hindered enough to greatly impact product formation. It was also suggested that the high amount of product retained following purification reflects the high solubility of *N*-(4-cyanophenyl)-*N'*-phenylurea in polar solvents. Although an acetyl group also withdraws electron density through the mesomeric effect, a yield of only 34% was achieved for *N*-(4-acetylphenyl)-*N'*-phenylurea (**Entry 4f**) when it was prepared using 4-acetylbenzoic acid.[75,76] However, it must be noted that unlike *N*-(4-cyanophenyl)-*N'*-phenylurea, *N*-(4-acetylphenyl)-*N'*-phenylurea was triturated with a

chloroform-EtOAc (90:10, v/v) solvent mixture instead of pure chloroform in order to remove unreacted 4-acetylbenzoic acid which had co-eluted with the product during FC. Although use of this highly polar solvent mixture likely resulted in lower product retention, it was determined to be necessary since TLC analysis revealed a 0.61 retention factor for *N*-(4-acetylphenyl)-*N'*-phenylurea while 4-acetylbenzoic acid was found to have a retention factor of 0.16.[93,119]

Following the trituration with a hexane-chloroform (90:10, v/v) solvent mixture, a yield of 23% was obtained for *N*-(*n*-butyl)-*N'*-phenylurea when it was prepared using *n*-butylamine. However, TLC analysis of the product indicated that an impurity remained. In contrast, it was previously observed that the trituration of *N*-(*n*-butyl)-*N'*-phenylurea using a hexane-chloroform (90:10, v/v) solvent mixture was sufficient to remove all remaining impurities when *n*-butylamine was used as the amine starting material. Therefore, the presence of this impurity is possibly a consequence of using valeric acid as the carboxylic acid starting material. Fortunately, the higher polarity of pure chloroform was found to effectively remove the impurity while only slightly lowering the yield obtained for *N*-(*n*-butyl)-*N'*-phenylurea (**Entry 4n**) to 20%.[93] Since the polarities of *N*-(*t*-butyl)-*N'*-phenylurea and *N*-cyclohexyl-N'phenylurea were previously determined to be similar to that of *N*-(*n*-butyl)-*N'*-phenylurea based on TLC analysis, the triturations of these two products were also performed using pure chloroform when the former was prepared using pivalic acid and the latter with cyclohexanoic acid. This was done to ensure the removal of any aryl amide side products that could similarly result from the use of these carboxylic acid starting materials.

Although the carbonyl carbon atom in valeric acid is not obstructed from nucleophilic attack by steric hindrance, the 20% yield obtained for *N*-(*n*-butyl)-*N'*-phenylurea (**Entry 4n**) was still quite low. Therefore, product formation was likely hindered instead by the high

electron density surrounding the carboxyl group of valeric acid and subsequently, the isocyanate group in *n*-butyl isocyanate. Much of this electron density is contributed by the alkyl group through the inductive effect and its distribution is restricted due to limited electron delocalization.[74,122] Evidence for this suggestion was gained when product precipitation was not observed following the addition of aniline to the reaction mixture despite its occurrence when *n*-butylamine was used as the amine starting material. Furthermore, similar observations were made when *N*-benzyl-*N'*-phenylurea, *N*-(*t*-butyl)-*N'*-phenylurea, and *N*-cyclohexyl-N'phenylurea were prepared using phenylacetic acid, pivalic acid, and cyclohexanoic acid respectively.

Unlike valeric acid, phenylacetic acid contains a conjugated π-electron system in its molecular structure. However, this conjugated π-electron system does not extend to the carboxyl group. As a result, the electron density surrounding the carboxyl group of phenylacetic acid is also not affected by electron delocalization.[74] Therefore, it was not surprising that only a slight difference existed between the 11% yield obtained for *N*-benzyl-*N'*-phenylurea (**Entry 4m**) when it was prepared using phenylacetic and the 20% yield achieved for *N*-(*n*-butyl)-*N'*-phenylurea (**Entry 4n**) which was prepared using valeric acid. In contrast, the particularly low 5% yield obtained for *N*-(*t*-butyl)-*N'*-phenylurea (**Entry 4o**) when it was prepared using pivalic acid was likely further limited by the high amount of steric hindrance exerted by the t-butyl group of the starting material. Similarly, it is expected that the superior 32% yield obtained for *N*-cyclohexyl-N'phenylurea (**Entry 4p**) when it was prepared using cyclohexanoic acid was mostly due to the cyclohexyl group of this starting material exerting a lower amount of steric hindrance than the *t*-butyl group in pivalic acid.[74]

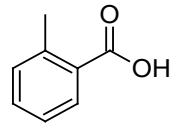
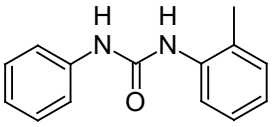
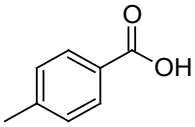
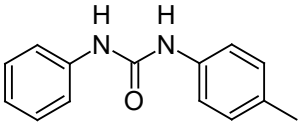
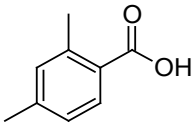
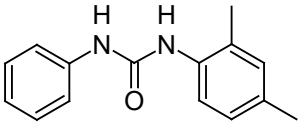
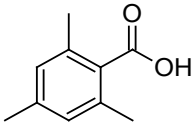
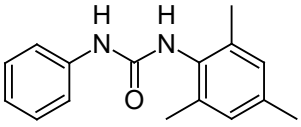
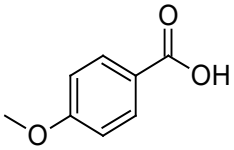
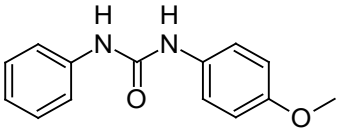
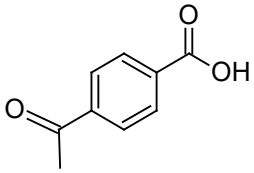
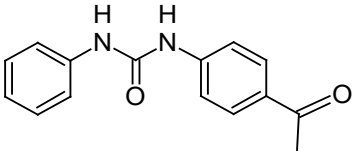
The yields obtained for the ten aryl ureas which were previously prepared by combining benzoic acid with various amines were mostly found to decrease when various carboxylic acids

and aniline were used as starting materials instead. The only exception to this trend was the slightly greater 94% yield obtained for *N*-(4-chlorophenyl)-*N'*-phenylurea when it was prepared using 4-chlorobenzoic acid (**Entry 4k**) in comparison to the 81% yield achieved when *n*-butylamine (**Entry 2h**) was used in its preparation. In addition, it was noted that high yields were obtained for the products that had been prepared by combining 4-fluorobenzoic acid, 4-bromobenzoic acid, or 4-cyanobenzoic acid with aniline. Therefore, it became evident that ideal carboxylic acid starting materials for the HATU method were those that had a low electron density surrounding the carboxyl group.[74] Furthermore, many of these ideal carboxylic acids likely contain conjugated π-electron systems throughout their molecular structures. In contrast, the high product yields achieved by combining benzoic acid with *n*-butylamine, *t*-butylamine, benzylamine, and cyclohexylamine indicated that amine starting materials which had a high electron density near the amino group were preferable for the HATU method. Based on this observation, it appears that the most suitable amine starting materials lack conjugated π-electron systems.

Although the influence of EDGs and EWGs on electron density distribution in starting materials clearly plays a large role in product formation when using the HATU method, the large difference in yield observed when certain aryl ureas were prepared using two different combinations of reagents indicated the additional impact of steric hindrance. For example, while the 56% yield achieved for *N*-(2,4,6-dimethylphenyl)-*N'*-phenylurea when it was prepared using 2,4,6-trimethylaniline (**Entry 2f**) was not particularly high, the use of 2,4,6-trimethylbenzoic acid (**Entry 4d**) as a starting material resulted in an extremely low yield of 1% being obtained instead. This demonstrates that while the two methyl groups adjacent to the amino group in 2,4,6-trimethylaniline interfere with its nucleophilic attack on phenyl isocyanate,

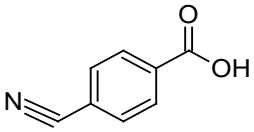
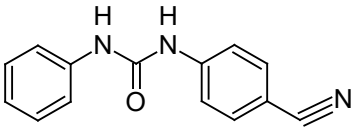
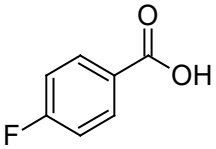
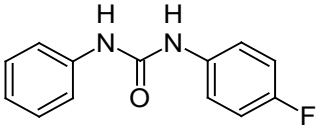
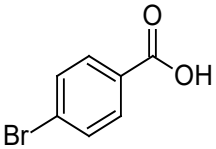
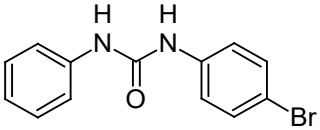
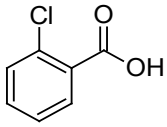
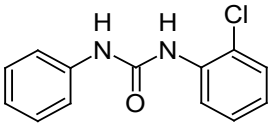
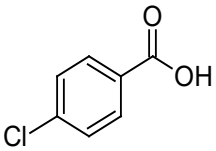
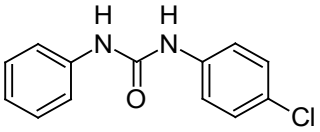
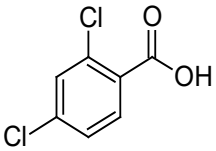
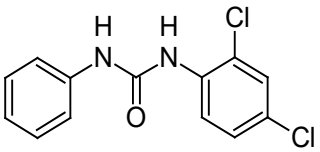
the two methyl groups adjacent to the carboxyl group in 2,4,6 trimethylbenzoic acid are far more detrimental to product formation. This is due to their steric hindrance interfering with the reactivity of 2,4,6-trimethylbenzoic acid as well as each intermediate that leads up to the formation of 2,4,6-trimethylphenyl isocyanate in the proposed mechanism.[74] Therefore, if the option exists to prepare a particular aryl urea from one of two starting material combinations, then the selected combination should involve the carboxylic acid with the simpler molecular structure. However, if both of the selectable carboxylic acids have molecular structures with similar complexity, then the decision is relegated to choosing the carboxylic acid with less electron density around the carboxyl group.

Table 3.4 - *Summary of yields obtained for aryl ureas under optimized conditions using various carboxylic acids and aniline as starting materials.*

Entry	Carboxylic Acid Reagent	Urea Product	Yield (%)
4a			(56) 41
	o-Toluic Acid	*N*-(2-Methylphenyl)-*N'*-phenylurea	
4b			(73) 54
	p-Toluic Acid	*N*-(4-Methylphenyl)-*N'*-phenylurea	
4c			(95) 64
	2,4-Dimethylbenzoic Acid	*N*-(2,4-Dimethylphenyl)-*N'*-phenylurea	
4d			(10) 1
	2,4,6-Trimethylbenzoic Acid	*N*-(2,4,6-Trimethylphenyl)-*N'*-phenylurea	
4e			(88) 23
	p-Anisic Acid	*N*-(4-Methoxyphenyl)-*N'*-phenylurea	
4f			(126) 34*
	4-Acetylbenzoic Acid	*N*-(4-Acetylphenyl)-*N'*-phenylurea	

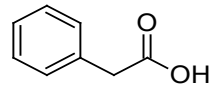
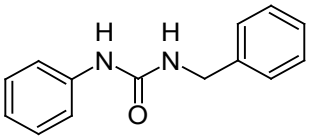
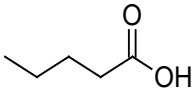
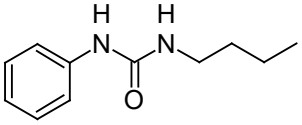
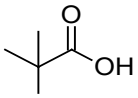
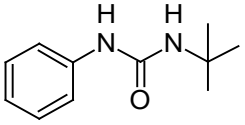
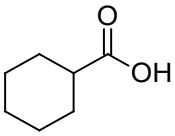
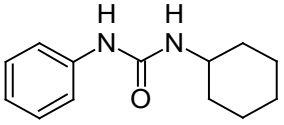
( ) Product yield prior to trituration.
* Product triturated with chloroform-EtOAc (90:10, v/v) instead of pure chloroform.

Table 3.4 (Cont.) - *Summary of yields obtained for aryl ureas under optimized conditions using various carboxylic acids and aniline as starting materials.*

Entry	Carboxylic Acid Reagent	Urea Product	Yield (%)
4g			(120) 98
	4-Cyanobenzoic Acid	*N*-(4-Cyanophenyl)-*N'*-phenylurea	
4h			(110) 87
	4-Fluorobenzoic Acid	*N*-(4-Fluorophenyl)-*N'*-phenylurea	
4i			(111) 97
	4-Bromobenzoic Acid	*N*-(4-Bromophenyl)-*N'*-phenylurea	
4j			(93) 70
	2-Chlorobenzoic Acid	*N*-(2-Chlorophenyl)-*N'*-phenylurea	
4k			(127) 94
	4-Chlorobenzoic Acid	*N*-(4-Chlorophenyl)-*N'*-phenylurea	
4l			(65) 20*
	2,4-Dichlorobenzoic Acid	*N*-(2,4-Dichlorophenyl)-*N'*-phenylurea	

( ) Product yield prior to trituration.
* Product triturated with chloroform-EtOAc (90:10, v/v) instead of pure chloroform.

Table 3.4 (Cont.) - *Summary of yields obtained for aryl ureas under optimized conditions using various carboxylic acids and aniline as starting materials.*

Entry	Carboxylic Acid Reagent	Urea Product	Yield (%)
4m			(49) 11
	Phenylacetic Acid	*N*-Benzyl-*N'*-phenylurea	
4n			(50) 20
	Valeric Acid	*N*-(*n*-Butyl)-*N'*-phenylurea	
4o			(33) 5
	Pivalic Acid	*N*-(*t*-Butyl)-*N'*-phenylurea	
4p			(75) 32
	Cyclohexanoic Acid	*N*-Cyclohexyl-*N'*-phenylurea	

( ) Product yield prior to trituration.

3.5 Modification of HATU Method for Aniline Preparation

Once the versatility of the HATU method had been evaluated through testing with different starting materials, an attempt was made to modify it for the purpose of amine preparation. As was indicated following the testing of the HATU method with different alcohol starting materials, the side reaction of water with phenyl isocyanate prior to the addition of the alcohol in the synthetic procedure results in the formation of aniline. Much of this aniline then reacts with the remaining phenyl isocyanate to form *N,N'*-diphenylurea. Although the formation of aniline as a by-product was not desired when the purpose of the synthetic procedure was to prepare various aryl carbamates, it was evident that this side reaction could possibly be developed into a secondary application. The potential for this application was tested by using benzoic acid and water as starting materials (**Table 3.5**). Initially, the test was conducted without any modifications to the synthetic procedure (**Entry 5a**) and it was expected that the use of water as a nucleophile would result in the conversion of all phenyl isocyanate into aniline. The formation of aniline as well as *N,N'*-diphenylurea was indicated by TLC analysis once product extraction had been conducted using EtOAc followed by washing with water. However, TLC analysis performed after FC indicated that aniline was not present in any of the solvent fractions that had been selected by the instrument software. Therefore, it was likely that the concentration of aniline was too low to be detected, causing it to remain on the column. Although the side reaction resulting in *N,N'*-diphenylurea likely consumed much of the aniline that was generated during the final step of the synthetic procedure, it is suggested that the weak nucleophilicity of water also limited product formation.

In an effort to reduce the amount of aniline lost to the formation of *N,N'*-diphenylurea, the synthetic procedure was modified to exclude heating of the reaction mixture following the

addition of water. Unfortunately, TLC analysis indicated that aniline was still not retained following FC, regardless of whether product extraction was attempted with EtOAc (**Entry 5b**) or DCM (**Entry 5c**). However, it was noted that benzanilide had also been formed as a by-product in addition to *N,N'*-diphenylurea. This suggests that when the reaction mixture was not heated following the addition of water, a larger amount of activated ester remained and therefore, a greater portion was able to subsequently react with some of the aniline that had formed.

A final attempt to improve aniline retention was conducted by increasing the amount of water used in the synthetic procedure while lowering the proportions of the other reagents (**Entry 5d**). Along with the absence of heating, it was anticipated these modifications would limit the abundance of residual phenyl isocyanate that was available to react with aniline as it formed. Once again, TLC analysis found that aniline had not been recovered subsequent to FC being performed. It is possible that the difficulty in recovering aniline following this purification step could be overcome by scaling up all reagent quantities since the corresponding increase in product would likely be detected during FC. However, this would not improve product yield and therefore, a stronger nucleophile such as a hydroxide salt may be necessary to increase the rate of phenyl isocyanate conversion to aniline.[89,124]

Table 3.5 - *Summary of yield obtained for aniline under various conditions using benzoic acid and water as starting materials.*

Entry	Benzoic Acid (eq)	HATU (eq)	HOSA (eq)	Water (eq)	Microwave Conditions	Yield (%)	Additional Conditions
5a	1.25	1.25	1.5	1	100°C, 5min.	0	N/A
5b	1.25	1.25	1.5	1	N/A	0	N/A
5c	1	1.05	1.3	1.3	N/A	0	N/A
5d	1.25	1.25	1.5	1	N/A	0	x2 DCM substituted for EtOAc during extraction

3.6 Incorporation of HATU Method Into Multi-step Sorafenib Preparation

After it had been determined that the HATU method could not be effectively employed to prepare amines when using water as a nucleophile, focus was shifted to incorporating it into a multi-step synthesis for the anticancer drug Sorafenib. As mentioned previously, the preparation of the product along with its two precursors used existing techniques in the literature which were modified to make use of the reagents as well as conditions employed in the HATU method (**Table 3.6**).[125,126,95]

The preparation of the first precursor, *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea, was attempted using 4-chloro-3-(trifluoromethyl)benzoic acid and 4-aminophenol as starting materials. Although a yield of 56% was initially achieved, the product could not be separated from unreacted 4-aminophenol once all purification steps had been completed. The persistence of 4-aminophenol as an impurity was suggested to be the result of several unfavourable chemical properties. One such property was its low water solubility, causing it to remain in the organic layer during product extraction and washing.[127] Once FC had been performed on the precipitate obtained from the organic layer, it was found that the similar polarity of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea, 4-aminophenol, and two other impurities caused them to co-elute. Furthermore, 4-aminophenol and the other two impurities remained after the precipitate obtained from the eluted fractions had been triturated with a chloroform-EtOAc (90:10, v/v) solvent mixture. It is possible that at least one of the two impurities aside from 4-aminophenol was an oxidized derivative that had self-reacted to form a dye. This postulate was supported by the brown colour of the product isolated from FC which was drastically different from the white colour of pure *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea. [127,128,114] Also, it is likely that some of 4-

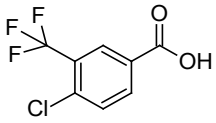
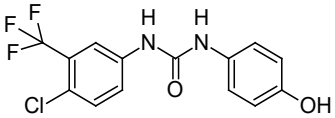
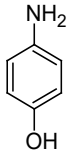
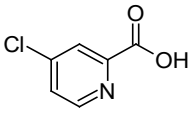
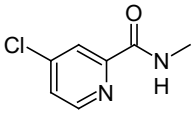
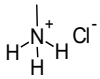
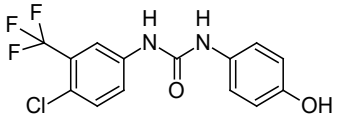
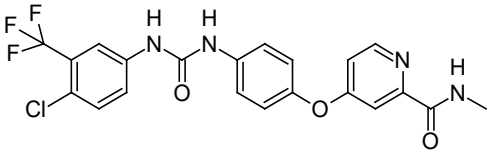
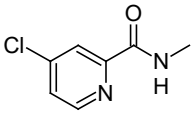
aminophenol starting material had become oxidized prior to its addition to the reaction mixture since it was not stored under an inert atmosphere. Therefore, it was suggested that the high susceptibility of 4-aminophenol to oxidation partially hindered product formation [129]

In attempt to eliminate the presence of residual 4-aminophenol in the reaction mixture following the synthesis of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea, the reagent was substituted with its corresponding hydrochloride salt. Since the solubility of 4-hydroxyanilinium in water is higher than that of 4-aminophenol, most of the unreacted salt that remained in the reaction mixture was expected to partition into the aqueous layer during product extraction and washing.[128] However, the product still contained impurities following FC. Furthermore, a lower yield of 30% accompanied the replacement of 4-aminophenol with 4-hydroxyanilinium chloride which likely indicated that the conversion of the latter into the former through deprotonation by DIPEA did not occur efficiently.[130,131] As a result, it was determined that alteration to the solvent gradient and flow rate used for FC was necessary in order to adequately separate 4-aminophenol as well as the other two impurities from the product. Fortunately, this modification was highly effective in its purpose. Furthermore, subsequent trituration with a chloroform-MeOH (90:10, v/v) solvent mixture was sufficient to remove any remaining impurities following FC. However, the high polarity of MeOH likely resulted in a large amount of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea being dissolved along with these impurities, resulting in a 47% yield being obtained.[93] Therefore, the molar quantities of the reagents and catalyst had to be tripled in order to prepare a sufficient amount of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea for the subsequent synthesis of Sorafenib. Fortunately, a similar yield of 45% when the increased molar quantities were used (**Entry 6a**), indicating that this alteration did not interfere with product formation.

The preparation of the second precursor, 4-chloro-*N*-methyl-2-pyridinecarboxamide, was attempted using 4-chloro-2-pyridinecarboxylic acid and methylammonium chloride as starting materials. Since the product of this step did not require the addition of HOSA in the synthetic procedure, the formation of by-products and side reactions caused by the addition of this reagent were avoided. However, isolation of 4-chloro-*N*-methyl-2-pyridinecarboxamide initially proved difficult since the product and all remaining impurities exhibited similar solubility in a hexane-chloroform (90:10, v/v) solvent mixture during trituration. Fortunately, this challenge was overcome by once again modifying the solvent gradient employed for FC such that the product did not co-elute with any detectable impurities. Therefore, subsequent trituration was no longer required, preventing a decrease in product yield that could result from this purification step. Despite the 74% yield achieved, the molar quantities of the reagents and catalyst had to be doubled in order to prepare a sufficient amount of 4-chloro-*N*-methyl-2-pyridinecarboxamide for the subsequent synthesis of Sorafenib. Once again, the increase in molar quantities did not appear to affect product formation based on the nearly identical 73% yield (**Entry 6b**) obtained when this alteration was employed.

Once both precursors had been prepared in adequate amounts, they were used as starting materials for a S_NAr reaction which was expected to result in the formation of Sorafenib. However, only starting materials as well as a few side products were recovered following FC, suggesting that Sorafenib had not formed (**Entry 6c**). This likely indicates that DIPEA did not effectively deprotonate the hydroxyl group in *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea, despite the reaction mixture being heated to 100°C for 30 minutes using a microwave synthesizer. Therefore, it is clear that the use of a catalyst with a much higher basicity is vital to the success of a S_NAr reaction.

Table 3.6 *- Summary of yields obtained for Sorafenib and precursors under optimized conditions using various starting materials.*

Entry	Starting Materials	Product	Yield (%)
6a	 4-Chloro-3-(trifluoromethyl)-benzoic Acid	 *N*-[4-Chloro-3-(trifluoromethyl)-phenyl]-*N'*-(4-hydroxyphenyl)urea	(86) 45*
	 4-Aminophenol		
6b	 4-Chloro-2-pyridinecarboxylic Acid	 4-Chloro-*N*-methyl-2-pyridinecarboxamide	73
	 Methylammonium Chloride		
6c	 *N*-[4-Chloro-3-(trifluoromethyl)-phenyl]-*N'*-(4-hydroxyphenyl)urea	 Sorafenib	0
	 4-Chloro-*N*-methyl-2-pyridinecarboxamide		

( ) Product yield prior to trituration.
*Product triturated with chloroform-MeOH (90:10, v/v) instead of pure chloroform.

4. CONCLUSION AND FUTURE WORK

Ureas and Carbamates are carbonyl functional groups that are noted for their chemical stability through resonance as well as their potential to form multiple hydrogen bonds. These chemical properties as well as others have resulted in these functional groups being incorporated into the molecular structures of foldamers as well as various drugs. In addition, they have found use in the development of host complexes for smaller molecules. Therefore, the efficient synthesis of ureas and carbamates has become an important research focus. Although early synthetic procedures for these functional groups were developed over a century ago, not much progress was made until the development of the Curtius, Hofmann, and Lossen rearrangement reactions. The isocyanate that ultimately formed from each rearrangement reaction could easily be converted into a urea or carbamate when combined with the appropriate nucleophile. Although all three rearrangement reactions have been applied to urea and carbamate synthesis since their discovery, the Lossen rearrangement has had the notable advantage of not involving highly toxic or explosive reagents. Unfortunately, the hydroxamic acid precursors from which the hydroxamate starting materials are often prepared have low commercial availability. This has led to their preparation from precursors that are more easily obtained such as carboxylic acids. However, the direct conversion of a carboxylic acid to a hydroxamate does not occur efficiently due to the hydroxide anion being a poor leaving group. In addition, the electrophilicity of the carbonyl carbon atom is often quite low. Therefore, the carboxylic acid must be transformed into an activated derivative in which the hydroxyl group is replaced by a strong EWG that exhibits high stability as an anion. This can be achieved by combining the carboxylic acid with one of several coupling reagents that have been developed over the past few decades. The hydroxamate can then be synthesized by combining the activated derivative with a hydroxylamine derivative.

The HATU method for the preparation of aryl ureas and carbamates that was presented herein was expected to improve upon the method developed by Bao *et al.* (2018), primarily through alterations to the synthetic procedure. The first alteration was the replacement of benzoyl chloride with various carboxylic acids that could be transformed into activated esters using HATU. HATU was selected as the coupling reagent due to the 1*H*-benzotriazole moiety of which it is partially comprised. Once this moiety is incorporated into the molecular structure of the activated ester, it is capable of interfering with product racemization if an α-carbon atom is also present in the intermediate. Additionally, the 1*H*-benzotriazole moiety stabilizes HOSA prior to its nucleophilic attack on the carbonyl carbon atom through hydrogen bonding, resulting in a higher rate of isocyanate formation. Along with the advantages provided by HATU, the use of a carboxylic acid instead of an acyl chloride as a starting material is preferable since the storage capability of the latter is hindered by rapid hydrolysis in the presence of moisture. Another alteration that was made to the synthetic procedure employed by Bao *et al.* (2018) was the use of MeCN instead of DCM as the solvent in which the reaction was conducted. This switch was made since the higher polarity of MeCN allows it to be heated more efficiently than DCM in the microwave synthesizer. In addition to the changes applied to the synthetic procedure, the purification procedure used by Bao *et al.* (2018) was also modified by extracting the reaction mixture into EtOAc or DCM and then performing a wash with water following heating in the microwave synthesizer. This extraction was included with the intention of eliminating highly polar impurities that would make product isolation difficult when using FC.

Optimization of the HATU method was carried out through the repeated preparation of *N,N'*-diphenylurea from benzoic acid and aniline using slightly different conditions as well as reagent proportions. Upon completion of optimization, it became evident that the conditions and

reagent proportions employed by Bao *et al.* (2018) did not require any drastic alterations. This made it possible to compare product yields obtained with each method solely based on changes in the synthetic and purification procedures. Several aryl ureas and carbamates were then synthesized from benzoic acid and various nucleophiles using the HATU method, including those which were previously reported by Bao *et al.* (2018). Most of the yields achieved for the aryl ureas ranged from 75% to 95% while the majority of those obtained for the aryl carbamates spanned 45% to 65%. The lower yields obtained for the aryl carbamates were mainly attributed to side reactions caused by the presence of water in the alcohol starting materials as well as acidic by-products that formed in solution. After yields for products that had been prepared by both methods were compared, it was found that many of the yields achieved using the new method were similar or superior to those reported by Bao *et al.* (2018). However, higher yields were reported by Bao *et al.* (2018) for a few products as well. Based on these comparisons, it is suggested that although use of the synthetic procedure employed in the HATU method generally results in higher product formation, the yield is hindered by subsequently triturating the product during purification. Unfortunately, this trituration is necessary due to the persistence of impurities such as HOAt following product isolation by FC. Therefore, the replacement of HATU with another coupling reagent that generates by-products which are all highly soluble in water could be necessary. Also, it is possible that a greater number of impurities could be separated from products by FC through appropriate adjustments to parameters such as elution time and gradient as well as the chemical properties of the silica gel. Finally, a better understanding of aryl urea and carbamate solubility trends in EtOAc as well as DCM would likely provide insight as to how the retention of products could be improved during their extraction from reaction mixtures.

Once comparison of the two methods was completed, several more aryl ureas were prepared from various carboxylic acids and aniline using the HATU method. This included aryl ureas which had already been synthesized through the HATU method using benzoic acid and certain nucleophiles. The use of two different pairs of starting materials to prepare the same aryl ureas allowed for a yield comparison that provided insight as to how the molecular structures as well as chemical properties of the starting materials affect product formation. As a result of this comparison, it was determined that aromatic carboxylic acids which have one or more EWGs are ideal for maximizing product yield since electron density near the carbonyl carbon atom is minimal, enhancing its electrophilicity. In addition, it was found that aliphatic amines which have one or more EDGs similarly contribute to a higher product yield by concentrating electron density near the amino group, enhancing its nucleophilicity. However, steric hindrance near the carbonyl carbon atom in a carboxylic acid or the amino group in an amine can greatly limit product yield, regardless of electron density distribution in either starting material. Furthermore, intramolecular steric hindrance in aromatic carboxylic acids caused by substituents directly adjacent to the carboxyl group can disrupt its co-planarity with the aryl group, increasing electron density near the carbonyl carbon atom due to a decrease in electron delocalization.

Although the preparation of aniline from benzoic acid and water using the synthetic procedure in the HATU method was indicated to be successful according to TLC analysis, the product could not be isolated by FC due to its low concentration in the reaction mixture. This low concentration was partially attributed to the weak nucleophilicity of water. In addition, it was suggested that some of the aniline in the reaction mixture reacted with the remaining phenyl isocyanate. This suggestion is based on *N,N'*-diphenylurea also being present in the reaction mixture. Therefore, it is likely that the HATU method cannot be effectively employed to

prepare primary amines unless a stronger nucleophilic starting material such as hydrogen peroxide is used instead of water.

The incorporation of the HATU method into the total synthesis of Sorafenib from *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea and 4-chloro-*N*-methyl-2-pyridinecarboxamide resulted in the formal synthesis of the two precursors. However, the use of DIPEA to catalyze the S_NAr reaction which was expected to form the final product from the two precursors was not successful. Therefore, it is likely that a catalyst with a much higher basicity is required to effectively deprotonate *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea. Also, the tendency for 4-aminophenol to become oxidized and participate in side reactions during the synthesis of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N′*-(4-hydroxyphenyl)urea suggests that future alterations to the synthetic procedure such as protecting the hydroxyl group or using the reagent in excess could improve product formation. Furthermore, an effective reduction in the formation of side products would likely eliminate the requirement for trituration following purification through FC.

As indicated previously, there exists potential to improve the method reported by Bao *et al.* (2018) beyond the alterations which were made in the HATU method. It is suggested that with further refinement, the HATU method could eventually be developed into a library synthesis. This library synthesis could then be employed for purposes such as the rapid preparation of multiple urea and carbamate analogues that could act as precursors to drug candidates with similar molecular structures. In addition, the library synthesis could be subsequently adapted into a flow chemistry method. Automation of the library synthesis would not only reduce the amount of time required for preparing each product, but also ensure that the synthetic and purification procedures are carried out consistently.

5. REFERENCES

(1) Lemke, Thomas L.; Roche, Victoria F.; Zito, S. W. *Review of Organic Functional Groups: Introduction to Medicinal Chemistry*, 5th ed.; Lippincott Williams & Wilkins: Baltimore, Maryland, 2012.

(2) Dewan, S. K. *Pharmaceutical Organic Chemistry*; Alpha Science International Ltd.: Oxford, England, 2009.

(3) Lortie, F.; Boileau, S.; Bouteiller, L. N,N′-Disubstituted Ureas: Influence of Substituents on the Formation of Supramolecular Polymers. *Chem. - A Eur. J.* **2003**, *9* (13), 3008–3014.

(4) Kozlova, T. V.; Zharkov, V. V. Spectroscopic Effects and Thermodynamic Parameters of Hydrogen Bonds in N-Substituted Ureas. *J. Appl. Spectrosc.* **1981**, *35* (2), 905–912.

(5) Bisson, A. P.; Carver, F. J.; Eggleston, D. S.; Haltiwanger, R. C.; Hunter, C. A.; Livingstone, D. L.; McCabe, J. F.; Rotger, C.; Rowan, A. E. Synthesis and Recognition Properties of Aromatic Amide Oligomers: Molecular Zippers. *J. Am. Chem. Soc.* **2000**, *122* (37), 8856–8868.

(6) Pendem, N.; Nelli, Y. R.; Douat, C.; Fischer, L.; Laguerre, M.; Ennifar, E.; Kauffmann, B.; Guichard, G. Controlling Helix Formation in the γ-Peptide Superfamily: Heterogeneous Foldamers with Urea/Amide and Urea/Carbamate Backbones. *Angew. Chemie - Int. Ed.* **2013**, *52* (15), 4147–4151.

(7) Nelli, Y. R.; Fischer, L.; Collie, G. W.; Kauffmann, B.; Guichard, G. Structural Characterization of Short Hybrid Urea/Carbamate (U/C) Foldamers: A Case of Partial Helix Unwinding. *Biopolymers* **2013**, *100* (6), 687–697.

(8) Pasco, M.; Dolain, C.; Guichard, G. Foldamers in Medicinal Chemistry. In *Comprehensive Supramolecular Chemistry II - Volume 5: Supramolecular Medicinal Chemistry and Chemical Biology*; Atwood, J.L., Gokel, G.W., Barbour, L.J., Wilson, A.J., Jayawickramarajah, J., Ed.; Elsevier: London, 2017; pp 89–125.

(9) Skurski, P.; Simons, J. An Excess Electron Bound to Urea Oligomers. II. Chains and Ribbons. *J. Chem. Phys.* **2001**, *115* (23), 10731–10737.

(10) Genio, F. A. F.; Paderes, M. C. Functional Supramolecular Gels Comprised of Bis-Urea Compounds and Cosmetic Solvents. *ChemistrySelect* **2021**, *6* (31), 7906–7911.

(11) Jones, C. D.; Steed, J. W. Gels with Sense: Supramolecular Materials That Respond to Heat, Light and Sound. *Chem. Soc. Rev.* **2016**, *45* (23), 6546–6596.

(12) Shi, A. C.; Huang, Z.; Kilic, S.; Xu, J.; Enick, R. M.; Beckman, E. J.; Carr, A. J.; Hamilton, A. D. The Gelation of CO2: A Sustainable Route to the Creation of Microcellular Materials. *Science* **1999**, *286* (5444), 1540–1543.

(13) Liu, K.; Steed, J. W. Triggered Formation of Thixotropic Hydrogels by Balancing Competitive Supramolecular Synthons. *Soft Matter* **2013**, *9* (48), 11699–11705.

(14) Vintiloiu, A.; Leroux, J. C. Organogels and Their Use in Drug Delivery - A Review. *J. Control. Release* **2008**, *125* (3), 179–192.

(15) Fages, F.; Vögtle, F.; Žinić, M. Systematic Design of Amide-and Urea-Type Gelators with Tailored Properties. In *Low Molecular Mass Gelators*; Fages, F., Ed.; Topics in Current Chemistry, 256; Springer Berlin Heidelberg: Berlin, Heidelberg, 2005; pp 77–131.

(16) Li, Q.; Mak, T. C. W. Novel Inclusion Compounds of Urea with Tetraalkylammonium Pentaborates. *Supramol. Chem.* **1997**, *8* (2), 147–156.

(17) Yang, Y.; Lu, Z. Novel Urea/Thiourea-Betaine Inclusion Compounds Consolidated by Host-Guest Hydrogen Bonds. *Mol. Cryst. Liq. Cryst.* **2021**, *722* (1), 47–57.

(18) Fischer, P. H. H.; McDowell, C. A. The Infrared Absorption Spectra of Urea-Hydrocarbon Adducts. *Can. J. Chem.* **1960**, *38* (2), 187–193.

(19) Lashua, A. F.; Smith, T. M.; Hu, H.; Wei, L.; Allis, D. G.; Sponsler, M. B.; Hudson, B. S. Commensurate Urea Inclusion Crystals with the Guest (E,E)-1,4-Diiodo-1,3- Butadiene. *Cryst. Growth Des.* **2013**, *13* (9), 3852–3855.

