Copper-Catalyzed Cascade C-H Functionalization and C-N Bond Formation: Synthesis of Functionalised Benzimidazoles

Synopsis Report

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STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati D. Mahesh

December 2017

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. D. Mahesh has been working under my supervision since July 2012. I am forwarding his thesis entitled "*Copper-Catalyzed Cascade C-H Functionalization and C-N Bond Formation: Synthesis of Functionalized Benzimidazoles*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati

December 2017

Prof. Tharmalingam Punniyamurthy

Supervisor

ACKNOWLEDGEMENT

I would like to express honest thanks to the kind people around me, who helped me directly and indirectly these significant milestones and provoked me on the path of success.

First and foremost, my heartfelt thanks to my thesis supervisor **Prof. Tharmalingam Punniyamurthy** for his continuous support, motivation, expert guidance and suggestions throughout my Ph.D. His true scientific spirit has helped me a lot during my research work. I am also thankful to him for giving me the freedom to explore organic chemistry. My everlasting gratitude goes towards him.

I express my sincere thanks to doctoral committee members **Prof. G. Krishnamoorthy**, **Dr. Lalmohan Kundu**, Department of Chemistry and **Prof. Arun Goyal**, Department of Biosciences and Bioengineering, for their evaluation and valuable suggestions during the entire period of my doctoral studies. My honest regards to all the faculty of the Department of Chemistry for their motivation and encouragement.

I am very greatful to the Ministry of Human Resource and Development (MHRD), India for financial support and IIT Guwahati for all the facilities that were made available to me. I also thank Central Instrument Facility (CIF), IIT Guwahati for providing the instrument facility and DST for providing the X-ray facility.

My special thanks goes to all my past and present group members, Dr. Rajesh Paul, Dr. T. Ramana, Dr. Murali Mohan Guru, Dr. Rapolu Kiran Kumar, Dr. Santhosh Kumar Alla, Dr. M. Kannan, Dr. M. Sengoden, Dr. G. Murgavel, Dr. G. Bharathiraja, Dr. Dinabandhu, Dr. Pradeep Sadhu, M. Vijay, V. Satheesh, Raghunath Bag, Pinaki, Sourav, Abhisikta, Tanumay, Bijay, Dr. S. Vivek Kumar, Dr. Subhasish Roy, Dr. Tariq Shah, Kangkan, Rahul, Manmath, Sonbidya and Rohith Pavan for the stimulating discussions, pleasant and helpful company and for all the fun we have had in the last five years.

I thank to other friends in IITG, Gopi, Radhakrishna, Belal, Karuna, Gopikrishna, Mohan, Nayak, Unnava, Srinu, Satish, Srinivas, Aravind, Aktar, Wajid, Hiranya, Suranjan, Manas Suresh and Ashraful for their everyday help and support in all aspects.

My heartful thanks also go to my dearest friends from outside IITG Sravan Kore, Rakesh, Rushi, Santhosh, Rajesh, Kotesh, Pavan, and Ravi for their constant support and encouragement.

I also take this opportunity to thank all of my Ph.D. batchmates (July, 2012), the other research scholars in the chemistry department and all my IITG friends, who have shared their thoughts and views with me.

Finally, I want to thank all of my family members. Without their love and support, none of this would have been possible. I wish to express my sincere gratitude to my parents (Devulapally Yadagiri and Rajyalakshmi), sisters (Rajitha and Anitha), brother (Rajesh) and I dedicate this work to them.

Devulapally Mahesh

List of Abbreviations

CAN	ceric ammonium nitrate
*m*CPBA	3-chloroperbenzoicacid
DCB	dichlorobenzene
DMAc	dimethylacetamide
DME	dimethoxyethane
DMEDA	dimethylenediamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DTBP	di-*tert*-butyl peroxide
EDG	electron donating group
EWG	electron wthdrawing group
ESI-MS	electrospray ionisation mass spectrometry
FT-IR	fourier-transform infrared spectroscopy
H_2O_2	hydrogen peroxide
MS	molecular sieve
NP	nano particle
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
OLED	organic light-emitting diode
PIDA	(diacetoxyiodo)benzene
TMEDA	tetramethylethylenediamine
1,10-Phen	1,10-phenanthroline
TMTU	tetramethylthioure
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TLC	thin layer chromatography
TsN_3	tosyl azide
TEA	triethylamine
$TMSN_3$	trimethylsilyl azide

