Facile synthesis of 1, 3-benzaoxazine fused triazoles via Pd-catalysed highly selective isocyanide insertion/cyclisation/N-N bond formation cascade

A thesis

Submitted in the partial fulfilment of the requirement for the award of degree of

MASTER OF SCIENCE
in
CHEMISTRY

Submitted by
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Under the supervision of
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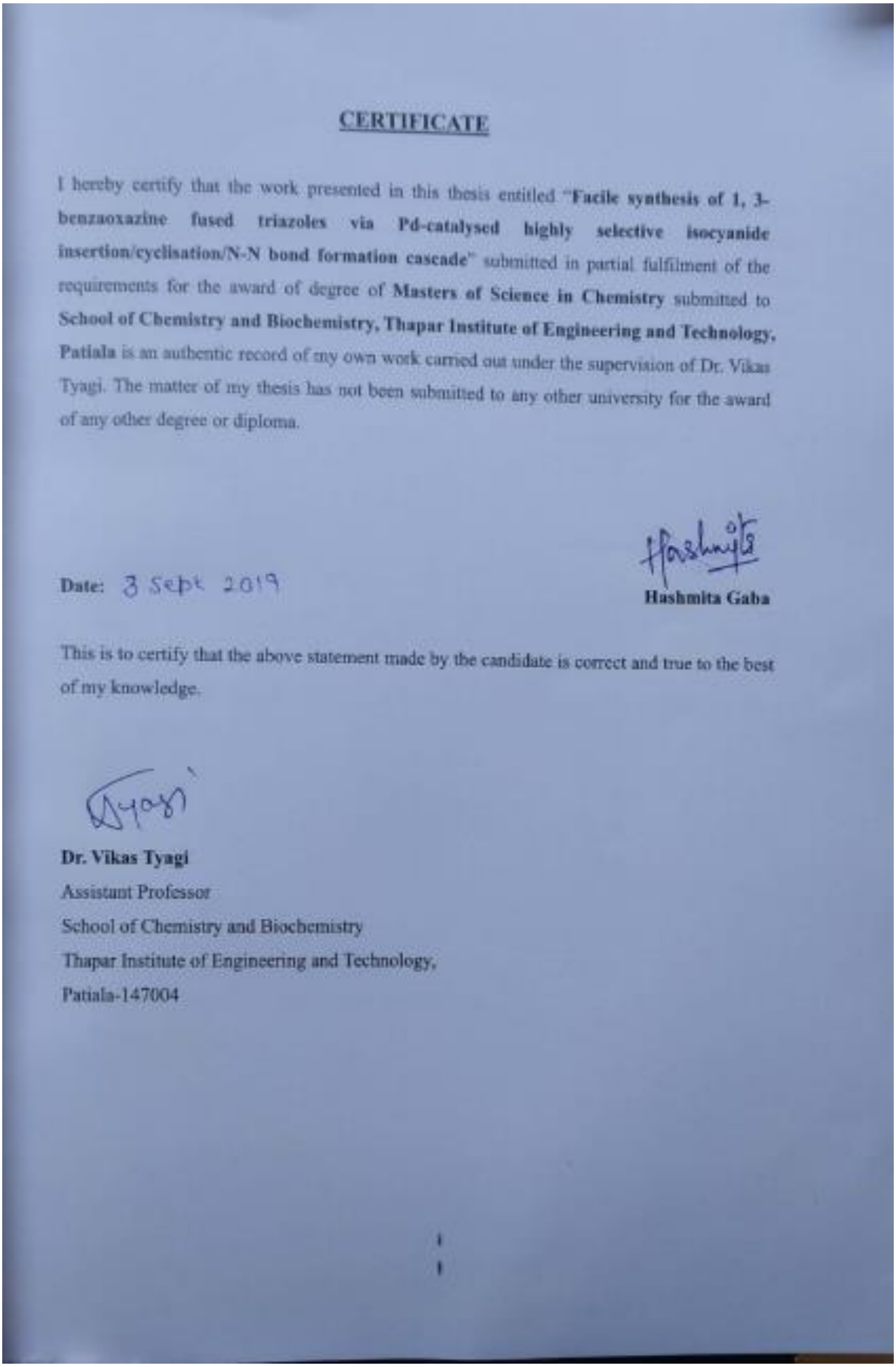
July 2019



CERTIFICATE

I hereby certify that the work presented in this thesis entitled "**Facile synthesis of 1, 3-benzaoxazine fused triazoles via Pd-catalysed highly selective isocyanide insertion/cyclisation/N-N bond formation cascade**" submitted in partial fulfilment of the requirements for the award of degree of **Masters of Science in Chemistry** submitted to **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** is an authentic record of my own work carried out under the supervision of Dr. Vikas Tyagi. The matter of my thesis has not been submitted to any other university for the award of any other degree or diploma.

Date: 3 Sept 2019

Hashmita Gaba

This is to certify that the above statement made by the candidate is correct and true to the best of my knowledge.

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SELF-DECLARATION

The work embodies is the project entitled **"Facile synthesis of 1, 3-benzaoxazine fused triazoles via Pd-catalysed highly selective isocyanide insertion/cyclisation/N-N bond formation cascade"** has been done by me in partial fulfilment of the requirement for the award of degree of **Masters of Science in Chemistry**, submitted in the **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** is an authentic record of my own work carried under the guidance and supervision of Dr. Vikas Tyagi, Assistant Professor, School of Chemistry and Biochemistry, Thapar Instititute of Engineering and Technology, Patiala, All the ideas and references has been duly acknowledged.

Hashmita

Date: 3 Sept 2019

Hashmita Gaba

This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

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ACKNOWLEDGEMENT

I would like to express my special thanks of gratitude to my research supervisor, Dr. Vikas Tyagi for the continuous support of my research, for his patience, motivation and immense knowledge. He has taught me the methodology to carry out the research and to present the same as clearly as possible. I would also like to thank him for his friendship, empathy and great sense of humour. His guidance helped me in all the time of research and writing of the thesis. I could not have asked for a better supervisor for my thesis.

Besides my advisor, I would like to express my sincere gratitude to our Head of Department, Dr. Amjad Ali for giving me this opportunity to work on wonderful project on the topic **Facile synthesis of 1, 3-benzaoxazine fused triazoles via Pd-catalysed highly selective isocyanide insertion/cyclisation/N-N bond formation cascade,** which helped me in doing a lot of research and I came to know about so many new things I am really thankful to.

My completetion of this project could not have been accomplished without the support of my fellow lab and class mates. Last but not the least I am extremely grateful to my family: my parents for supporting me spiritually throughout my life.

Date: 03-09-2019 **Hashmita Gaba**

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ABSTRACT

Triazoles are a significant class of N-heterocycles that are well known for their biological activities. In recent years, many advances and practices have been performed to synthesise triazole containing compounds. In this work we have demonstrated an effective protocol for the synthesis of benzoxazine fused triazoles which are known for their diuretic activities.

The synthesis comprises of Pd-catalysed one pot cascade reaction involving isocyanide insertion, cyclisation and N-N bond formation from N-arylamides based hydrazones. N-aryl diazoamides are basically used in the synthesis of oxindoles but herein we have used them as starting material for the synthesis of fused triazoles. This method is really easy to carry out and to extract the product. The final product is formed in good to excellent yields with no side products leading to less chemical waste making this protocol eco-friendly.

CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

1.1. Introduction

There is a growing interest in triazoles containing compounds because of their significant applications and popularity in various areas of chemistry inclusive of material science, supramolecular, medicinal and pharmaceutical chemistry. Further, triazole fused heterocyclic compounds have been found showing a wide range of biological activities for example antibacterial[1], anti-HIV[2,3], antitrypanosomal[4] (**A**), antiallergic, anti-fungal[6] (**B**), cardiovascular[7] (**C**), antileishmanial[4] (**D**), anti-cancer[8] (**E**), and chemotherapeutic[9] (**F**) activities (**Fig. 1**). Among various triazole containing heterocycles, benzoxazine fused trizaoles have been interesting scaffolds due to their diuretic activities (**G**).[10]

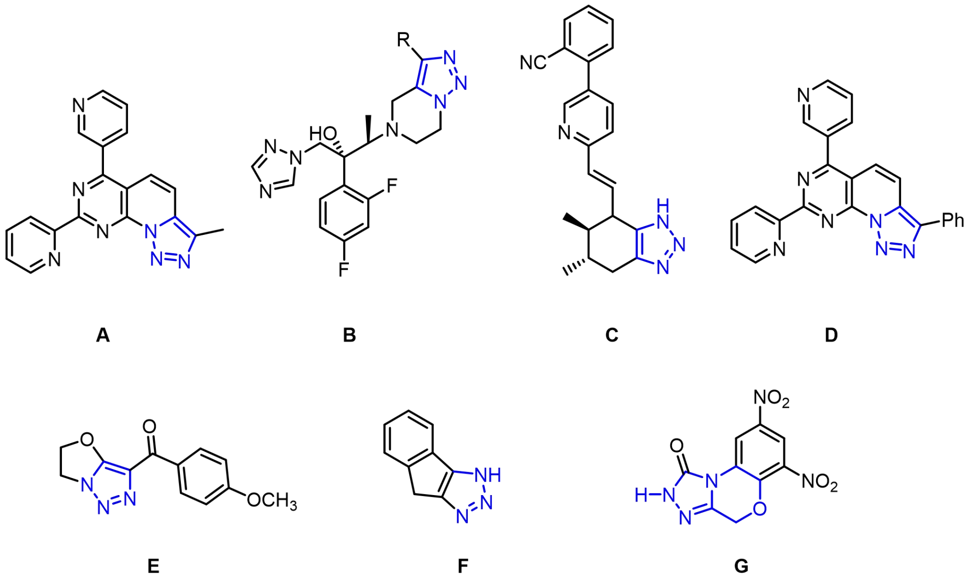


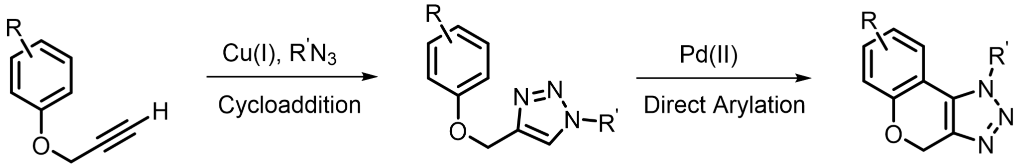
Fig. 1: Biologically active triazole fused heterocycles

On the other hand, tandem reactions (cascade) have gain lots of attention in last few years due to a number of advantages such as multiple bond formations in one-pot process deprived of isolating the intermediate species and varying the reaction conditions. Also, tandem protocols are highly economic and eco-friendly, since they generate less amount of chemical wastes.[11,12] In last few years, a number of Pd-catalysed tandem reactions have been reported for synthesizing various heterocyclic compounds from activated alkenes and 4-chloroacetoacetates leading to the formation of 4-substituted-3-(2H)-furanones[13], spiro-oxindole from two aryl iodides involving four times C-C bond formation followed by triple C-H activation[14]. In addition, Pd-catalyzed tandem isocyanide insertions followed by intramolecular cyclisation have been advantageous in the preparation of various heteroatoms containing compounds e.g. isoquinolines, oxindoles or isoindoline.[15]

1.2. Literature review

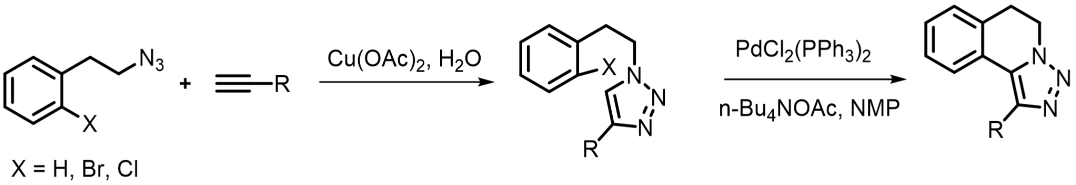
1.2.1. Recent strategies for synthesizing triazole fused heterocycles

The synthesis of fused triazole moiety has attracted a great attention from the chemical community in last few decades. The furthermost conventional method is the Click reaction which involves dipolar cycloaddition reaction using azides with alkynes for the preparation of heterocyclic fused triazoles which include both bicyclic and polycyclic[18]. Recently, a wide range of methods have been established for the preparation of heterocyclic fused triazoles. In this context, Schulman *et al.* reported a highly efficient approach towards three different heterocyclic fused 1,2,3-triazoles (**Scheme 1**).[19] This method involves Cu-catalysed alkyne azide cycloaddition followed by an intramolecular Pd-catalysed C-H functionalization or direct annulation and furnished the products in good yields and has been proved very useful in chemical and biological science.