(20) Thakral, S.; Madan, A. K. Reduction in Moisture Sensitivity/Uptake of Moisture Sensitive Drugs through Adduction in Urea. *J. Pharm. Innov.* **2008**, *3* (4), 249–257.

(21) Inoue, Y.; Niiyama, D.; Murata, I.; Kanamoto, I. Usefulness of Urea as a Means of Improving the Solubility of Poorly Water-Soluble Ascorbyl Palmitate. *Int. J. Med. Chem.* **2017**, *2017*, 1–9.

(22) Sureshbabu, V. V.; Narendra, N. Protection Reactions. In *Amino Acids, Peptides and Proteins in Organic Chemistry - Volume 4: Protection Reactions, Medicinal Chemistry, and Combinatorial Synthesis*; Huges, A. B., Ed.; Wiley-VCH: Weinheim, 2011; Vol. 4, pp 1–97.

(23) Ghosh, A. K.; Brindisi, M. Organic Carbamates in Drug Design and Medicinal Chemistry. *J. Med. Chem.* **2015**, *58* (7), 2895–2940.

(24) Testa, B.; Mayer, J. M. The Hydrolysis of Carboxylic Acid Ester Prodrugs. In *Hydrolysis in Drug and Prodrug Metabolism*; Wiley Online Books; Verlag Helvetica Chimica Acta: Zurich, 2003; pp 419–534.

(25) Ghosh, A. K.; Brindisi, M. Urea Derivatives in Modern Drug Discovery and Medicinal Chemistry. *J. Med. Chem.* **2020**, *63* (6), 2751–2788.

(26) Azam, F. Pharmacological Recognition of Urea Derivatives in Brain Disorders. In *Urea: Synthesis, Properties and Uses*; Fernandez, A. M., Munoz, C. M., Eds.; Nova Science Publishers Inc.: New York, 2012; pp 183–200.

(27) Maher, T. A.; Johnson, D. A. Receptors and Drug Action. In *Foye's Principles of Medicinal Chemistry*; Lemke, T. L., Roche, V. F., Williams, D. A., Zito, S. W., Eds.; Lippincott Williams & Wilkins: Philadelphia, 2008; pp 85–98.

(28) Marcovici-Mizrahi, D.; Gottlieb, H. E.; Marks, V.; Nudelman, A. On the Stabilization of the Syn-Rotamer of Amino Acid Carbamate Derivatives by Hydrogen Bonding. *J. Org. Chem.* **1996**, *61* (24), 8402–8406.

(29) Cui, Y. Hydrotropic Solubilization by Urea Derivatives: A Molecular Dynamics Simulation Study. *J. Pharm.* **2013**, *2013*, 1–15.

(30) Alex, A.; Millan, D. S.; Perez, M.; Wakenhut, F.; Whitlock, G. A. Intramolecular Hydrogen Bonding to Improve Membrane Permeability and Absorption in beyond Rule of Five Chemical Space. *Medchemcomm* **2011**, *2* (7), 669–674.

(31) Suissa, S.; Dennis, R.; Ernst, P.; Sheehy, O.; Wood-Dauphinee, S. Effectiveness of the Leukotriene Receptor Antagonist Zafirlukast for Mild-to-Moderate Asthma: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann. Intern. Med.* **1997**, *126* (3), 177–183.

(32) Sevrioukova, I. F.; Poulos, T. L. Structure and Mechanism of the Complex between Cytochrome P4503A4 and Ritonavir. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107* (43), 18422–18427.

(33) Perrone, M. H.; Barrett, J. A. Preclinical Pharmacology of Celiprolol: A Cardioselective β-Adrenergic Antagonist and Mild Vasodilator. *Am. Heart J.* **1991**, *121* (2 [Pt 2]), 677–683.

(34) Meessen, J. Urea Synthesis. *Chemie-Ingenieur-Technik* **2014**, *86* (12), 2180–2189.

(35) Wöhler, F. Ueber Künstliche Bildung Des Harnstoffs. *Ann. Phys.* **1828**, *88* (2), 253–256.

(36) Joseph, D.; Chakraborty, K. Justus Liebigs Annalen Der Chemie. *J. Aquat. Food Prod. Technol.* **2017**, *26* (9), 1042–1056.

(37) Liebig, J. von; Wohler, F. Cyansaures Aethyl-Und Methyloxyd. *Justus Liebigs Ann. Chem.* **1845**, *54* (3), 370–371.

(38) Bazarov, A. I. Obtaining Urea from Carbon Dioxide and Ammonia. *J. für Prakt. Chemie* **1870**, *2*, 283–312.

(39) Cotarca, L.; Heiner, E. *Phosgenations - A Handbook*; Wiley-VCH: Weinheim, 2003.

(40) Liu, A. H.; Li, Y. N.; He, L. N. Organic Synthesis Using Carbon Dioxide as Phosgene-Free Carbonyl Reagent. *Pure Appl. Chem.* **2012**, *84* (3), 581–602.

(41) Shi, F.; Deng, Y.; SiMa, T.; Peng, J.; Gu, Y.; Qiao, B. Alternatives to Phosgene and Carbon Monoxide: Synthesis of Symmetric Urea Derivatives with Carbon Dioxide in Ionic Liquids. *Angew. Chemie - Int. Ed.* **2003**, *42* (28), 3257–3260.

(42) Grego, S.; Aricoì, F.; Tundo, P. Highly Selective Phosgene-Free Carbamoylation of Aniline by Dimethyl Carbonate under Continuous-Flow Conditions. *Org. Process Res. Dev.* **2013**, *17* (4), 679–683.

(43) Hoshino, Y.; Ohtsuka, N.; Okada, T.; Honda, K. One-Pot Synthesis of Primary Amines from Carboxylic Acids through Rearrangement of in Situ Generated Hydroxamic Acid Derivatives. *Tetrahedron Lett.* **2016**, *57* (48), 5304–5307.

(44) Singh, A. S.; Kumar, D.; Mishra, N.; Tiwari, V. K. An Efficient One-Pot Synthesis of N,N′-Disubstituted Ureas and Carbamates from N-Acylbenzotriazoles. *RSC Adv.* **2016**, *6* (87), 84512–84522.

(45) Saraiva Rosa, N.; Glachet, T.; Ibert, Q.; Lohier, J. F.; Franck, X.; Reboul, V. A Straightforward Synthesis of N-Substituted Ureas from Primary Amides. *Synth.* **2020**, *52* (14), 2099–2105.

(46) Laue, Thomas; Plagens, A. *Named Organic Reactions*, 2nd ed.; John Wiley & Sons Ltd.: Chichester, England, 2005.

(47) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds. *Angew. Chemie Int. Ed.* **2005**, *44* (33), 5188–5240.

(48) Kulkarni, A. R.; Garai, S.; Thakur, G. A. Scalable, One-Pot, Microwave-Accelerated Tandem Synthesis of Unsymmetrical Urea Derivatives. *J. Org. Chem.* **2017**, *82* (2), 992–999.

(49) Chaloner, P. *Organic Chemistry: A Mechanistic Approach*, 1st ed.; CRC Press: Boca Raton, 2014.

(50) Yoshimura, A.; Middleton, K. R.; Luedtke, M. W.; Zhu, C.; Zhdankin, V. V. Hypervalent Iodine Catalyzed Hofmann Rearrangement of Carboxamides Using Oxone as Terminal Oxidant. *J. Org. Chem.* **2012**, *77* (24), 11399–11404.

(51) Pereira, M. M. A.; Santos, P. P. Rearrangement of Hydroxylamines, Oximes, and Hydroxamic Acids. In *The Chemistry of Hydroxylamines, Oximes, and Hydroxamic Acids*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons Ltd.: Chichester, 2009; pp 343–498.

(52) Thalluri, K.; Manne, S. R.; Dev, D.; Mandal, B. Ethyl 2-Cyano-2-(4-Nitrophenylsulfonyloxyimino)Acetate-Mediated Lossen Rearrangement: Single-Pot Racemization-Free Synthesis of Hydroxamic Acids and Ureas from Carboxylic Acids. *J. Org. Chem.* **2014**, *79* (9), 3765–3775.

(53) Shioiri, T. Degradation Reactions. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry (Volume 1)*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; pp 795–828.

(54) Niu, T.; Wang, K. H.; Huang, D.; Xu, C.; Su, Y.; Hu, Y.; Fu, Y. One-Pot Transition-Metal-Free Synthesis of Weinreb Amides Directly from Carboxylic Acids. *Synth.* **2014**, *46* (3), 320–330.

(55) Woo, J. C. S.; Fenster, E.; Dake, G. R. A Convenient Method for the Conversion of Hindered Carboxylic Acids to N -Methoxy- N -Methyl (Weinreb) Amides Since Their Initial Appearance in 1981 , N -Methoxy- N - Acylating Reagents in Organic Chemistry . 1 The Predictable Ensured Their Use as Inter. **2004**, 8984–8986.

(56) Bodanszky, M. *Peptide Chemistry: A Practical Textbook*, 2nd ed.; Spring-Verlag: Berlin, 1998.

(57) Montalbetti, C. A. G. N.; Falque, V. Amide Bond Formation and Peptide Coupling. *Tetrahedron* **2005**, *61* (46), 10827–10852.

(58) Ulijn, R. V.; Moore, B. D.; Janssen, A. E. M.; Halling, P. J. A Single Aqueous Reference Equilibrium Constant for Amide Synthesis-Hydrolysis. *J. Chem. Soc. Perkin Trans. 2* **2002**, *2* (5), 1024–1028.

(59) Jursic, B. S.; Zdravkovski, Z. A Simple Preparation of Amides from Acids and Amines by Heating of Their Mixture. *Synth. Commun.* **1993**, *23* (19), 2761–2770.

(60) Beckwith, A. L. J. Synthesis of Amides. In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience: London, 1970; pp 105–109.

(61) Valeur, E.; Bradley, M. Amide Bond Formation: Beyond the Myth of Coupling Reagents. *Chem. Soc. Rev.* **2009**, *38* (2), 606–631.

(62) Sheehan, J. C.; Hess, G. P. A New Method of Forming Peptide Bonds. *J. Am. Chem. Soc.* **1955**, *77* (4), 1067–1068.

(63) Williams, A.; Ibrahim, I. T. Carbodiimide Chemistry: Recent Advances. *Chem. Rev.* **1981**, *81* (6), 589–636.

(64) Anderson, G. W.; Callahan, F. M. Racemization by The Dicyclohexylcarbodiimide Method of Peptide Synthesis: Sir. *J. Am. Chem. Soc.* **1958**, *80* (11), 2902–2903.

(65) König, W.; Geiger, R. A new method for synthesis of peptides: Activation of the carboxyl group with dicyclohexylcarbodiimide using 1-hydroxybenzotriazoles as additives. *Chem. Reports* **1970**, *103* (3), 788–798.

(66) König, W.; Geiger, R. Racemization in Peptide Syntheses. *Chem. Reports* **1970**, *103* (7), 2024–2033.

(67) Carpino, L. A. 1-Hydroxy-7-Azabenzotriazole. An Efficient Peptide Coupling Additive. *J. Am. Chem. Soc.* **1993**, *115* (10), 4397–4398.

(68) Albericio, F.; Bofill, J. M.; El-Faham, A.; Kates, S. A. Use of Onium Salt-Based Coupling Reagents in Peptide Synthesis. *J. Org. Chem.* **1998**, *63* (26), 9678–9683.

(69) Malow, M.; Wehrstedt, K. D.; Neuenfeld, S. On the Explosive Properties of 1H-Benzotriazole and 1H-1,2,3-Triazole. *Tetrahedron Lett.* **2007**, *48* (7), 1233–1235.

(70) Wehrstedt, K. D.; Wandrey, P. A.; Heitkamp, D. Explosive Properties of 1-Hydroxybenzotriazoles. *J. Hazard. Mater.* **2005**, *126* (1–3), 1–7.

(71) Subirós-Funosas, R.; Prohens, R.; Barbas, R.; El-Faham, A.; Albericio, F. Oxyma: An Efficient Additive for Peptide Synthesis to Replace the Benzotriazole-Based HOBt and HOAt with a Lower Risk of Explosion. *Chem. - A Eur. J.* **2009**, *15* (37), 9394–9403.

(72) El-Faham, A.; Albericio, F. COMU: A Third Generation of Uronium-Type Coupling Reagents. *J. Pept. Sci.* **2010**, *16* (1), 6–9.

(73) Jad, Y. E.; Khattab, S. N.; De La Torre, B. G.; Govender, T.; Kruger, H. G.; El-Faham, A.; Albericio, F. TOMBU and COMBU as Novel Uronium-Type Peptide Coupling Reagents Derived from Oxyma-B. *Molecules* **2014**, *19* (11), 18953–18965.

(74) Sykes, P. *A Guidebook to Mechanism in Organic Chemistry*, 6th ed.; Longman, 1986.

(75) Firme, C. L. Substituent Groups and Electrophilic Aromatic Substitution. In *Introductory Organic Chemistry and Hydrocarbons*; CRC Press, 2020; pp 386–417.

(76) Rice, J. E. Functional Groups. In *Organic Chemistry Concepts and Applications for Medicinal Chemistry*; Academic Press: Boston, 2014; pp 51–65.

(77) Davis, M. M.; Hetzer, H. B. Relative Strengths of Forty Aromatic Carboxylic Acids in Benzene at 25-Degrees-C. *J. Res. Natl. Bur. Stand. (1934).* **1958**, *60* (6), 569–592.

(78) Stewart, R.; Granger, M. R. The Basicities of Ortho-Substituted Benzoic Acids. *Can. J. Chem.* **1961**, *39* (12), 2508–2515.

(79) Mistry, L.; Mapesa, K.; Bous, T. W.; Camp, J. E. Synthesis of Ureas in the Bio-Alternative Solvent Cyrene. *Green Chem.* **2017**, *19* (9), 2123–2128.

(80) Peterson, S. L.; Stucka, S. M.; Dinsmore, C. J. Parallel Synthesis of Ureas and Carbamates From Amines and CO 2 under Mild Conditions. *Org. Lett.* **2010**, *12* (6), 1340–1343.

(81) Ren, Y.; Rousseaux, S. A. L. Metal-Free Synthesis of Unsymmetrical Ureas and Carbamates from CO2 and Amines via Isocyanate Intermediates. *J. Org. Chem.* **2018**, *83* (2), 913–920.

(82) Oosthoek-De Vries, A. J.; Nieuwland, P. J.; Bart, J.; Koch, K.; Janssen, J. W. G.; Van Bentum, P. J. M.; Rutjes, F. P. J. T.; Gardeniers, H. J. G. E.; Kentgens, A. P. M. Inline Reaction Monitoring of Amine-Catalyzed Acetylation of Benzyl Alcohol Using a Microfluidic Stripline Nuclear Magnetic Resonance Setup. *J. Am. Chem. Soc.* **2019**, *141* (13), 5369–5380.

(83) Kolodziej, K.; Romanowska, J.; Stawinski, J.; Kraszewski, A.; Sobkowski, M. The Case of Triethylammonium Cation Loss during Purification of Certain Nucleotide Analogues: A Cautionary Note. *Anal. Bioanal. Chem.* **2015**, *407* (6), 1775–1780.

(84) Reichardt, C.; Welton, T. *Solvent and Solvent Effects in Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, 2011.

(85) Okamoto, K.; Fukui, S.; Nitta, I.; Shingu, H. Kinetic Studies of Bimolecular Nucleophilic Substitution. VIII. The Effect of Hydroxylic Solvents on the Nucleophilicity of Aliphatic Amines in the Menschutkin Reaction. *Bull. Chem. Soc. Jpn.* **1967**, *40* (10), 2354–2357.

(86) Feit, B. A.; Bigon, Z. The Effect of Dipolar Aprotic Solvents on the Nucleophilic Addition of Alcohols to Activated Olefins. *J. Org. Chem.* **1969**, *34* (12), 3942–3948.

(87) Devine, William G.; Pollastri, M. P. Microwave Synthesis. In *Green Techniques for Organic Synthesis and Medicinal Chemistry*; Zhang, Wei; Cue Jr., B. W., Ed.; John Wiley & Sons Ltd.: Chichester, England, 2012; pp 325–341.

(88) Ouellette, R. J.; Rawn, J. D. Haloalkanes and Alcohols Nucleophilic Substitution and Elimination Reactions. In *Organic Chemistry: Structure, Mechanisms, Synthesis*; Academic Press, 2018; pp 255–298.

(89) Bao, J.; Kuik, D.; Tranmer, G. K. An Efficient One-Pot Synthesis of N,N′-Disubstituted Phenylureas and N-Aryl Carbamates Using Hydroxylamine-O-Sulfonic Acid. *Tetrahedron* **2018**, *74* (38), 5546–5553.

(90) Luknitskii, F. I.; Vovsi, B. A. Ketens in Situ and Cycloaddition to Them . *Russ. Chem. Rev.* **1969**, *38* (6), 487–494.

(91) Sánchez-Sancho, F.; Mann, E.; Herradón, B. Efficient Syntheses of Polyannular Heterocycles Featuring Microwave-Accelerated Bischler-Napieralski Reaction, Stereoselective Heck Cyclization, and Claisen Rearrangement. *Synlett* **2000**, *2000* (4), 509–513.

(92) Carpino, L. A.; Imazumi, H.; Foxman, B. M.; Vela, M. J.; Henklein, P.; El-Faham, A.; Klose, J.; Bienert, M. Comparison of the Effects of 5- and 6-HOAt on Model Peptide Coupling Reactions Relative to the Cases for the 4- and 7-Isomers. *Org. Lett.* **2000**, *2* (15), 2253–2256.

(93) Snyder, L. R.; Kirkland, J. J.; Glajch, J. L. Appendix II: Properties of Solvents Used in HPLC. In *Practical HPLC Method Development*; John Wiley & Sons, Inc., 1997; pp 721–728.

(94) Cranwell, P. B.; Harwood, L. M.; Moody, C. J. *Experimental Organic Chemistry*, 3rd ed.; John Wiley & Sons Ltd.: Chichester, 2017.

(95) Kumar, A.; Kumar, N.; Sharma, R.; Bhargava, G.; Mahajan, D. Direct Conversion of Carboxylic Acids to Various Nitrogen-Containing Compounds in the One-Pot Exploiting Curtius Rearrangement. *J. Org. Chem.* **2019**, *84* (17), 11323–11334.

(96) Matsuda, Y.; Wakai, T. Sorafenib. *Encyclopedia of Cancer*; Spring-Verlag, 2017; pp 4286–4289.

(97) Hill, A.; Gotham, D.; Fortunak, J.; Meldrum, J.; Erbacher, I.; Martin, M.; Shoman, H.; Levi, J.; Powderly, W. G.; Bower, M. Target Prices for Mass Production of Tyrosine Kinase Inhibitors for Global Cancer Treatment. *BMJ Open* **2016**, *6*, 1–9.

(98) pERC. Final Recommendation for Sorafenib (Nexavar) for Differentiated Thyroid Cancer. In *Pan-Canadian Oncology Drug Review*; Canadian Agency For Drugs And Technologies In Health: Ottawa, 2015; pp 1–8.

(99) Henderson, A. S.; Medina, S.; Bower, J. F.; Galan, M. C. Nucleophilic Aromatic Substitution (SNAr) as an Approach to Challenging Carbohydrate-Aryl Ethers. *Org. Lett.* **2015**, *17* (19), 4846–4849.

(100) Smith, M. B. *Organic Synthesis*, 4th ed.; Academic Press: London, 2017.

(101) Hayashi, Y. Pot Economy and One-Pot Synthesis. *Chem. Sci.* **2016**, *7* (2), 866–880.

(102) Clarke, P. A.; Santos, S.; Martin, W. H. C. Combining Pot, Atom and Step Economy (PASE) in Organic Synthesis. Synthesis of Tetrahydropyran-4-Ones. *Green Chem.* **2007**, *9* (5), 438–440.

(103) Vaxelaire, C.; Winter, P.; Christmann, M. One-Pot Reactions Accelerate the Synthesis of Active Pharmaceutical Ingredients. *Angew. Chemie Int. Ed.* **2011**, *50* (16), 3605–3607.

(104) Lehmann, H.; Lavecchia, L. Scale-up of Organic Reactions in a Pharmaceutical Kilo-Lab Using a Commercial Microwave Reactor. *Org. Process Res. Dev.* **2010**, *14* (3), 650–656.

(105) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic Synthesis Provides Opportunities to Transform Drug Discovery. *Nat. Chem.* **2018**, *10* (4), 383–394.

(106) Wang, L.; Wang, H.; Wang, Y.; Shen, M.; Li, S. Photocatalyzed Synthesis of Unsymmetrical Ureas via the Oxidative Decarboxylation of Oxamic Acids with PANI-g-C3N4-TiO2 Composite under Visible Light. *Tetrahedron Lett.* **2020**, *61* (23), 151962–151966.

(107) Zhang, C.; Wang, W.-K.; He, T. Dramatic Solvent Effect in the One-Pot Synthesis of Substituted Ureas Directly from Primary Alcohols Using the Combined Reagent of Iodobenzene Dichloride and Sodium Azide in Ethyl Acetate. *Synthesis (Stuttg).* **2012**, *44* (19), 3006–3014.

(108) Malviya, B. K.; Jaiswal, P. K.; Verma, V. P.; Badsara, S. S.; Sharma, S. Electrochemical Synthesis of Carbodiimides via Metal/Oxidant-Free Oxidative Cross-Coupling of Amines and Isocyanides. *Org. Lett.* **2020**, *22* (6), 2323–2327.

(109) Kotecki, B. J.; Fernando, D. P.; Haight, A. R.; Lukin, K. A. A General Method for the Synthesis of Unsymmetrically Substituted Ureas via Palladium-Catalyzed Amidation. *Org. Lett.* **2009**, *11* (4), 947–950.

(110) Atahan, A.; Gencer, N.; Bilen, C.; Yavuz, E.; Genc, H.; Sonmez, F.; Zengin, M.; Ceylan, M.; Kucukislamoglu, M. Synthesis, Biological Activity and Structure-Activity Relationship of Novel Diphenylurea Derivatives Containing Tetrahydroquinoline as Carbonic Anhydrase I and II Inhibitors. *ChemistrySelect* **2018**, *3* (2), 529–534.

(111) Zeng, H.; Du, H.; Gong, X.; Zhang, J.; Han, W. Palladium-Catalyzed Aerobic Oxidative Carbonylation of Amines Enables the Synthesis of Unsymmetrical N,N′-Disubstituted Ureas. *Synlett* **2021**, *32* (12), 1223–1226.

(112) Adler, T.; Bonjoch, J.; Clayden, J.; Font-Bardía, M.; Pickworth, M.; Solans, X.; Solé, D.; Vallverdú, L. Slow Interconversion of Enantiomeric Conformers or Atropisomers of Anilide and Urea Derivatives of 2-Substituted Anilines. *Org. Biomol. Chem.* **2005**, *3* (17), 3173–3183.

(113) Casula, A.; Fornasier, M.; Montis, R.; Bettoschi, A.; Argent, S. P.; Blake, A. J.; Lippolis, V.; Marongiu, L.; Picci, G.; Tidey, J. P.; et al. Halogen-Substituted Ureas for Anion Binding: Solid State and Solution Studies. *Supramol. Chem.* **2017**, *29* (11), 875–886.

(114) Anderson, R. G.; Jett, B. M.; McNally, A. A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angew. Chemie - Int. Ed.* **2018**, *57* (38), 12514–12518.

(115) Sun, W.; Fang, S.; Yan, H. Discovery of Novel Picolinamide-Based Derivatives as Novel VEGFR-2 Kinase Inhibitors: Synthesis,: In Vitro Biological Evaluation and Molecular Docking. *Medchemcomm* **2018**, *9* (6), 1054–1058.

(116) Brotzel, F.; Ying, C. C.; Mayr, H. Nucleophilicities of Primary and Secondary Amines in Water. *J. Org. Chem.* **2007**, *72* (10), 3679–3688.

(117) Kumara, M. N.; Nakahara, T.; Kobayashi, S.; Fujio, M.; Mishima, M. Nucleophilicities of Alcohols and Water in Acetonitrile Based on Reactivities of Benzhydrylium Ions. *Bull. Chem. Soc. Jpn.* **2018**, *91* (4), 523–530.

(118) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. Nucleophilic Reactivities of Primary and Secondary Amines in Acetonitrile. *European J. Org. Chem.* **2009**, *2009* (36), 6379–6385.

(119) Wall, P. E. *Thin-Layer Chromatography: A Modern Practical Approach*; The Royal Society of Chemistry: Cambridge, England, 2005.

(120) Tan, B.; Melius, P.; Ziegler, P. Simple Gas Chromatographic Method for the Study of Organic Solvents: Moisture Analysis, Hygroscopicity, and Evaporation. *J. Chromatogr. Sci.* **1982**, *20* (5), 213–217.

(121) Talbot, R. J. E. The Hydrolysis of Carboxylic Acid Derivatives. In *Comprehensive Chemical Kinetics (Vol.10)*; Bamford, C.H., Tipper, C. F. H., Ed.; Elsevier B.V.: Amsterdam, ND, 1972; pp 209–293.

(122) Kaplan, M. Reactivity of Isocyanates in Terms of the Hammett Equation: Meta- and Para-Substituted Phenyl Isocyanates. *J. Chem. Eng. Data* **1961**, *6* (2), 272–275.

(123) Uneyama, K. Fundamentals in Organic Fluorine Chemistry. In *Organofluorine Chemistry*; Blackwell Publishing: Oxford, UK, 2006; pp 1–100.

(124) Martin, R. B. Nucleophilicities of Metal Ion Bound Hydroxide. *J. Inorg. Nucl. Chem.* **1976**, *38* (3), 511–513.

(125) Džolić, Z. R.; Perković, I.; Pavelić, S. K.; Sedić, M.; Ilić, N.; Schols, D.; Zorc, B. Design, Synthesis, and Cytostatic Activity of Novel Pyrazine Sorafenib Analogs. *Med. Chem. Res.* **2016**, *25* (12), 2729–2741.

(126) Gathirwa, J. W.; Maki, T. Benzylation of Hydroxy Groups with Tertiary Amine as a Base. *Tetrahedron* **2012**, *68* (1), 370–375.

(127) Ibanez, P. S. 2. Final Report on the Safety Assessment of p-Aminophenol, m-Aminophenol, and o-Aminophenol. *J. Am. Coll. Toxicol.* **1988**, *7* (3), 279–333.

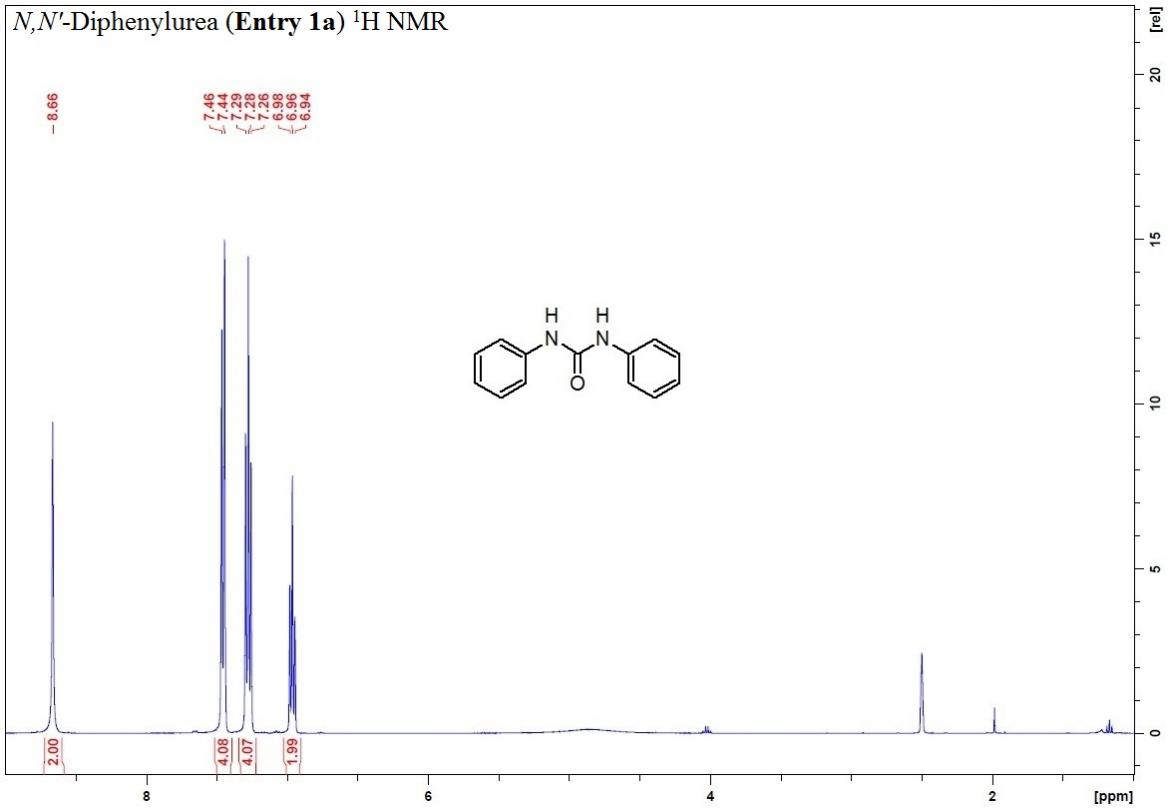
(128) Khandavilli, U. B. R.; Keshavarz, L.; Skořepová, E.; Steendam, R. R. E.; Frawley, P. J. Organic Salts of Pharmaceutical Impurity P-Aminophenol. *Molecules* **2020**, *25* (8), 1–10.

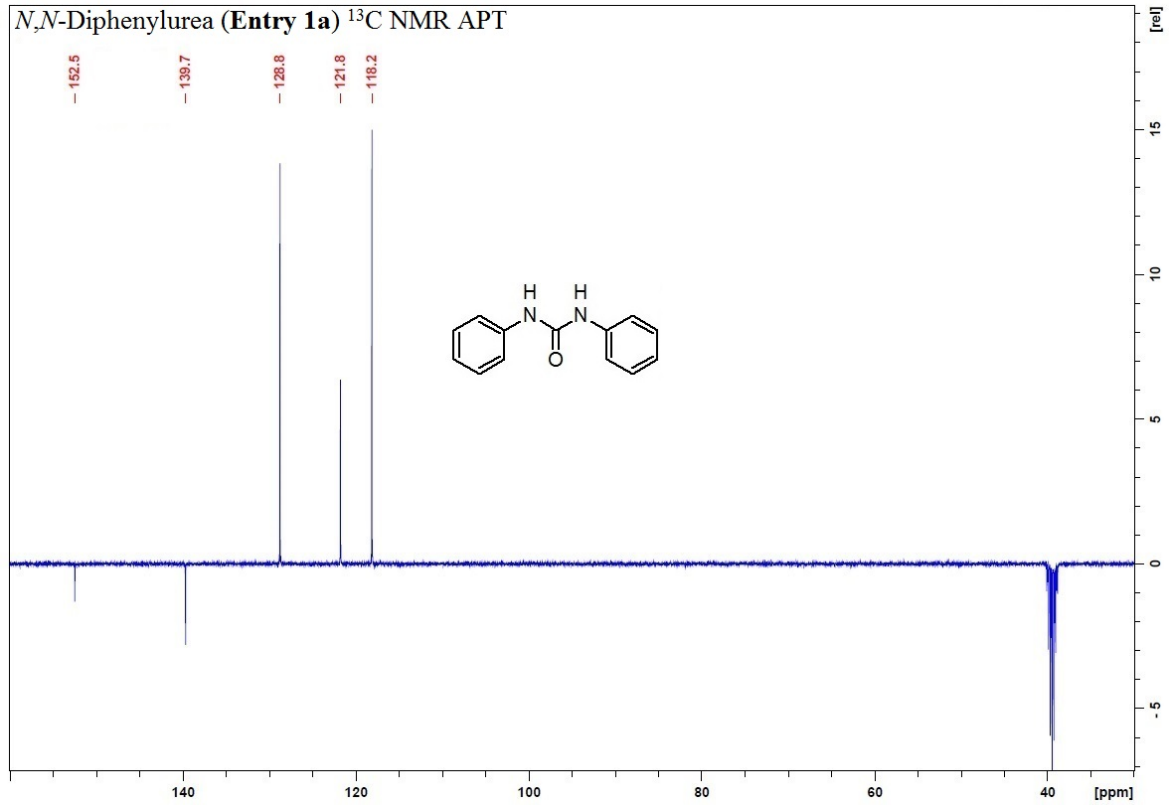
(129) Mitchell, S. C.; Carmichael, P.; Waring, R. Aminophenols. *Kirk-Othmer Encyclopedia of Chemical Technology - Volume 2*; John Wiley & Sons, Inc., 2004; pp 652–678.

(130) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev.* **2016**, *20* (2), 140–177.

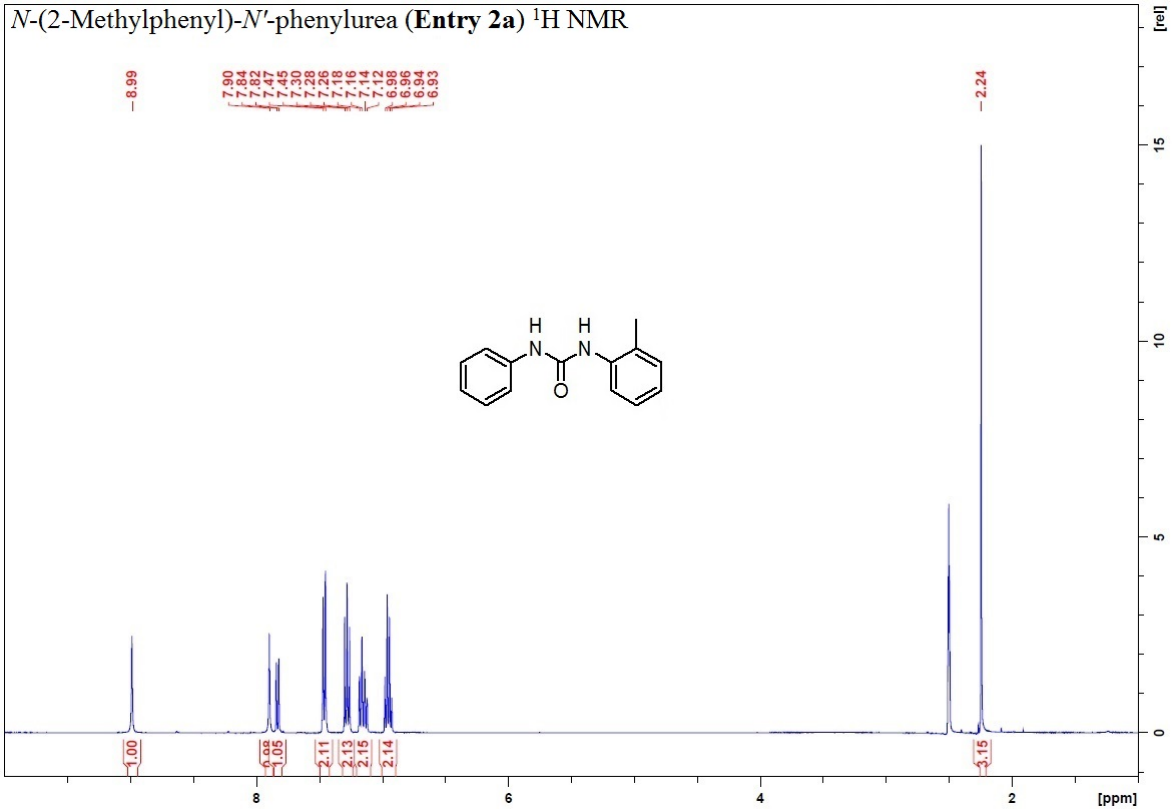
(131) Ito, T.; Ikemoto, T.; Isogami, Y.; Wada, H.; Sera, M.; Mizuno, Y.; Wakimasu, M. Practical Synthesis of Low-Density Lipoprotein Receptor Upregulator, N-[1-(3-Phenylpropane-1-Yl)Piperidin-4-Yl]-5-Thia-1,8b-Diazaacenaphthylene- 4-Carboxamide. *Org. Process Res. Dev.* **2002**, *6* (3), 238–241.