Abstract

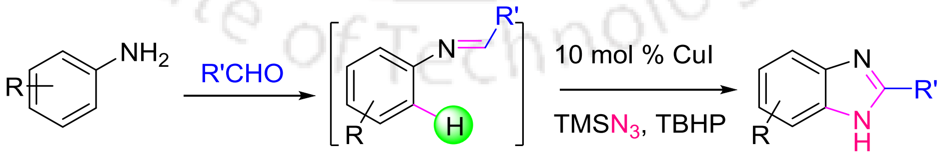
The thesis contains five chapters. The chapter one covers the methods that are developed for the construction of benzimidazoles The chapter two focuses on the Cu-catalyzed oxidative coupling of anilines, aldehydes and $TMSN_3$. The chapter three deals with the Cu-catalyzed oxidative coupling of anilines, benzylamine and NaN_3. The chapter four describes the Cu-catalyzed oxidative coupling of anilines and methyl arenes with $TMSN_3$.

Chapter 1. Recent Developments in the Synthesis of Benzimidazoles

'Benzimidazole' is an important scaffold and found in numerous compounds that are of biological and medicinal interests. Common methods used for their preparation involves the condensation of 1,2-diaminobenzene with aldehydes or carboxylic acid followed by oxidative cyclization. These methods are however limited due to the requirement of harsh reaction conditions during the oxidative cyclization. Further suitably substituted 1,2-diaminobenzene is not available. Efforts are thus made to develop new strategies for the benzimidazoles synthesis using cross-coupling and C-H functionalization routes.

Chapter 2. Cu-Catalyzed Oxidative Coupling of Anilines, Aldehydes and $TMSN_3$

This chapter describes multicomponent oxidative coupling of aryl amines, aldehydes and azide to provide benzimidazole frameworks in the presence of TBHP at moderate temperature. The reaction involves the formation of imine followed by imine directed sp^2 C-H azidation and sp^2 oxidative cyclization (Scheme 1). The reaction of aryl and alkyl aldehydes can be accomplished. The use of simple substrates tandem C-H functionalization/C-N bond formation, broad substrate scope and functional group diversity are the important practical features.



R = EWG, EDG

R' = anthracene, aryl, naphthyl, thiophene, isopropyl

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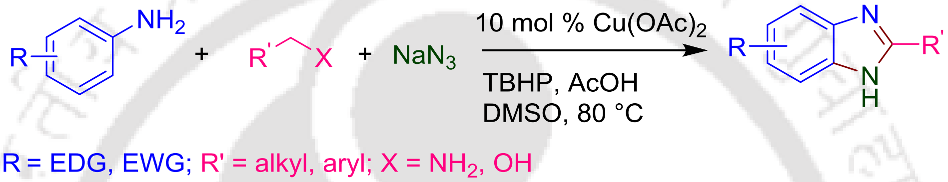
Scheme 1

Chapter 3. Cu-Catalyzed Oxidative Cross-Coupling of Anilines, Benzylamine and NaN_3

This chapter presents the copper-catalyzed oxidative coupling of anilines with benzylamine and NaN_3/AcOH in the presence of TBHP at moderate temperature (Scheme 2). The reaction conditions can be extended to benzyl alcohols in the place of benzylamine. The reaction involves the formation of *N*-benzylaniline followed by oxidation to imine, *ortho*-selective sp^2 C-H azidation and sp^2 C-H oxidative cyclization to give benzimidazoles. The use of simple substrates, functional group tolerance and product diversity are the important practical features. The synthetic and mechanistic aspects have been demonstrated.