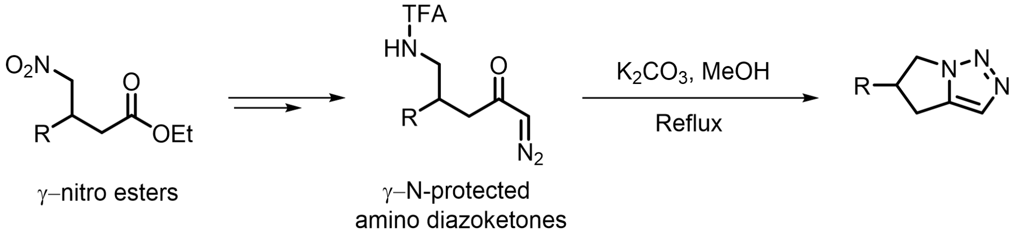
Scheme 1: Synthesis of polycyclic fused triazoles

Further, Fiandanese and co-workers synthesised isoindoles fused with 1,2,3-triazole and dihydroisoindoles in appreciable yields from terminal alkynes and (2-haloaryl)alkylazides (**Scheme 2**).[20] This synthesis involves preliminary cycloaddition of alkynes and alkyl azides and after that direct intramolecular Pd-catalysed C-H bond functionalization takes place.



Scheme 2: Synthesis of isoindoles and dihydroisoquinolines fused with 1,2,3-triazoles

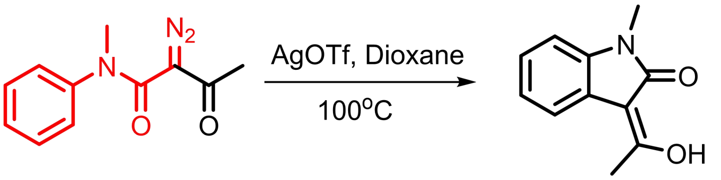
The Santiago's group demonstrated a direct synthesis of five membered rings fused with 1,2,3-triazoles rings in 63-95% yields after using γ-N-protected amino diazoketones (**Scheme 3**).[21] The strategy include three sequential steps such as deprotection of protecting group followed by formation of α-diazo imine and cyclisation.



Scheme 3: Synthetic sequence 1,2,3-triazoles containing bicyclic compounds from γ-N-(trifluoroacetyl) aminodiazoketones

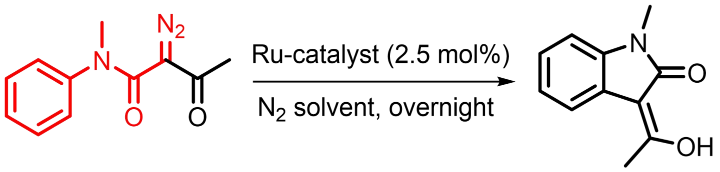
1.2.2. Recent approaches using N-aryl diazoamide as starting precursor

Previously, aryl α-diazoamides has been used in a number of approaches as a starting material for synthesizing various heterocyclic scaffolds. In this context, Li and Gao reported synthesis of 3-alkylideneoxindoles by environmentally friendly method that is Ag-catalysed intramolecular cyclization of N-aryl-α-diazoamide via in-situ formation of Ag-carbene complex (**Scheme 4**).[22] The mechanism involves nitrogen dissociation and Ag carbene addition followed by proton transfer.



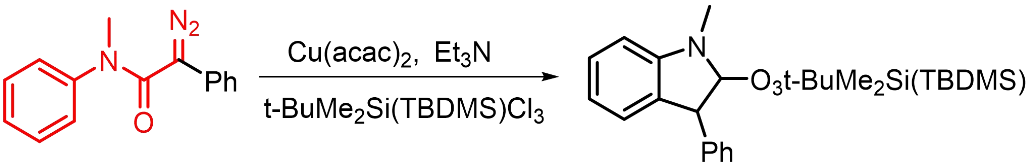
Scheme 4: Indole synthesis via Ag-carbene complex from aryl α-diazoamides

Further, Chan and co-workers synthesised same product as in Li and Gao that is 3-alkylideneoxindoles with the help of catalyst, [Ru (p-cymene)Cl_2]$_2$ (**Scheme 5**).[23] This synthesis involves intramolecular C-H bond functionalization of carbenoid arene in diazo β-ketoanilides under trivial reaction conditions. This synthesis affords the yield of the product, 3-alkylideneoxindoles up to 92%.



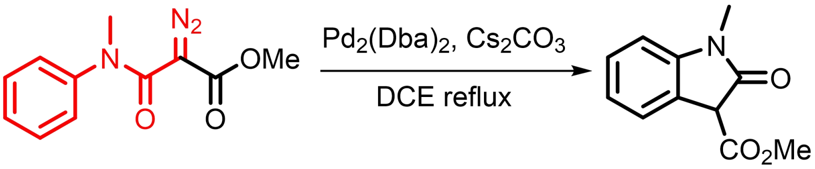
Scheme 5: Ru-catalysed C-H functionalization of diazo-β-ketoanilides to synthesise 3-alkyideneoxindoles

One pot synthesis of 2-acetoxyindole-3-carbonitriles was done by Mo *et al.* in excellent chemo specificity (**Scheme 6**)[24] via treating 2-cyano diazoacetanilides with acetyl chloride and triethylamine in presence of Cu(acac)$_2$ as catalyst.



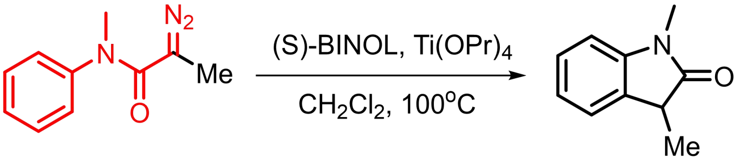
Scheme 6: Synthesis of 2-acetoxyindole-3- carbonitriles from 2-cyano diazoacetanilides

Moreover, Sole *et al.* reported a selective $Pd_2(dba)_3$ catalysed C-H addition of α-diazo-α-(methoxycarbonyl)acetanilides which synthesise oxindole derivatives (**Scheme 7**).[25]



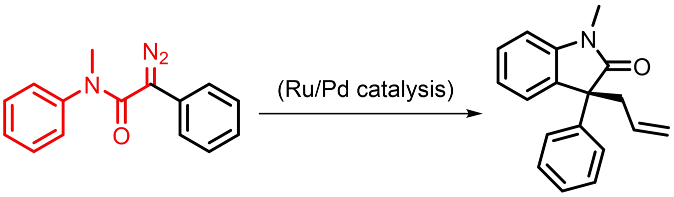
Scheme 7: α-diazo-α-(methoxycarbonyl)acetanilides undergoing carbenoid C-H insertion

N-aryl diazoamides undergoing intramolecular cyclization with the help of chiral Ti-BINOLate for asymmetric C-H addition and cyclization reported by Hashimoto and his fellow workers (**Scheme 8**).[26] The catalyst acts as chiral lewis acid which protonates the substrate in asymmetric manner. It gave corresponding oxindoles in 96% yield with modest enantioselectivity.



Scheme 8: Intramolecular cyclisation of N-aryl diazoamides with Ti-BINOLate complex

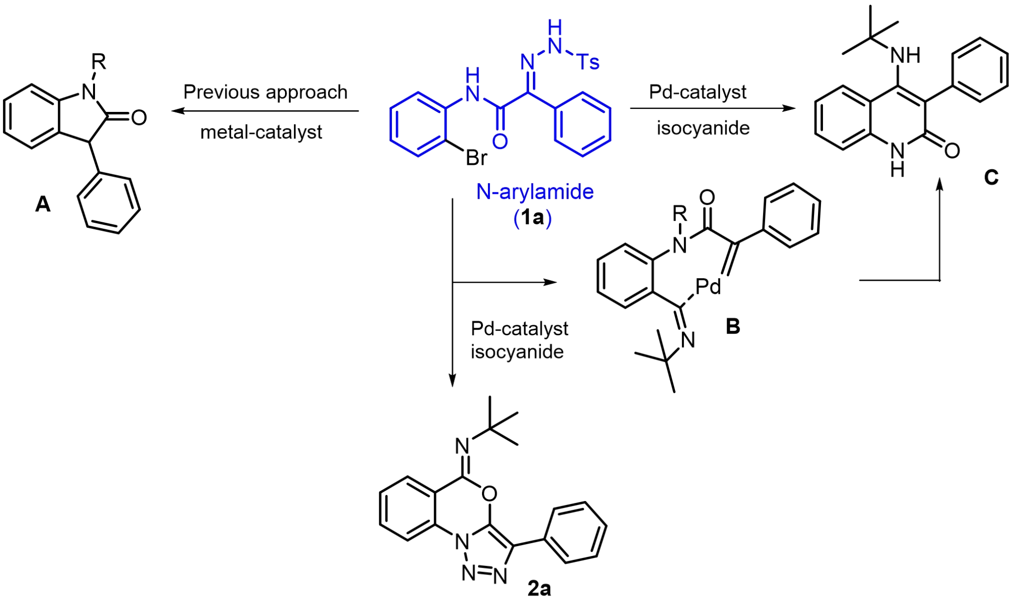
Yamamoto *et al.* reported one-pot ruthenium catalysed C-H functionalization along with the palladium catalysed allylic alkylation of N-aryl α-diazoamides (**Scheme 9**).[27] This strategy leading to product formation in outstanding yield of 3-allyl-3-aryl oxindoles possessing modest enantioselectivity.



Scheme 9: Novel dual-metal-catalysed reaction of α-diazoamides giving rise to aryl oxindoles

1.2.3. Our hypothesis

In accordance to previous approaches, it have been shown that N-aryl dizoamide in presence of metal-catalyst gives substituted oxindoles (**A**).[22] Herein, we envisaged that if we use isocyanide with N-aryldizoamides along with the palladium species as catalyst, the reaction would provide 4-aminoquinoline (**C, Scheme 10**). However, the NMR and mass studies showed the formation of some unusual product. To find the structure, we crystalize the product by slow evaporation method and got the X-ray crystal structure which suggested that product was benzoxzazine fused triazole (**Fig. 2**).



Scheme 10: Expected products from the starting material by Pd-catalysed tandem reaction.

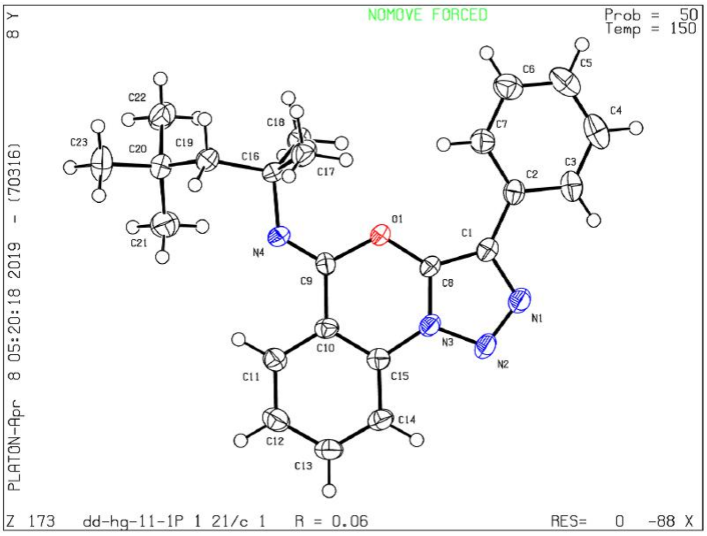


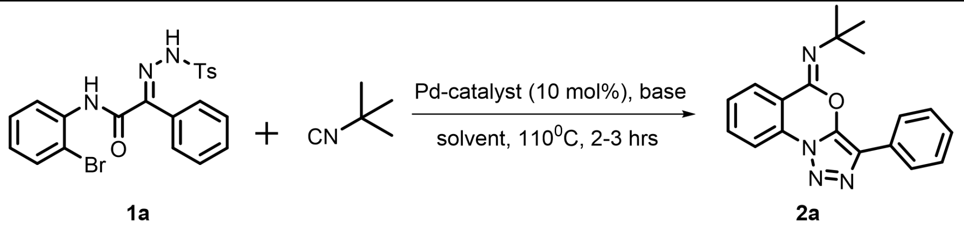
Fig. 2: Single crystal structure of product (**2b**)

CHAPTER 2: RESULTS AND DISCUSSION

2.1. Reaction condition optimisation

Initially, to verify the feasibility of Pd-catalysed cascade process for the preparation of benzoxazine fused triazoles (**2a**), *tert*-butyl isocyanide and corresponding hydrazone (**1a**) were chosen as the template reaction substrates for investigation. The formation of product (**2a**) was achieved in 75.7% yield after implementing 10 mol% of $Pd(OAc)_2$ and carried out the transformation in 1,4-dioxane as solvent at 110°C in a glass tube (**Table 1**, entry 1).