6. ^{1}H NMR AND ^{13}C NMR APT SPECTRA





N-(2-Methylphenyl)-*N'*-phenylurea (**Entry 2a**) ^{1}H NMR



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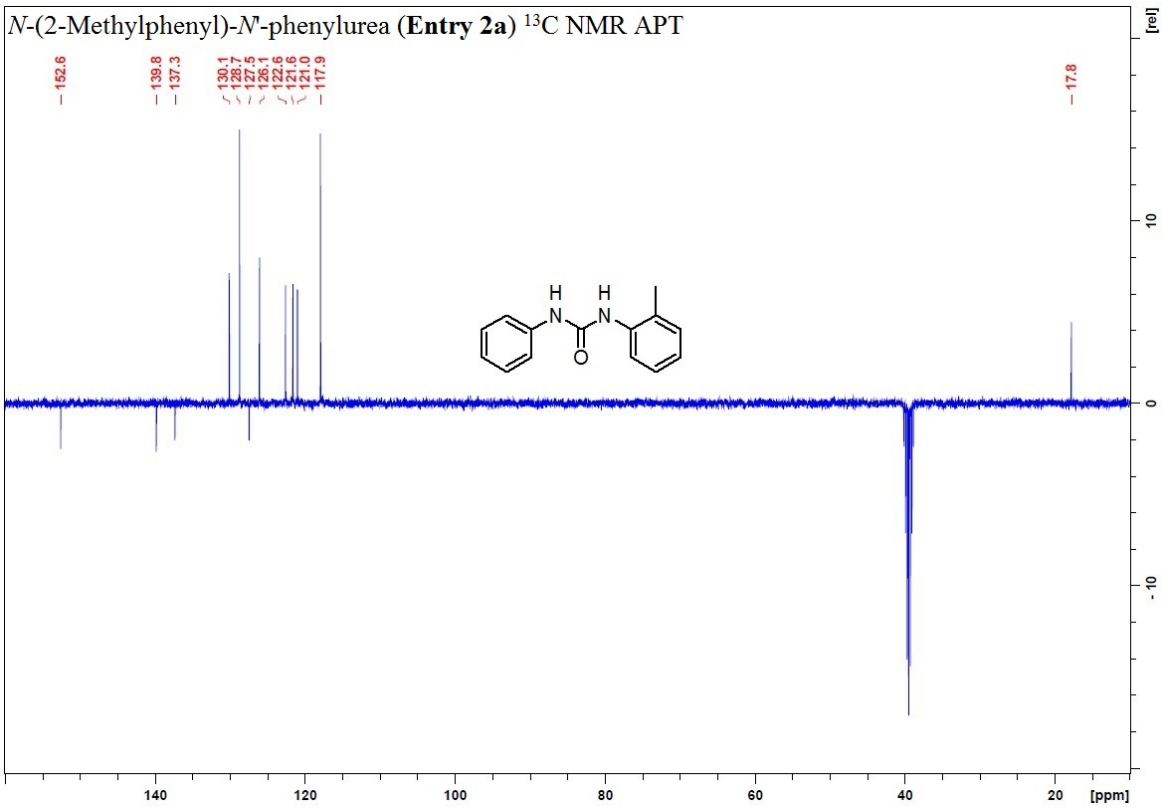

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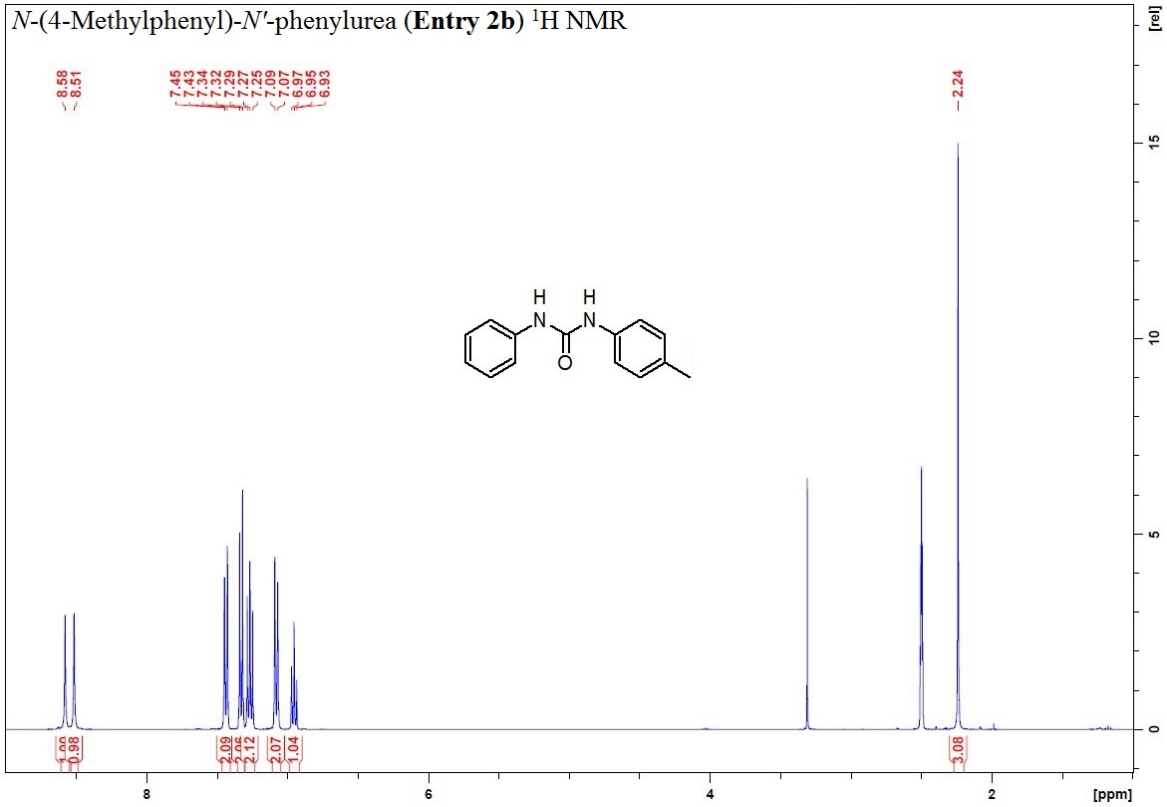

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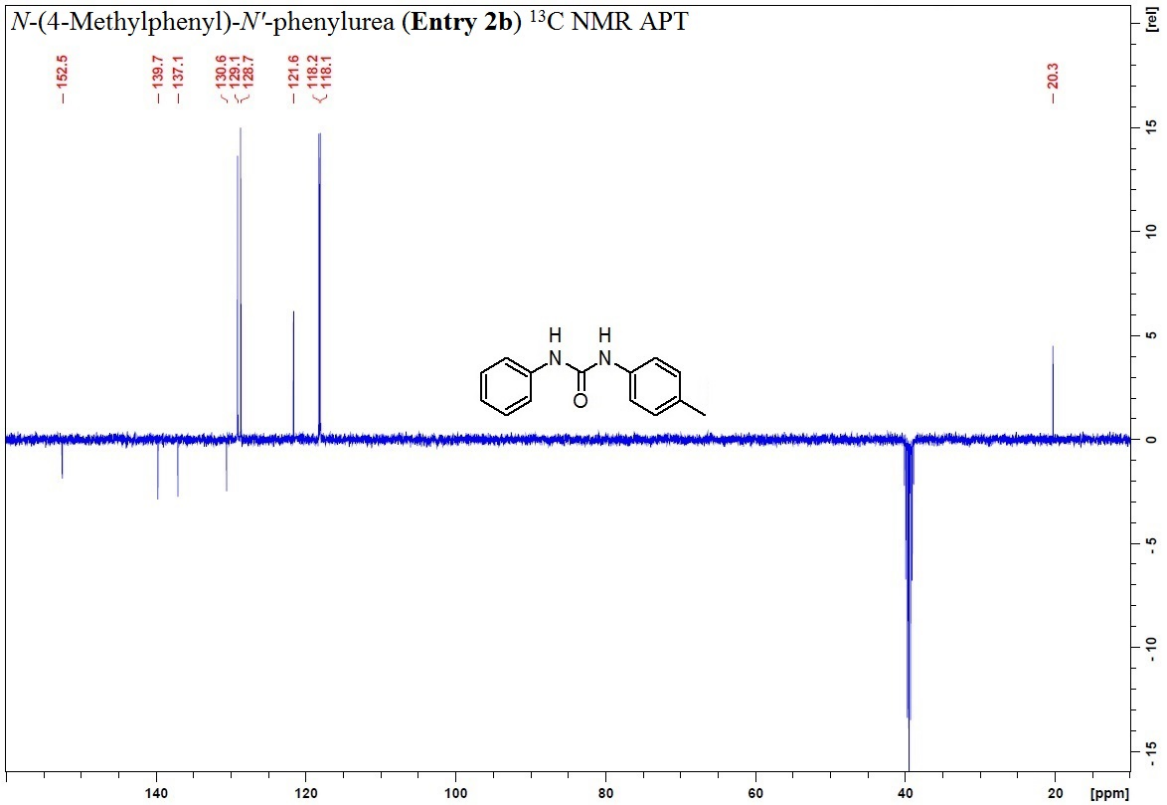

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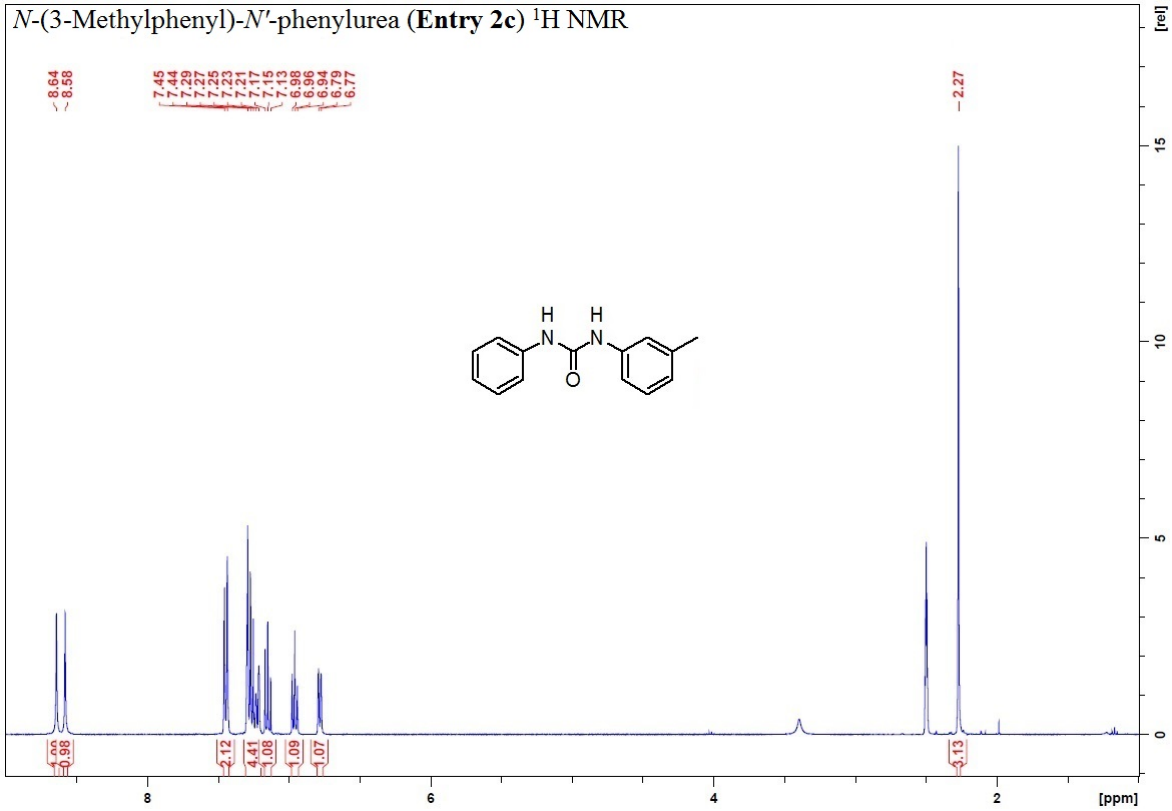

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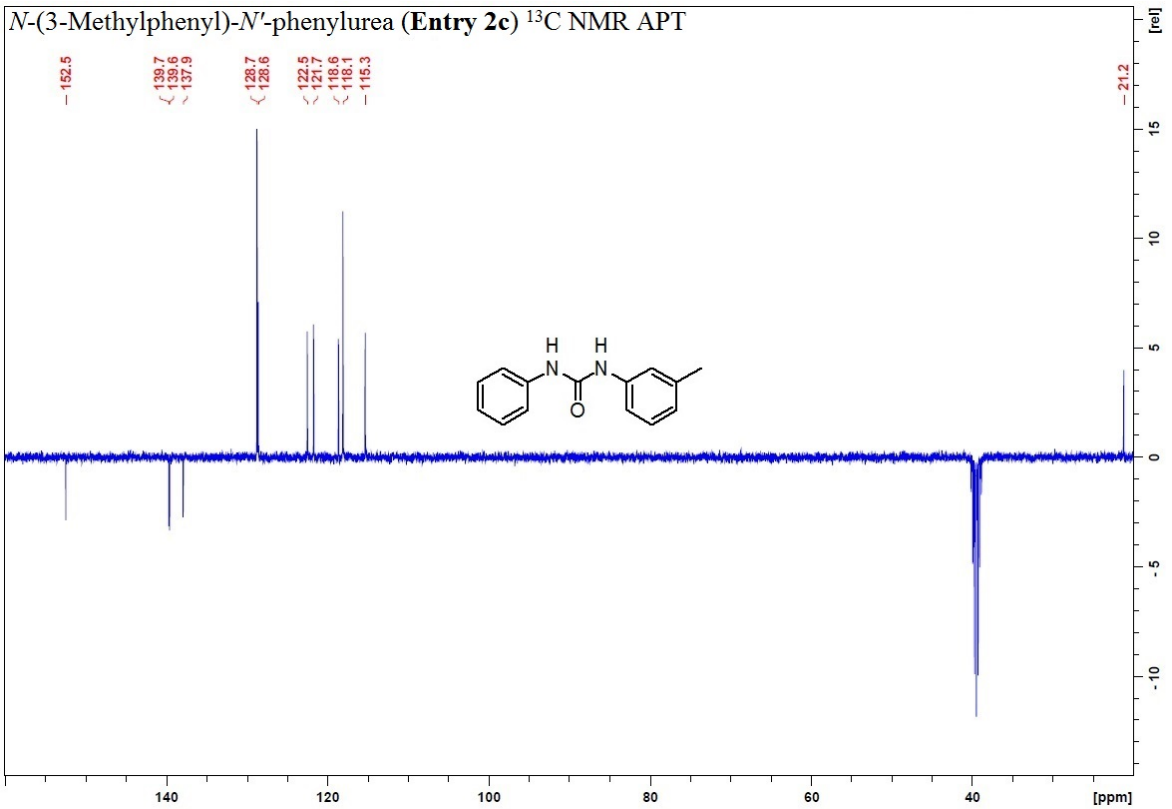

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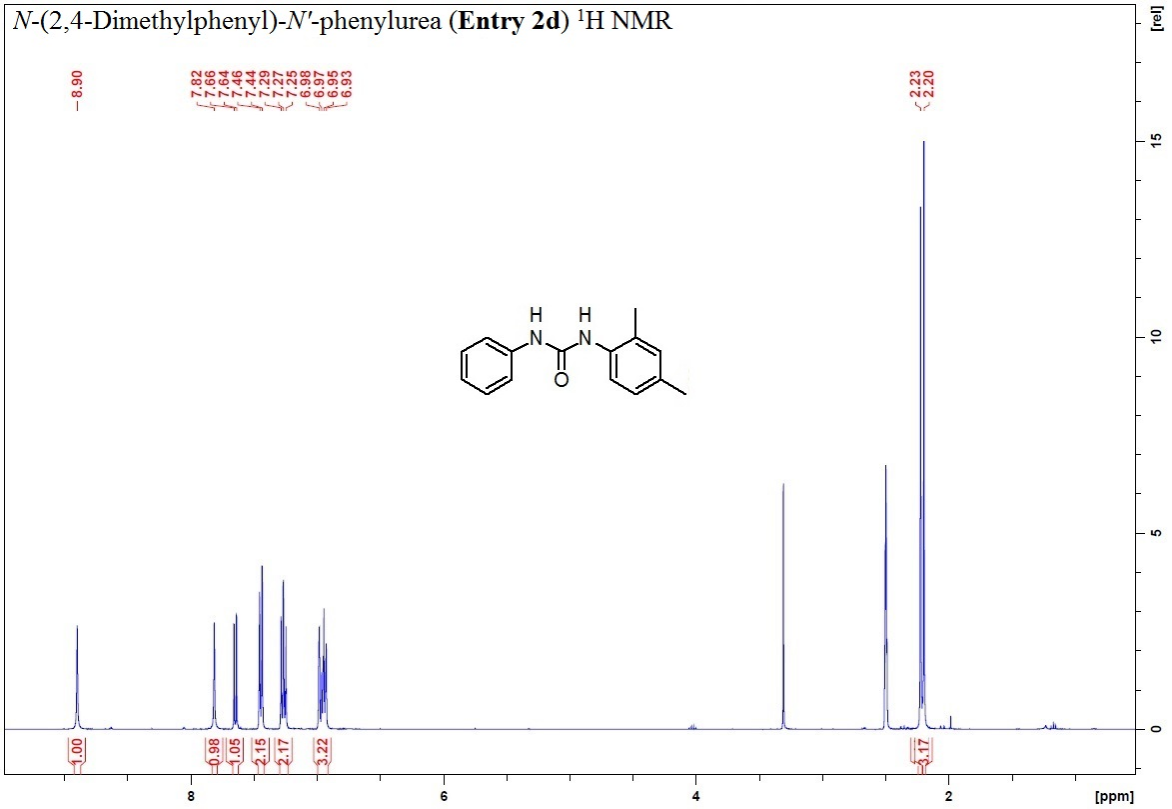

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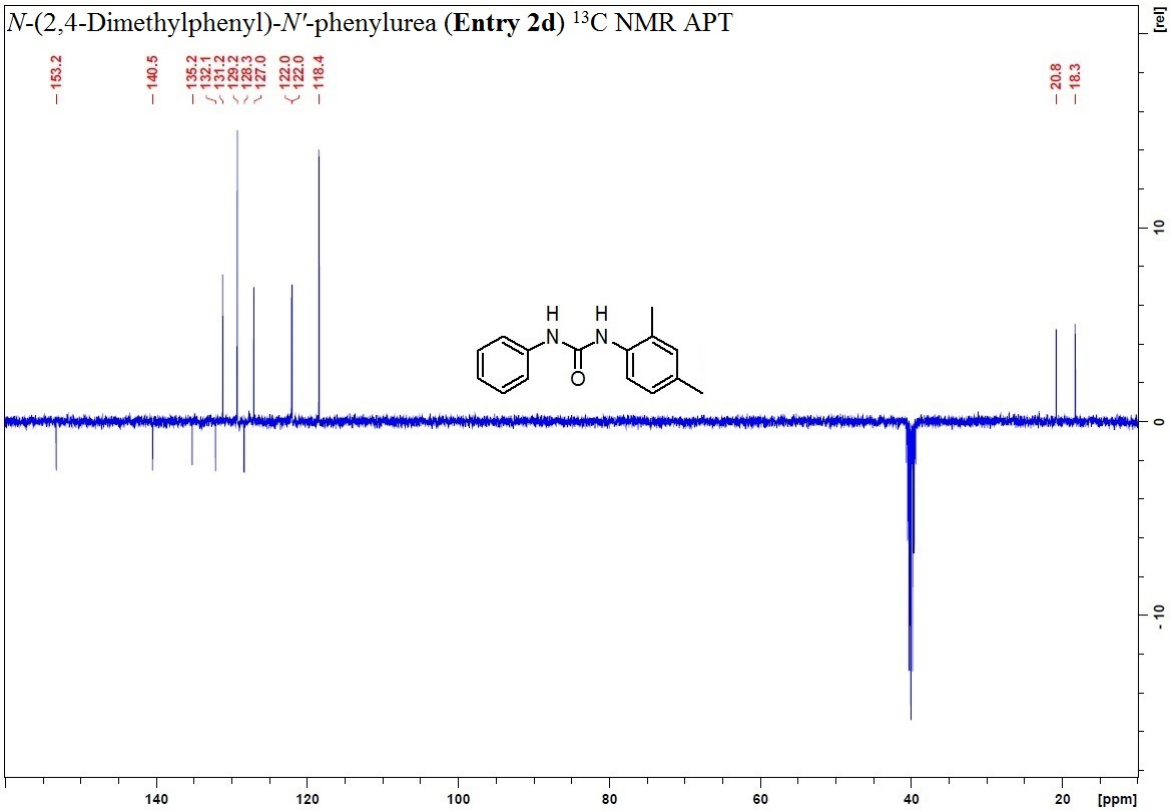

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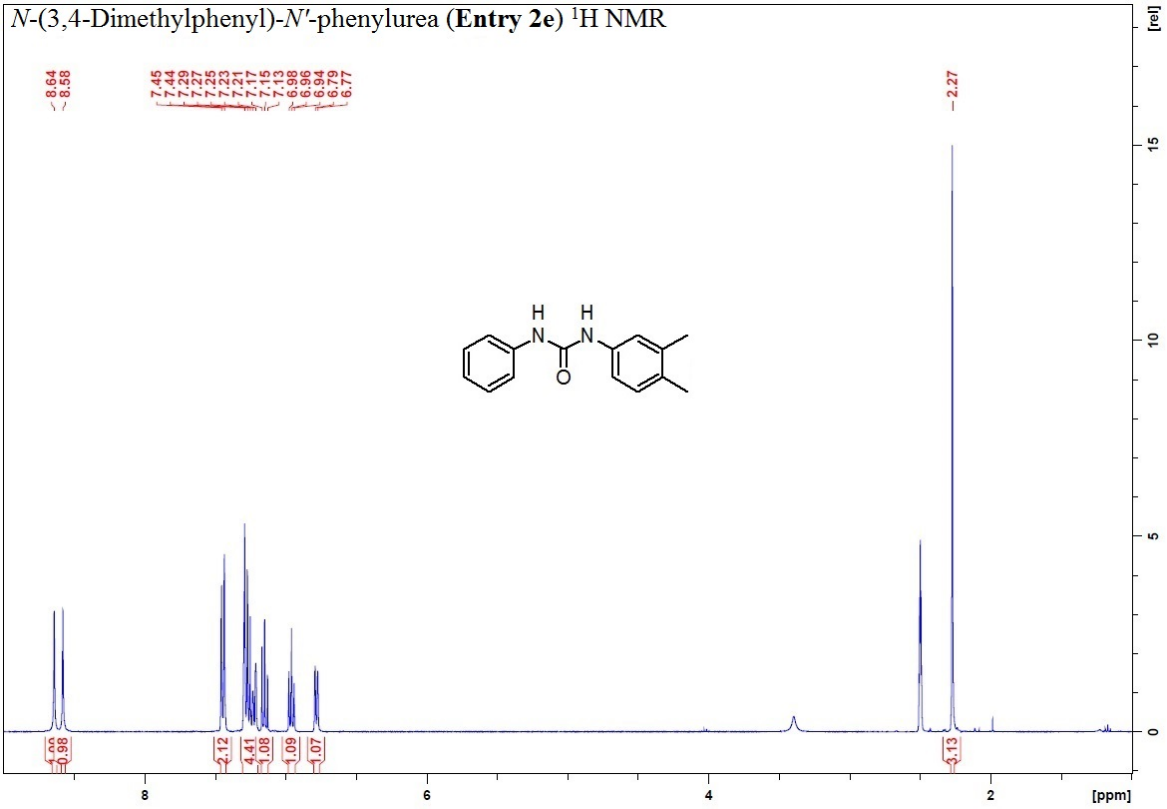

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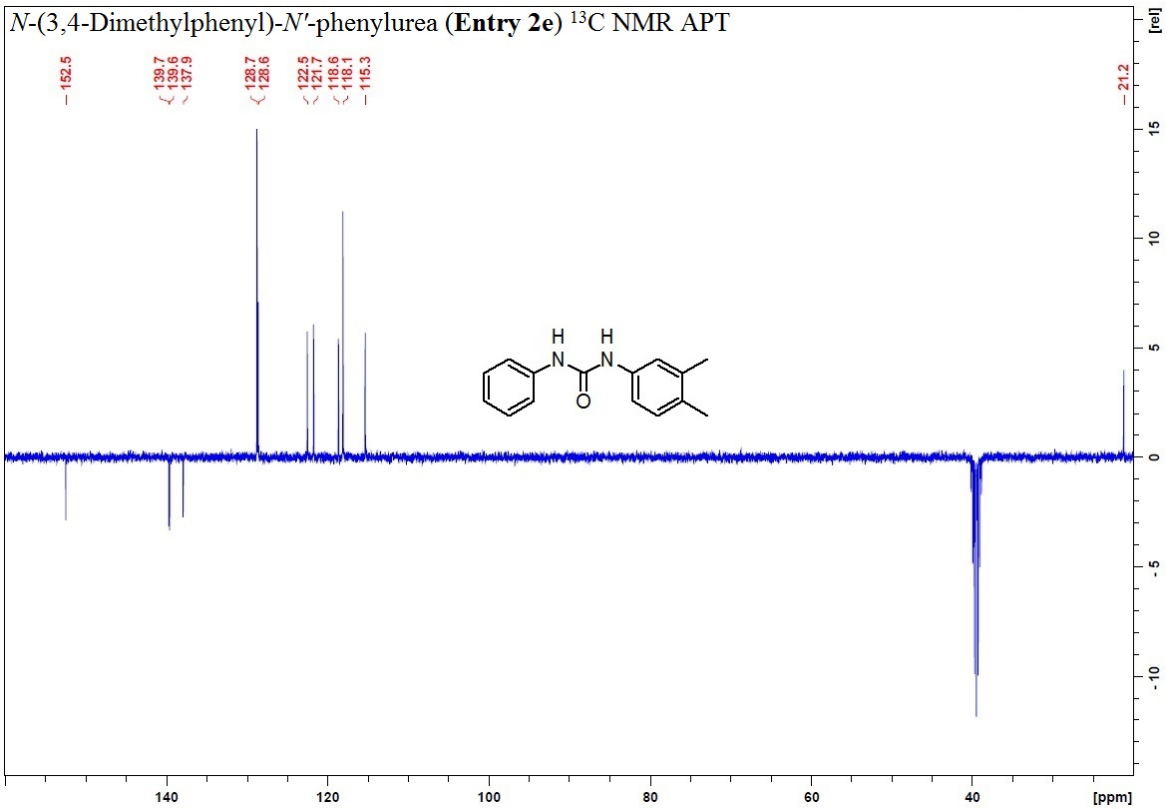

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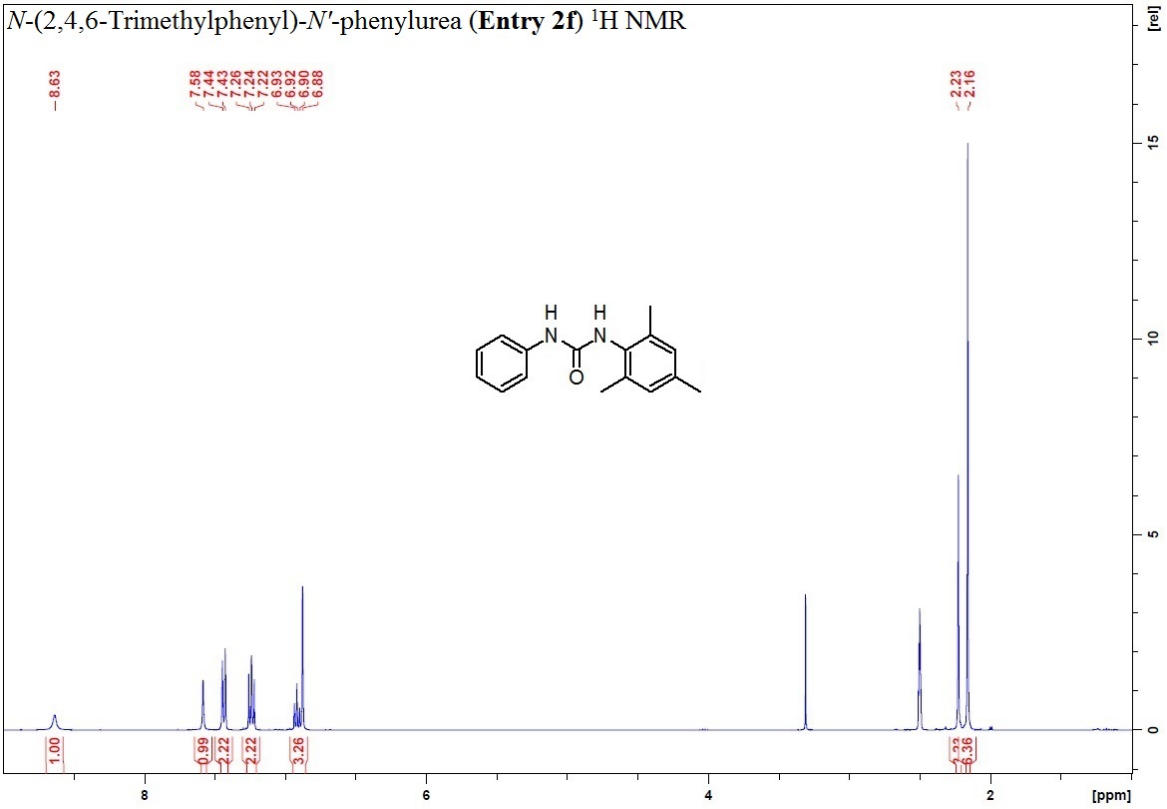

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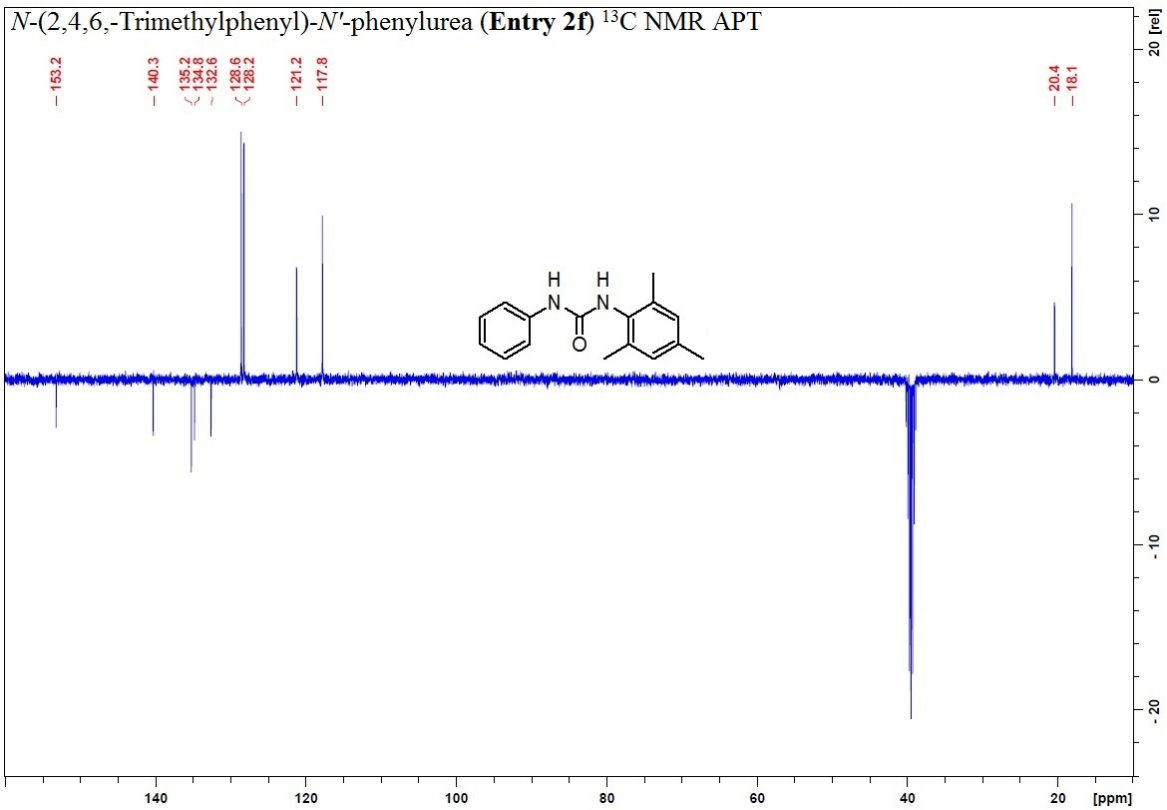

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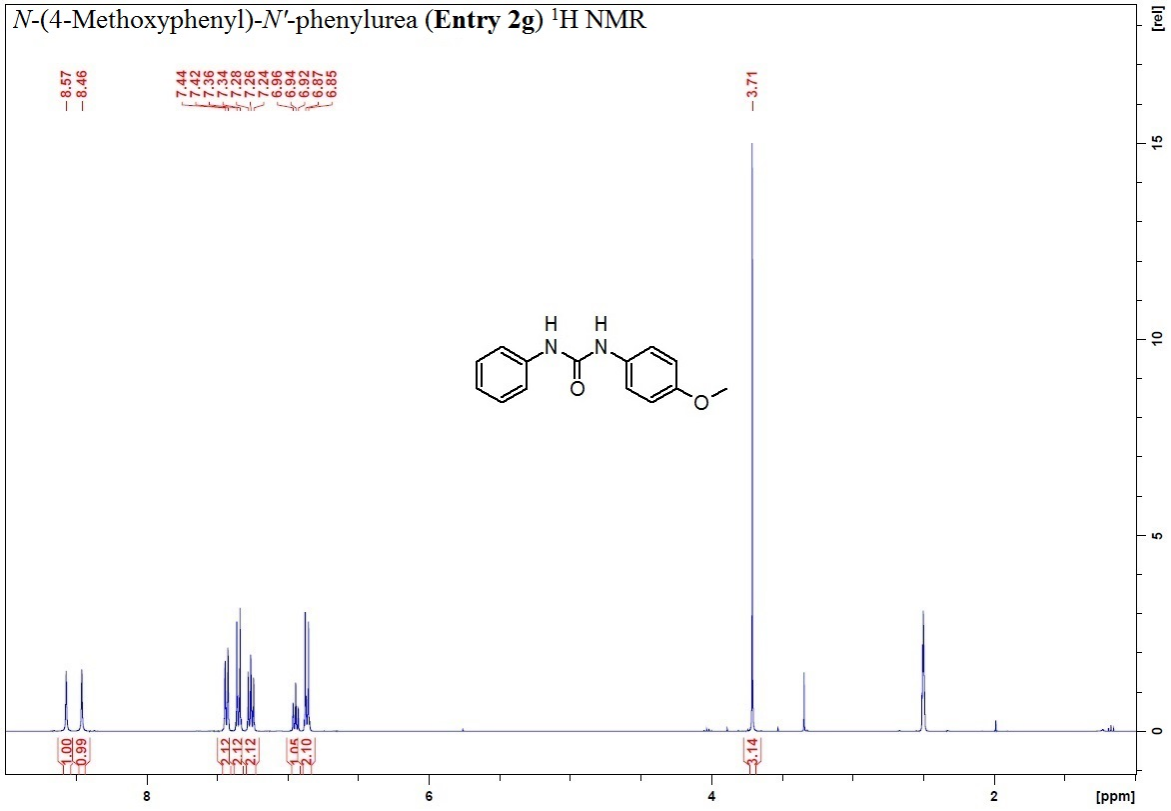