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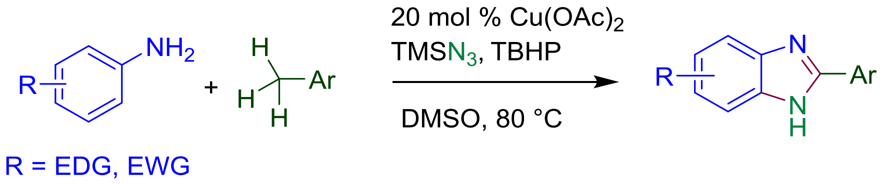
Scheme 2

Chapter 4. Cu-Catalyzed C-H Functionalization of Anilines, Methyl Arenes and $TMSN_3$

The chapter four covers the copper-catalyzed oxidative coupling of anilines, methyl arenes and $TMSN_3$ in the presence of TBHP to produce benzimidazoles (Scheme 3). This tandem $C(sp^3/sp^2)$-H functionalization and C-N bonds formation reaction involves the formation of N-benzylamine, oxidation to imine, *ortho*-selective sp^2 C-H azidation and intramolecular oxidative sp^2 C-H cyclization. The use of the readily available methyl arene, substrate scope and functional group diversity are the important practical features. The mechanistic and synthetic aspects have been covered.



Mahesh et al, *Org. Lett.* **2017**, DOI: 10.1021/acs.orglett.7b03264

Scheme 3

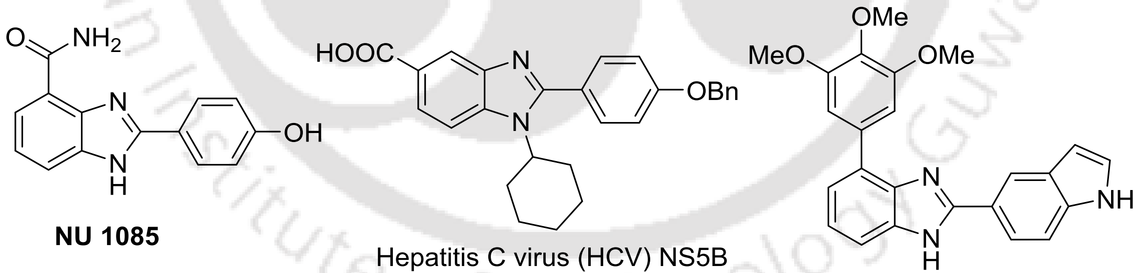
Chapter 5. Summary and Outlook

The methods developed provide effective synthetic tools for the transformation of simple substrates into diverse medicinally important benzimidazoles, which can find broad utilities in biological and medicinal sciences. These studies described are demonstrated well in context of the synthetic and mechanistic aspects, which find utilities in the synthetic chemistry for the further development of C-H functionalization strategies for the benzofuzed azol

Contents

Recent Developments in the Synthesis of Benzimidazoles

Tandem metal-catalyzed transformations involved in carbon-heteroatom bond formation hold a central place in synthetic organic chemistry. This field has been especially productive allowing the functionalization of a broad variety of nitrogen nucleophiles through Pd and Cu-catalyzed reactions. In addition, new strategies involving multiple bond formations have appeared in the literature for the synthesis of heterocycles.[1] Benzimidazole is an isosteric with indole and purine nuclei, which is present in a number of cellular and bioactive compounds. This heterocycle represents a kind of privileged substructure, which interacts with different proteins and enzymes. Indeed, a number of important drugs used in different therapeutics contain the benzimidazole ring,[2] as proton pump inhibitors (omeprazole), anti-hypertensive (candesartan and telmisartan), anti-histamines (astemizole), anti-helmintics (albendazole and mebendazole), and several other kinds of still investigational therapeutic agents, including anti-tumoral and antivirals (Figure 1). These moieties constitute an important class of compounds and found various applications in pharmaceutical industry and OLEDs. Considerable attention is thus focused on the development of effective synthetic methods for the construction of functionalized benzimidazoles. These

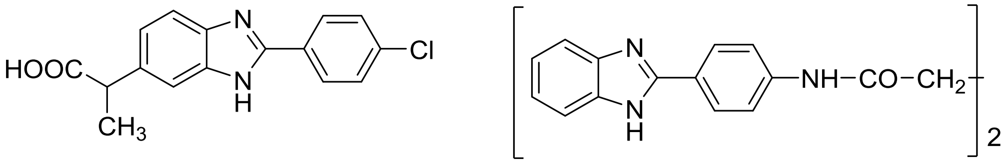


NU 1085

Antagonist and Inhibitor

Hepatitis C virus (HCV) NS5B polymerase inhibitor

Anti-cancer



Benoxaprofen Analog

HCV helicase

Figure 1. Examples of Biologically Important substituted 2-Aryl Benzimidazoles

structural frameworks are commonly made by condensation of 1,2-diaminoarenes with carboxylic acids or aldehydes followed by oxidative cyclization (Figure 2, a).[3] However, these approaches often suffer due to limited substrate scope, and sometimes with the requirement of strong acid and high temperature. Efforts are thus made on the development of new strategies to construct the benzimidazole structural motifs using *C-N* cross-coupling of 2-haloarylamidines (Figure 2, b)[4] and intramolecular cyclization of 2-azido *N*-aryl imines (Figure 2, c).[5] Attention has also been made to C-H functionalization of *N*-arylamidines (Figure 2, d and e).[6]