Table 1. Optimisation of reaction criteria[a]



Entry	Catalyst	Base	Solvent	Temperature(°C)	Yield[b] (%)
1.	**$Pd(OAc)_2$**	**KO*t*-Bu**	**1,4-dioxane**	**110**	**75.7**
2.	$PdCl_2$	KO*t*-Bu	1,4-dioxane	110	26
3.	$PdCl_2(NCC_6H_5)_2$	KO*t*-Bu	1,4-dioxane	110	50
4.	**$Pd(DPPF)Cl_2$**	**KO*t*-Bu**	**1,4-dioxane**	**110**	**75**
5.	$Pd(dba)_3$	KO*t*-Bu	1,4-dioxane	110	47
6.	$Pd(PPh_3)_4$	KO*t*-Bu	1,4-dioxane	110	Trace
7.	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	110	55
8.	$Pd(OAc)_2$	Cs_2CO_3	1,4-dioxane	110	Trace
9.	$Pd(OAc)_2$	KOH	1,4-dioxane	110	50
10.	$Pd(OAc)_2$	NaH	1,4-dioxane	110	60
11.	$Pd(OAc)_2$	$NaHCO_3$	1,4-dioxane	110	25
12.	$Pd(OAc)_2$	DBU	1,4-dioxane	110	38
13.	$Pd(OAc)_2$	LiO*t*-Bu	1,4-dioxane	110	63
14.	$Pd(OAc)_2$	KO*t*-Bu	Toluene	110	30
15.	$Pd(OAc)_2$	KO*t*-Bu	DMF	110	Trace
16.	$Pd(OAc)_2$	KO*t*-Bu	DMSO	110	27
17.	$Pd(OAc)_2$	KO*t*-Bu	THF	110	33

[a] Reaction conditions: substrate **1a** (1.0 equivalent), *tert*-butyl isocyanide (1.2 equivalents), Pd-catalyst (10 mol%), base (3.0 equivalents), solvent (2 ml), temperature of the reaction (110°C) and time (2-3 hrs). [b] isolated yield.

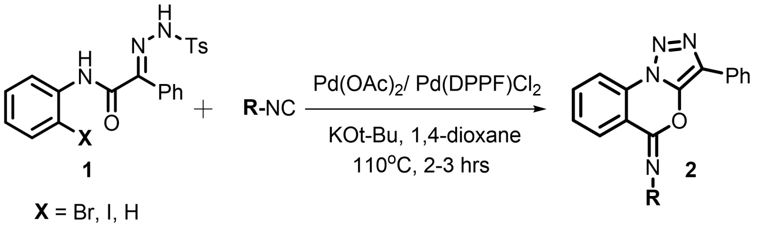
Encouraged by this preliminary result, a series of Pd-catalysts were afterwards tested (**Table 1**, entries 2-6), and the outcome showed that $Pd(OAc)_2$ and $Pd(DPPF)Cl_2$ were superior than other Pd-catalysts giving almost equivalent product yields (75%) (**Table 1**, entries 1 and 4) which made them the best out of all. Although, beside these catalysts, $PdCl_2(NCC_6H_5)_2$ and $Pd(dba)_3$ also gave a good yield of 50% and 47% respectively (**Table 1**, entries 3 and 5). A comparatively less yield i.e. 26% was obtained in the case of $PdCl_2$ (**Table 1**, entry 2). Moreover, when we used $Pd(PPh_3)_4$ as catalyst, only trace amount of product was formed (**Table 1**, entry 6). Thus, we chose $Pd(OAc)_2$ as the best catalyst for remaining optimisation of reaction conditions that is with different bases and solvents

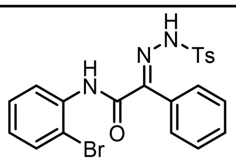
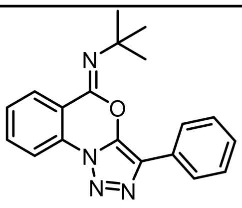
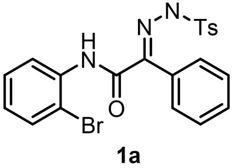
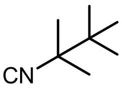
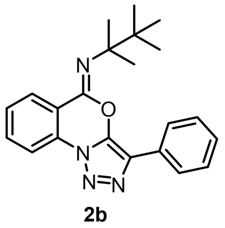
(**Table 1**, entries 7-17). On augmenting the reaction with different bases, KO*t*-Bu gave the maximum conversion among the bases screened for this reaction (**Table 1**, entry 1). However, LiO*t*-Bu also afforded 63% yield of the expected product (**Table 1**, entry 13). A respectable amount of product was formed in the case of K_2CO_3, KOH, NaH with the isolated yield (50-60%) (**Table 1**, entries 7, 9 and 10). The product was formed when $NaHCO_3$ and DBU were implemented as base but inferior yields were achieved (**Table 1**, entry 11 and 12). Further, the trace amount of product was formed when Cs_2CO_3 was used as a base (**Table 1**, entry 8). After having best catalyst and base such as $Pd(OAc)_2$ and KO*t*-Bu, the screening of solvent was done (**Table 1**, entries 14-17). We observed that variations in solvent have a substantial effect on the product formation in this reaction. Among the solvents tried, 1,4-dioxane appeared to be the best appropriate reaction media, giving the targeted product in 75.7% (**Table 1**, entry 1). When we used solvents including toluene, THF and DMSO, we attained the product in 27-33% yield (**Table 1**, entries 14, 16 & 17). When DMF was used, product was obtained in only trace amount (**Table 1**, entry 15).

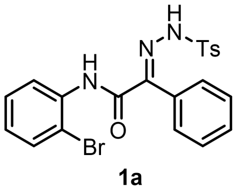
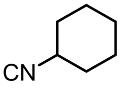
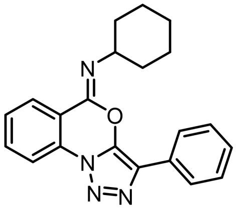
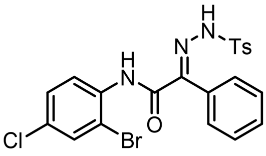
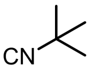
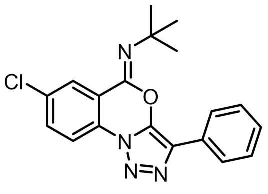
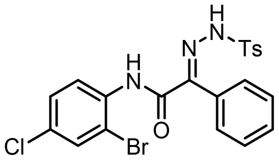
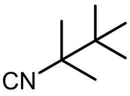
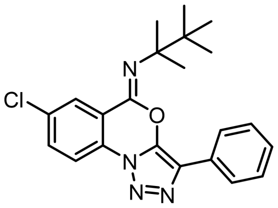
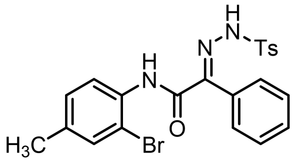
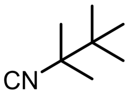
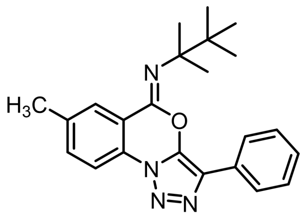
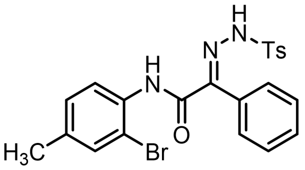
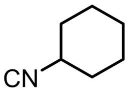
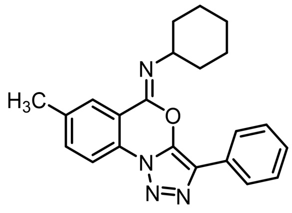
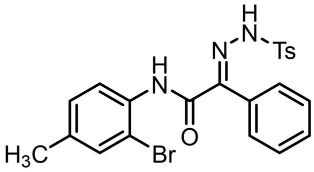
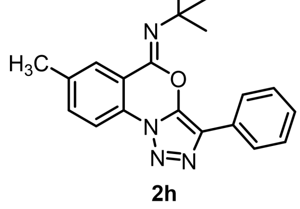
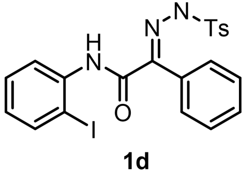
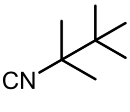
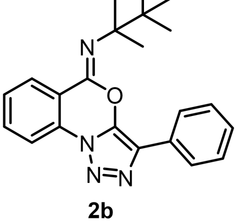
2.2. Substrate scope

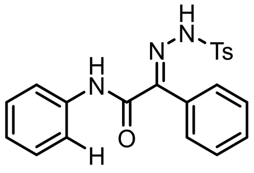
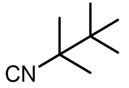
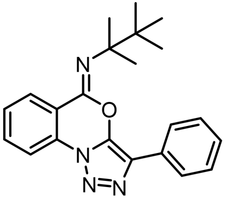
After having the best conditions in hand such as KO*t*-Bu as base, ($Pd(OAc)_2$ or $Pd(DPPF)Cl_2$ as catalyst and 1,4-dioxane in place of solvent, next, we tested the scope of reaction after having various substitutions on (**1a**) and using different isocyanides and collected all the results in **Table 2**.

Table 2. Effect of various substitutions on Pd-catalysed transformation[a]



Entry	Substrate (**1**)	CN-**R**	Product (**2**)	Yield[b] (%)
1.	 **1a**		 **2a**	75.7%
2.	 **1a**		 **2b**	72%

3.	 **1a**		 **2c**	65.5%
4.	 **1b**		 **2d**	55.9%
5.	 **1b**		 **2e**	36.2%
6.	 **1c**		 **2f**	80%
7.	 **1c**		 **2g**	72%
8.	 **1c**		 **2h**	74%
9.	 **1d**		 **2b**	72.1%

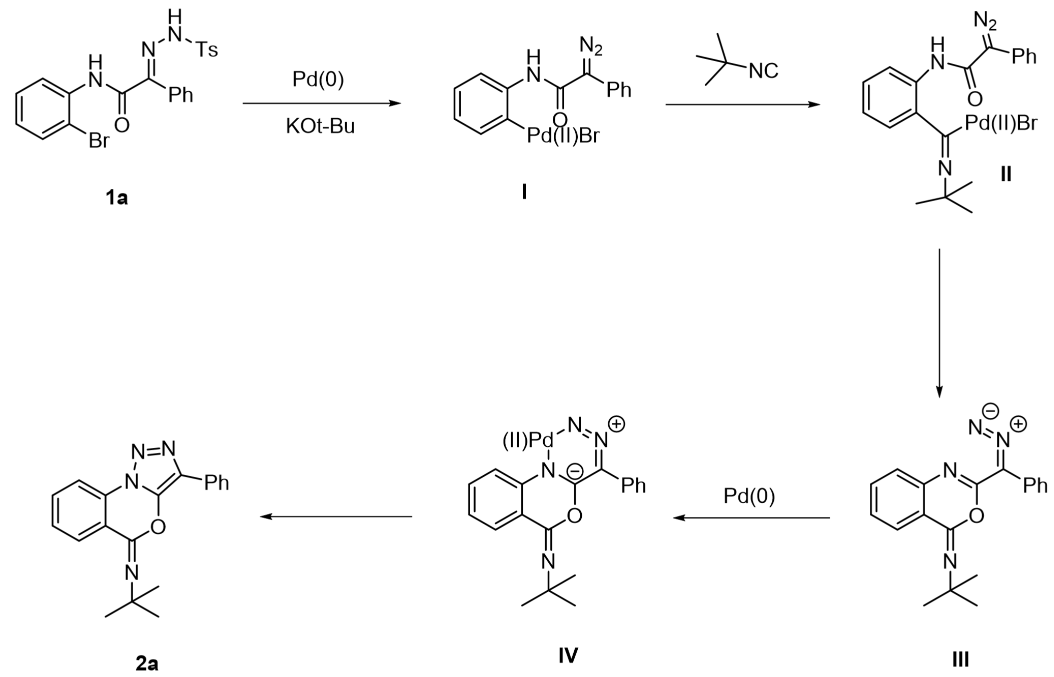
10.	 **1e**		 **2b**	Traces

[a]Reaction conditions: substrate (1.0 equivalent), isocyanide (1.2 equivalent), Pd(OAc)$_2$/Pd(DPPF)Cl$_2$ (10 mol%), KO*t*-Bu (3.0 equivalents), 1,4-dioxane (2 ml), 110°C. [b]Isolated yields.