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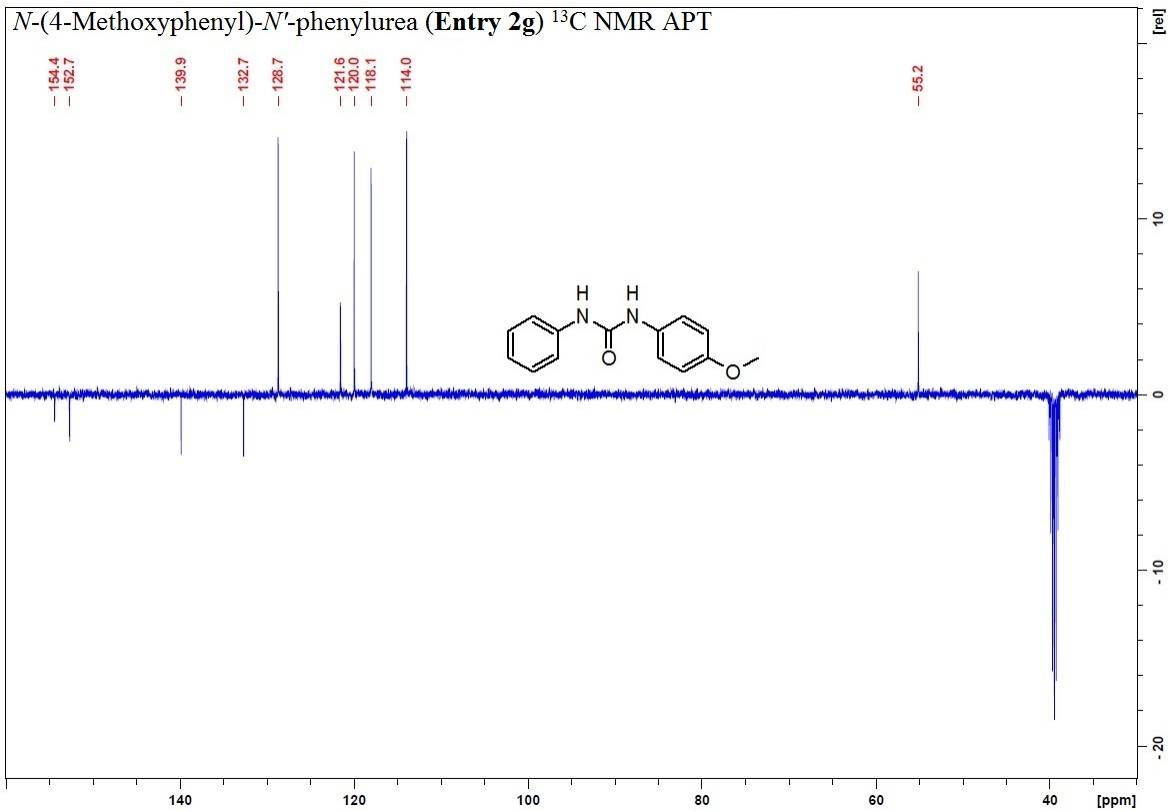

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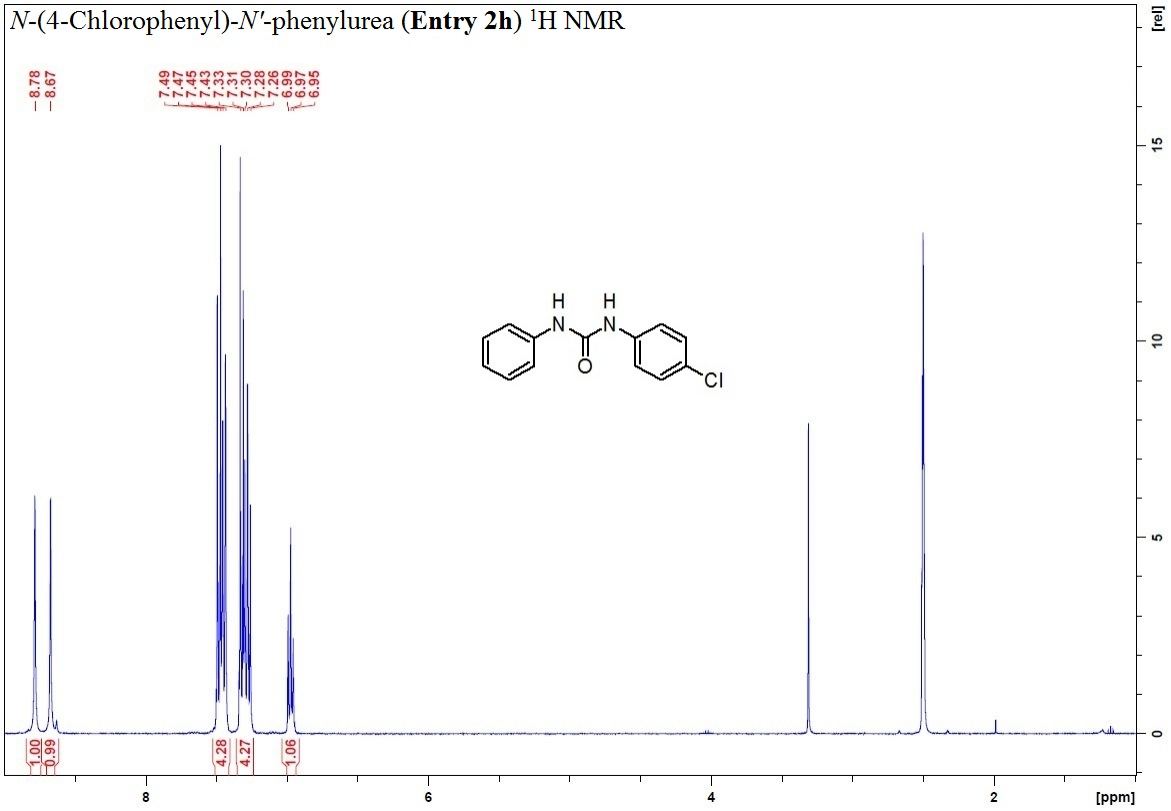

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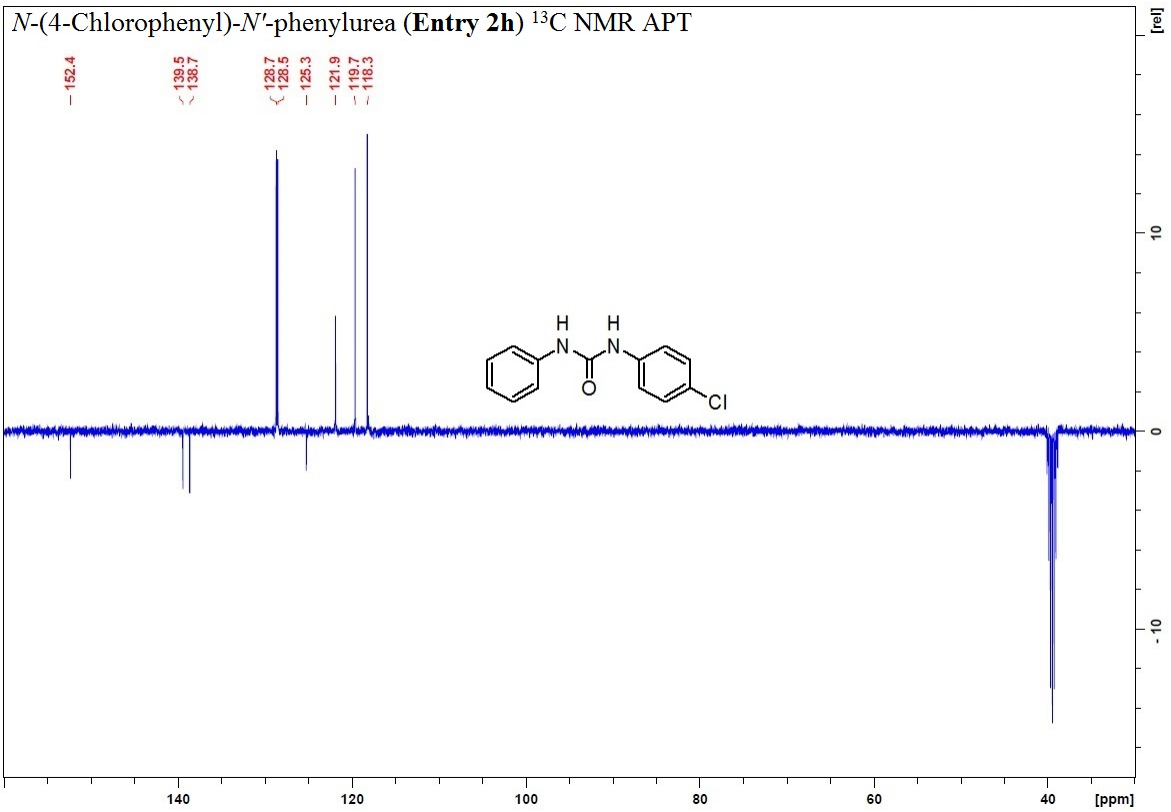
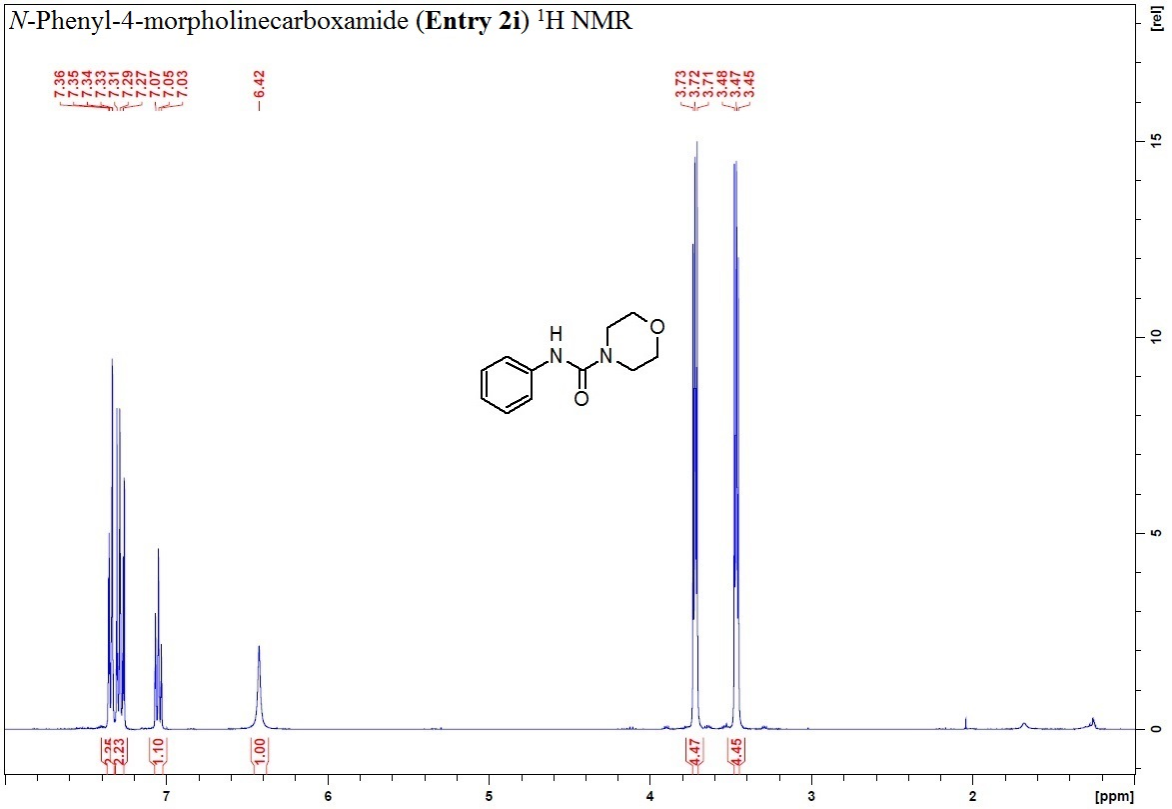


N-Phenyl-4-morpholinecarboxamide (**Entry 2i**) ^{1}H NMR



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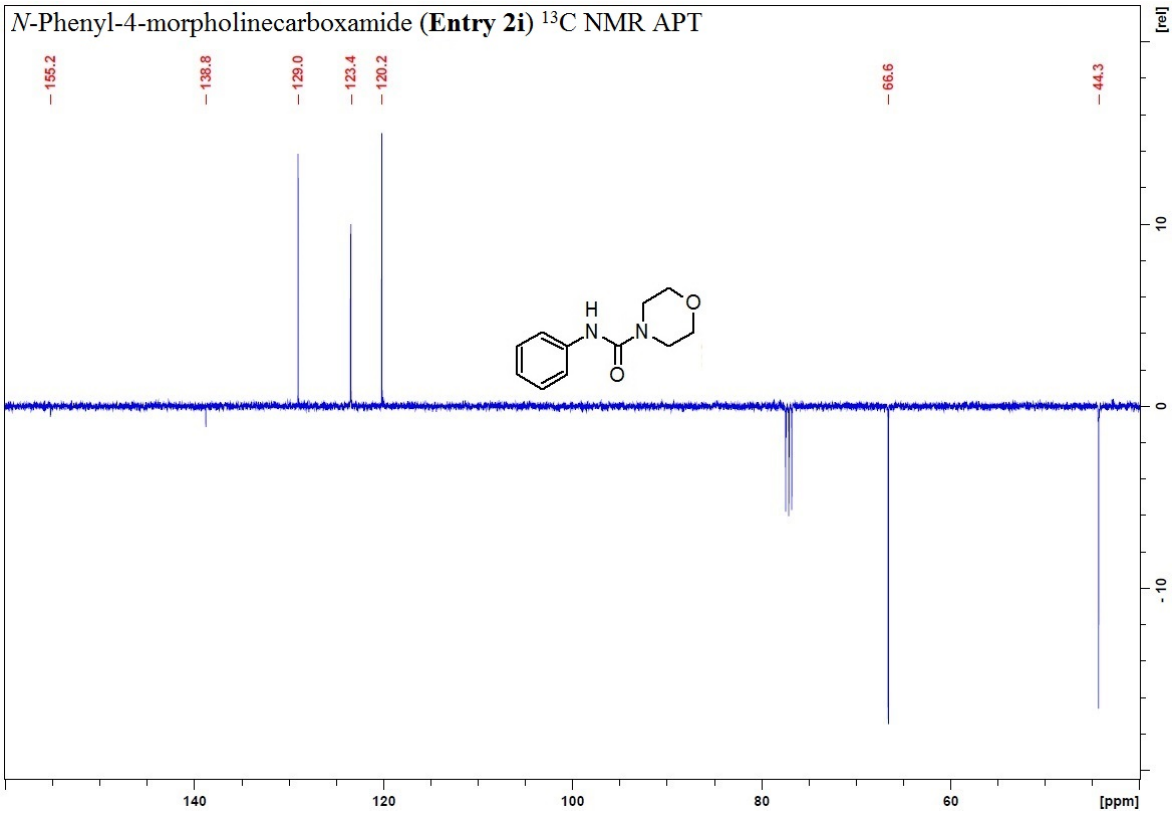
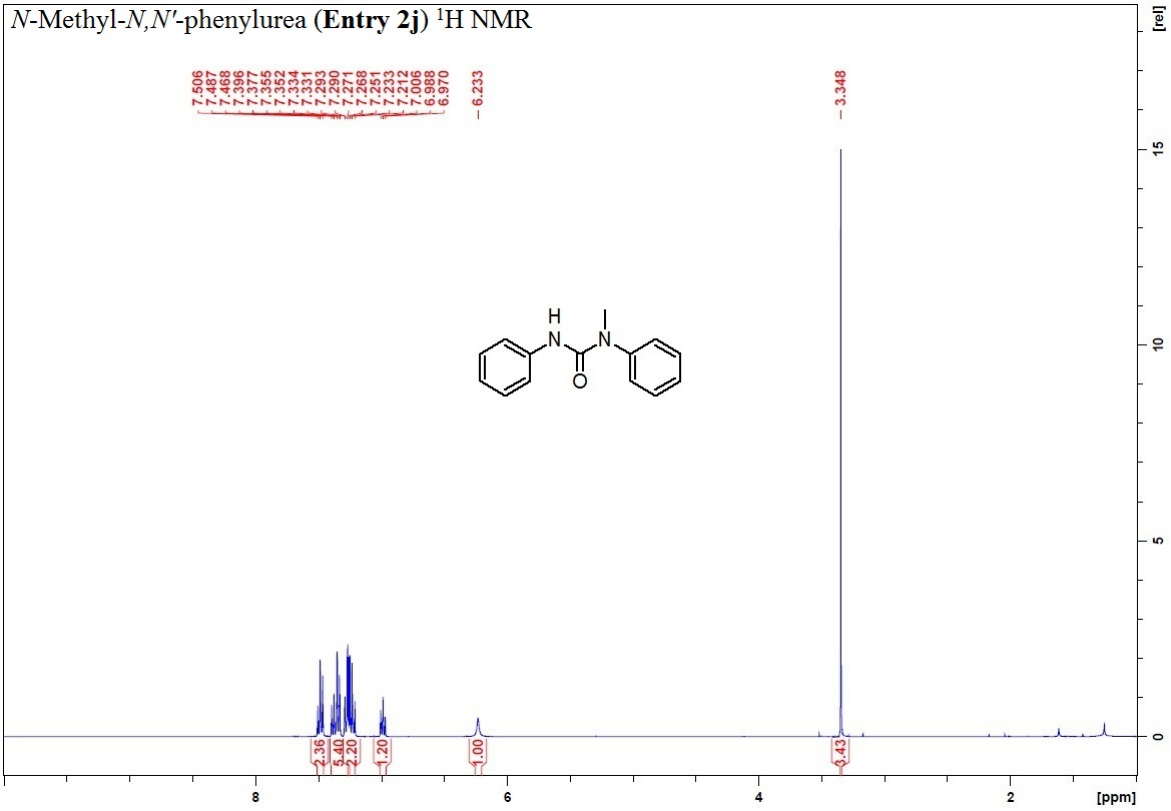
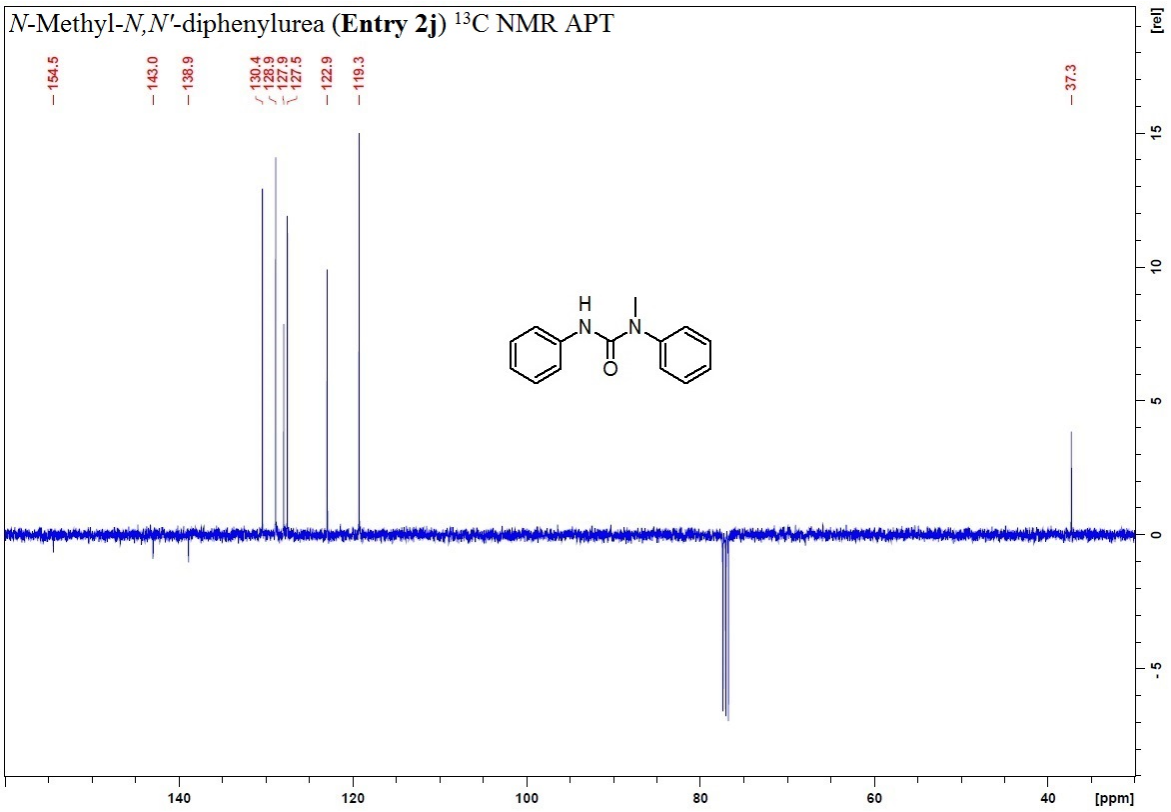


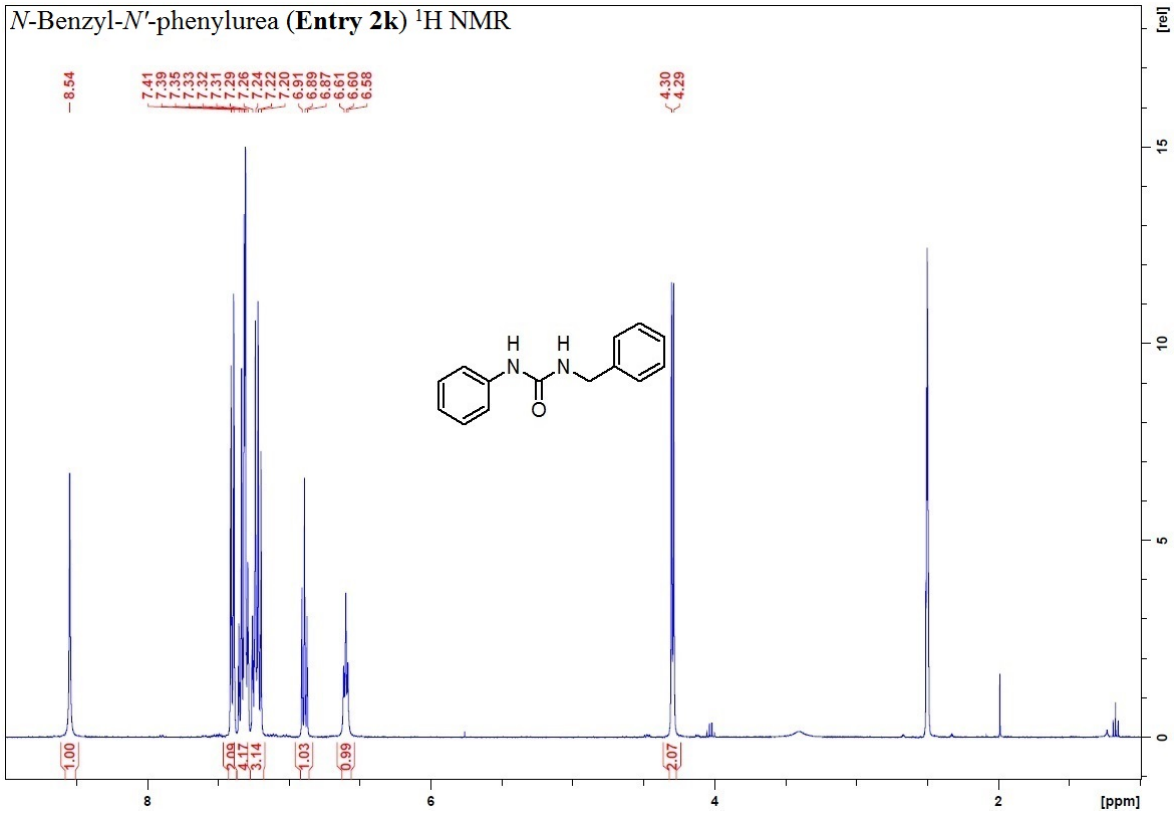
N-Methyl-*N,N'*-phenylurea (**Entry 2j**) ^{1}H NMR



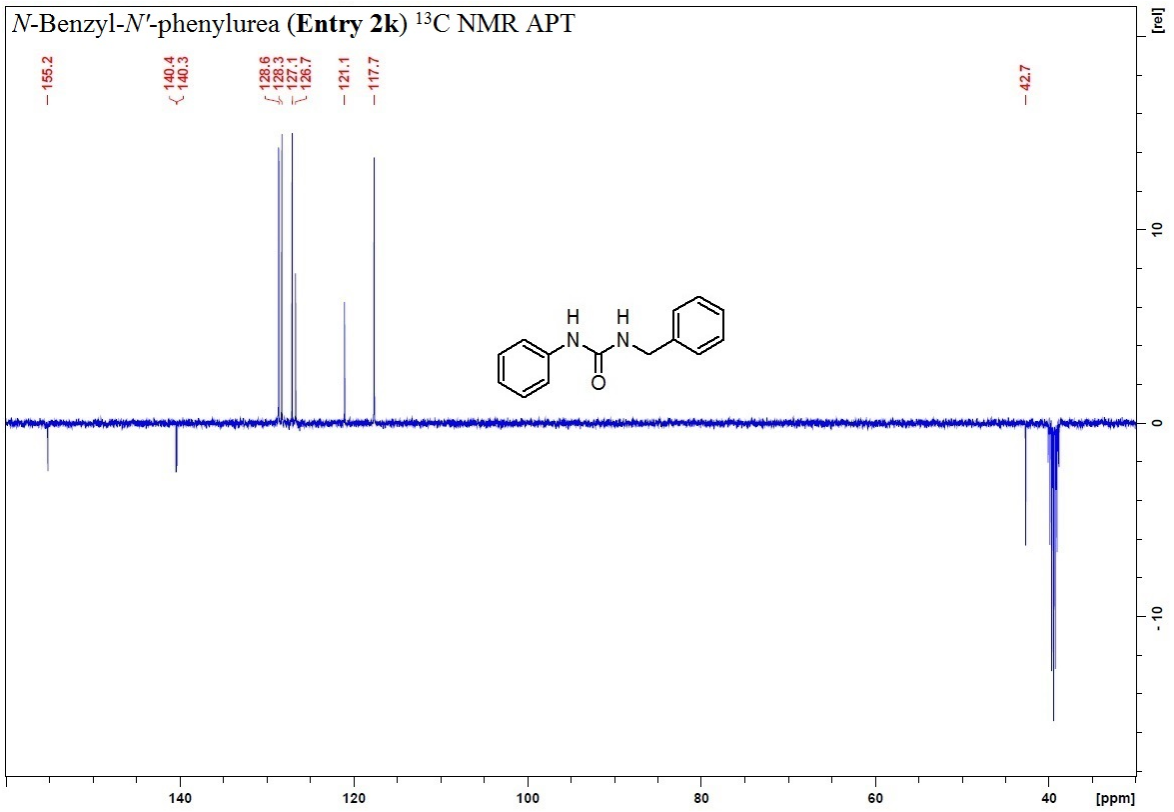
N-Methyl-*N,N'*-diphenylurea (**Entry 2j**) ^{13}C NMR APT



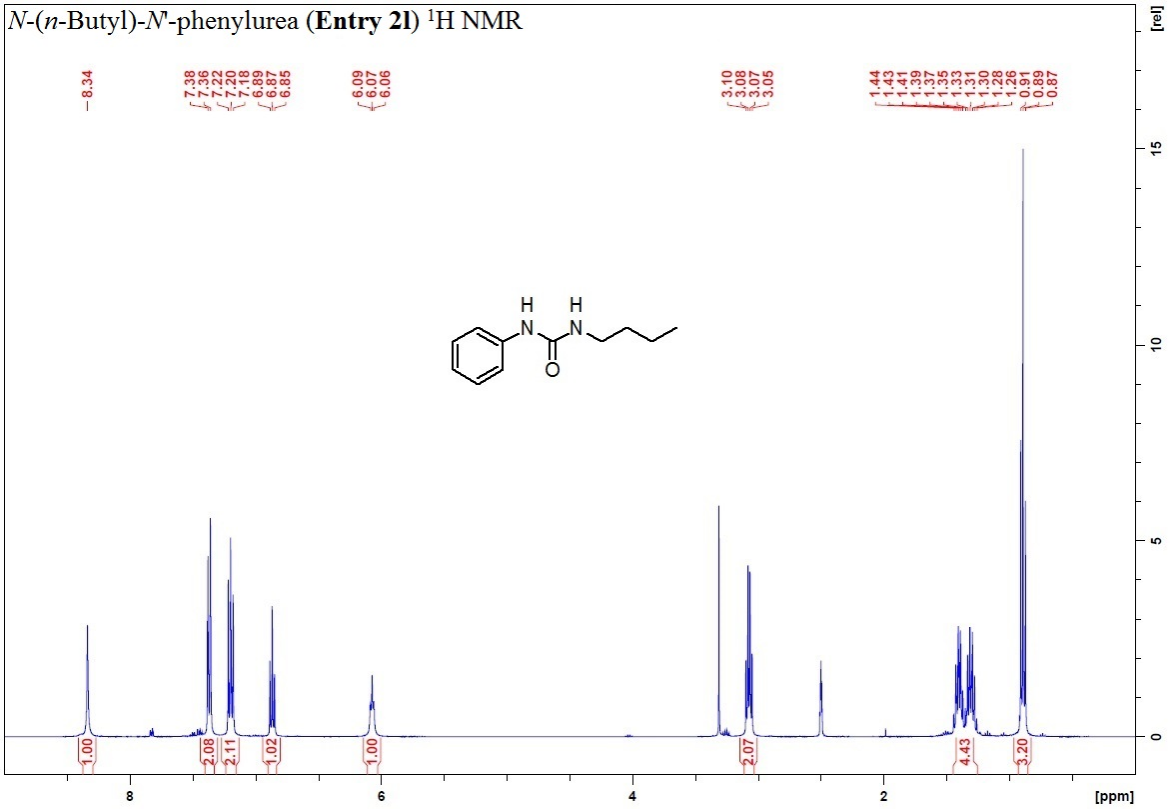
N-Benzyl-*N*′-phenylurea (**Entry 2k**) ^{1}H NMR



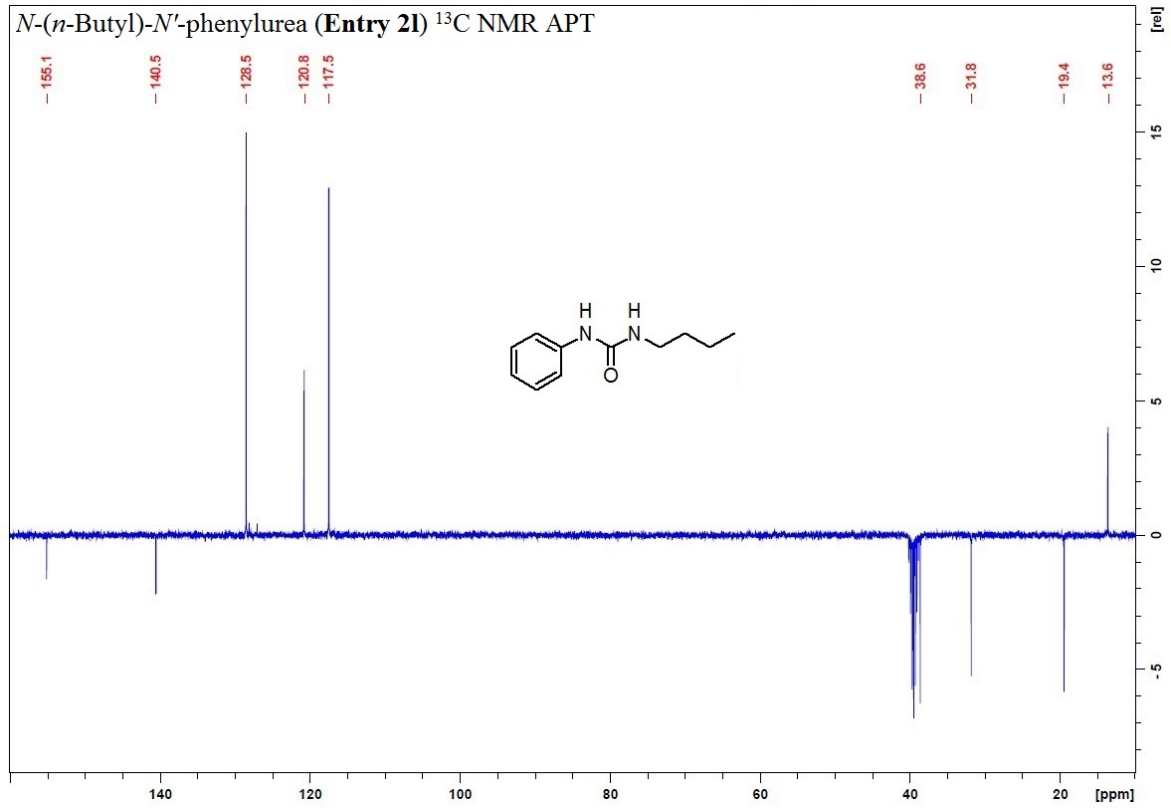
N-Benzyl-*N*′-phenylurea (**Entry 2k**) ^{13}C NMR APT



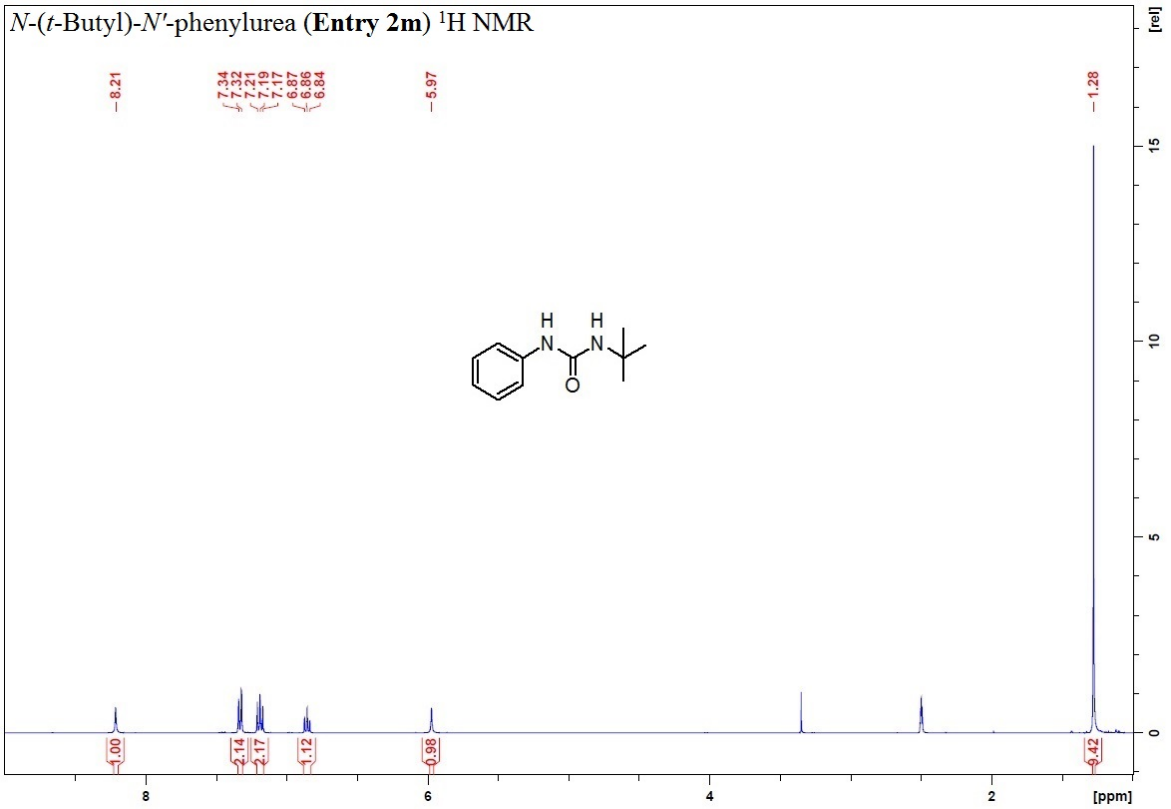
N-(*n*-Butyl)-*N*′-phenylurea (**Entry 2l**) ^{1}H NMR