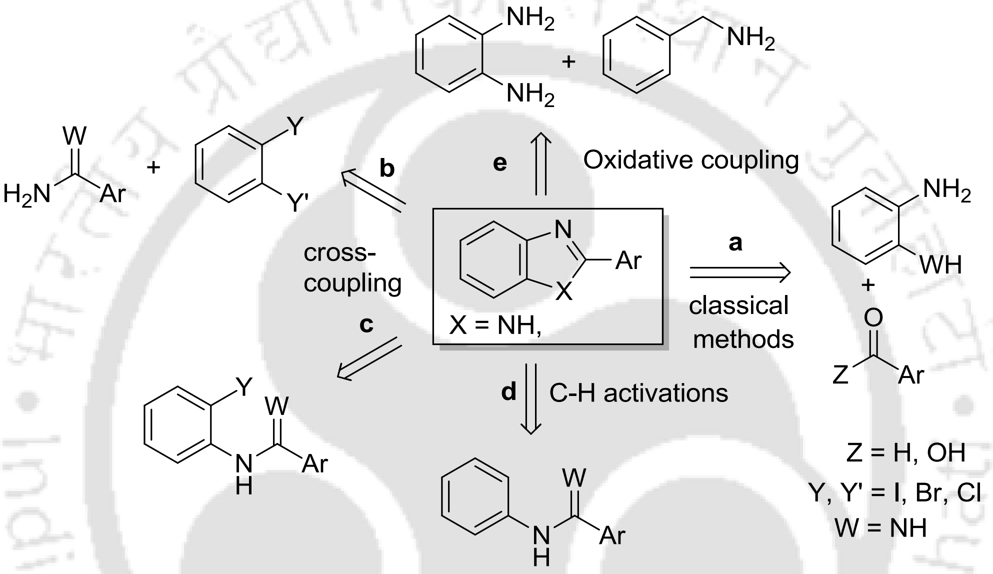
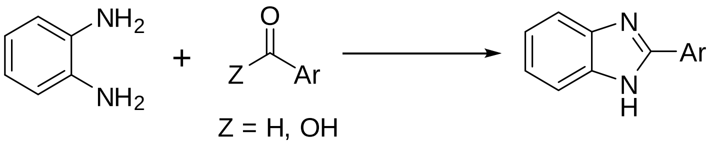


Figure 2. Synthetic Pathways for the Synthesis of Benzimidazoles

1.1 Traditional Methods

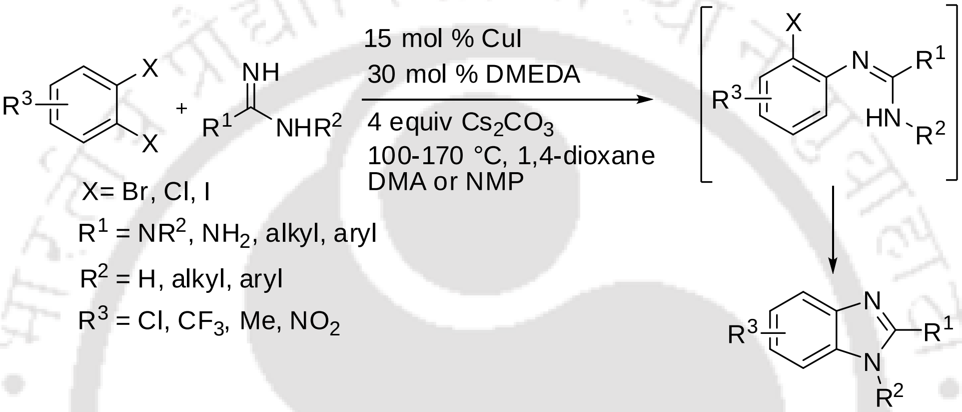
Benzimidazoles are commonly prepared by condensation and oxidative cyclization of 1,2-diaminobenzene with carbonyl derivatives under harsh reaction conditions, such as use of strong acid in combination with high temperature is required. In addition, this reaction often suffers due to limited substrate scope as substituted 1,2-diaminobenzene is not available (Scheme 1).[3]