When we treated (**1a**) as substrate with 1,1,3,3-tertramethylbutyl isocyanide, (**2b**) was exclusively obtained in yield 72% (**Table 2**, entry 2) which is almost equivalent to yield of (**2a**) synthesised from same substrate (**1a**) along with *tert*-butyl isocyanide (**Table 2**, entry 1). But, in the case where cyclohexyl isocyanide is reacted with substrate (**1a**), yield of product (**2c**) is lowered to 65.5% (**Table 2**, entry 3). Further, substrate (**1a**) bearing chloro at *para*-position, the product is formed in lesser amount (**Table 2**, entry 4-5). This shows substrates having mild electron withdrawing groups at the anilide ring are less reactive for the cyclization reaction. Additionally, when 1,1,3,3-tetramethylbutyl isocyanide has put into the reaction with 4-chloro-substituted substrate (**1b**), 36.2% yield of the desired product (**2e**) was achieved (**Table 2**, entry 5). Also, transformation gave moderate yield after using *tert*-butyl isocyanide with (**1b**) (**Table 2**, entry 4). Therefore, it might be established that the presence of a mild electron withdrawing atom on *para*-position gives the product in poor to moderate yield. While, in the presence of an electron releasing groups such as methyl at the 4-position of **1a,** obtained the product in a little bit higher yield (**Table 2**, entry 6-8). When, we used 1,1,3,3-tertramethylbutyl isocyanide with substrate (**1c**), the product (**2f)** was formed in an excellent yield (**Table 2**, entry 6). Also, with cyclohexyl and *tert*-butyl isocyanide, appreciable yields of product (**2g**) and (**2h**) were obtained with 4-methyl-substituted substrate (**Table 2**, entry 7-8). In addition to these, scope of substrate was also examined by changing the substituent at *ortho*-position (**Table 2**, entry 1, 9, 10). We found that Pd-catalysed cyclisation is more facile in substrates having halides like bromo (**1a**) and iodo (**1d**) at *ortho*-position, giving comparatively equivalent amount of product (**2b**) (**Table 2**, entry 1 & 9). While, when there is an absence of any halide on *ortho*-position (**1e**), the product is formed in trace amount (**Table 2**, entry 10). This explains the importance of presence of a halide on the *ortho*-position.

2.3. Plausible mechanism

The probable mechanism for the synthetic sequence of product (**2a**), constructed on the basis of our observations and prior mechanistic studies[15] has been described in **Scheme 11**. The conversion of (**1a**) to the first intermediate (**I**) take place by two steps occurring simultaneously that is conversion of tosyl hydrazone to diazo due to the addition of base and oxidative addition of Palladium leading to the formation of a species (**I**). Then, isocyanide insertion takes place through migratory insertion to Pd(II) species (**I**), giving rise to an intermediate (**II**). The intermediate (**II**) via intramolecular cyclisation involving oxygen atom followed by abrupt reductive elimination giving rise to species (**III**) and regeneration of Pd(0) via reductive elimination. Then, intermediate (**III**) undergoes another cycle of Pd-catalysis for N-N bond formation as reported previously[17]. This involves oxidative addition of Pd metal and leads to formation of a Pd-complex (**IV**). Further, reductive elimination along with the N-N bond formation gives the product (**2a**) and removal of Pd(0) for another cycle of catalysis (**Scheme 11**).



Scheme 11. Plausible mechanism to prepare the triazole fused benzoxazine

CHAPTER 3: EXPERIMENTAL

3.1. General information

All the reagents and solvents were procured from marketable sources and used without purification. The Jeol & Bruker spectrometer at 300 (400) for ^{1}H-NMR and 75 (100) for ^{13}C-NMR were used for recording NMR spectra in $CDCl_3$ with internal reference taken as tetramethylsilane. The chemical shifts is represented by δ (ppm) and coupling constant in J (Hz). HRMS was taken in TOF MS ESI-positive mode. Silica gel glass plates were used for Thin Layer Chromatography (TLC) for the monitoring of reaction progress. The column chromatography was performed using silica gel (100-120 micron). All the compounds were characterised by TLC, ^{1}H NMR, ^{13}C NMR and HRMS.

3.2. General methodology for synthesis of N-aryl amides based tosylhydrazone derivatives (1a-1e)

A mixture of aniline (1.0 equivalent), benzoyl formic acid (1.5 equivalents), DMAP (1.5 equivalents) and DCC (1.5 equivalents) were added in dichloromethane as solvent (~ 10 mL) at 25°C and stirred the resulting mixture for overnight. Upon complete conversion of the starting materials, work up of the reaction with ethyl acetate and distilled water in 2:1 ratio was done and the volatiles were removed by using high vacuum. The mixture was purified using gradient column chromatography to obtain the equivalent amides. To the corresponding amide (1.0 equivalent), tosyl hydrazine (1.5 equivalents) and p-TSA (1.0 equivalent) in methanol (10 mL) were added and the resulted mixture was heated at 70°C for 3 hrs. The reaction conversion was monitored by TLC and upon complete consumption of the reactants, the volatiles were removed and the desired product was purified by column chromatography to obtain N-aryl amide based tosyl hydrazones.

3.3. Methodology for the preparation of triazole fused benzoxazine (2a-2h)

To the mixture of N-arylamides based tosyl hydrazones (1.0 equivalent) and base (3 equivalents) in solvent (5 ml), Pd-catalyst (10 mol%) was added in the reaction tube followed by the addition of isocyanide (1.2 equivalents) in the same reaction tube. The resulted mixture was refluxed at 110°C for 2-3 hrs and the product formation was monitored by TLC. After completion of transformation, the volatiles were removed using high vacuum and the product was purified by column chromatography using ethyl acetate in hexanes.

3.4. Characterisation of compounds

N-(tert-butyl)-3-phenyl-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2a):

Solid, yield = 75.7%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.14 (m, 2H), 8.04-8.02 (m, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.50-7.41 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 1H), 1.52 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 138.6, 133.2, 132.3, 129.3, 128.9, 128.2, 127.9, 127.8, 125.3, 115.3, 114.9, 55.0, 30.0 ppm, HRMS calculated for $C_{19}H_{19}N_4O$ $[M+H]^+$ 319.3800 Found 319.3871.

3-phenyl-N-(2,3,3-trimethylbutan-2-yl)-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2b):

Solid, yield = 72%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 7.6, 2H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.45-7.54 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 1.60 (s, 6H), 1.08 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 137.0, 132.9, 132.4, 129.3, 129.3, 128.8, 128.1, 127.8, 127.7, 125.3, 115.5, 114.8, 58.6, 55.7, 31.8, 30.0 ppm, HRMS calculated for $C_{22}H_{25}N_4O$ $[M+H]^+$ 361.4610 Found 361.4681.

N-cyclohexyl-3-phenyl-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2c):

Solid, yield = 65.5%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H), 8.03 (d, *J* = 8 Hz, 2H), 7.72 (t, *J* = 8.4 Hz, 1H), 7.54-7.45 (m, 3H), 7.38 (t, *J* = 6.8 Hz, 1H), 4.12-4.06 (m, 1H), 1.97-1.89 (m, 2H), 1.62-1.36 (m, 8H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 141.1, 133.3, 132.2, 129.3, 128.8, 128.6, 128.2, 127.7, 125.0, 114.9, 114.5, 55.7, 33.3, 29.7, 25.7, 24.7 ppm, HRMS calculated for $C_{21}H_{21}N_4O$ $[M+H]^+$ 345.4180 Found 345.4181.

N-(tert-butyl)-7-chloro-3-phenyl-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2d):

Solid, yield = 55.9%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (s, 1H), 8.1 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 1.2 Hz, 1H), 8.03 (d, *J* = 1.2 Hz, 1H), 7.6 (d, *J* = 8.4 Hz, 1H), 7.5 (t, *J* = 8 Hz, 2H), 7.3 (t, *J* = 7.6 Hz, 1H), 1.55 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 137.3, 134.0, 133.3, 130.8, 129.0, 128.9, 128.8, 128.0, 127.9, 125.3, 116.7, 116.4, 55.2, 29.8 ppm, HRMS calculated for $C_{19}H_{18}N_4OCl$ $[M+H]^+$ 353.8220 Found 353.8224.

7-chloro-3-phenyl-N-(2,3,3-trimethylbutan-2-yl)-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2e) :

Solid, yield = 36.2%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 2 MHz, 1H), 8.13 (s, 1H), 8.0 (d, *J* = 1.2 Hz, 1H), 8.0 (d, *J* = 1.2 Hz, 1H), 7.6 (d, *J* = 8.8 Hz, 1H), 7.5 (t, *J* = 8.0 Hz, 2H), 7.3 (t, *J* = 7.6 Hz, 1H), 1.5 (s, 6H), 1.0 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 136.0, 134.0, 133.1, 130.8, 129.1, 128.9, 128.8, 128.0, 127.9, 125.3, 116.9, 116.5, 58.9, 55.4, 31.7, 30.0 ppm, HRMS calculated for $C_{22}H_{24}N_4OCl$ $[M+H]^+$ 395.9030 Found 395.9032.

7-methyl-3-phenyl-N-(2,3,3-trimethylbutan-2-yl)-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2f):

Solid, yield = 80%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.06 (m, 3H), 7.9 (s, 1H), 7.52-7.48 (m, 3H), 7.3 (t, *J* = 7.6 Hz, 1H), 2.4 (s, 3H), 1.6 (s, 6H), 1.0 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 138.4, 137.4, 133.8, 130.2, 129.4, 129.1, 128.8, 127.7, 127.6, 125.3, 115.2, 114.0, 58.6, 55.4, 32.0, 31.8, 30.1, 21.4 ppm, HRMS calculated for $C_{23}H_{27}N_4O$ $[M+H]^+$ 375.4880 Found 375.4881.

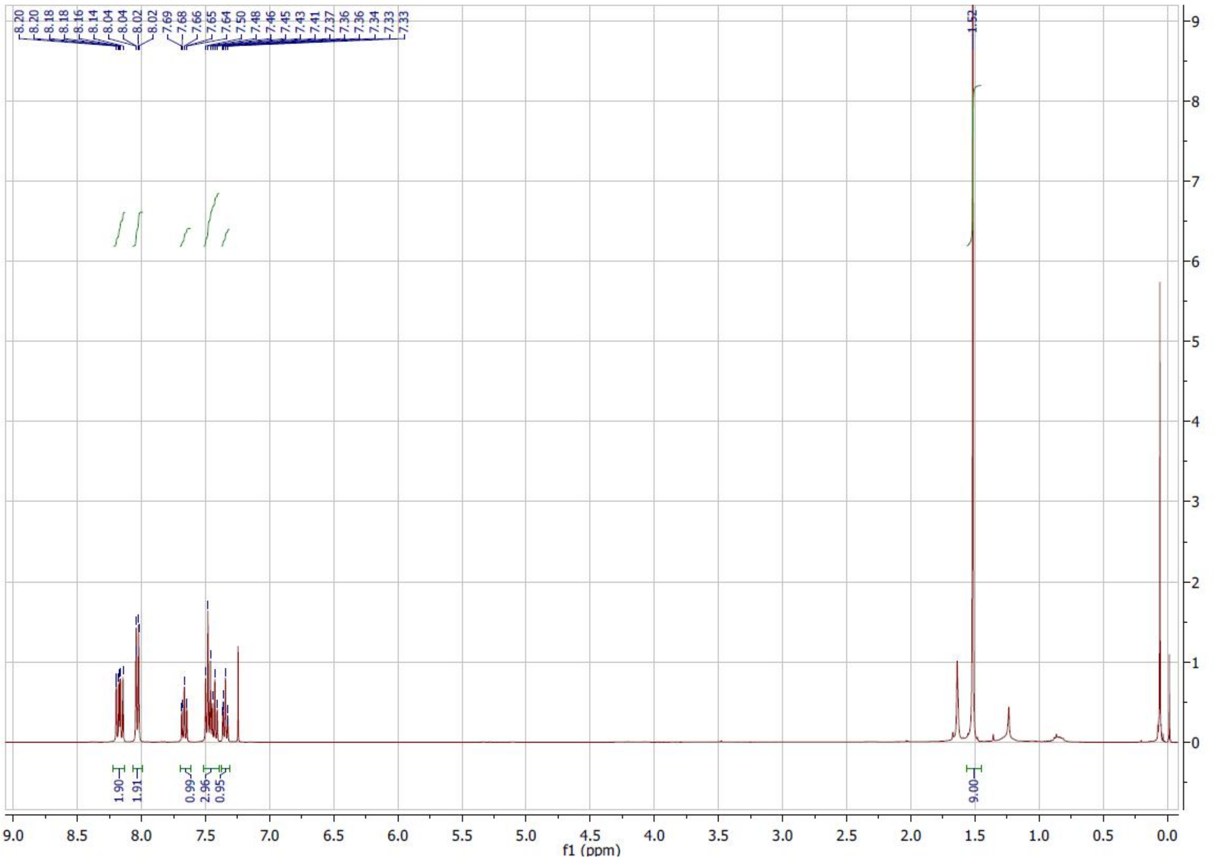
N-cyclohexyl-7-methyl-3-phenyl-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2g):