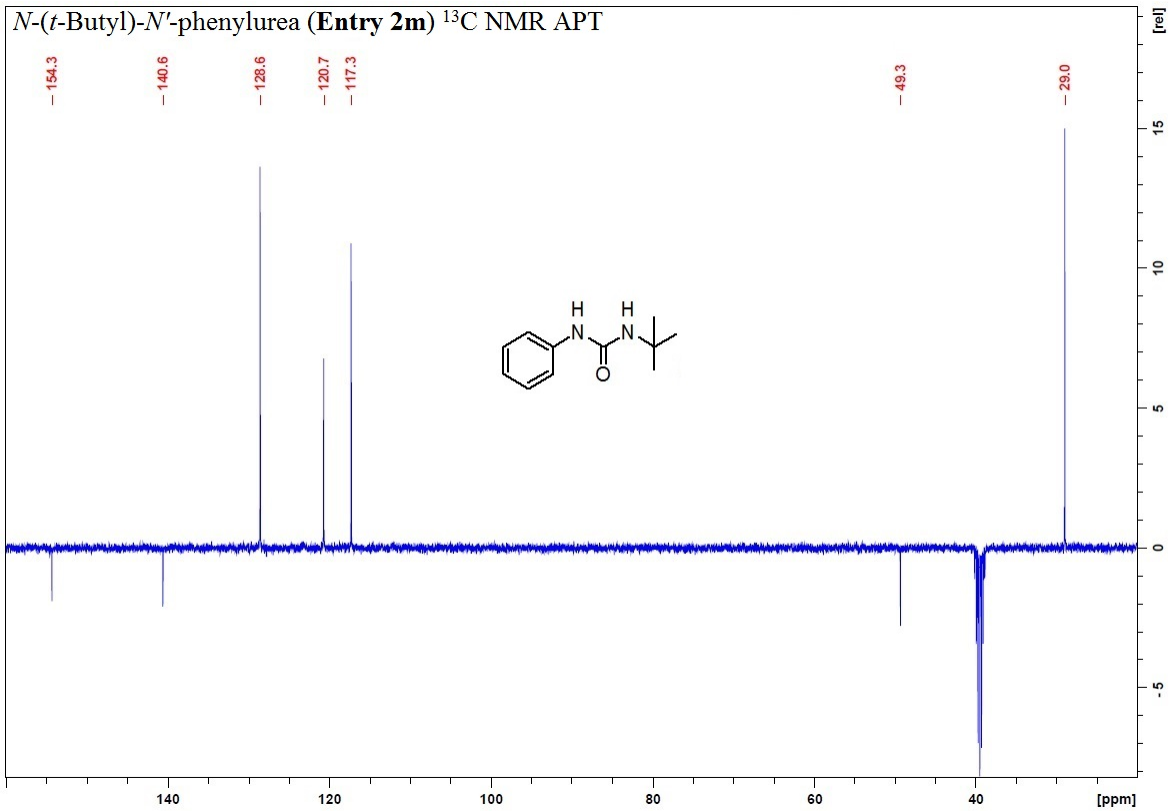
N-(*n*-Butyl)-*N*′-phenylurea (**Entry 2l**) ^{13}C NMR APT



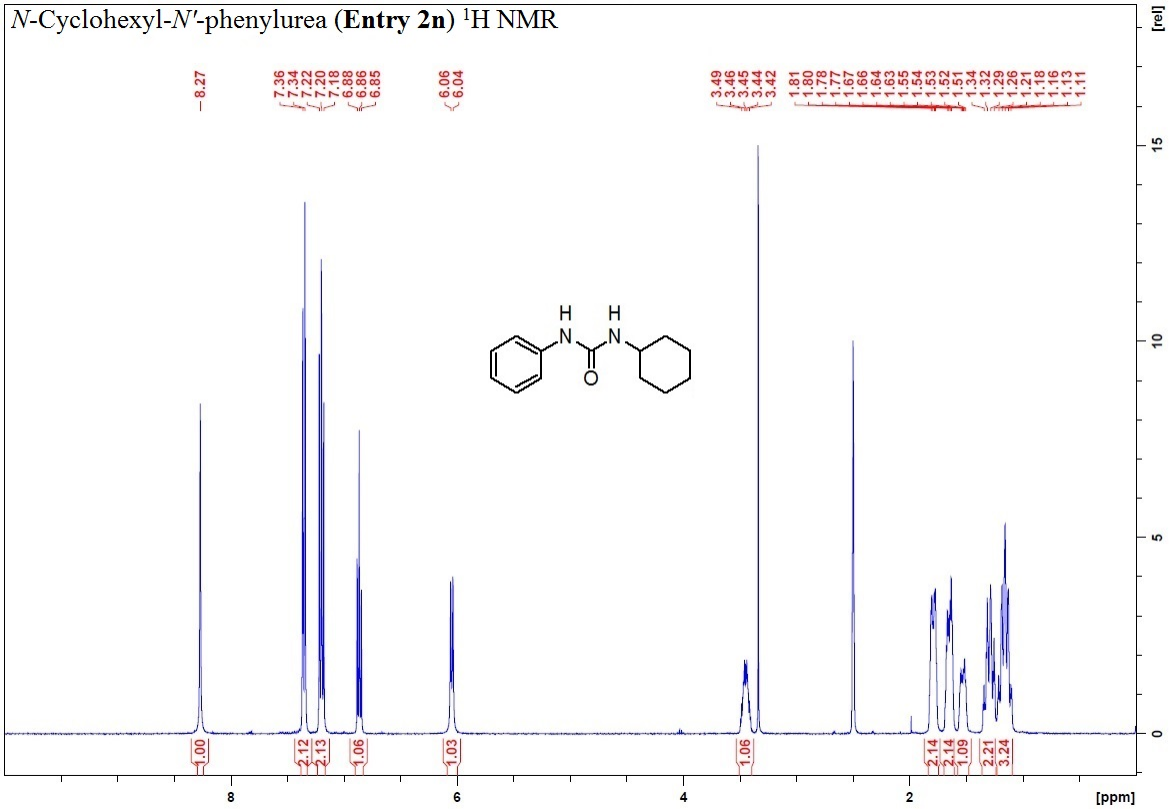
N-(*t*-Butyl)-*N*′-phenylurea (**Entry 2m**) ^{1}H NMR



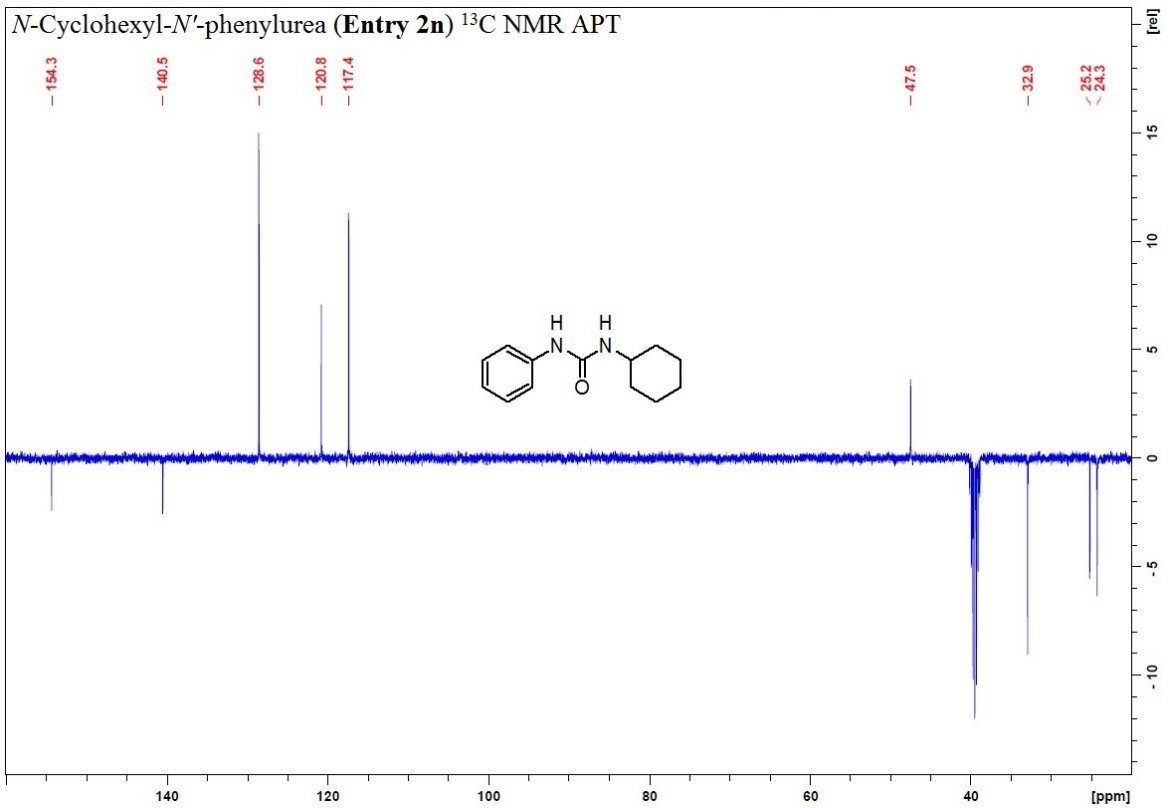
N-(*t*-Butyl)-*N*′-phenylurea (**Entry 2m**) ^{13}C NMR APT



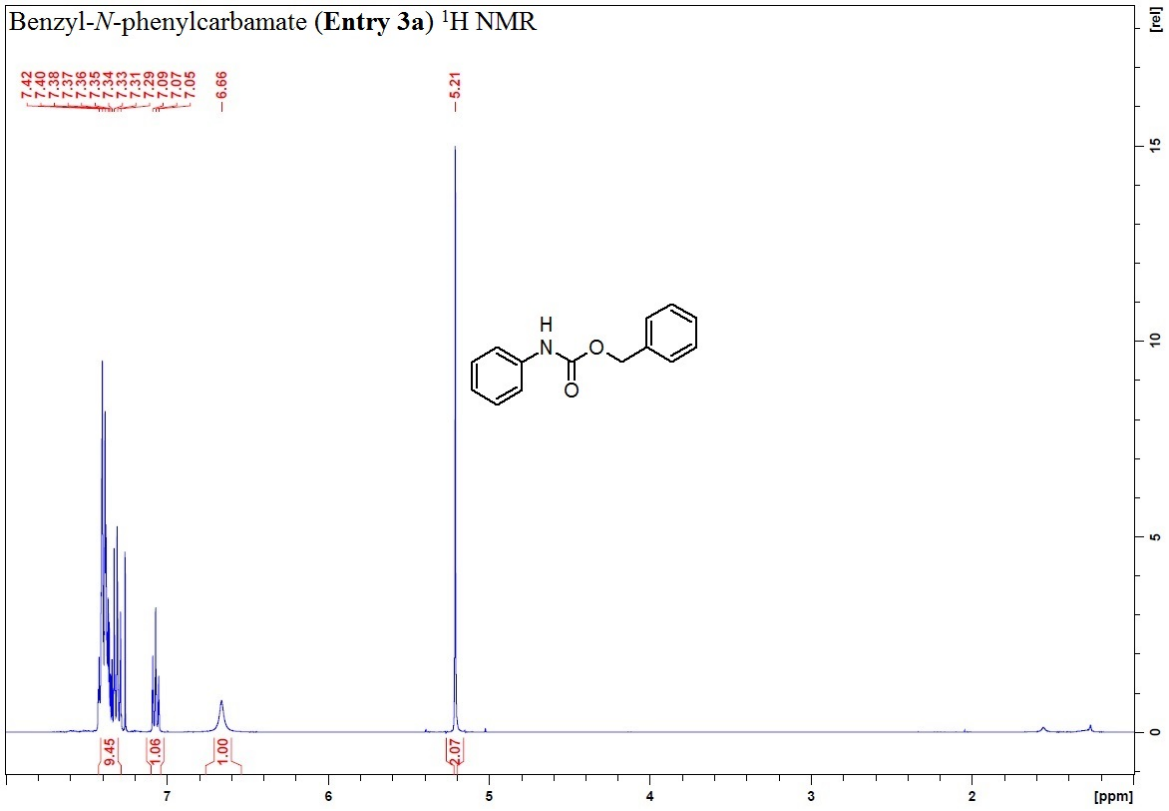
N-Cyclohexyl-*N*′-phenylurea (**Entry 2n**) ^{1}H NMR



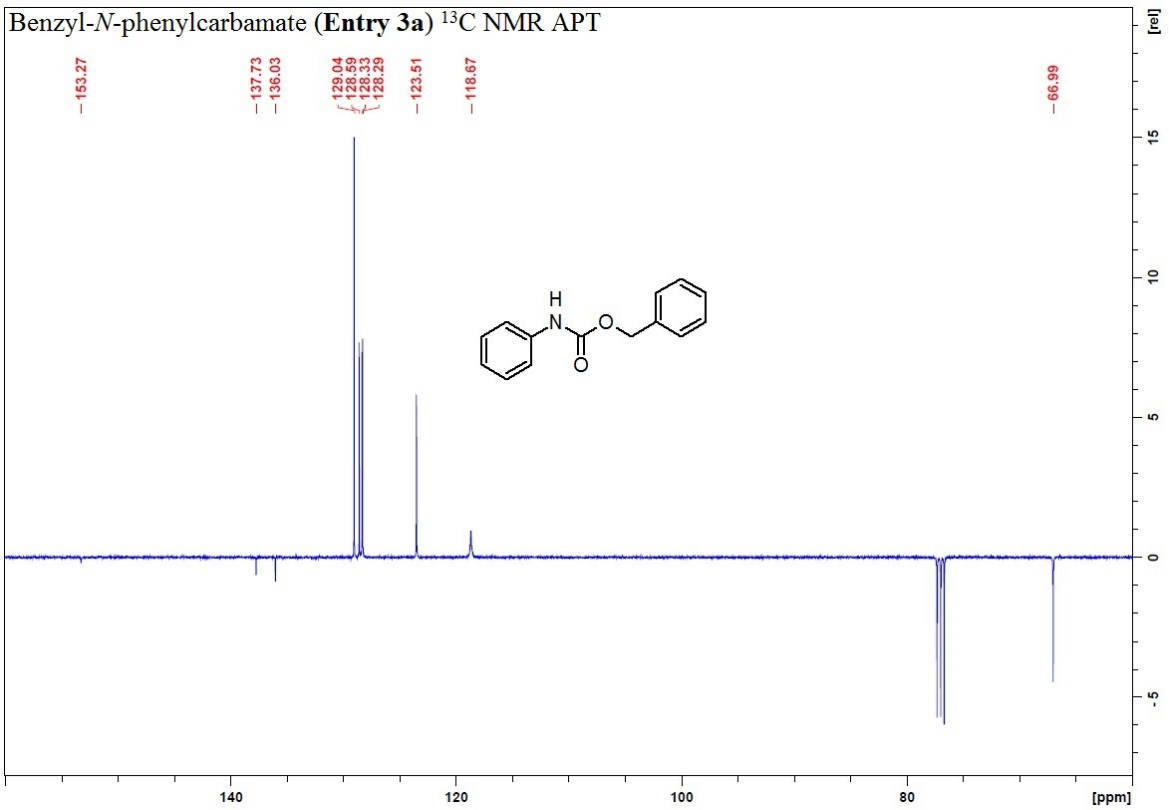
N-Cyclohexyl-*N*′-phenylurea (**Entry 2n**) ^{13}C NMR APT



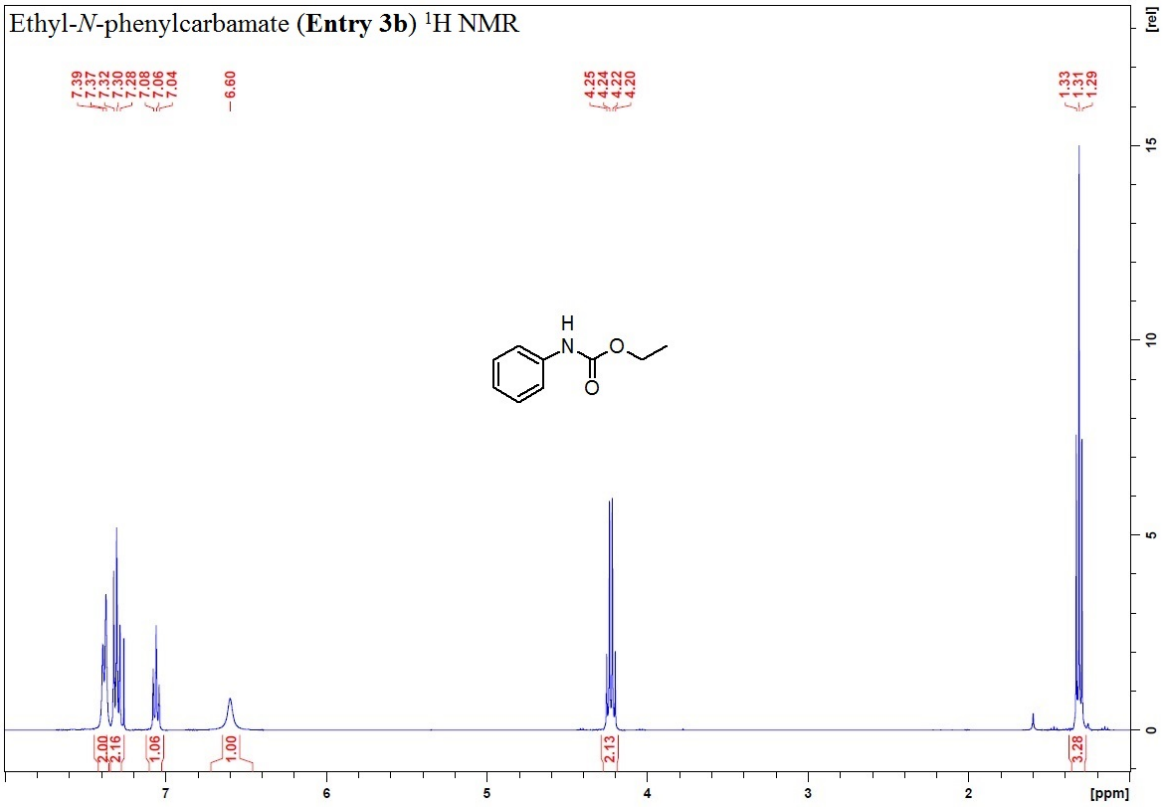
Benzyl-*N*-phenylcarbamate (**Entry 3a**) ^{1}H NMR



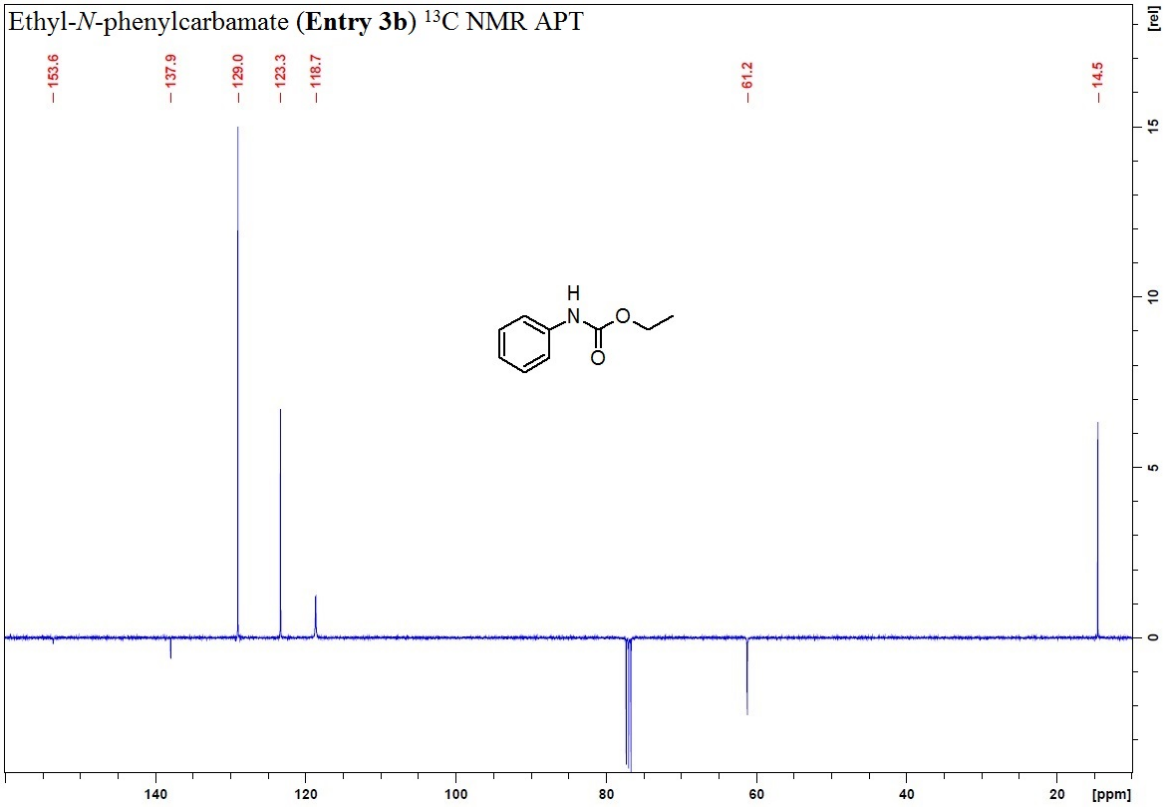
Benzyl-*N*-phenylcarbamate (**Entry 3a**) ^{13}C NMR APT



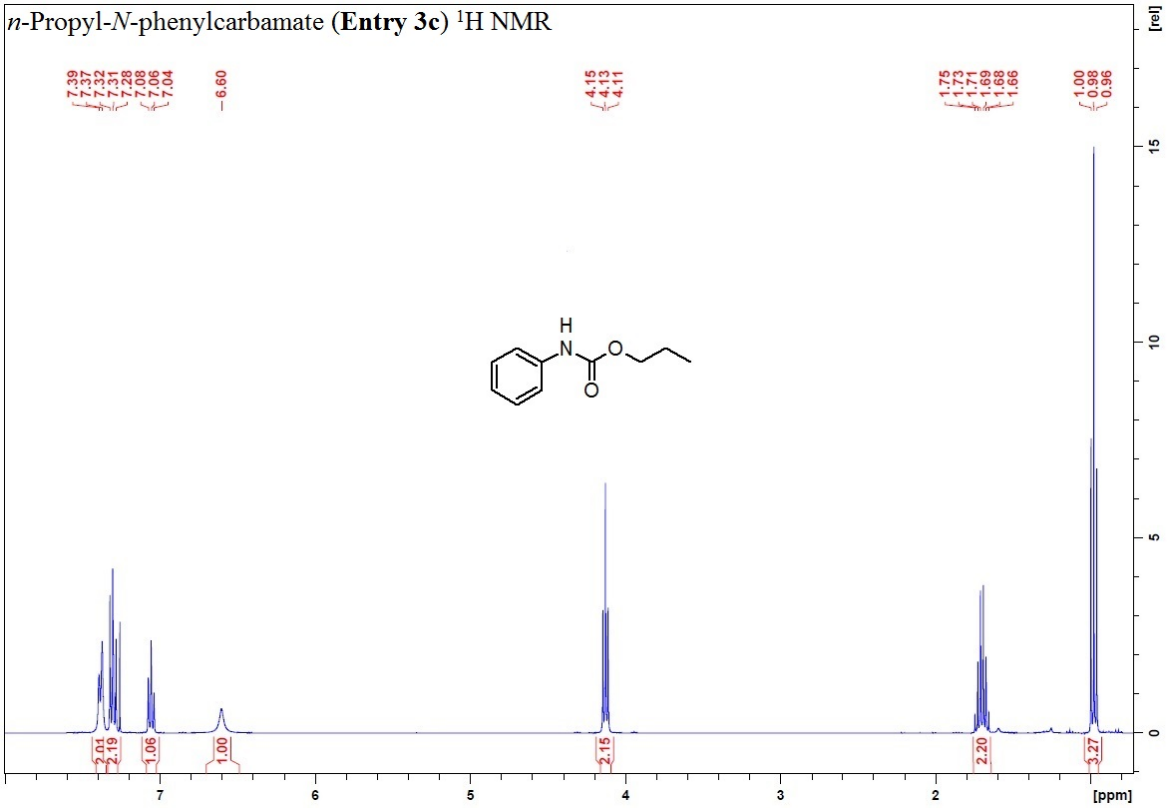
Ethyl-*N*-phenylcarbamate (**Entry 3b**) ^{1}H NMR



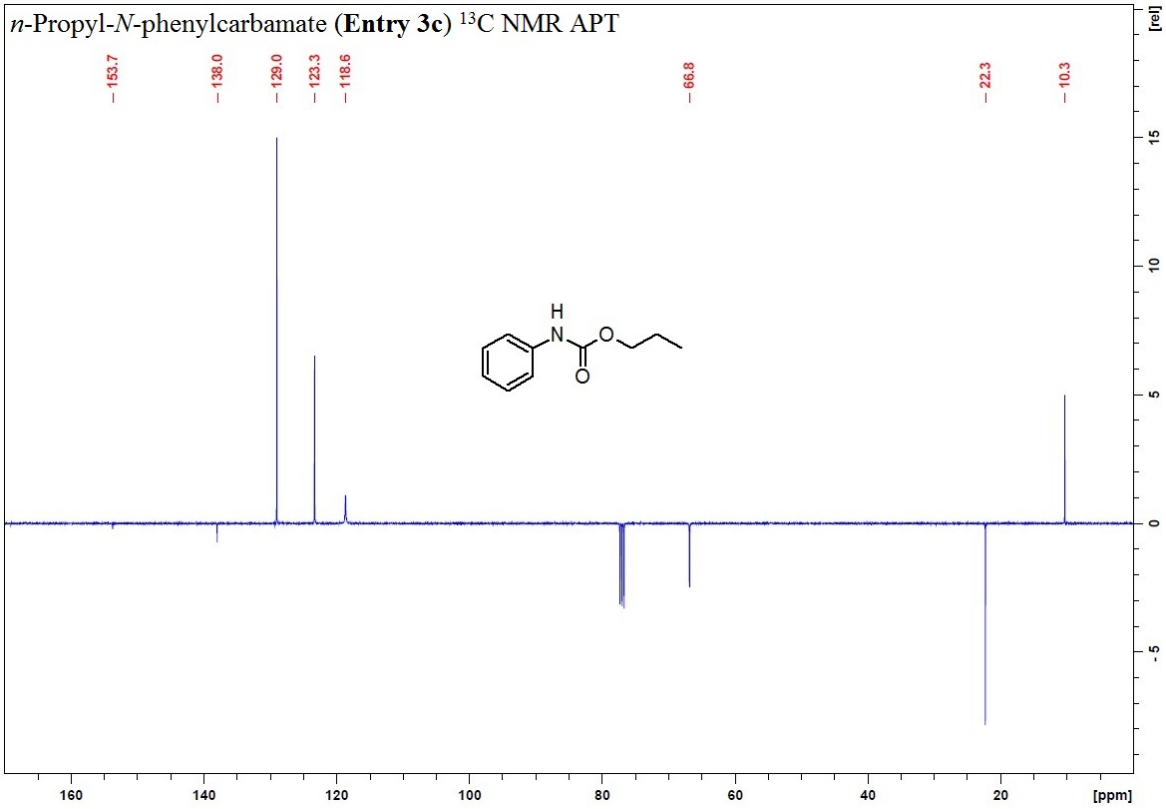
Ethyl-*N*-phenylcarbamate (**Entry 3b**) ^{13}C NMR APT



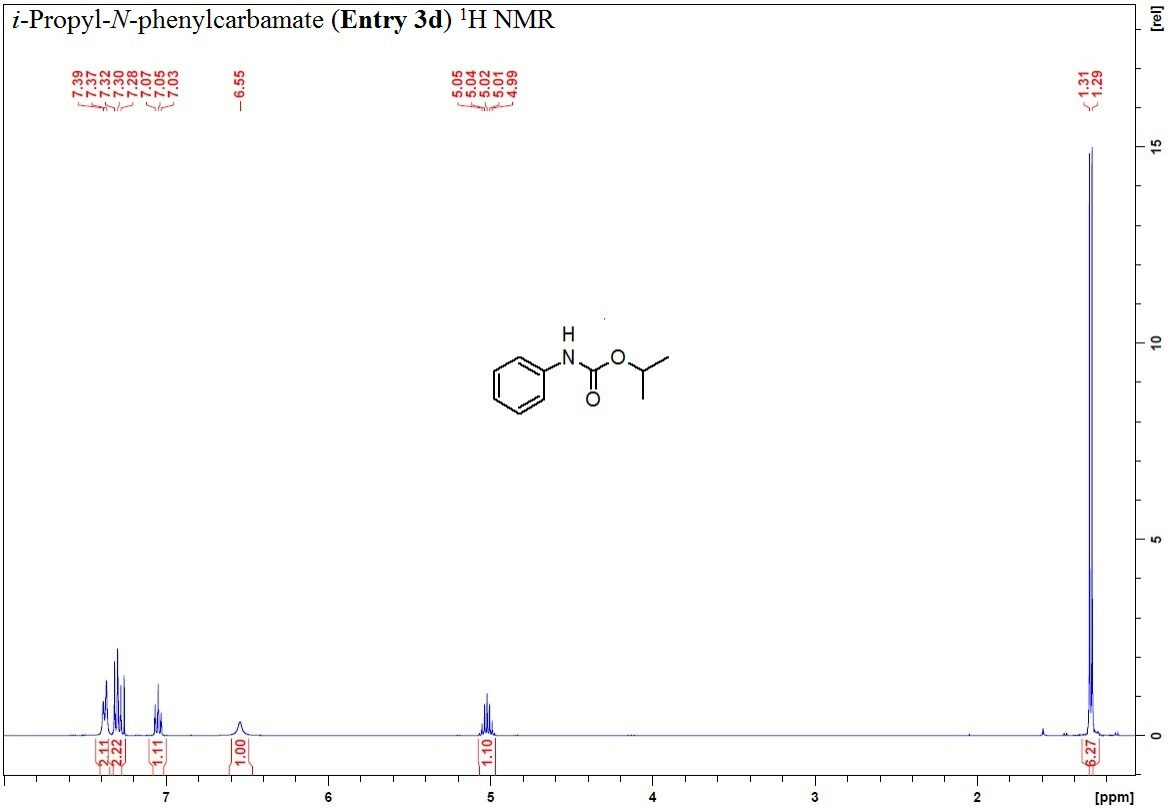
n-Propyl-*N*-phenylcarbamate (**Entry 3c**) ^{1}H NMR



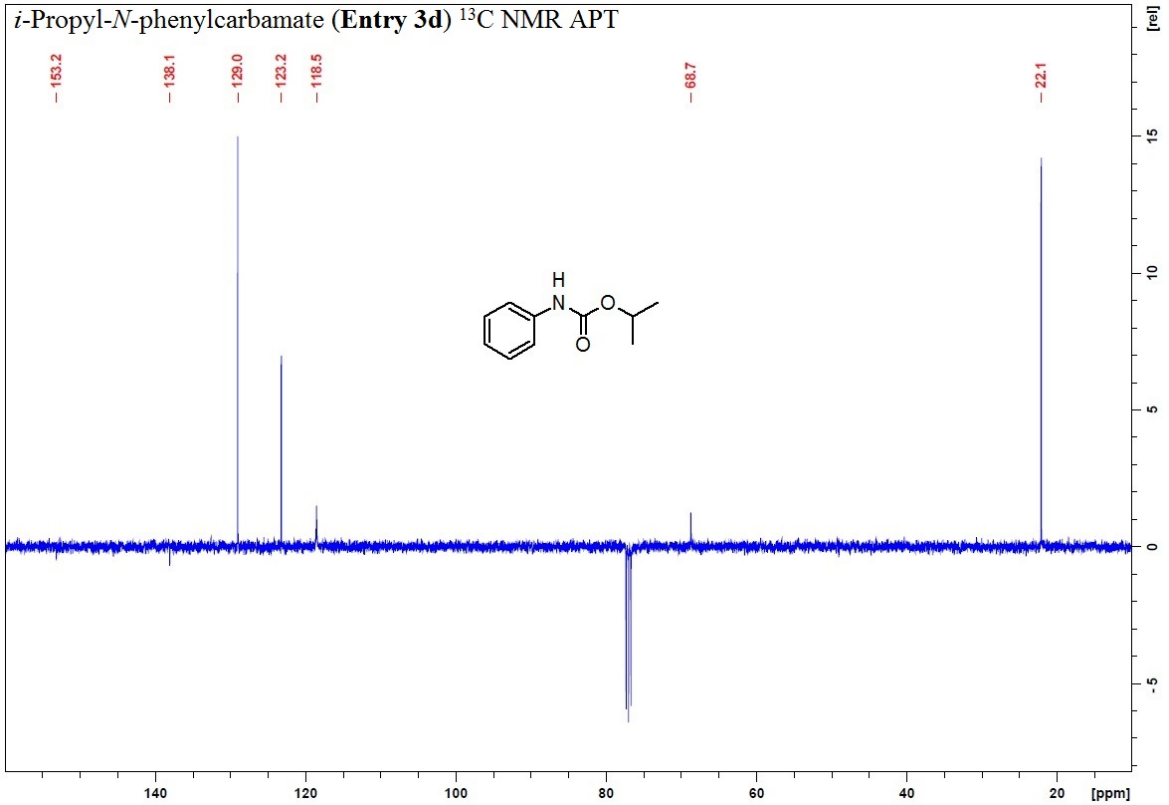
n-Propyl-*N*-phenylcarbamate (**Entry 3c**) ^{13}C NMR APT



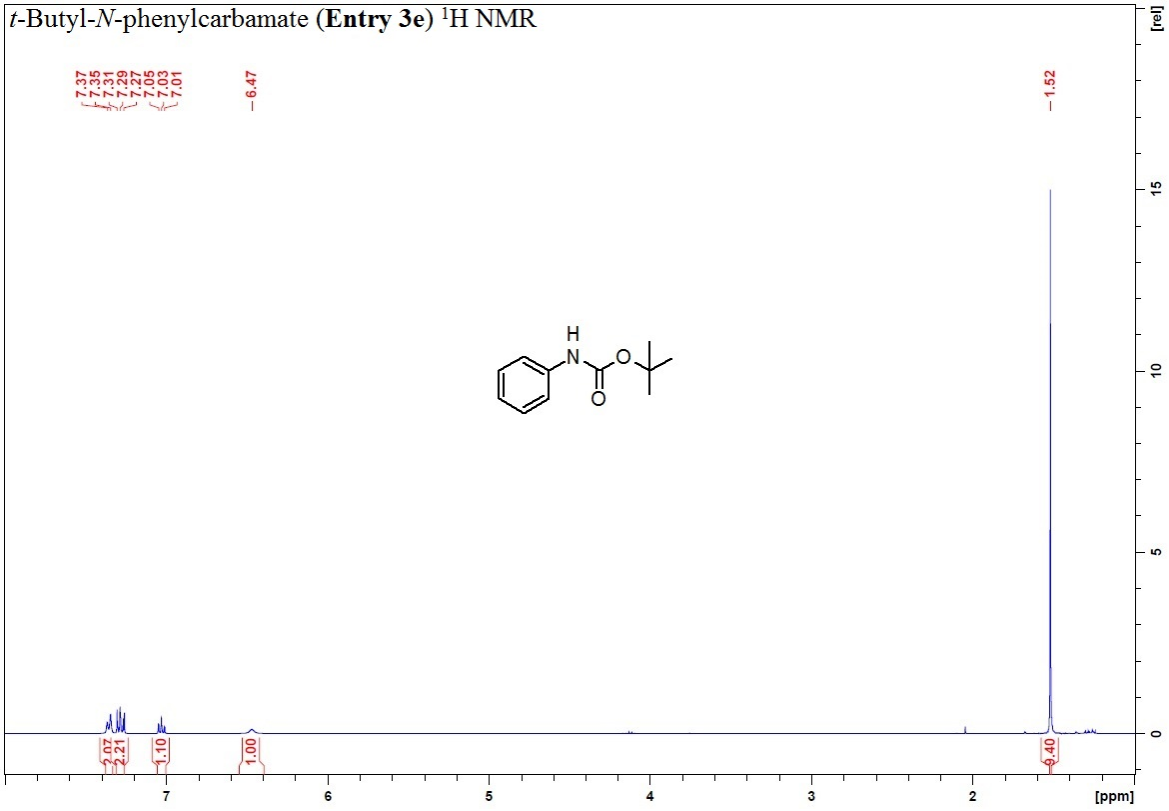
i-Propyl-*N*-phenylcarbamate (**Entry 3d**) ^{1}H NMR