Scheme 1. Synthesis of Benzimidazole

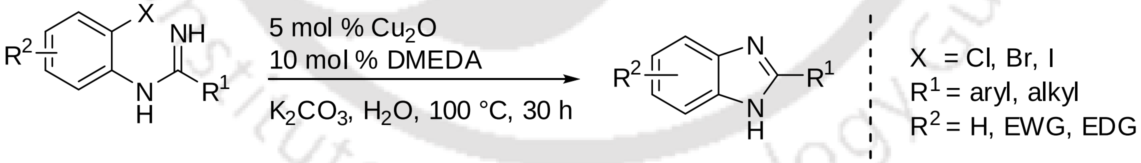
1.2 Cross-Coupling Methods

During the past decade efforts have been made on the development *C-N* cross-coupling for the construction of benzimidazoles. This section covers some of the effective methods that have been developed. Deng and co-workers showed CuI/*N*,*N*'-dimethylethylendiamine catalysed inter-/intramolecular amination of 1,2-dihalobenzene with guanidines to give benzimidazoles (Scheme 2).[4]



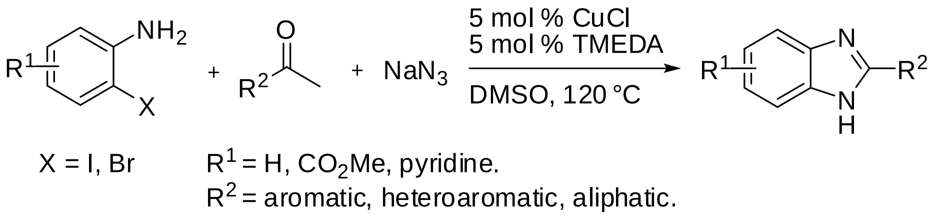
Scheme 2. Copper-Catalyzed Synthesis of Benzimidazole

Peng and co-workers reported an intramolecular *C-N* cross-coupling of *N*-(2-haloaryl)amidines to produce benzimidazoles using Cu_2O (5 mol %)/DMEDA (10 mol %) in the presence of K_2CO_3 in water (Scheme 3).[7]



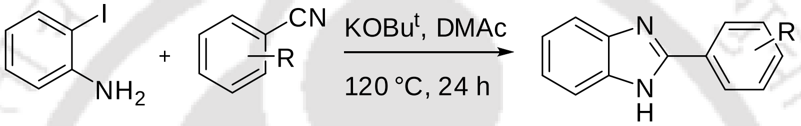
Scheme 3. Cu-Catalyzed Intramolecular *C-N* Bond Formation

Lee and co-workers reported a three-component cross-coupling of 2-haloanilines, aldehydes and NaN_3 using CuCl (5 mol%)/TMEDA (5 mol%) in DMSO at 120 °C to give benzimidazoles in good yields (Scheme 4).[8]



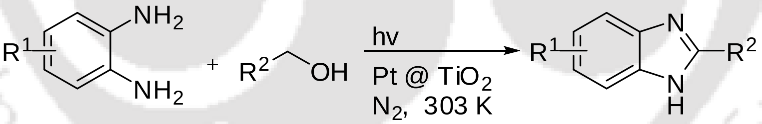
Scheme 4. Copper-Catalyzed Condensation and Intramolecular *C-N* Bond Formation

Xiang and co-workers reported a metal-free synthesis of benzimidazoles by intermolecular cyclization of 2-iodoanilines with aryl nitriles. This reaction has been demonstrated using KOBu^t at 120 ^{o}C to produce the target heterocycles in good yields (Scheme 5).[9]



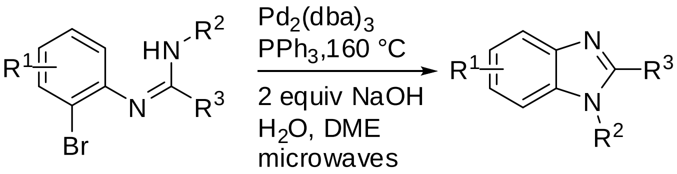
Scheme 5. Metal-Free Base Mediated *C-N* Bond Formation