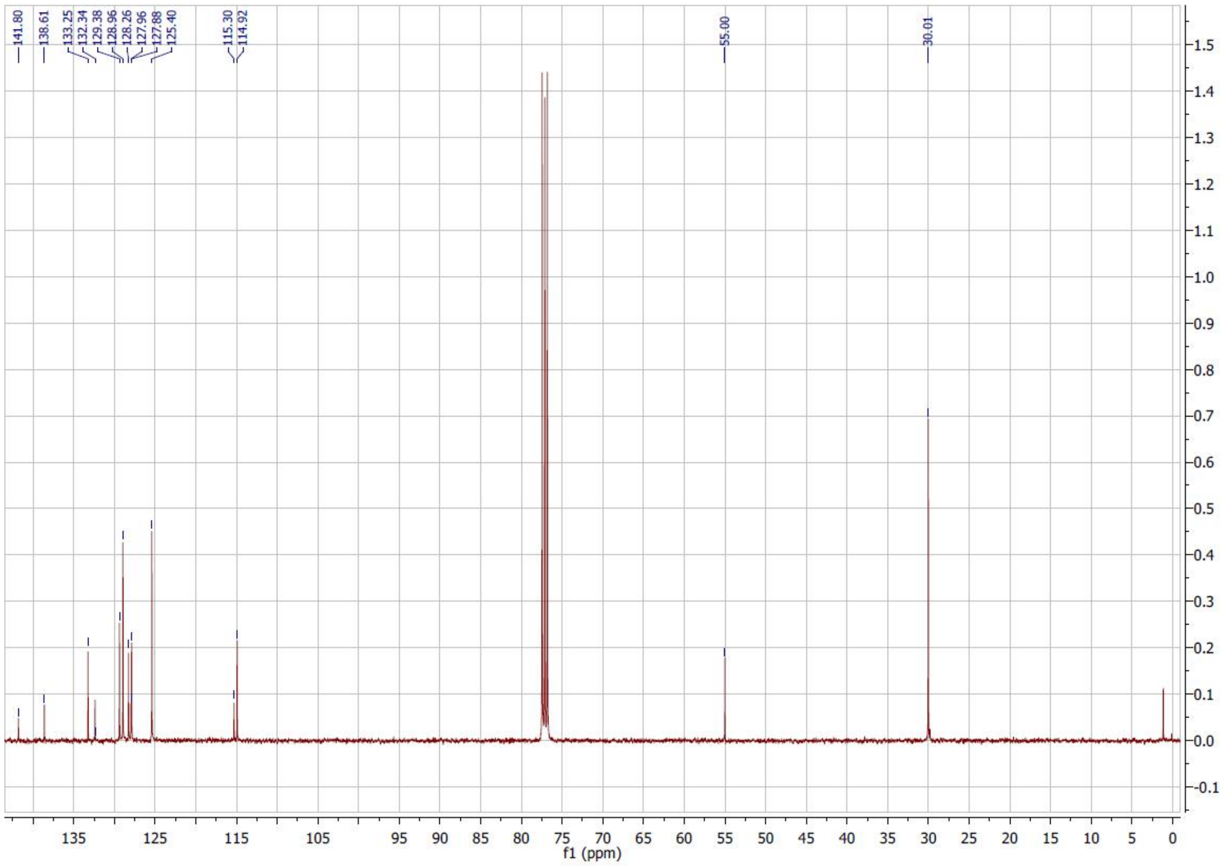
Solid, yield = 72%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.02 (m, 4H), 7.53-7.49 (m, 3H), 7.3 (t, *J* = 7.6 Hz, 1H), 2.48 (s, 3H), 4.11-4.06 (m, 1H), 1.97-1.91 (m, 2H), 1.63-1.40 (m, 8H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 141.5, 138.5, 134.2, 130.1, 129.4, 128.8, 128.3, 127.6, 125.0, 114.8, 114.1, 55.8, 33.4, 29.7, 24.8, 21.2 ppm, HRMS calculated for $C_{22}H_{23}N_4O$ $[M+H]^+$ 359.4450 Found 359.4452.

N-(tert-butyl)-7-methyl-3-phenyl-5H-benzo[d][1,2,3]triazolo[5,1-b][1,3]oxazin-5-imine (2h):

Solid, yield = 74%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.05 (m, 3H), 8.01 (s, 1H), 7.52-7.48 (m, 3H), 7.3 (t, *J* = 7.2 Hz, 1H), 2.47 (s, 3H), 1.55 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 138.9, 138.4, 134.0, 130.2, 129.4, 129.0, 128.8, 127.8, 127.7, 125.3, 114.9, 114.7, 54.8, 29.9, 21.3 ppm.

^{1}H NMR and ^{13}C NMR spectra of 2a





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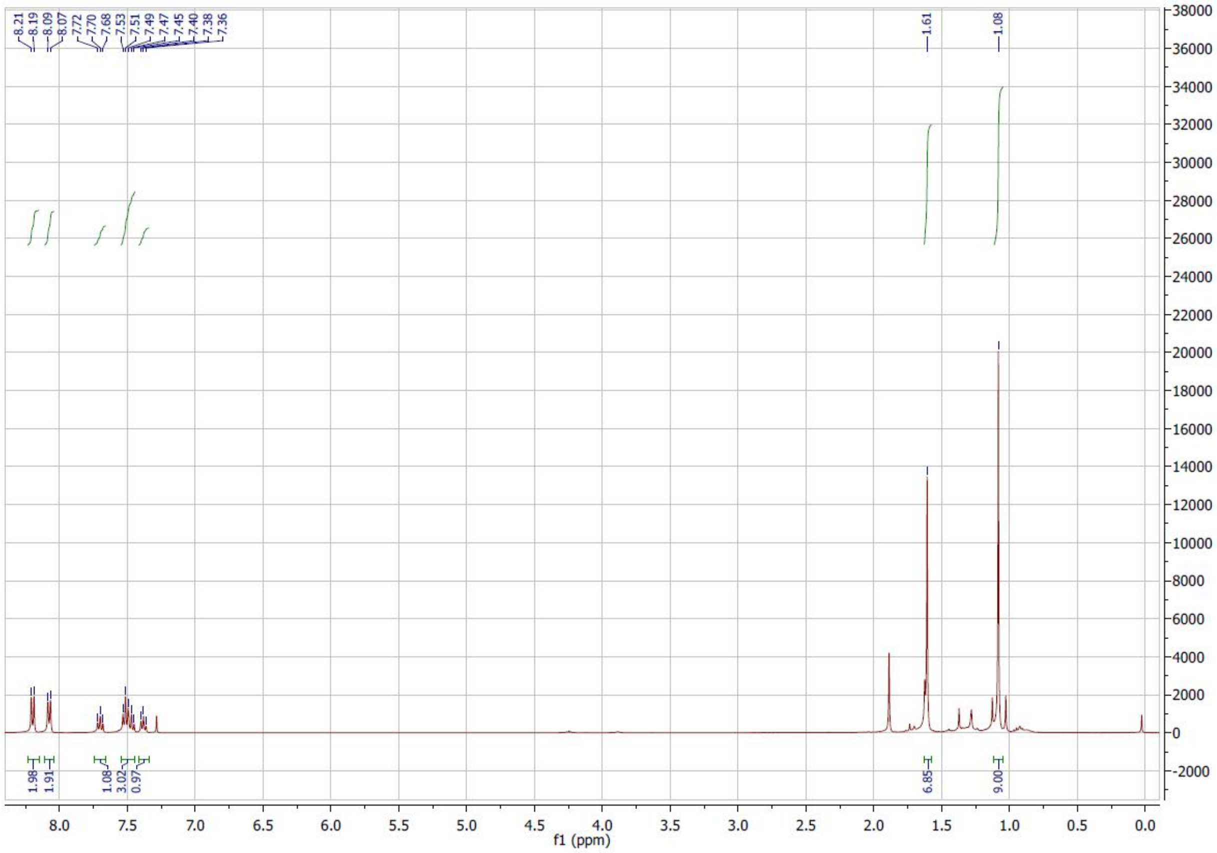

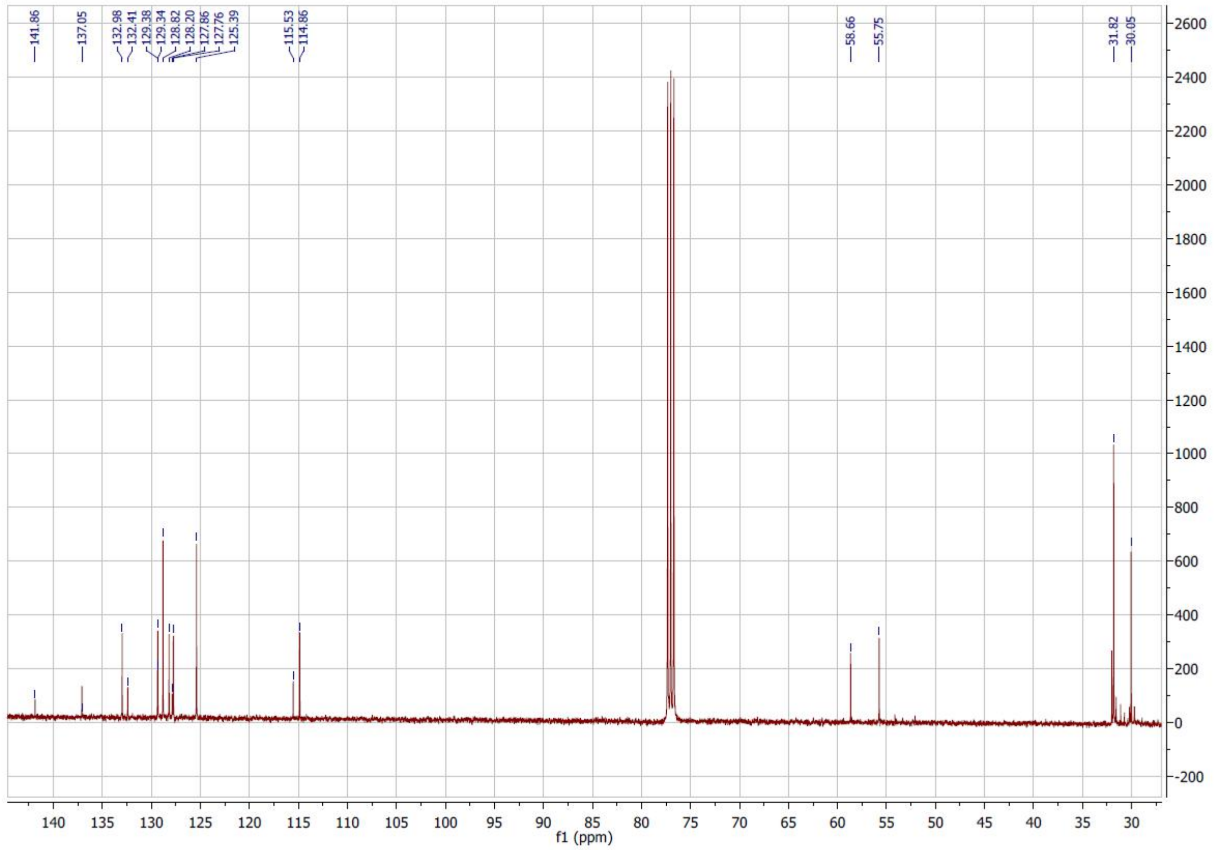

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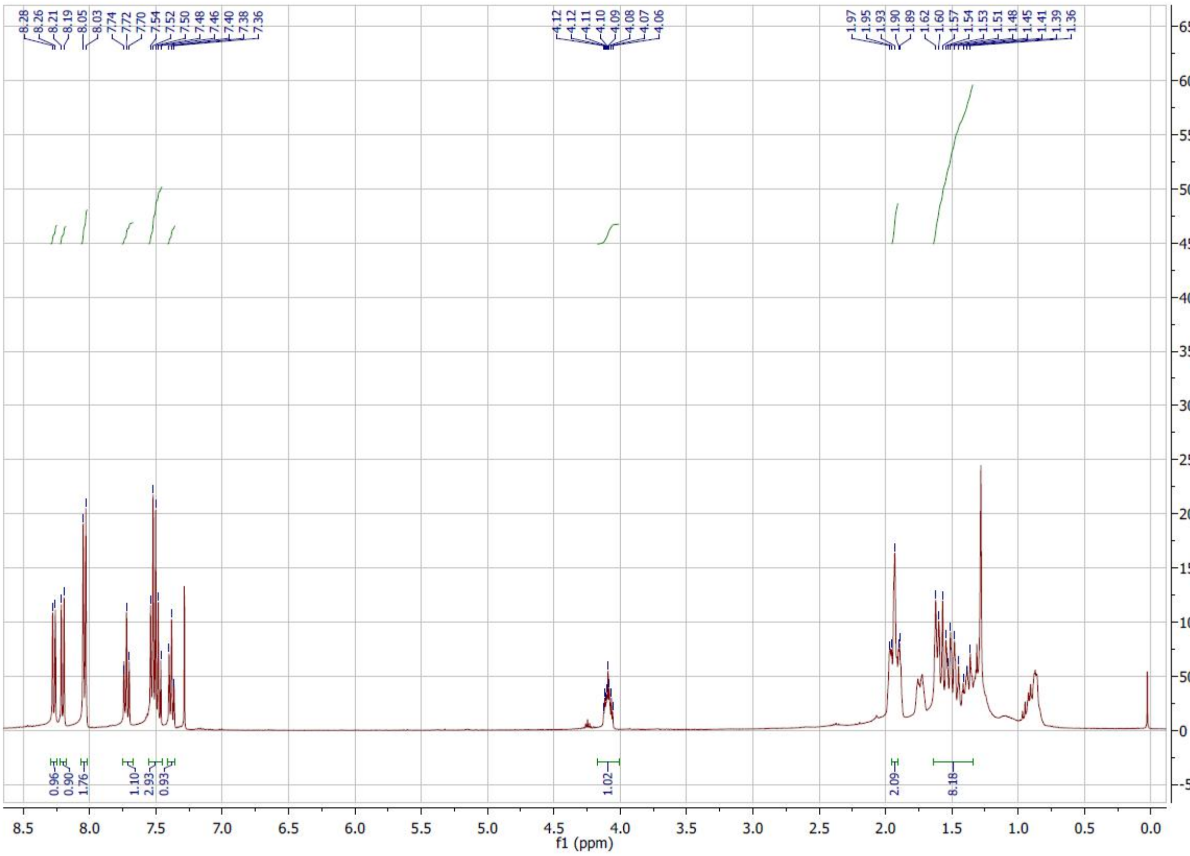