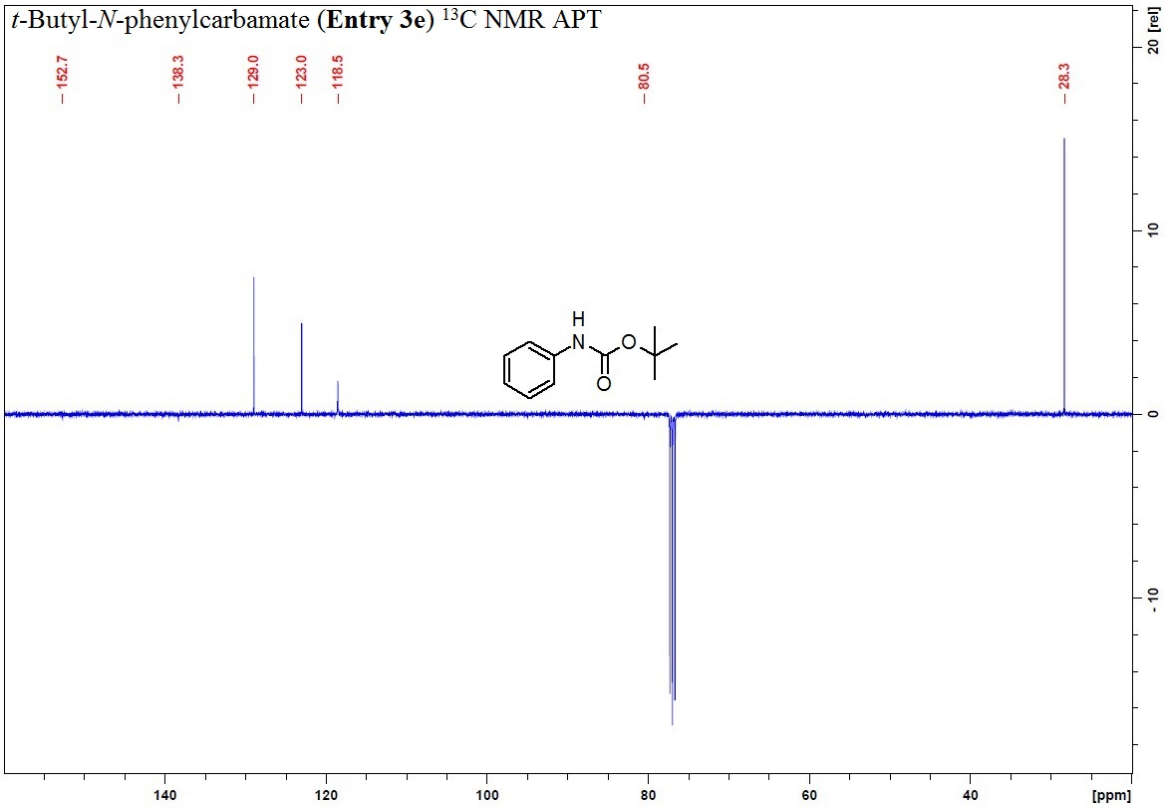
i-Propyl-*N*-phenylcarbamate (**Entry 3d**) ^{13}C NMR APT



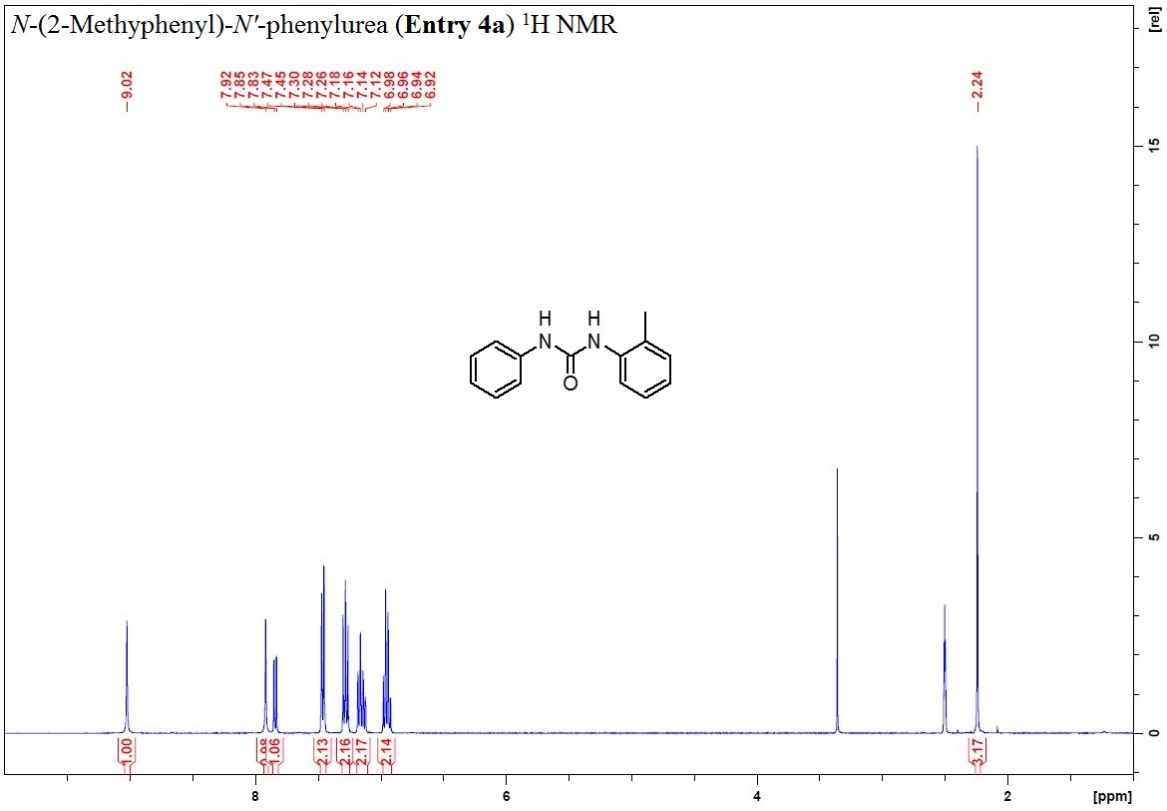
t-Butyl-*N*-phenylcarbamate (**Entry 3e**) ^{1}H NMR



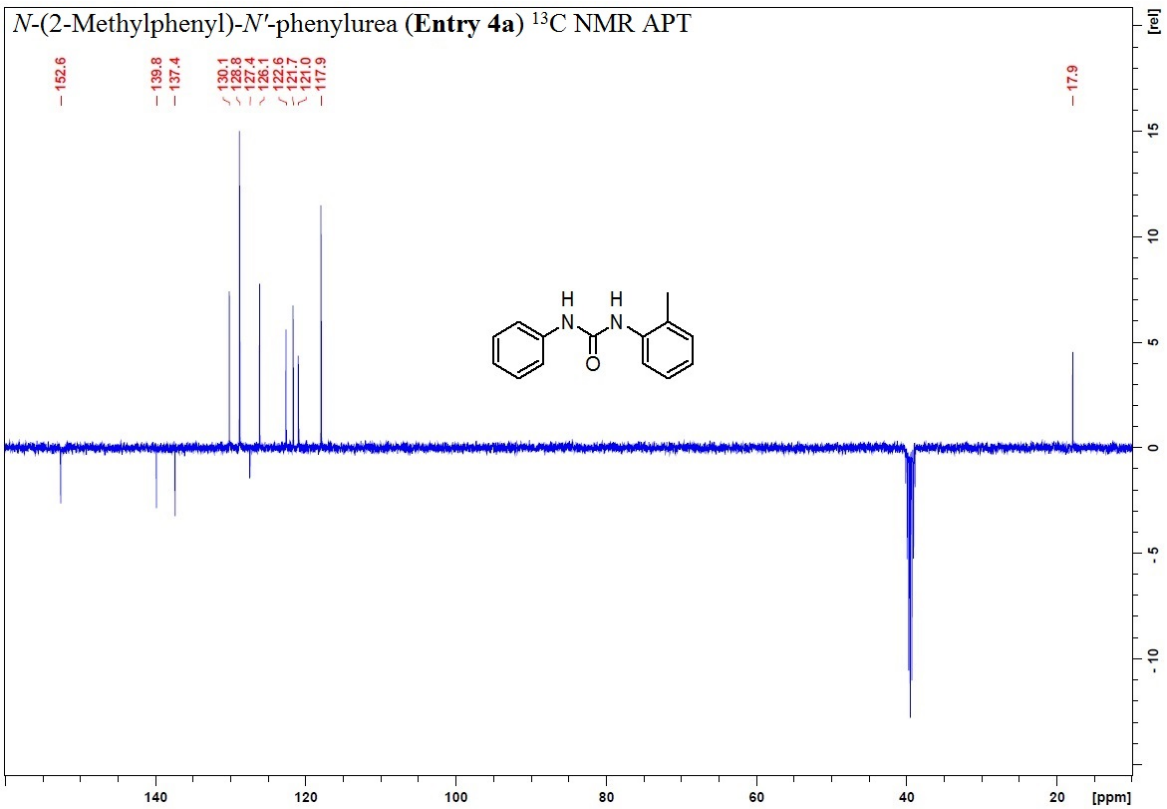
t-Butyl-*N*-phenylcarbamate (**Entry 3e**) ^{13}C NMR APT



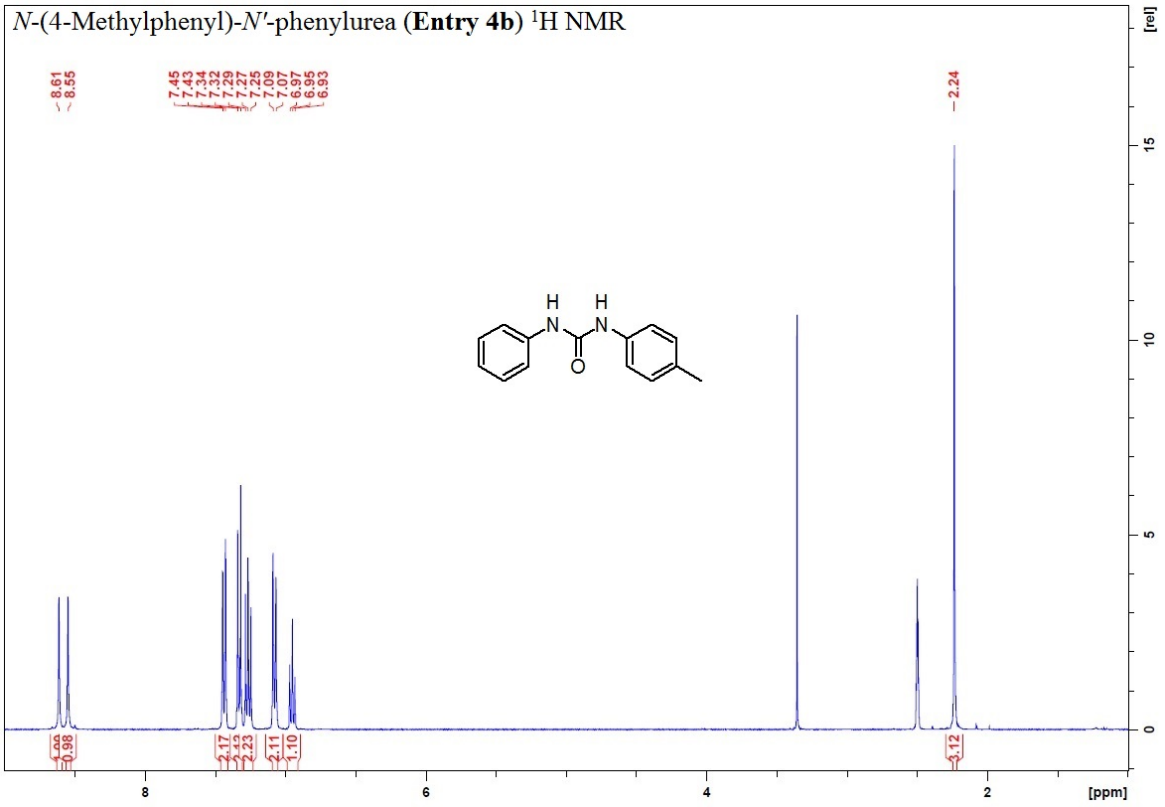
N-(2-Methyphenyl)-*N*′-phenylurea (**Entry 4a**) ^{1}H NMR



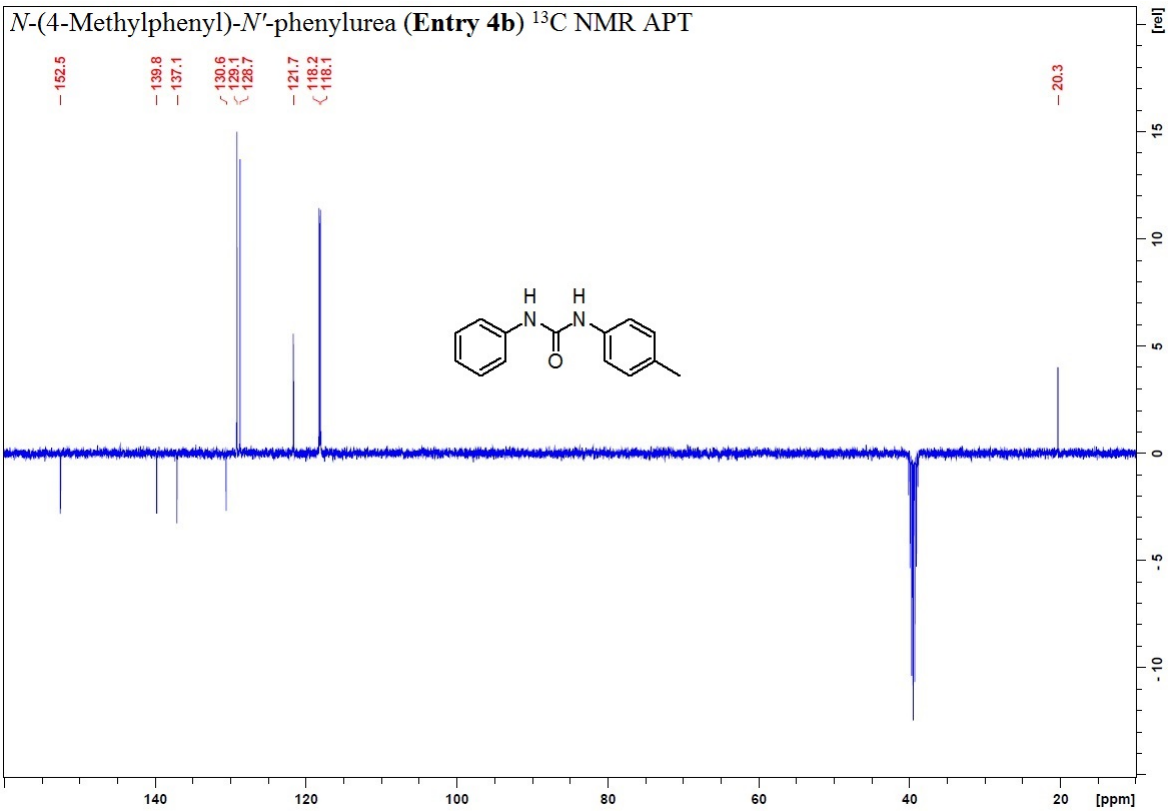
N-(2-Methylphenyl)-*N*′-phenylurea (**Entry 4a**) ^{13}C NMR APT



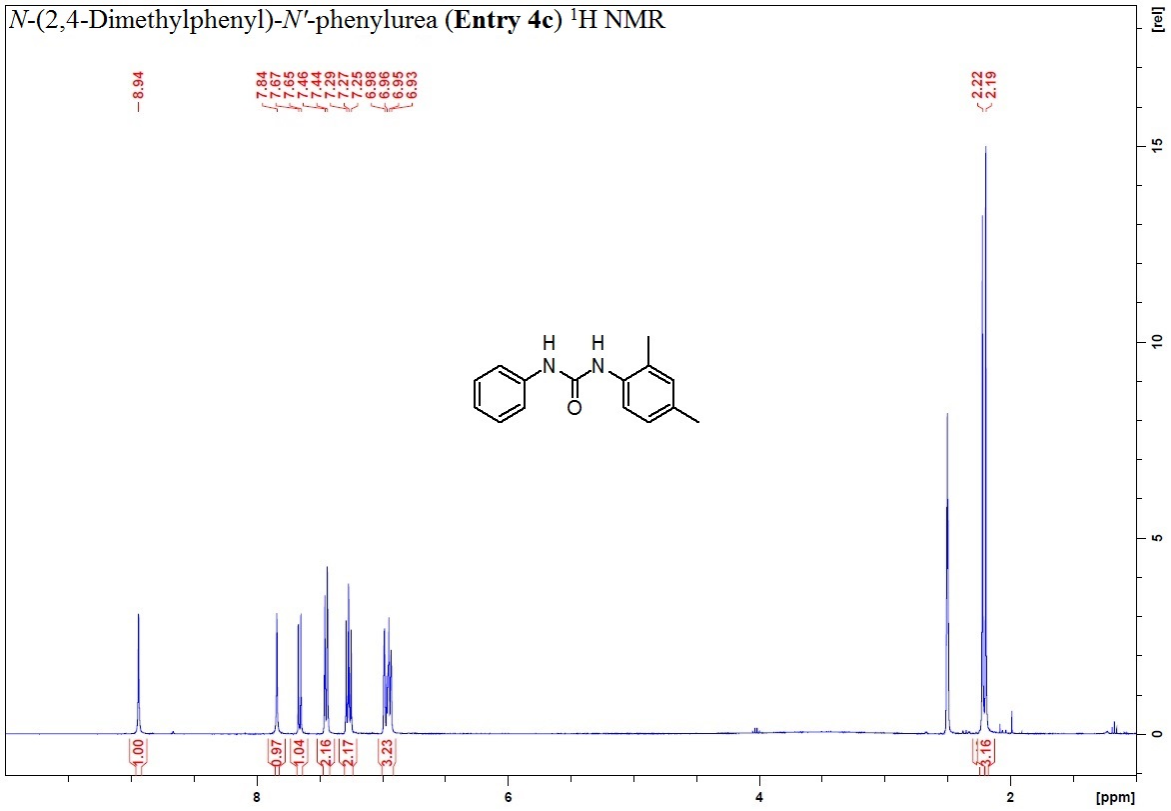
N-(4-Methylphenyl)-*N*′-phenylurea (**Entry 4b**) ^{1}H NMR



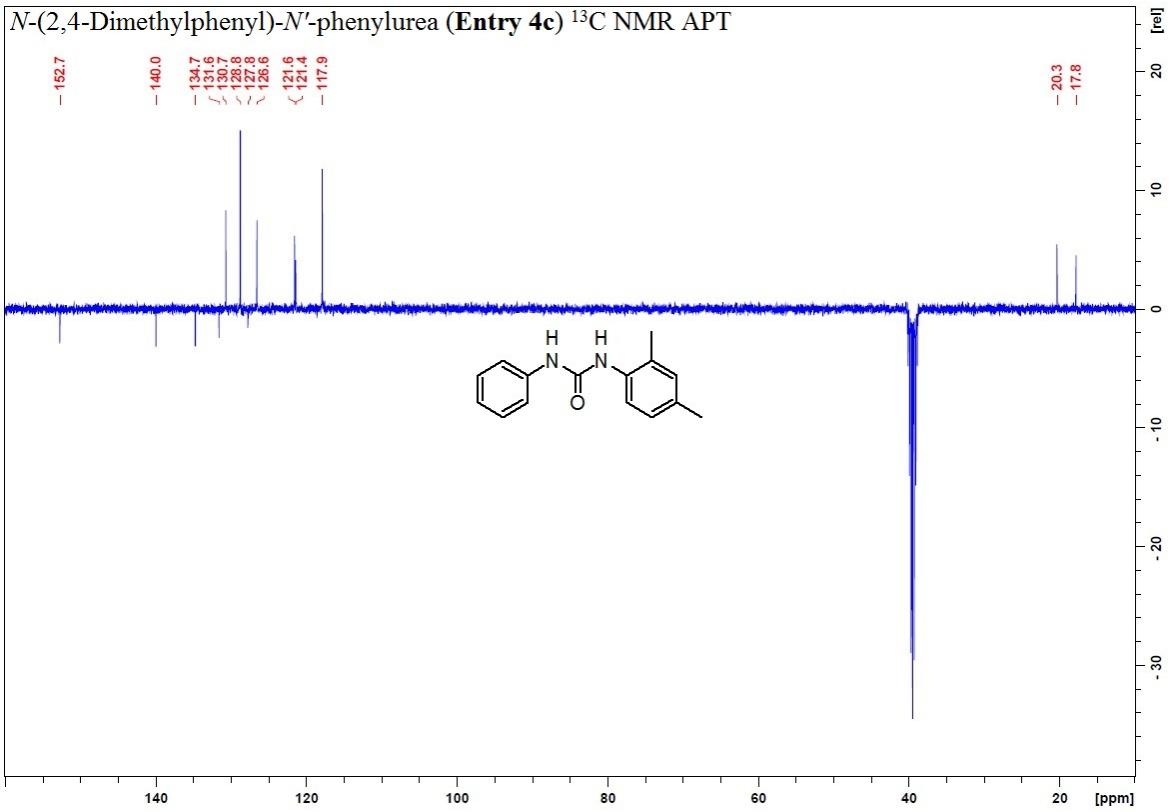
N-(4-Methylphenyl)-*N*′-phenylurea (**Entry 4b**) ^{13}C NMR APT

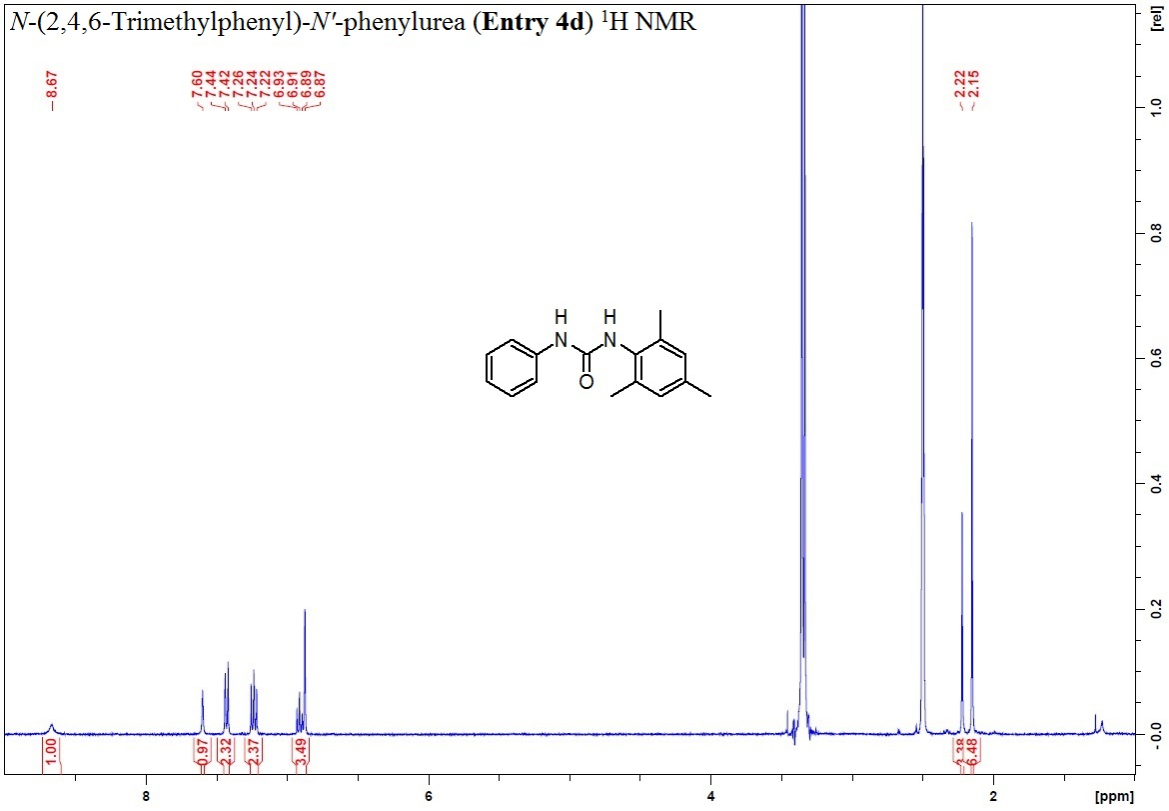


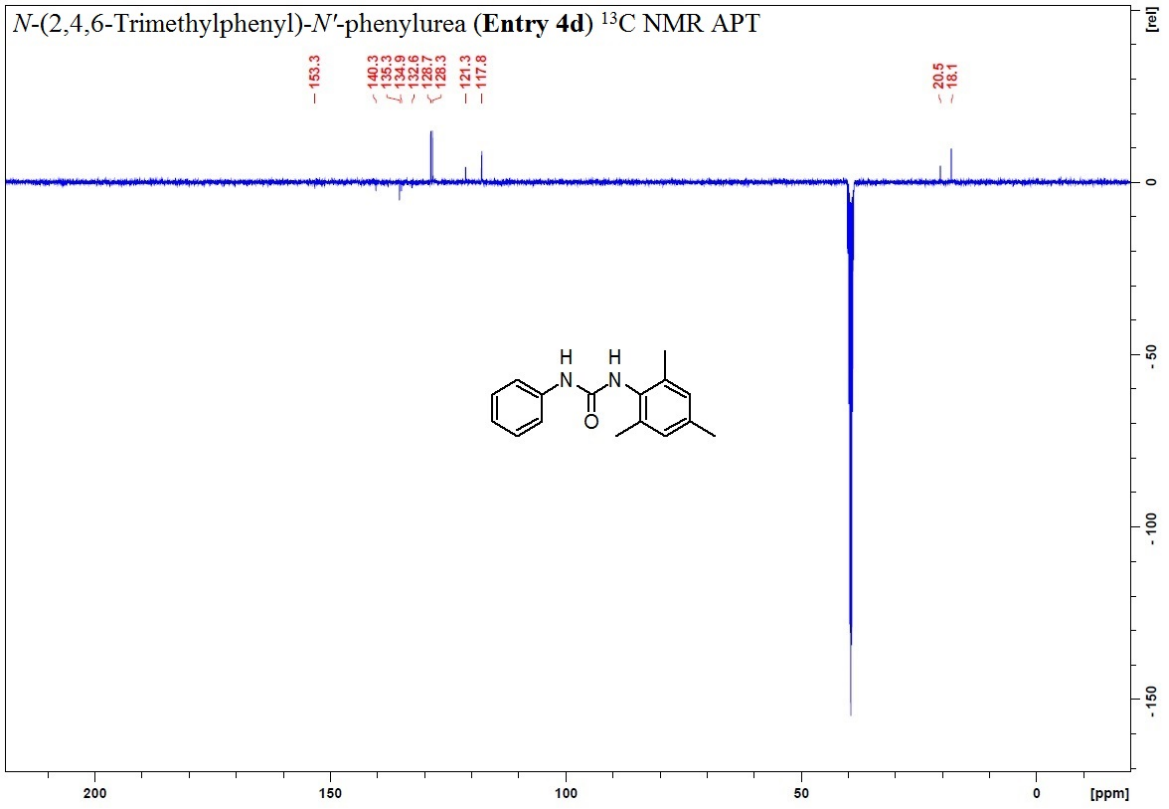
N-(2,4-Dimethylphenyl)-*N'*-phenylurea (**Entry 4c**) ^{1}H NMR



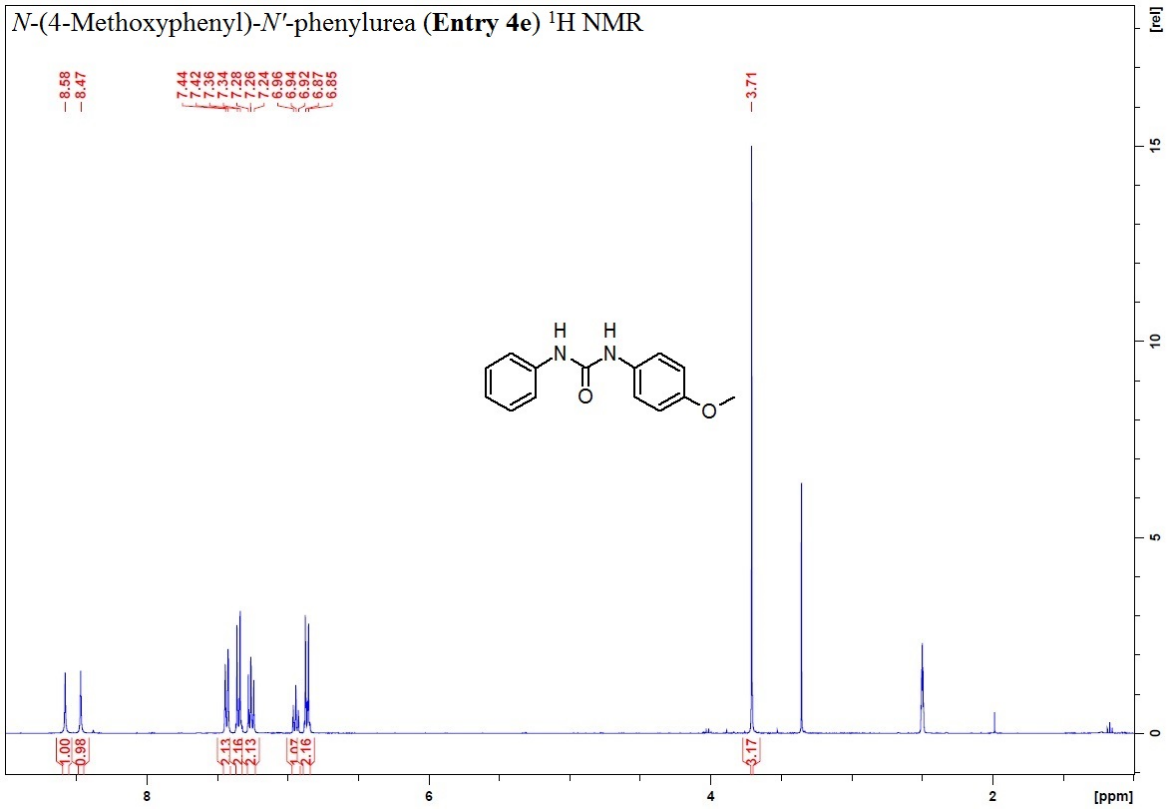
N-(2,4-Dimethylphenyl)-*N'*-phenylurea (**Entry 4c**) ^{13}C NMR APT



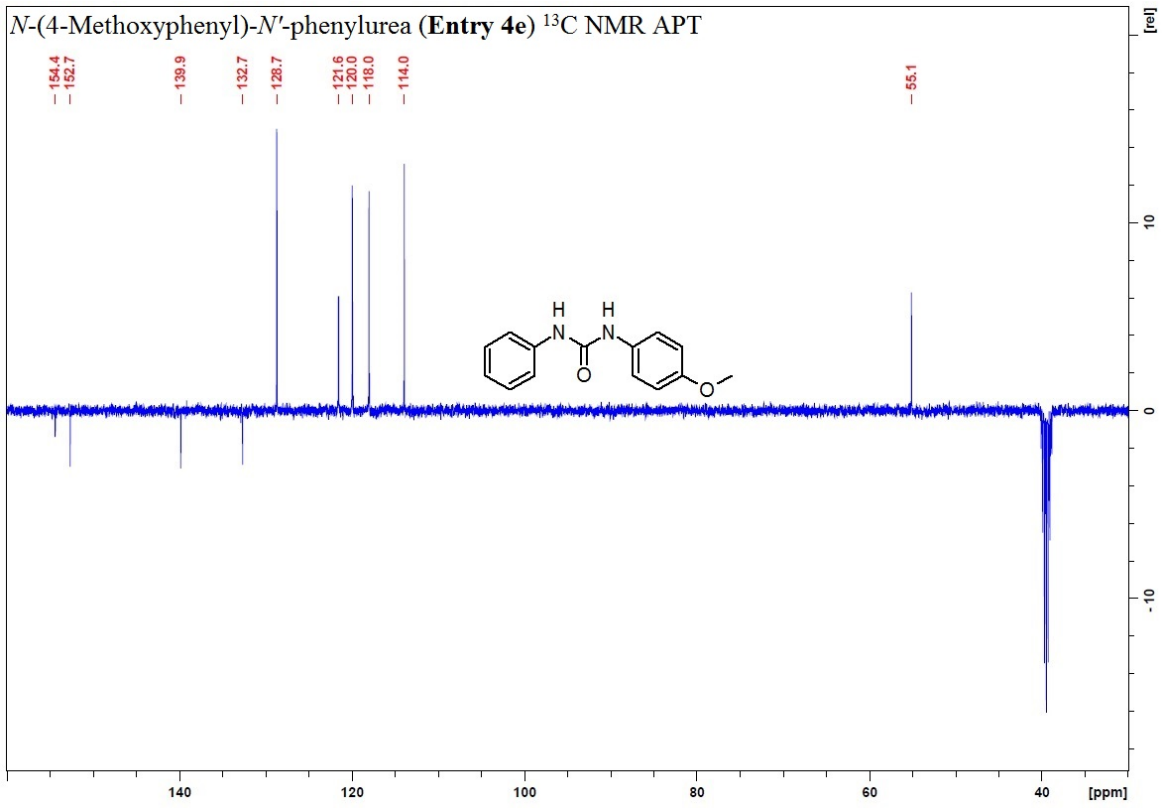

N-(2,4,6-Trimethylphenyl)-N′-phenylurea (Entry 4d) 1H NMR
8.67
7.60
7.44
7.42
7.26
7.24
7.22
6.93
6.91
6.89
6.87
2.22
2.15
1.00
0.97
2.32
2.37
3.49
2.38
6.48
8
6
4
2
[ppm]
[rel]


N-(2,4,6-Trimethylphenyl)-N′-phenylurea (Entry 4d) 13C NMR APT
153.3
140.3
135.3
134.9
132.6
128.7
128.3
121.3
117.8
20.5
18.1
200
150
100
50
0
[ppm]
[rel]

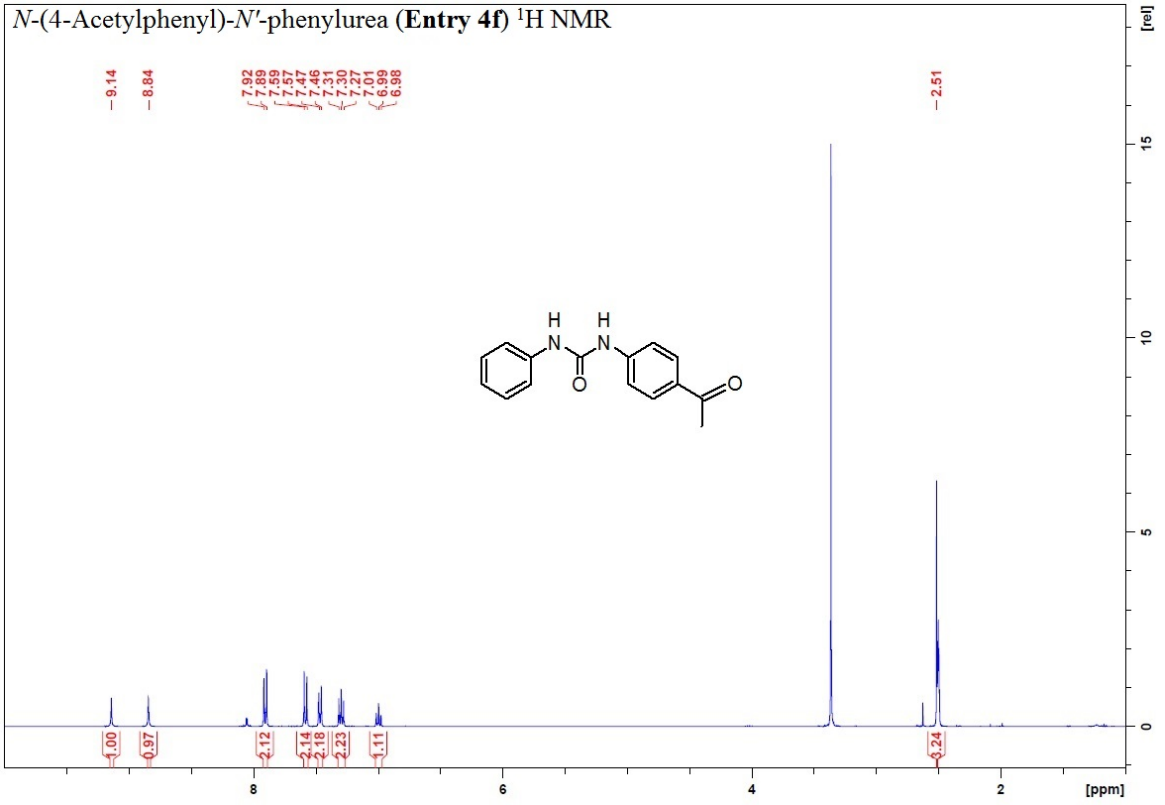
N-(4-Methoxyphenyl)-*N*′-phenylurea (**Entry 4e**) ^{1}H NMR