Shiraishi and co-workers developed Pt@TiO$_2$ catalyzed benzimidazole synthesis under photo irradiation. This is promoted by multiple catalytic transformations on Pt@TiO$_2$, which involves a Pt-assisted photo catalytic oxidation on TiO$_2$ and a catalytic dehydrogenation on the surface of the Pt particles (Scheme 6).[10]



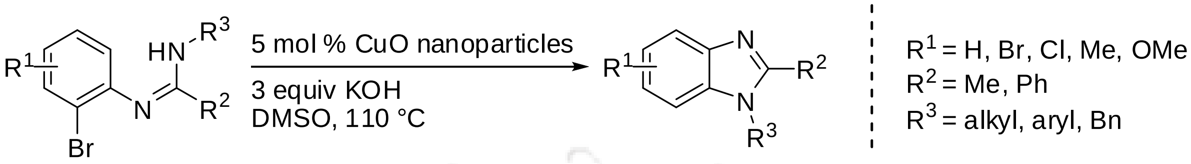
Scheme 6. Pt-Assisted Photocatalytic *C-N* Bond Formation

Brain and co-workers reported the synthesis of benzimidazoles by intramolecular Pd-catalyzed aryl-amination chemistry (Scheme 7).[11]



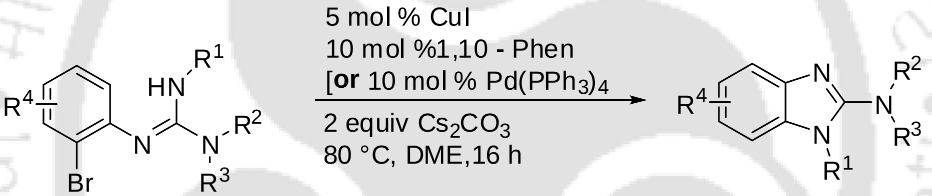
Scheme 7. Pd-Catalyzed Intramolecular C-N Bond Formation

Our group reported the synthesis of substituted benzimidazoles and 2-aminobenzimidazoles *via* intramolecular cyclization of *O*-bromoaryl derivatives using CuO nanoparticles. In this method, the CuO nanoparticles can be recovered and recycled (Scheme 8).[12]



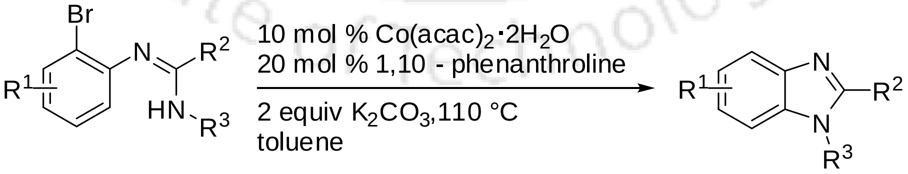
Scheme 8. CuO Nanoparticle Catalyzed *C-N* Bond Formation

The formation of 2-aminobenzimidazoles *via* intramolecular *C-N* bond formation between an aryl halide and a guanidine moiety can be achieved using either copper or palladium catalysis. Regioselective cyclization can be achieved under CuI/1,10-phenanthroline-catalyzed condition, whereas the palladium catalysis results in the formation of regioisomeric products (Scheme 9).[13]



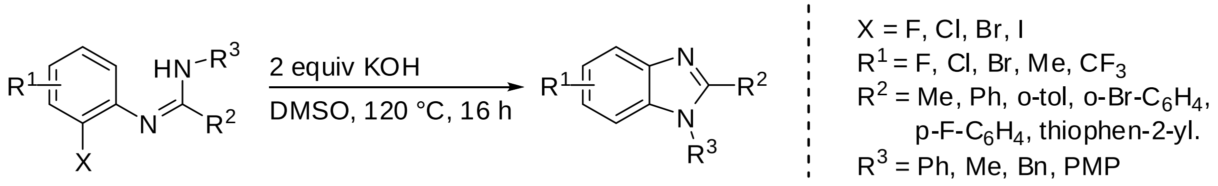
Scheme 9. Pd-Catalyzed Intramolecular *C-N* Bond Formation