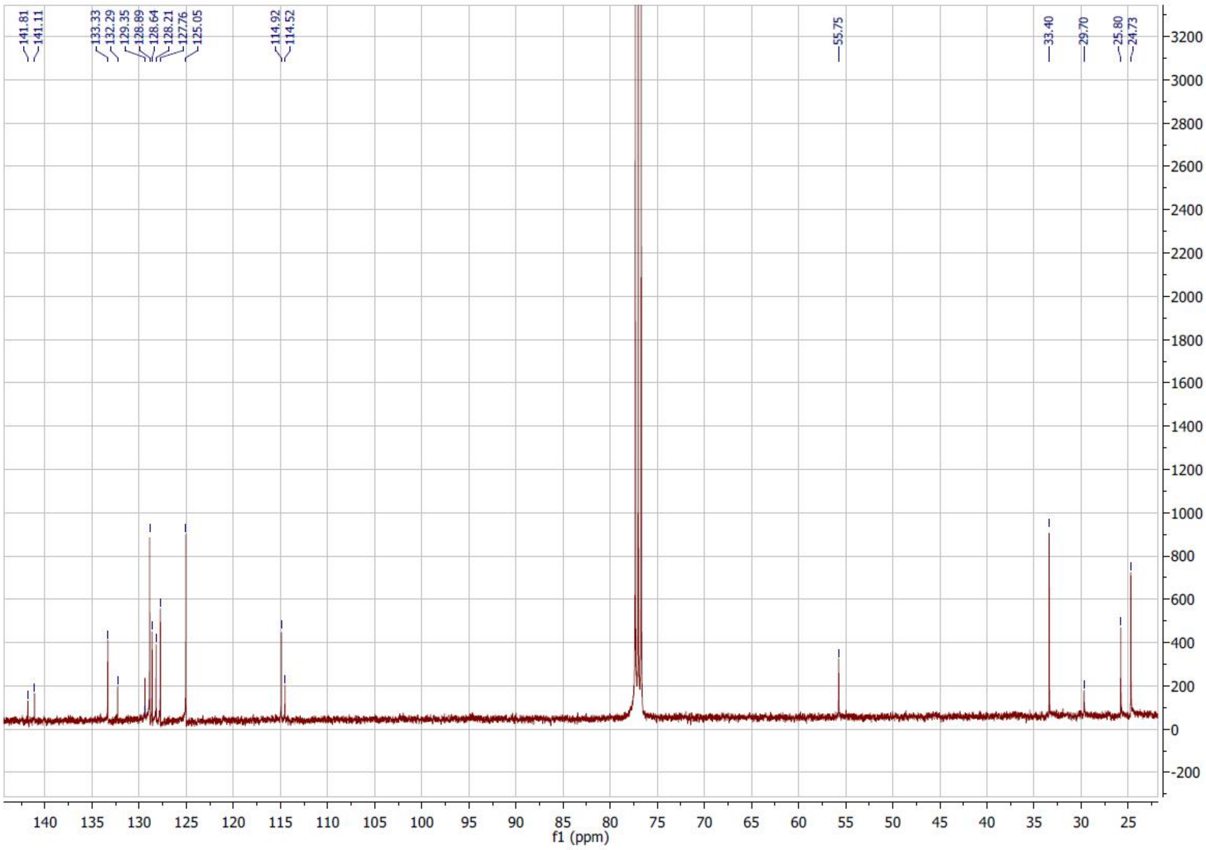

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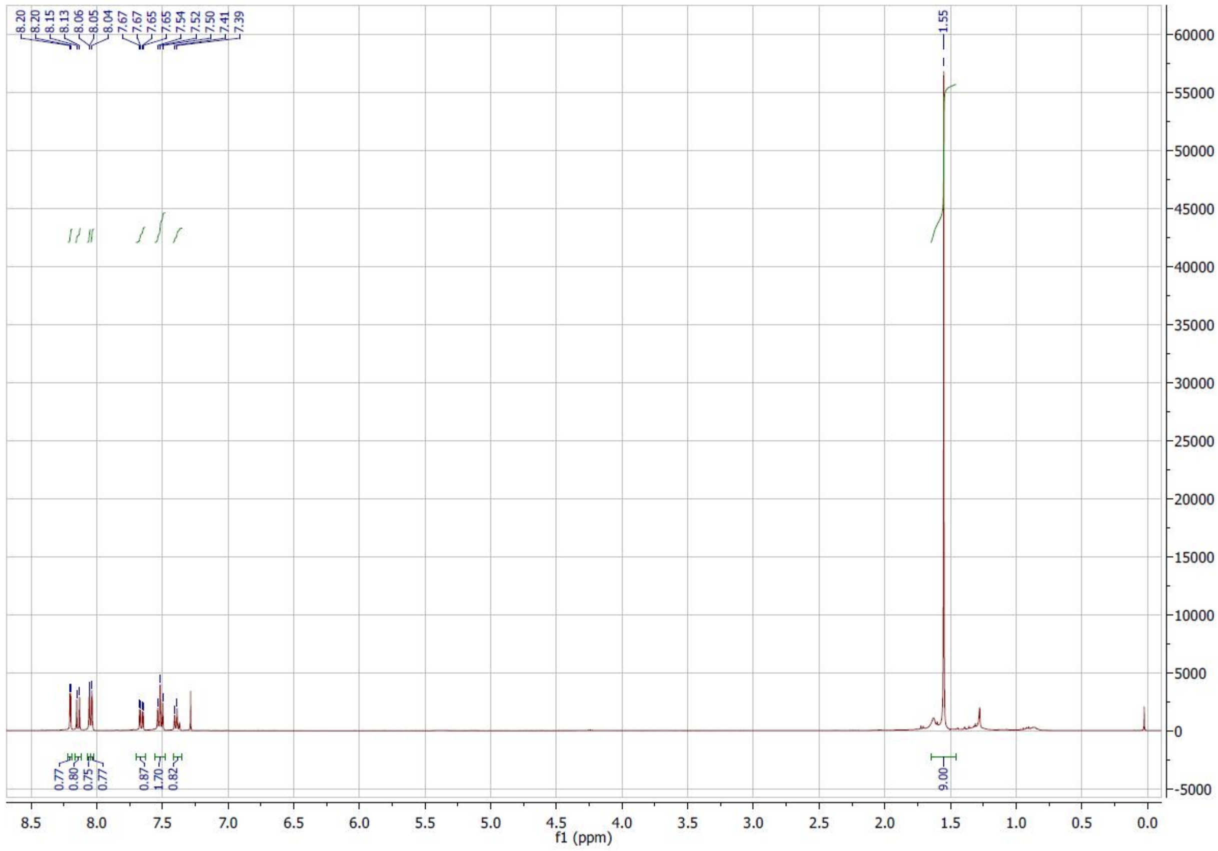