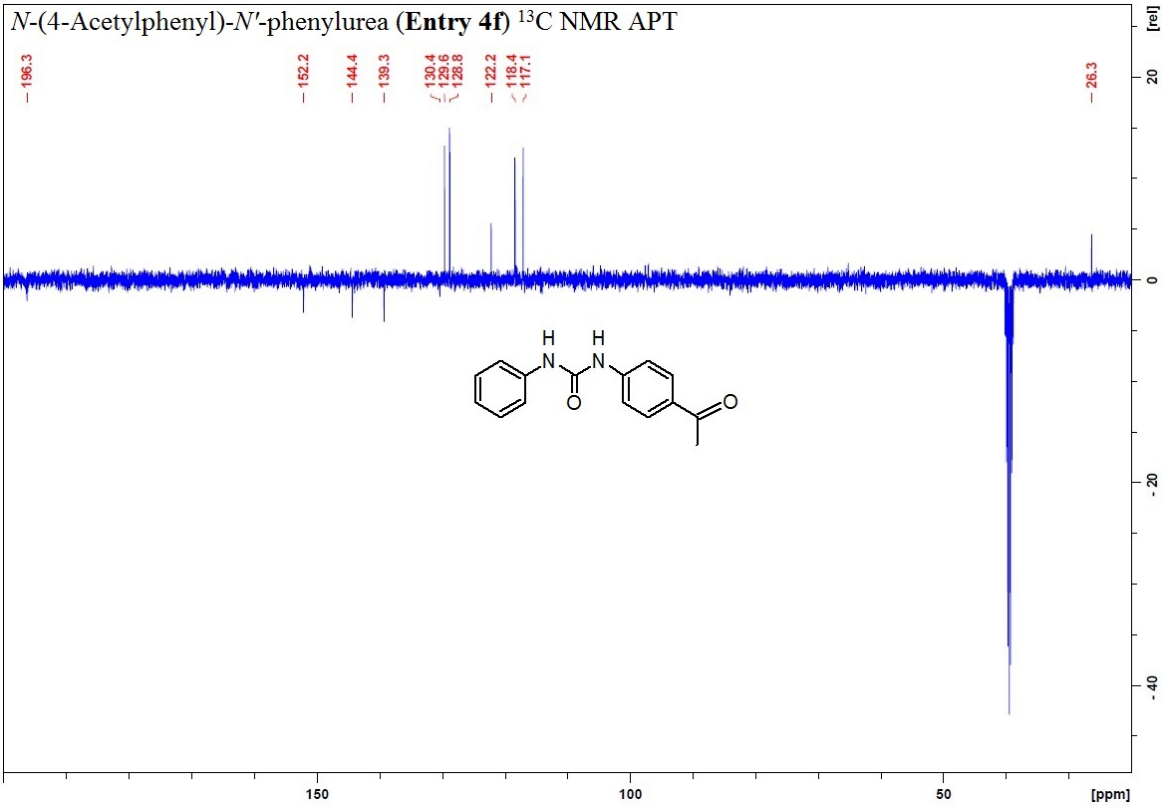
N-(4-Methoxyphenyl)-*N*′-phenylurea (**Entry 4e**) ^{13}C NMR APT



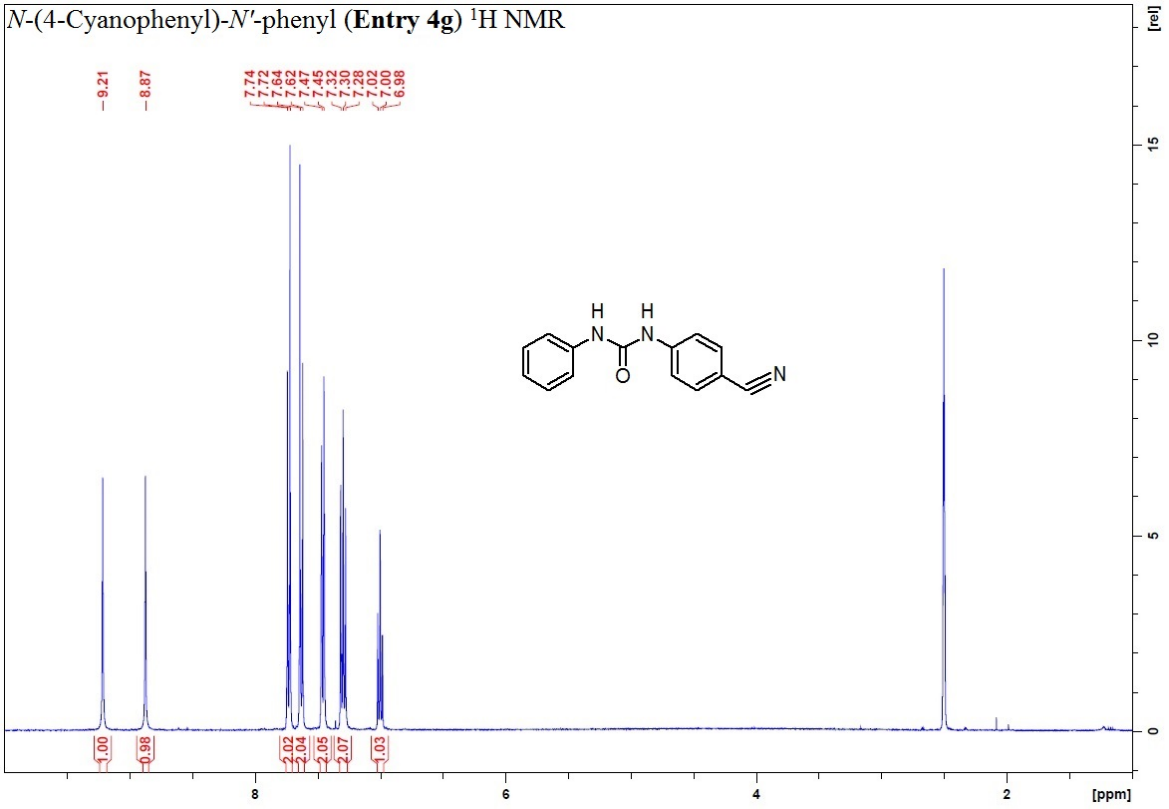
N-(4-Acetylphenyl)-*N*′-phenylurea (**Entry 4f**) ^{1}H NMR



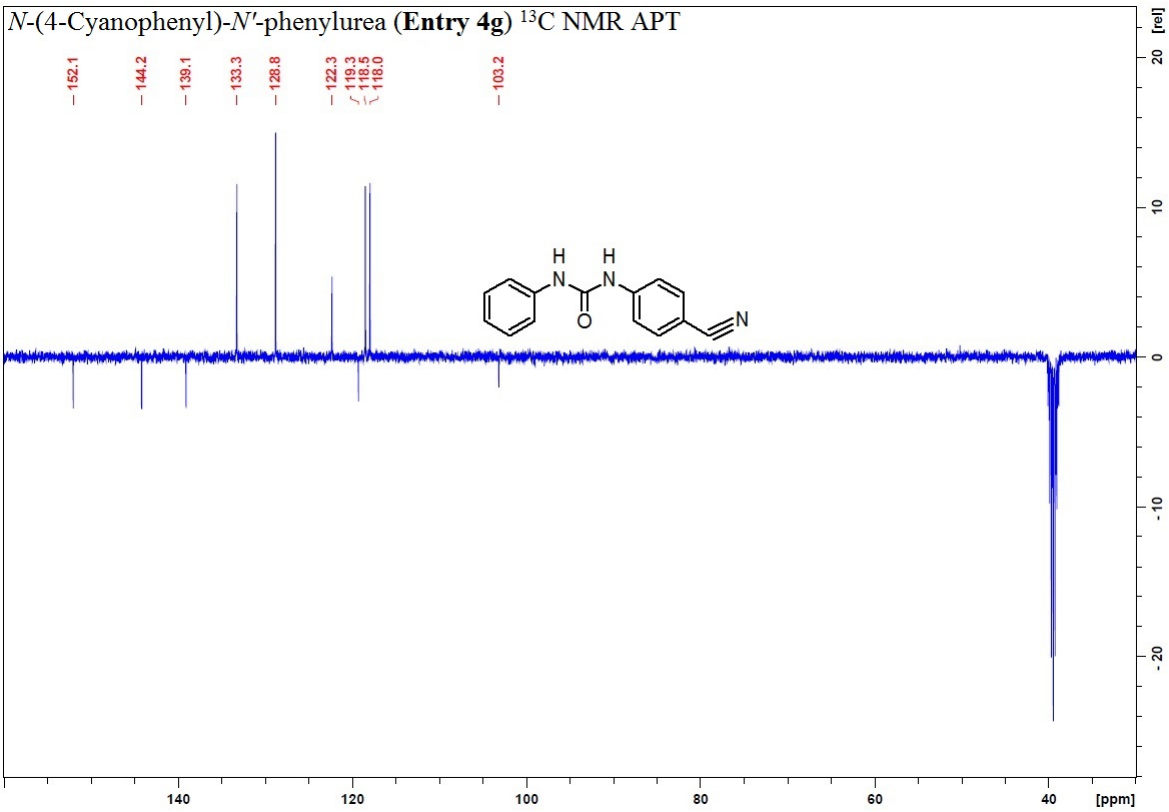
N-(4-Acetylphenyl)-*N*′-phenylurea (**Entry 4f**) ^{13}C NMR APT



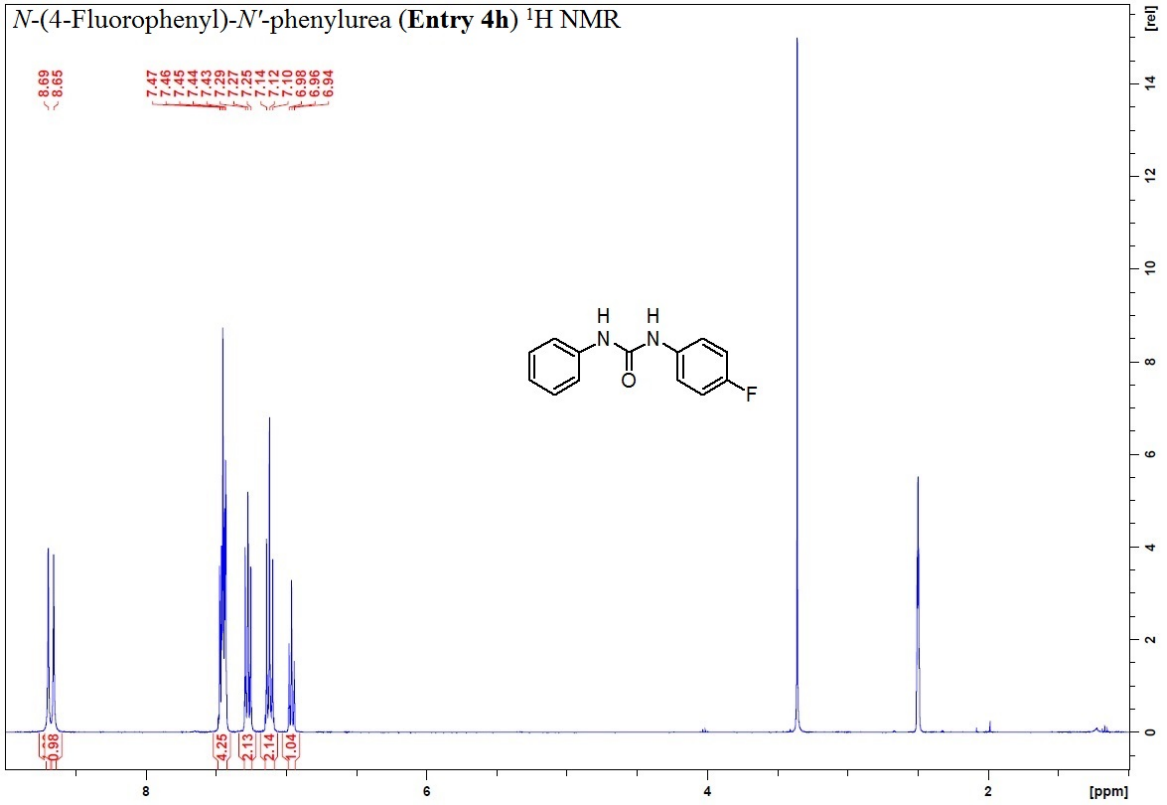
N-(4-Cyanophenyl)-*N'*-phenyl (**Entry 4g**) ^{1}H NMR



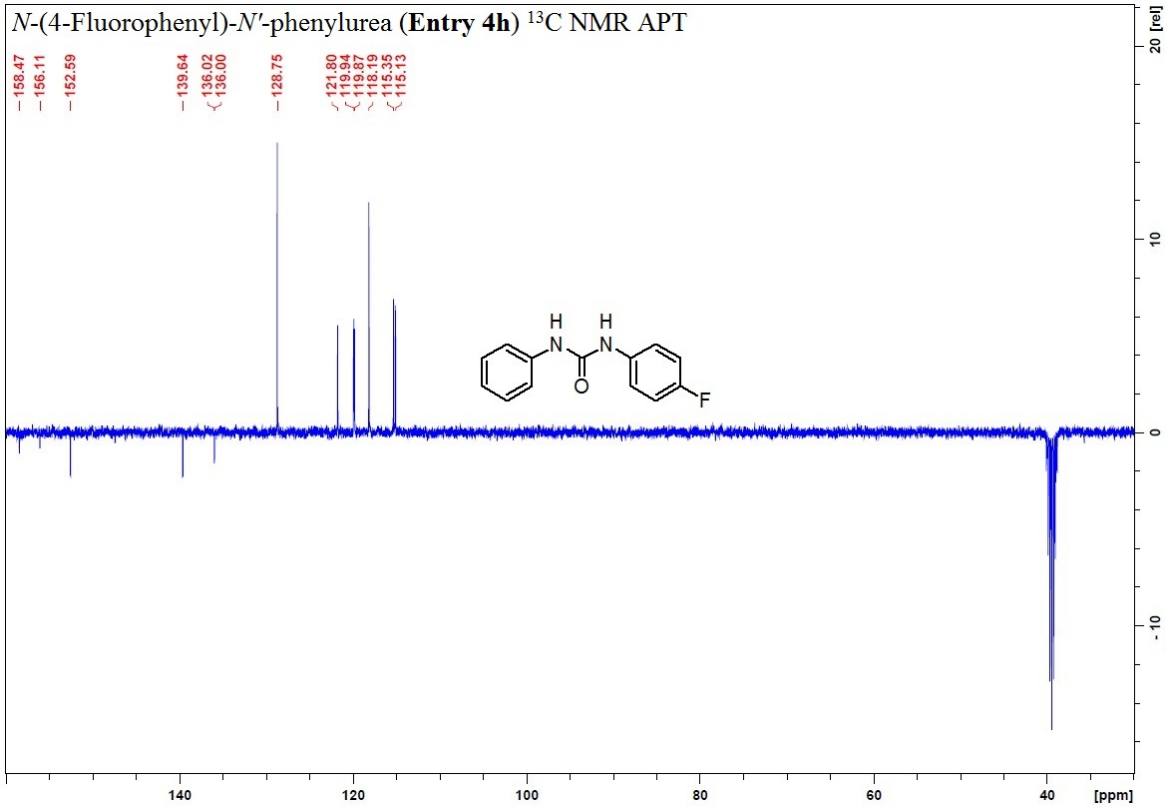
N-(4-Cyanophenyl)-*N'*-phenylurea (**Entry 4g**) ^{13}C NMR APT



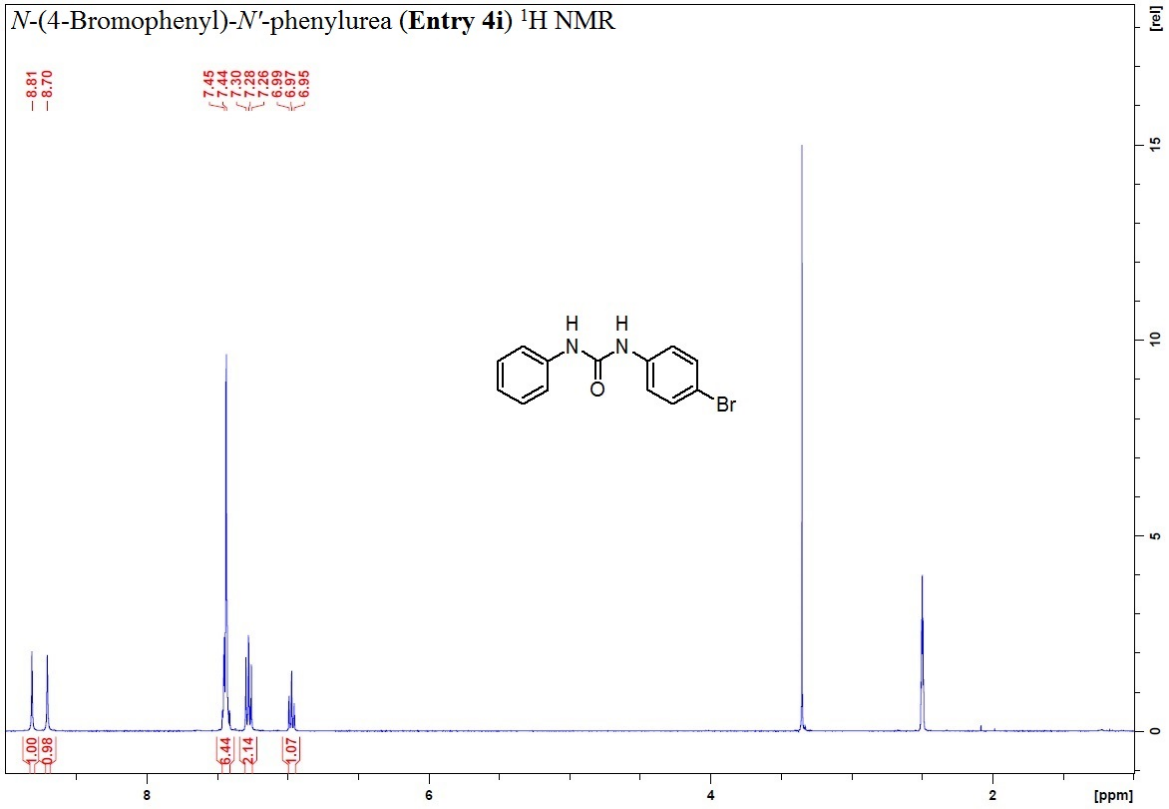
N-(4-Fluorophenyl)-*N*′-phenylurea (**Entry 4h**) ^{1}H NMR



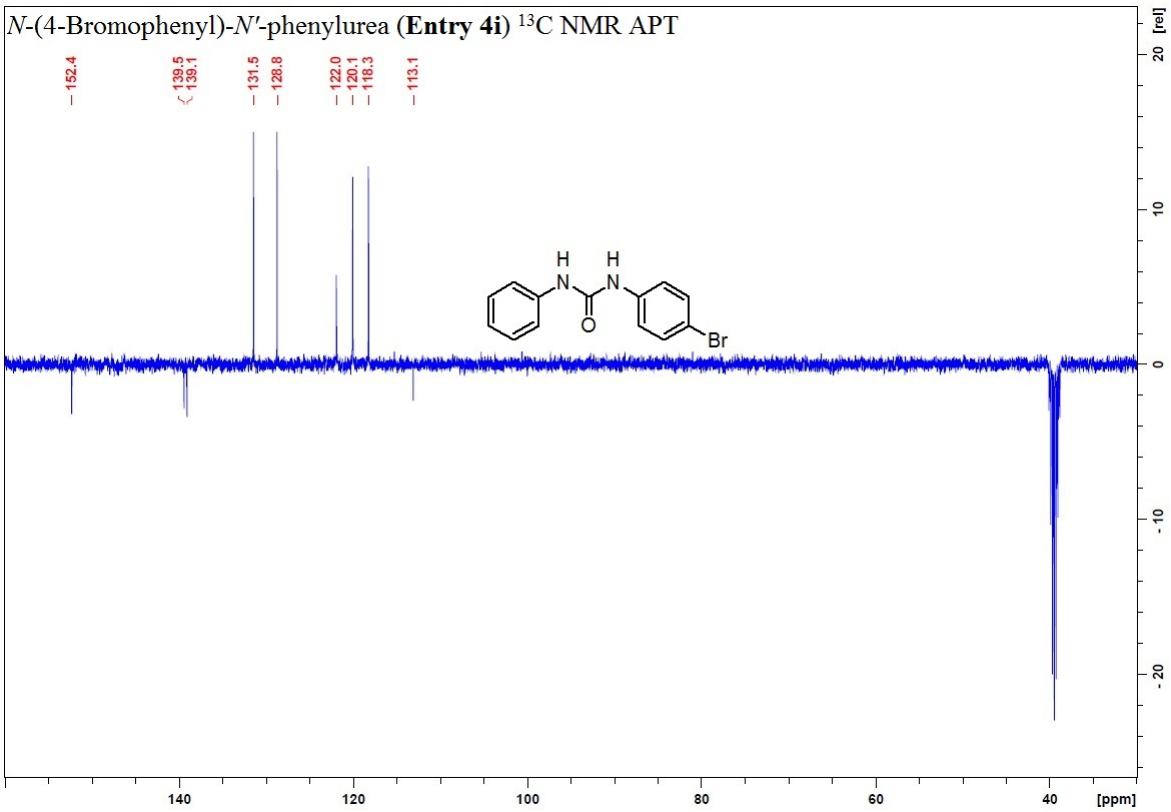
N-(4-Fluorophenyl)-*N*′-phenylurea (**Entry 4h**) ^{13}C NMR APT



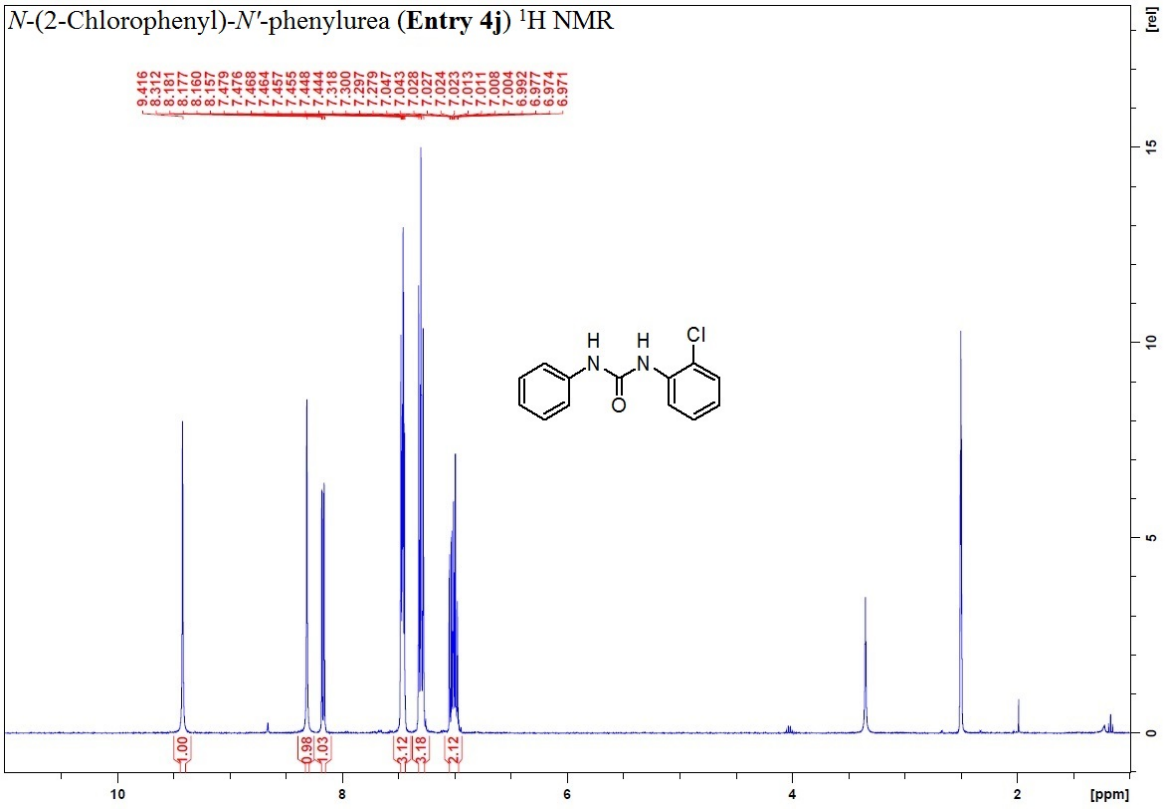
N-(4-Bromophenyl)-*N*′-phenylurea (**Entry 4i**) ^{1}H NMR



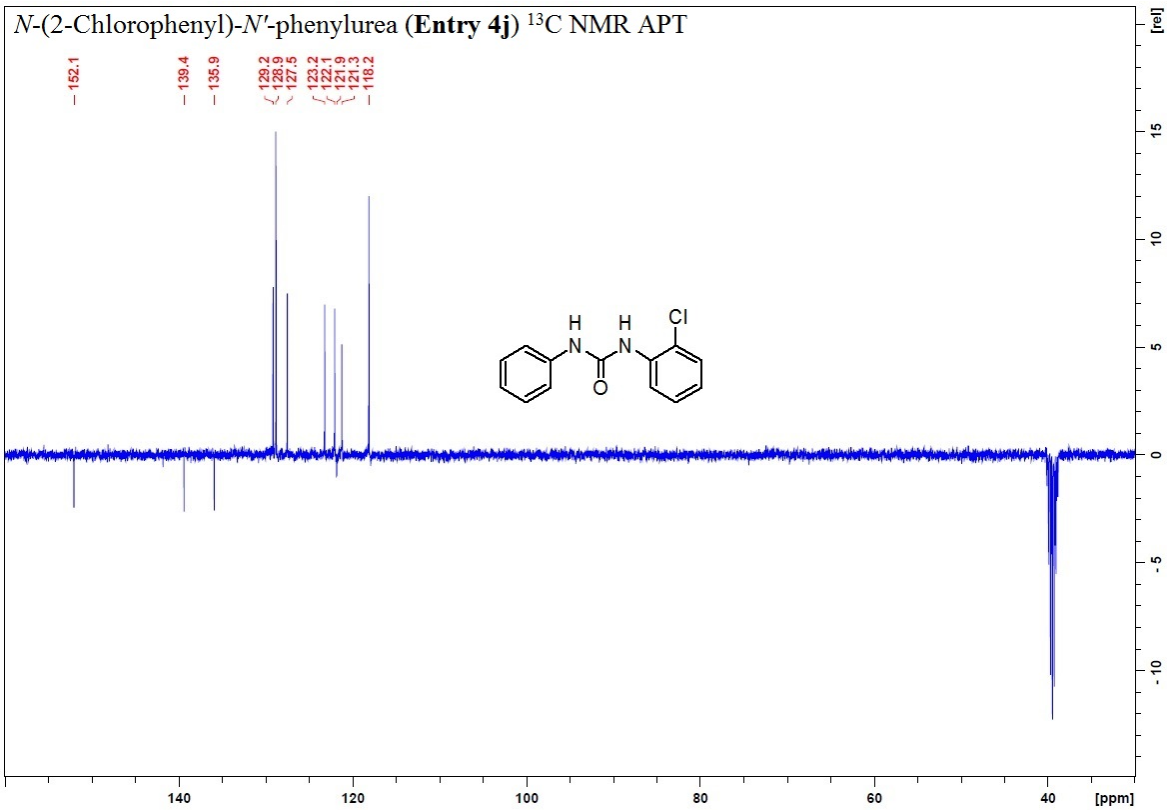
N-(4-Bromophenyl)-*N*′-phenylurea (**Entry 4i**) ^{13}C NMR APT



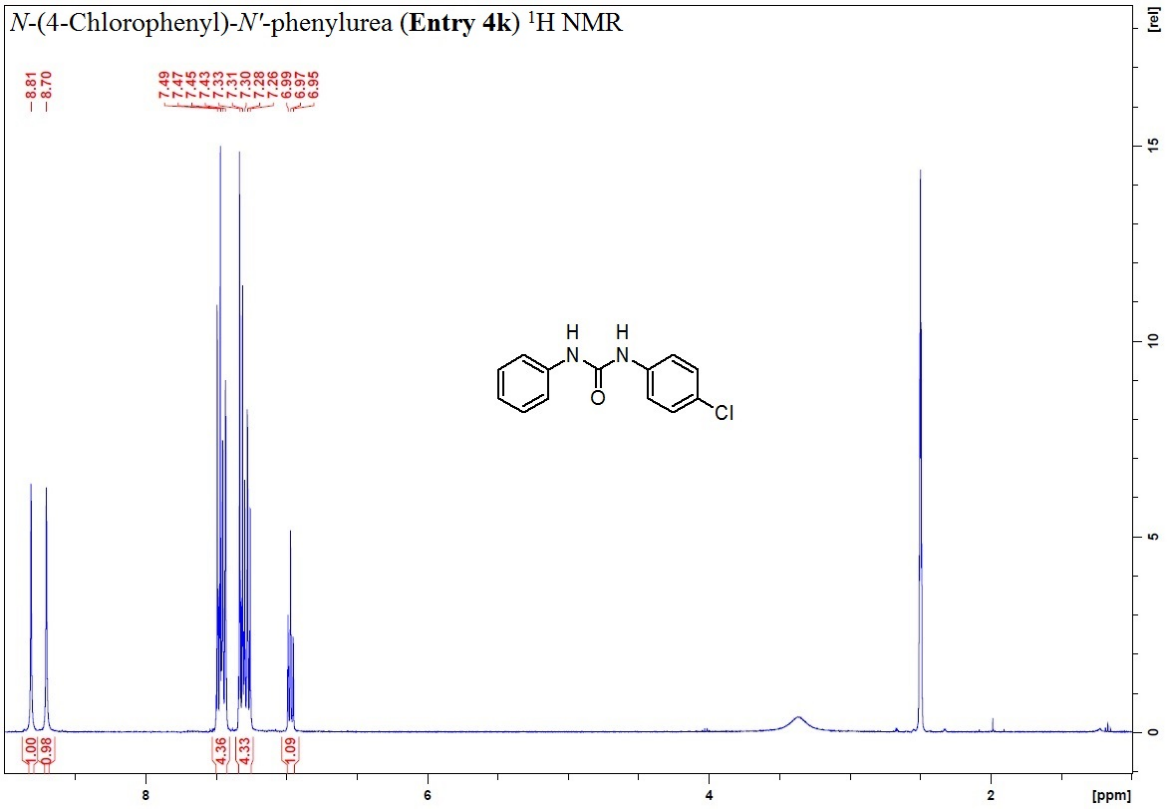
N-(2-Chlorophenyl)-*N'*-phenylurea (**Entry 4j**) ^{1}H NMR



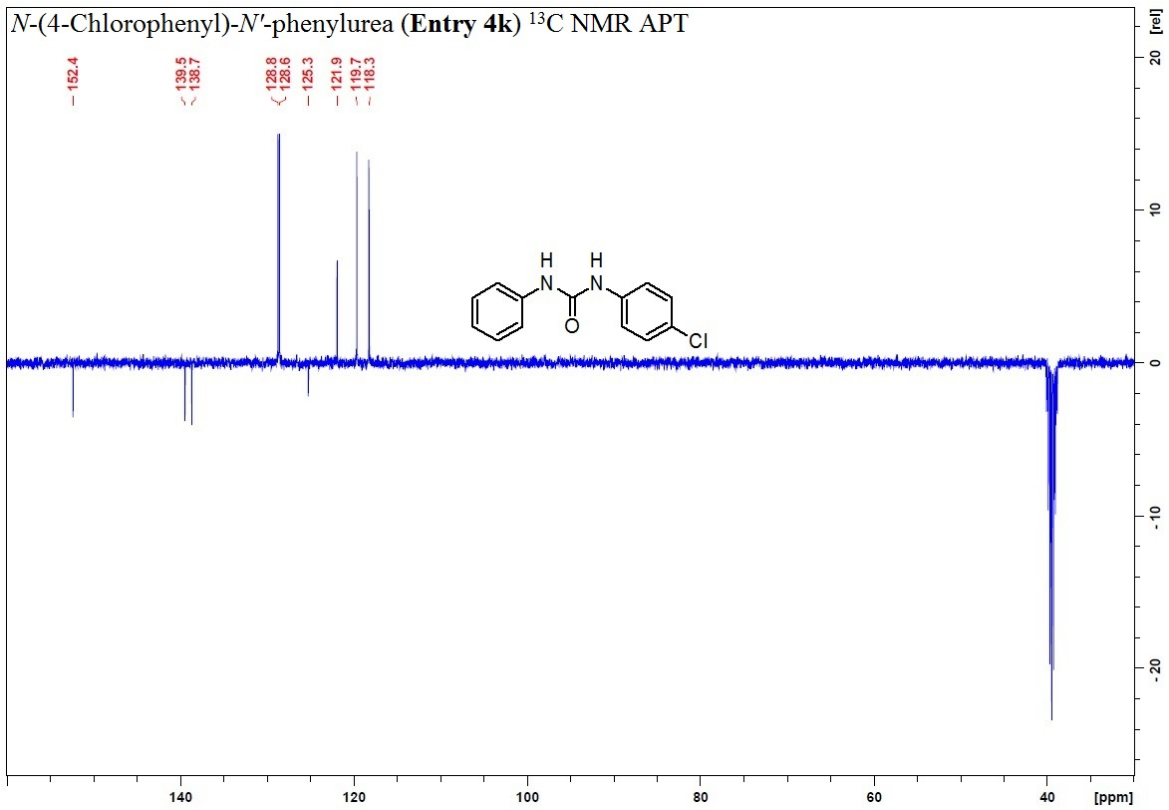
N-(2-Chlorophenyl)-*N'*-phenylurea (**Entry 4j**) ^{13}C NMR APT



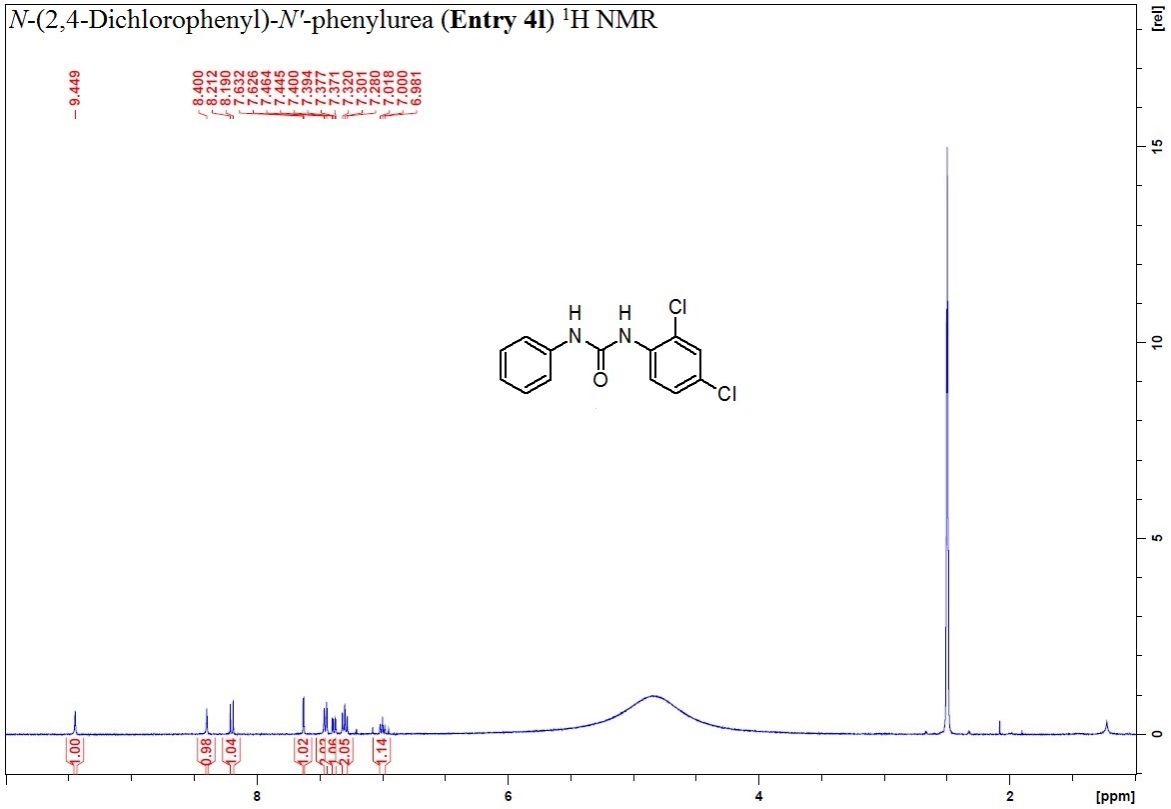
N-(4-Chlorophenyl)-*N'*-phenylurea (**Entry 4k**) ^{1}H NMR



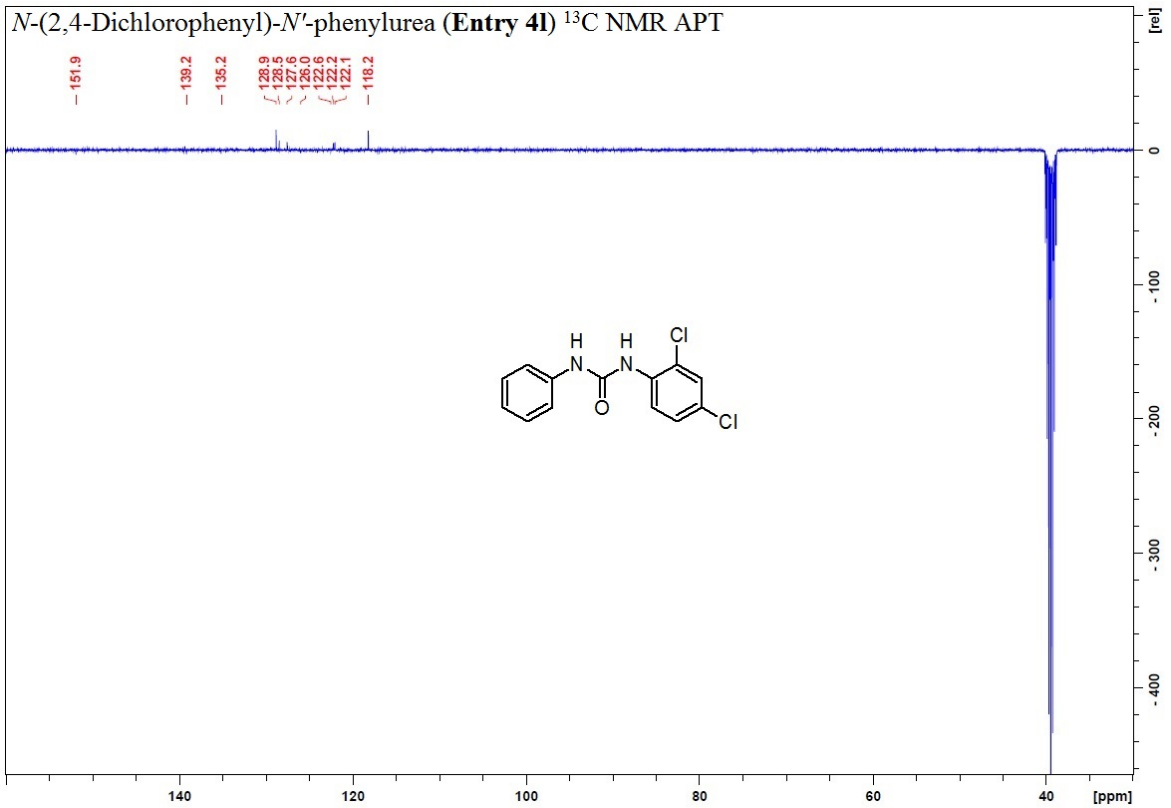
N-(4-Chlorophenyl)-*N'*-phenylurea (**Entry 4k**) ^{13}C NMR APT



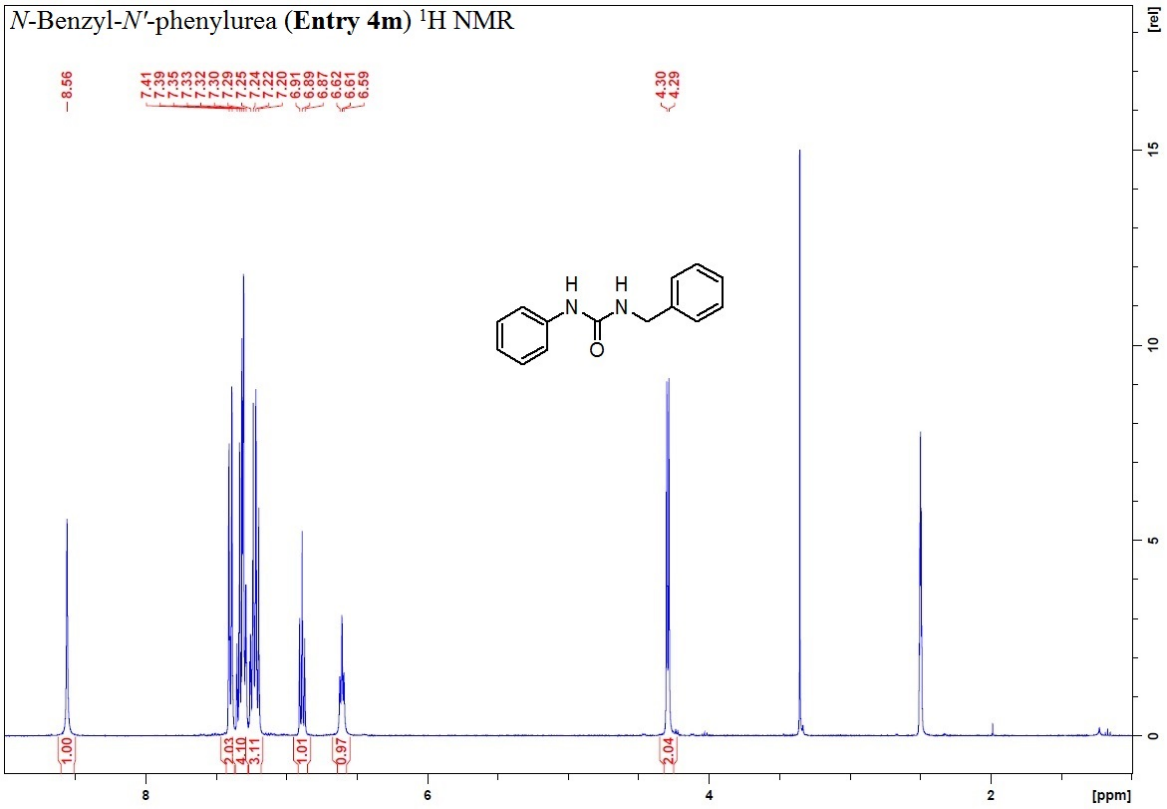
N-(2,4-Dichlorophenyl)-*N'*-phenylurea (**Entry 4l**) ^{1}H NMR



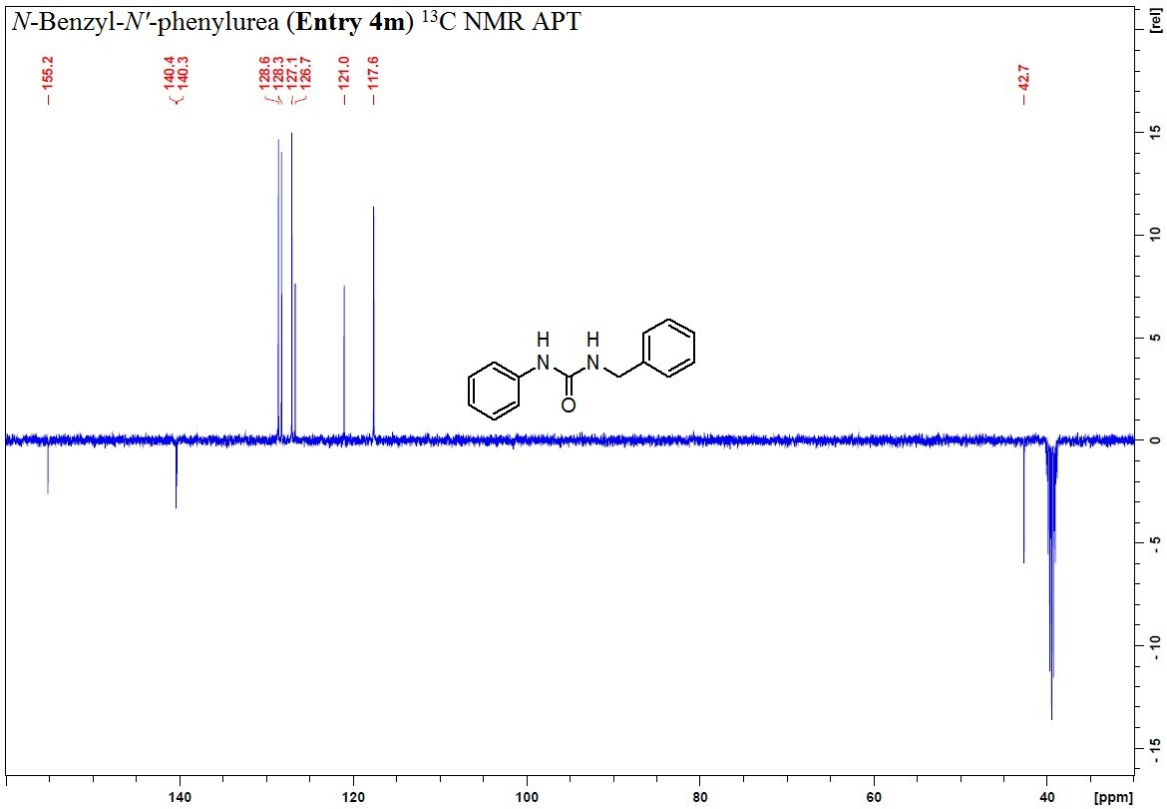
N-(2,4-Dichlorophenyl)-*N'*-phenylurea (**Entry 4l**) ^{13}C NMR APT



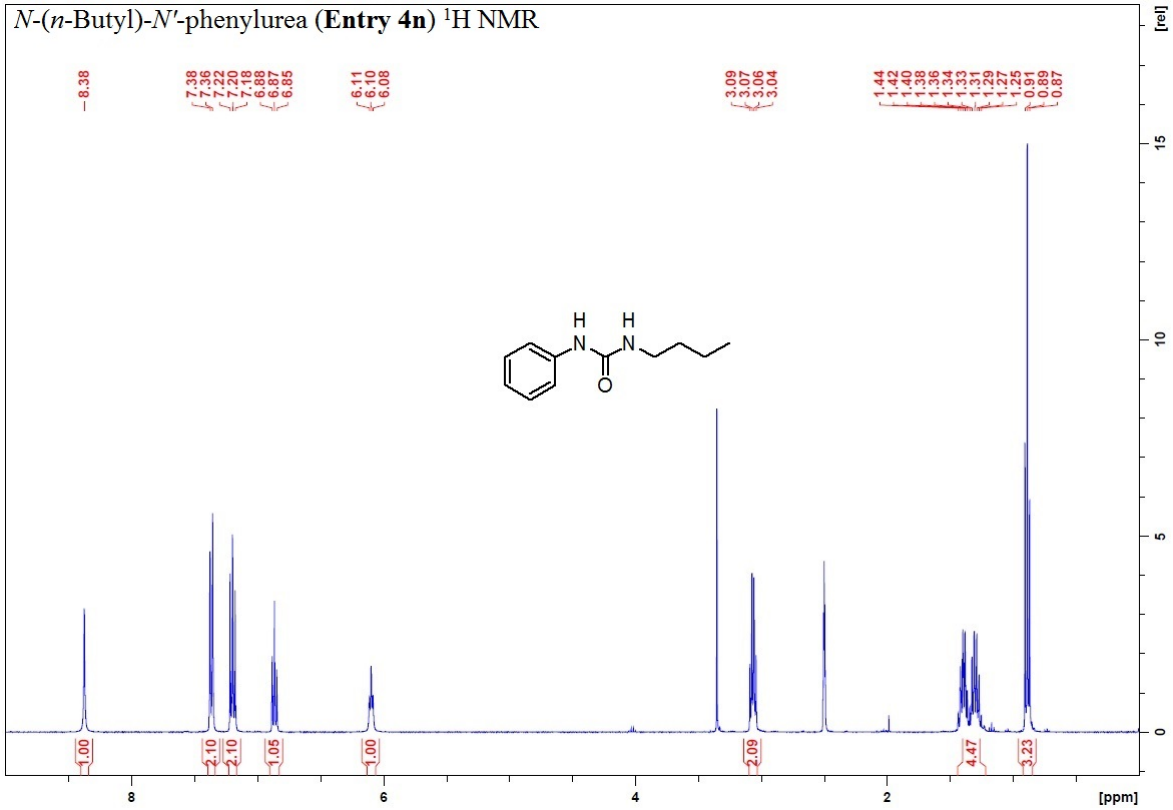
N-Benzyl-*N*′-phenylurea (**Entry 4m**) ^{1}H NMR



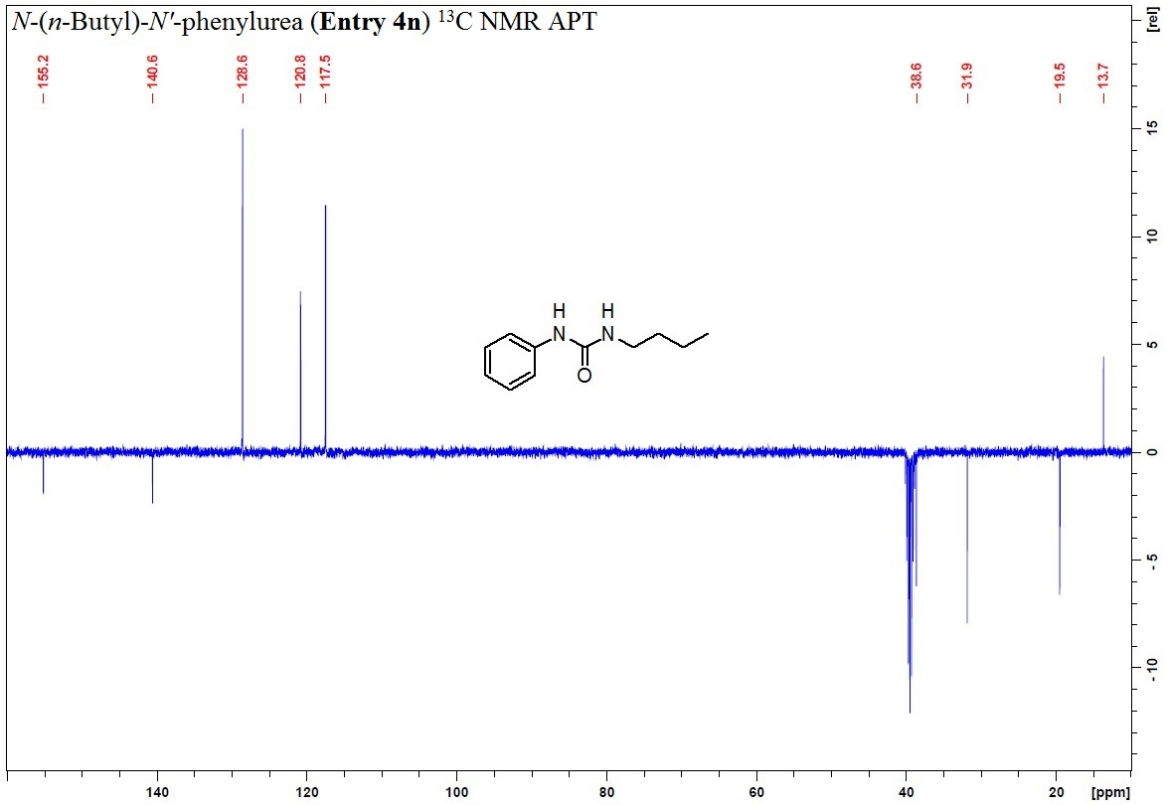
N-Benzyl-*N*′-phenylurea (**Entry 4m**) ^{13}C NMR APT



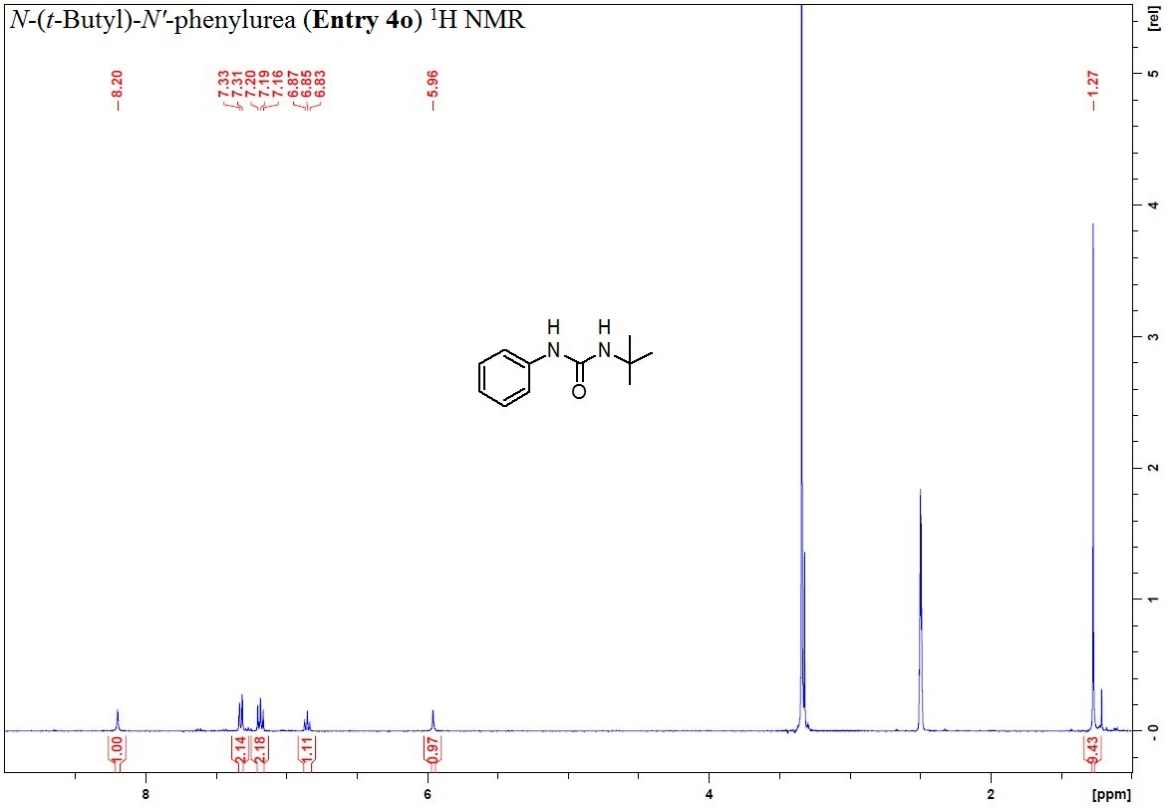
N-(*n*-Butyl)-*N*′-phenylurea (**Entry 4n**) ^{1}H NMR



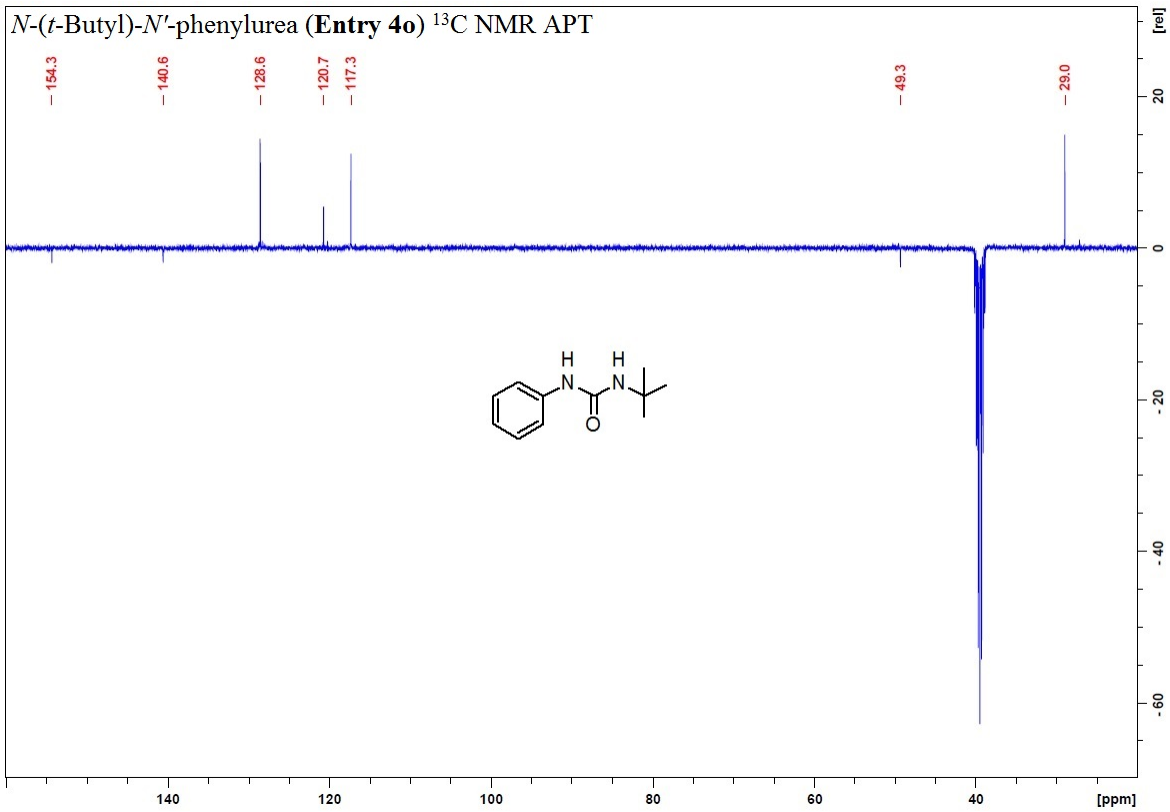
N-(*n*-Butyl)-*N*′-phenylurea (**Entry 4n**) ^{13}C NMR APT



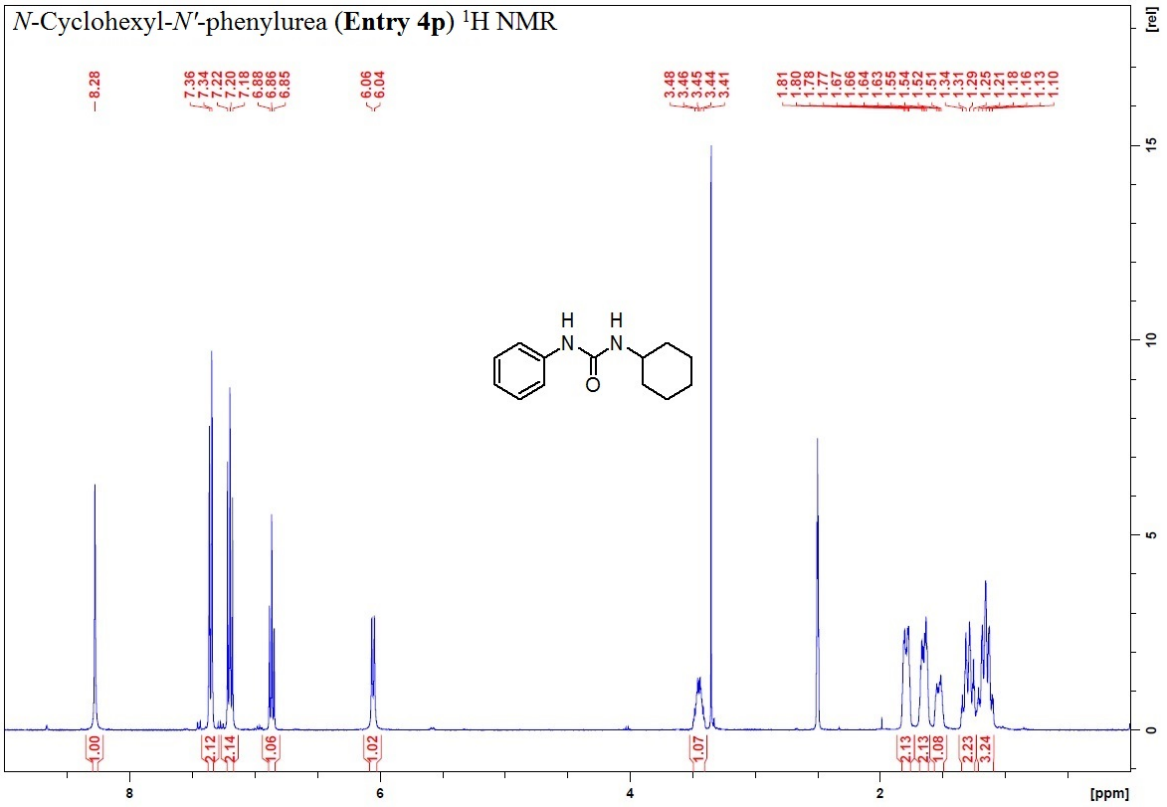
N-(*t*-Butyl)-*N*′-phenylurea (**Entry 4o**) ^{1}H NMR



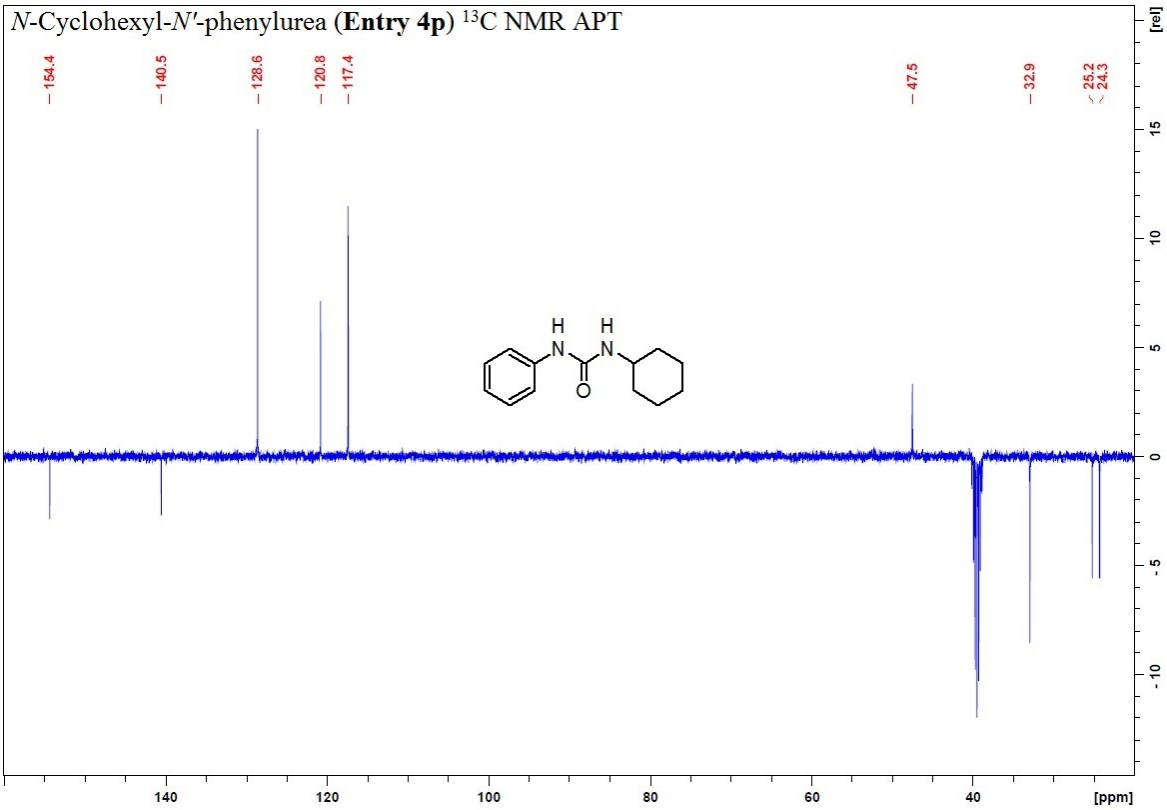
N-(*t*-Butyl)-*N*′-phenylurea (**Entry 4o**) ^{13}C NMR APT



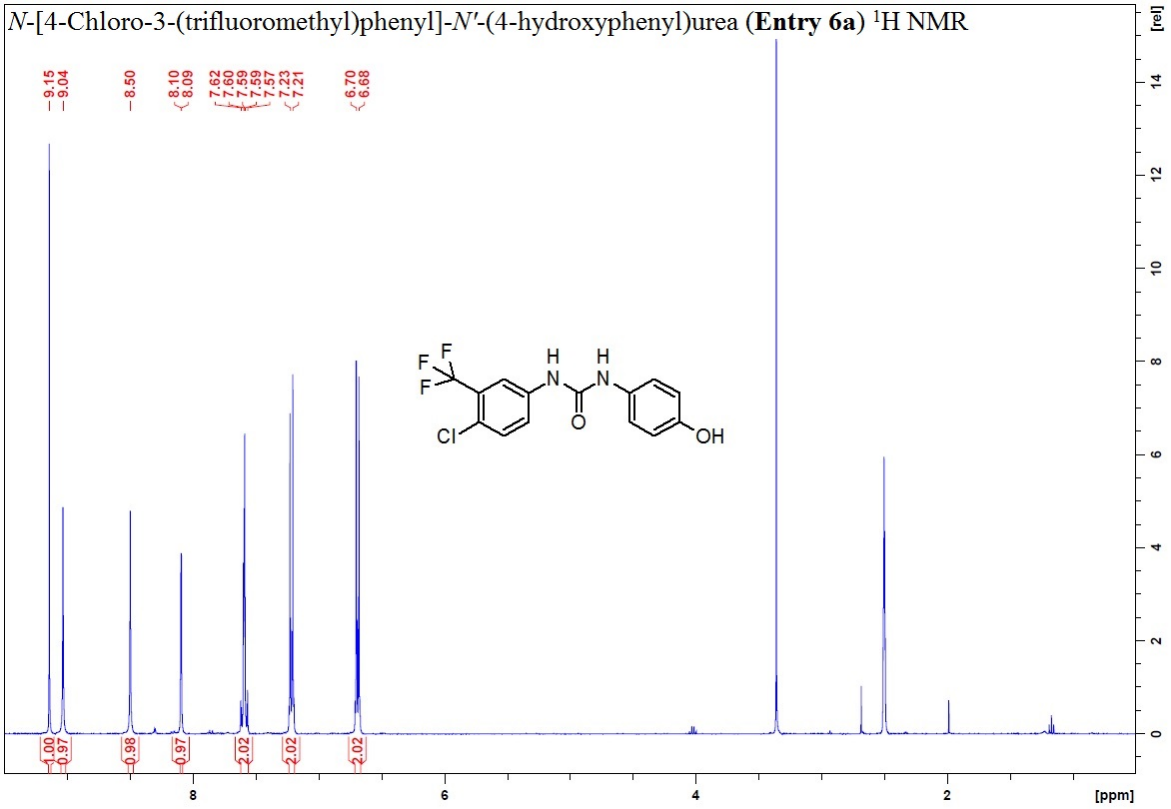
N-Cyclohexyl-*N*′-phenylurea (**Entry 4p**) ^{1}H NMR



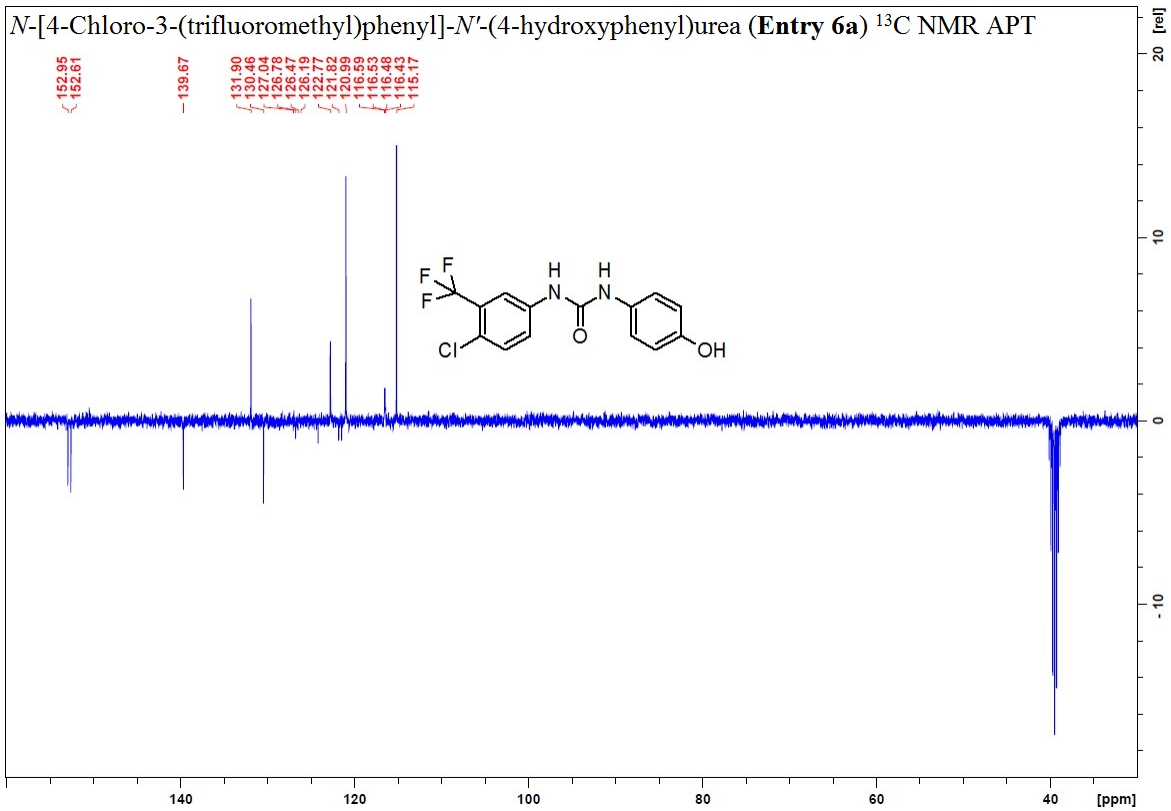
N-Cyclohexyl-*N*′-phenylurea (**Entry 4p**) ^{13}C NMR APT



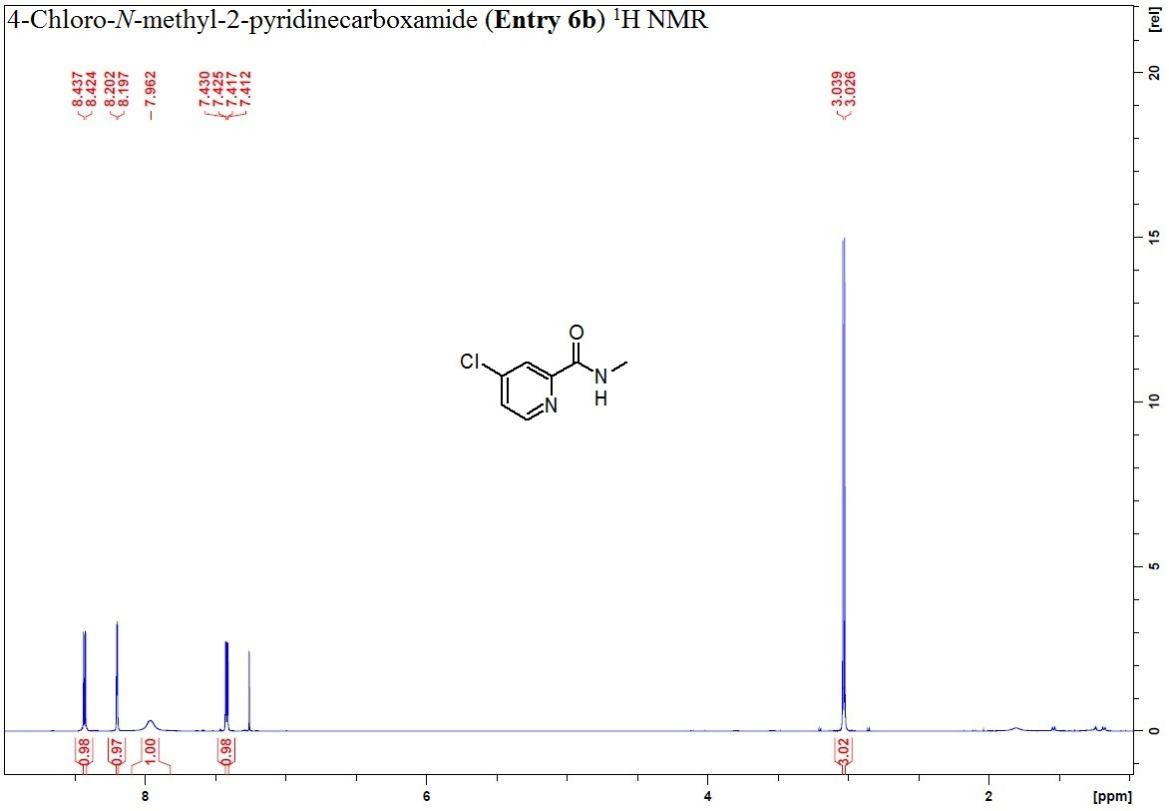
N-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-hydroxyphenyl)urea (**Entry 6a**) ^{1}H NMR



N-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-hydroxyphenyl)urea (**Entry 6a**) ^{13}C NMR APT



4-Chloro-*N*-methyl-2-pyridinecarboxamide (**Entry 6b**) ^{1}H NMR



4-Chloro-*N*-methyl-2-pyridinecarboxamide (**Entry 6b**) ^{13}C NMR APT