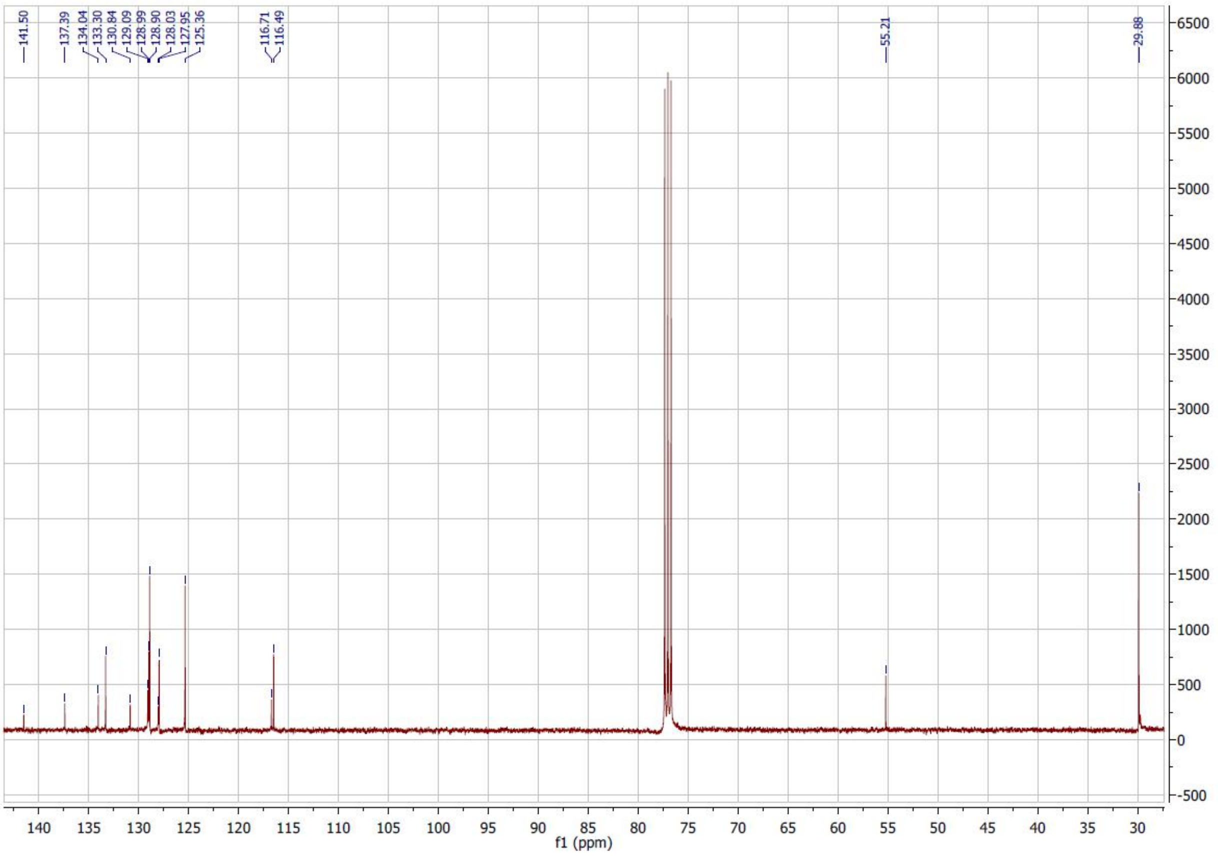

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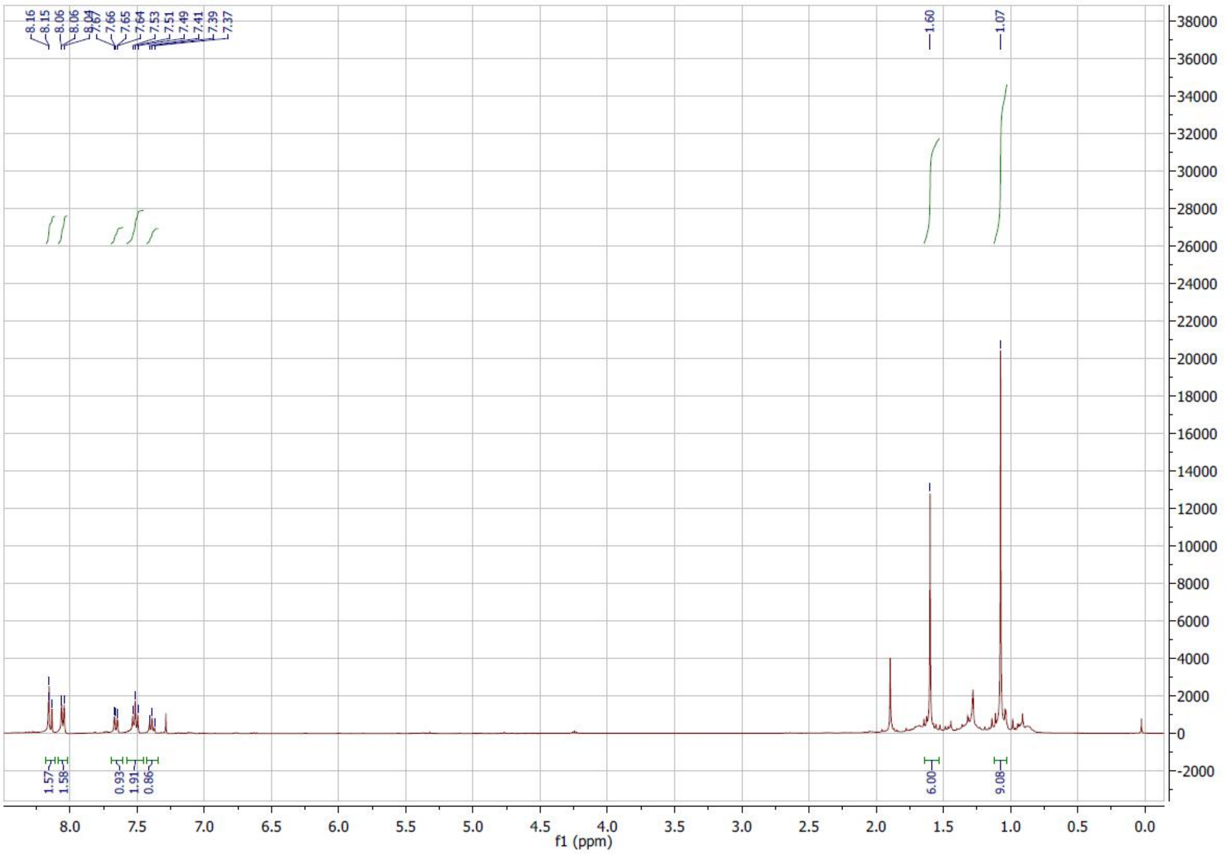
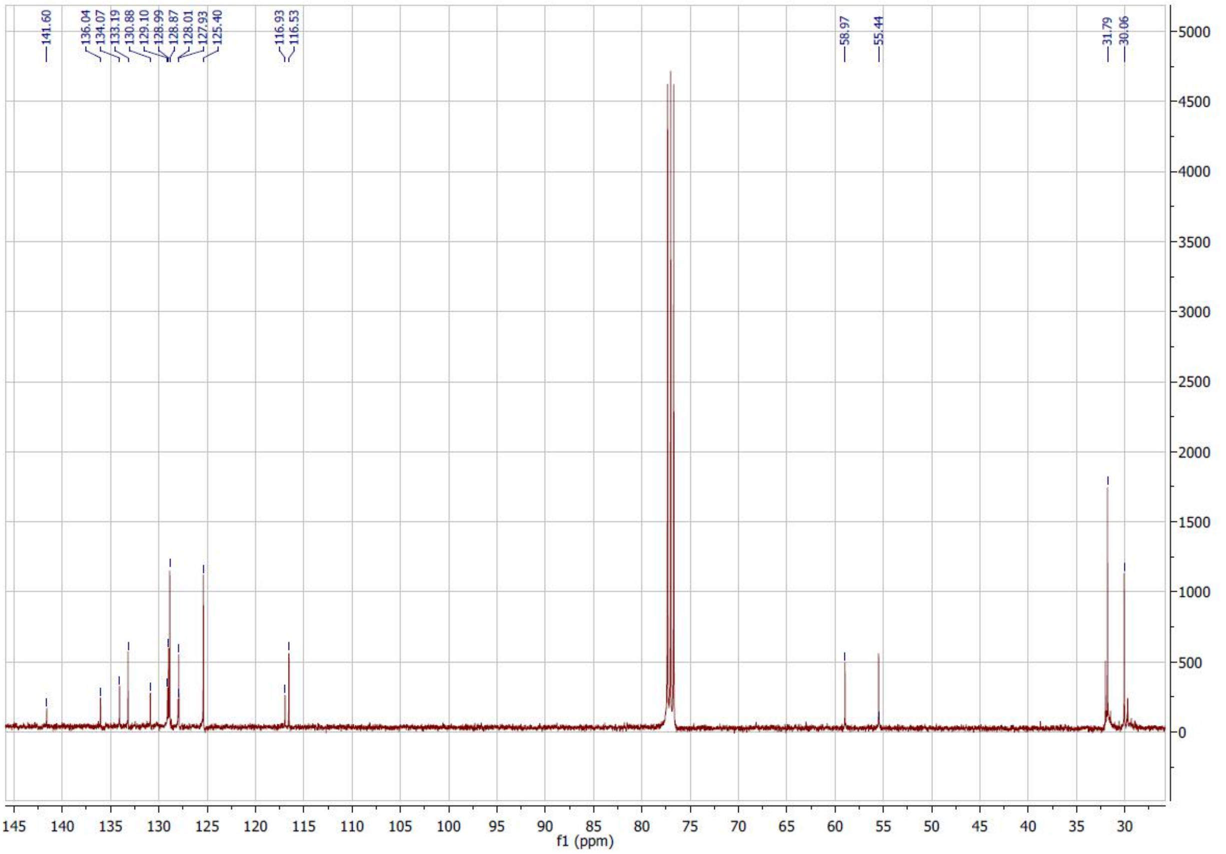
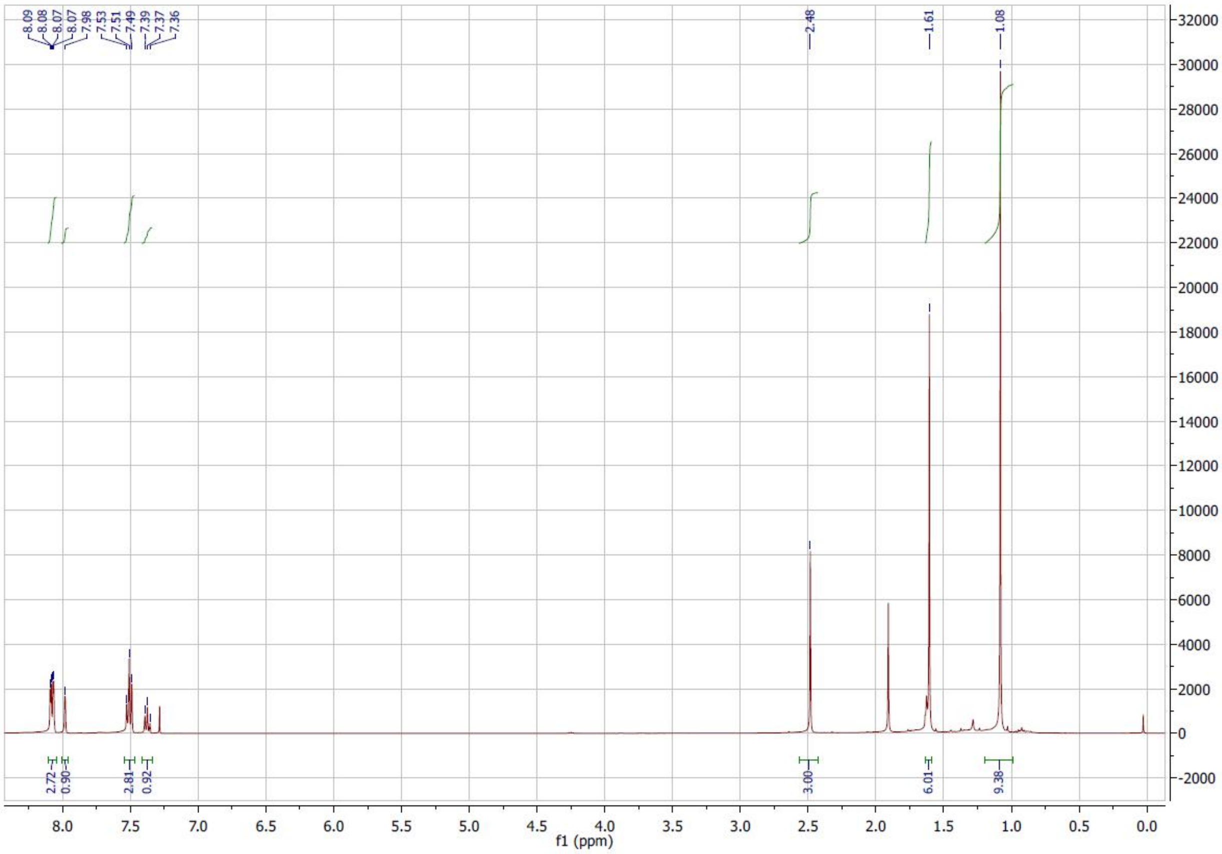
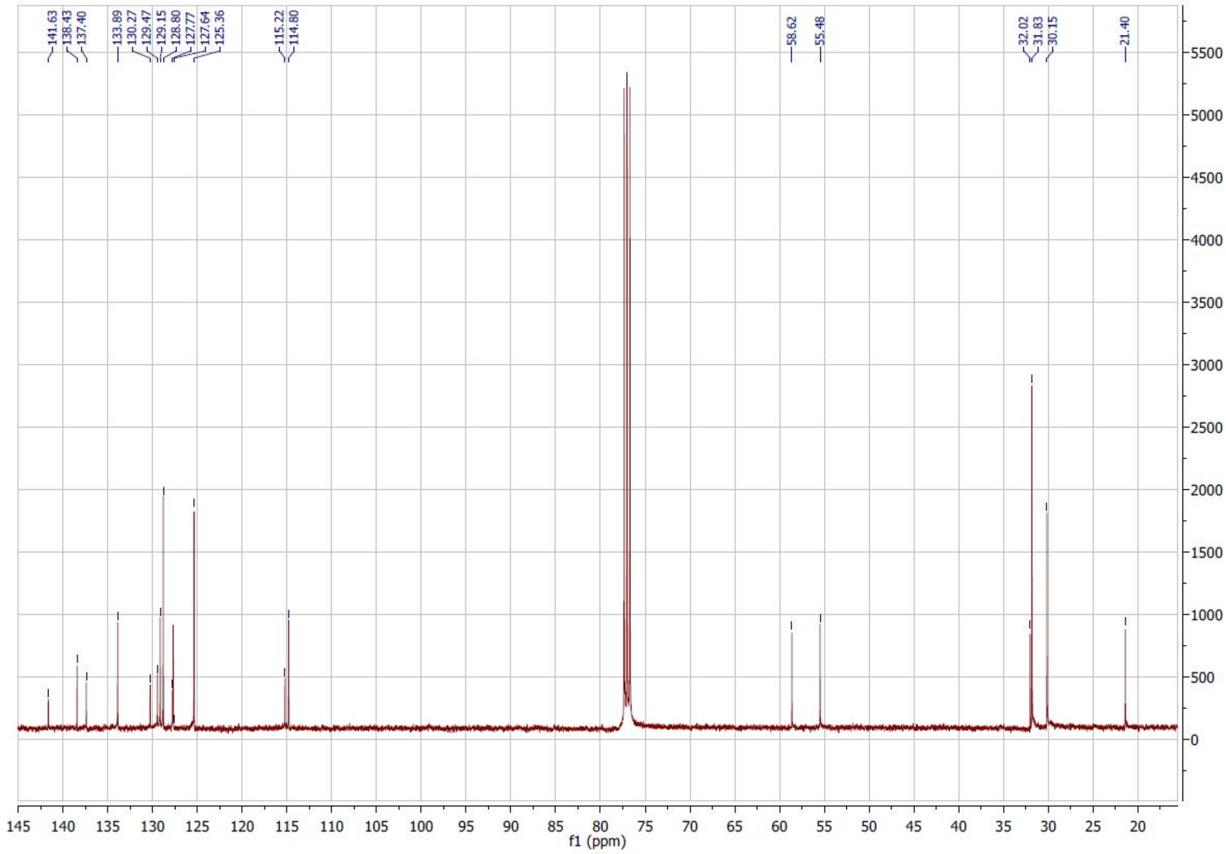




^{1}H NMR and ^{13}C NMR spectra of 2f





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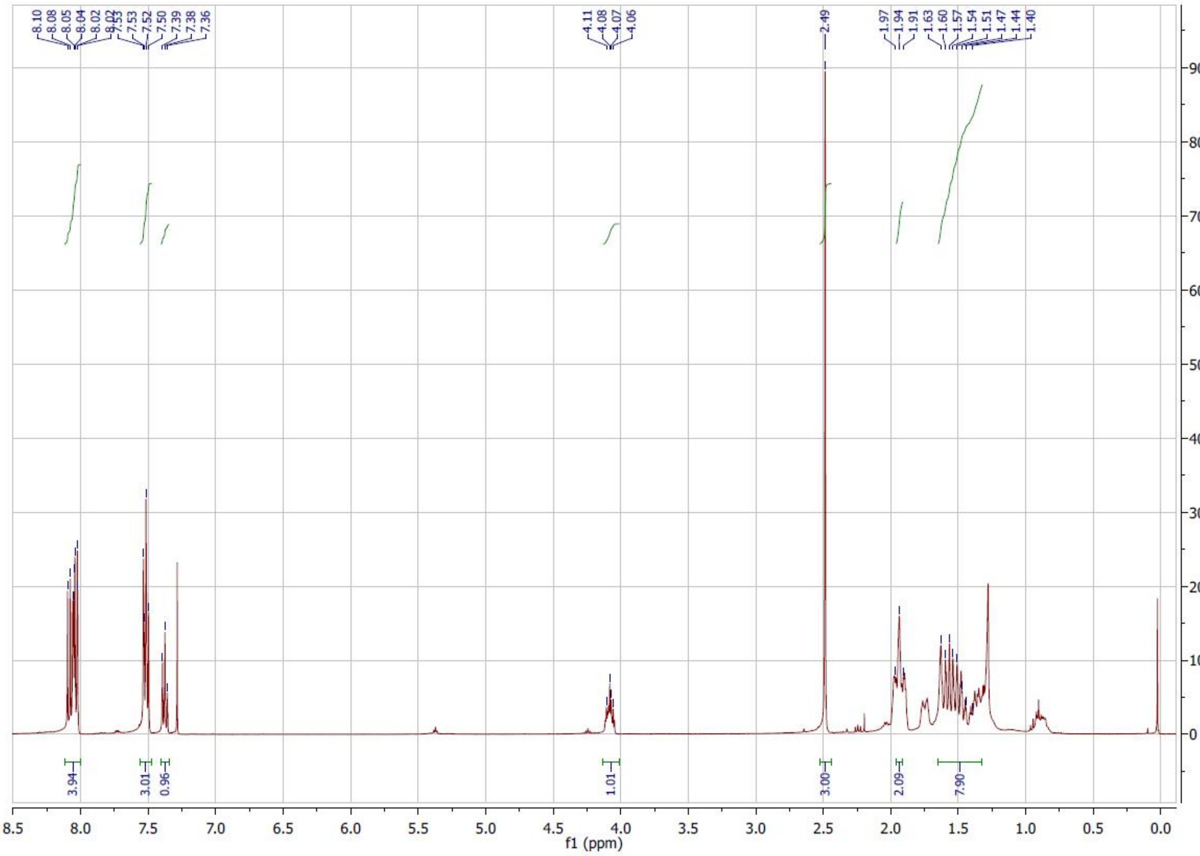

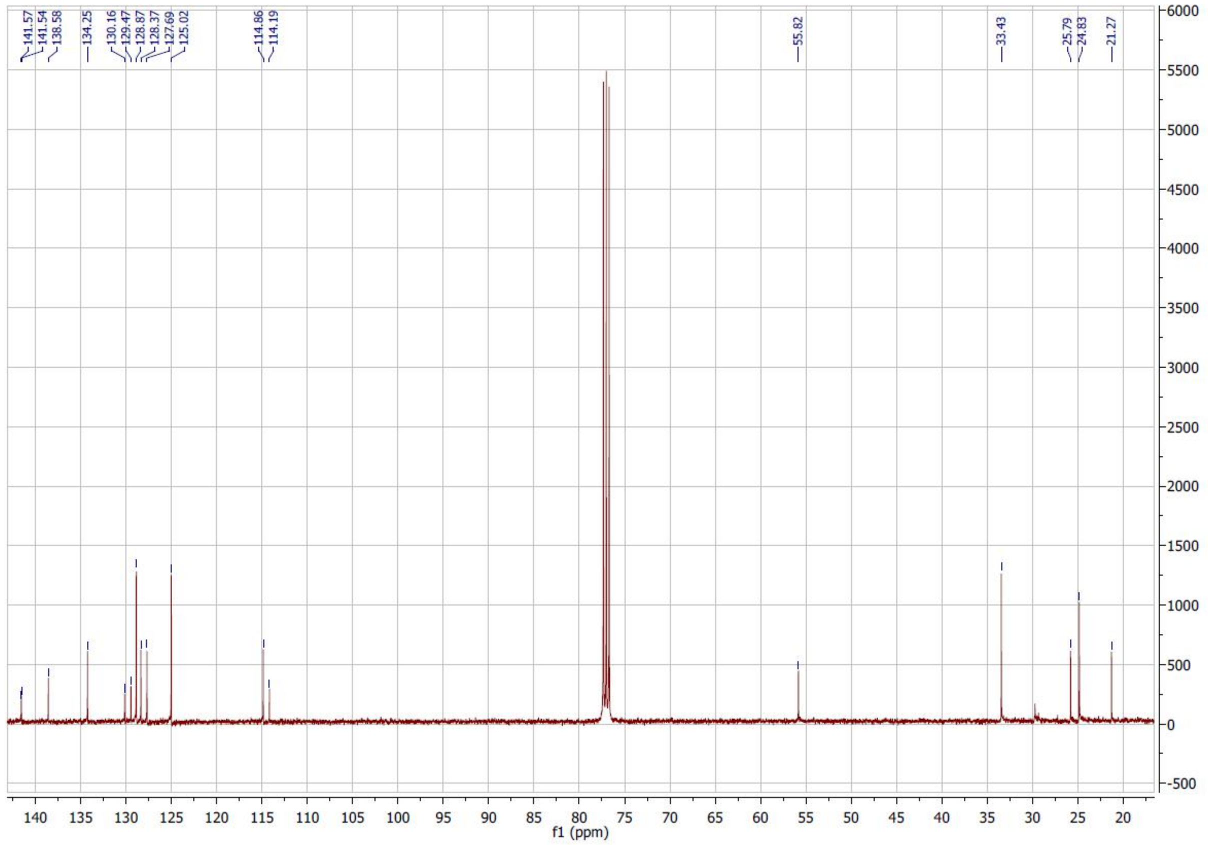

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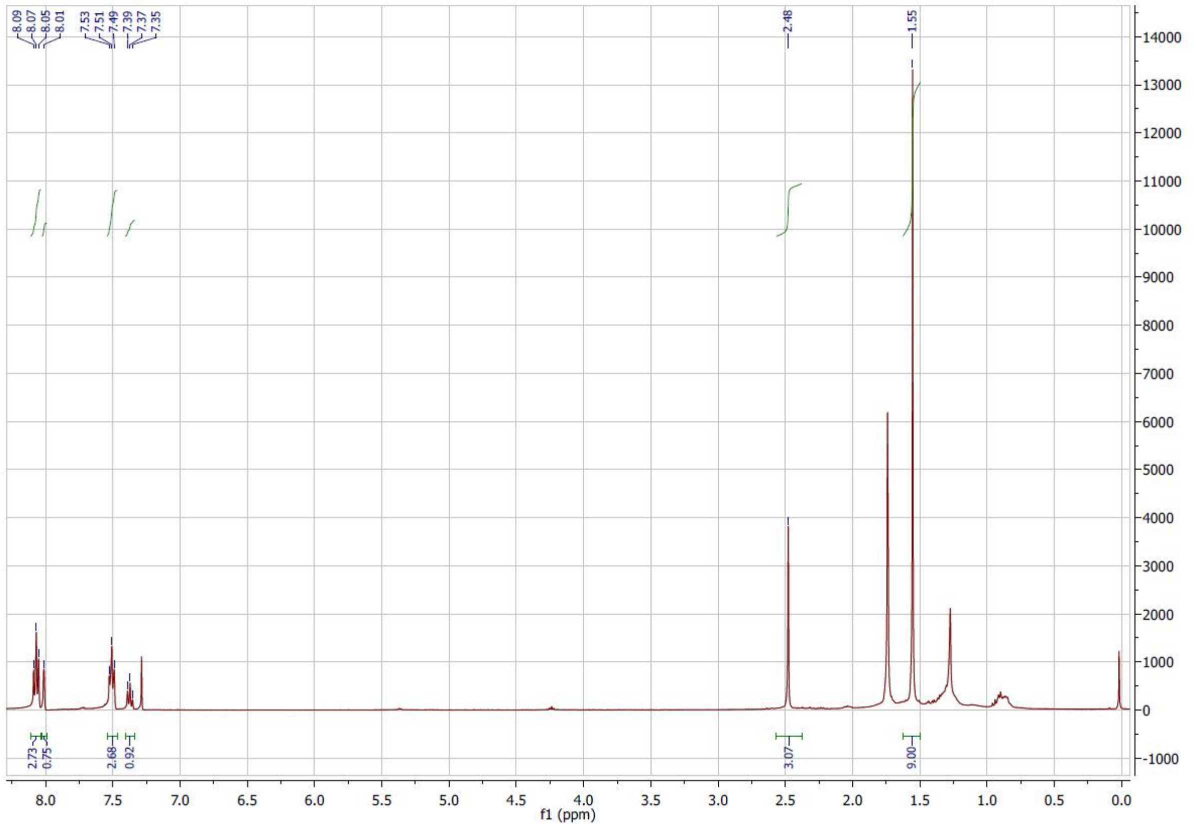

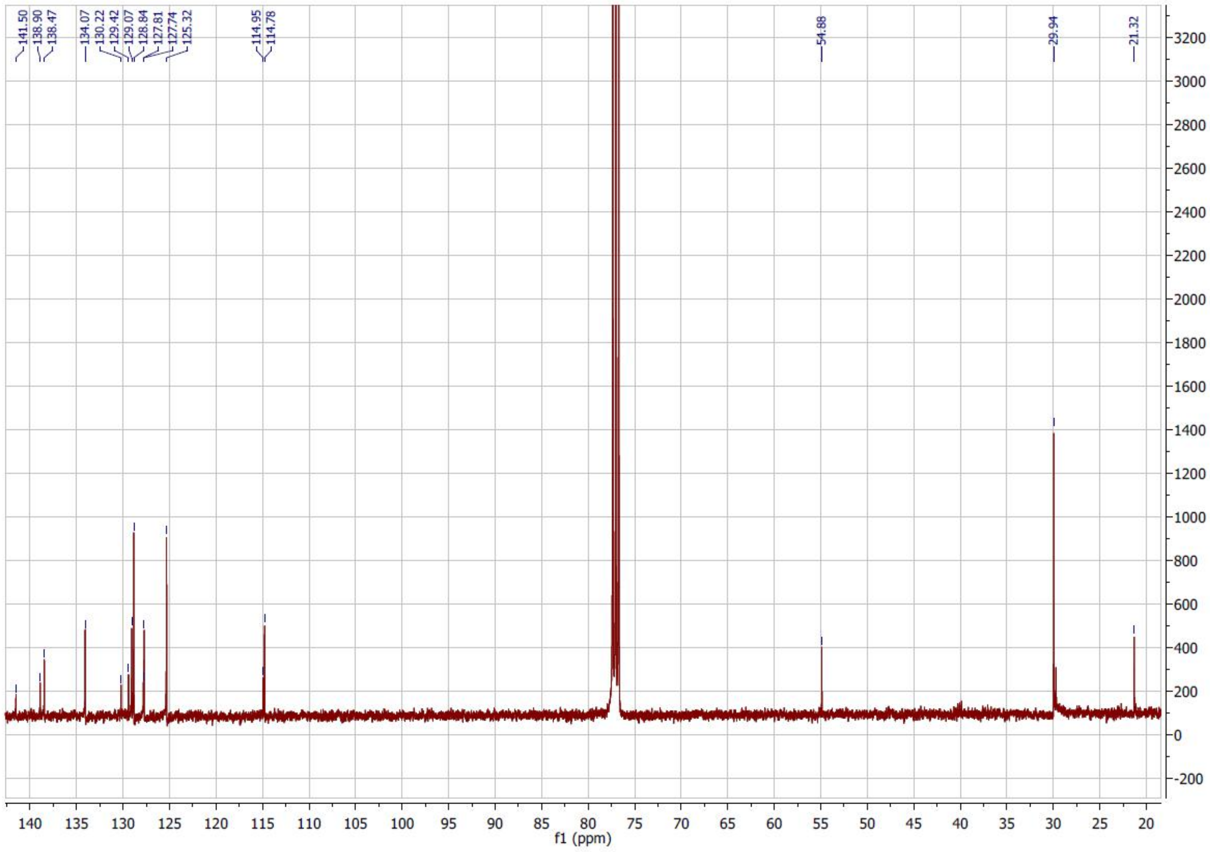

CHAPTER 4: CONCLUSION

In conclusion, we have developed a novel method for the preparation of benzoxazine fused 1,2,3-triazoles derivatives from N-arylamide based hydrazones via Pd-catalysed isocyanide insertion/cyclisation/N-N bond formation cascade reaction.

The strategy allows synthesis of molecules which are useful in various areas of chemistry such as material science, supramolecular, medicinal and pharmaceutical. Moreover, the synthesis involves one pot hypothesis and the product formed is really easy to extract. This protocol affords the desired product in decent to outstanding yields with no side products. Therefore, less waste is produced in whole synthesis process. Further, tandem (cascade) reactions are highly economic and eco-friendly.

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