Our group showed a Co-catalyzed intramolecular *C–N* cross-coupling of *Z*-*N*'-(2-halophenyl)-*N*-phenylamidines to give benzimidazoles in the presence of K_2CO_3 at moderate temperature (Scheme 10).[14]



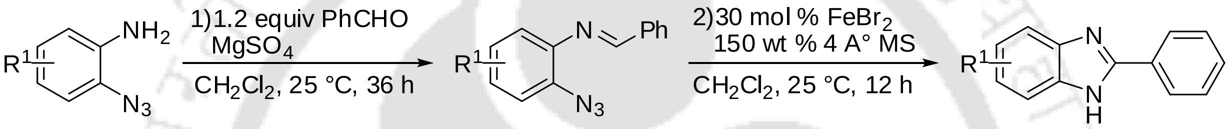
Scheme 10. Co-Catalyzed Intramolecular *C-N* Bond Formation

Bolm and co-workers developed base-mediated synthesis of benzimidazoles by intramolecular *N*-arylations of amidines at 120 °C (Scheme 11).[15]



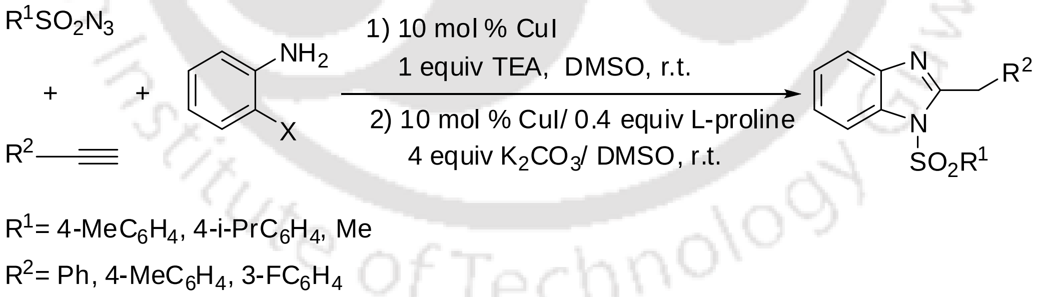
Scheme 11. Fe-Catalyzed Intramolecular *C-N* Bond Formation

Driver and co-workers reported the *O*-substituent of an aryl azide influences its reactivity toward transition metals. Substitution of a vinyl group with an imine disables Rh(II)-mediated C-H amination and triggers a Lewis acid mechanism catalyzed by iron(II) bromide to facilitate benzimidazole formation (Scheme 12).[5]



Scheme 12. Fe-Catalyzed Intramolecular C-H Functionalization/*C-N* Bond Formation

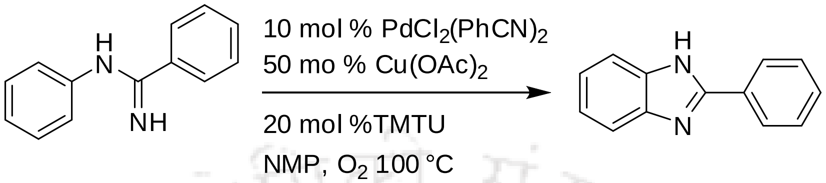
Wang and co-workers developed a Cu-catalyzed cascade reaction of RSO_2N_3, alkynes and 2-bromoaniline *via* intramolecular *N*-arylation of sulfonamides to produce benzimidazoles in good yields (Scheme 13).[16]



Scheme 13. Cu-Catalyzed Multi-Component *C-N* Bond Formations

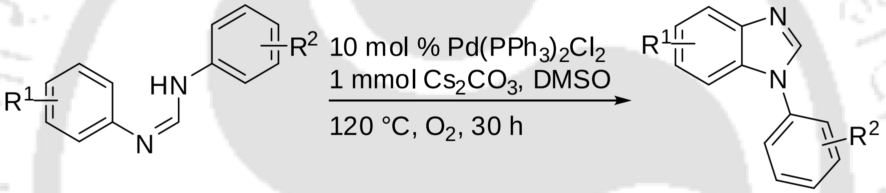
1.3 Metal-Catalyzed C-H Functionalization Methods

During the recent years, efforts have also been made on the development of regioselective C-H functionalization and *C-N* bond formation for the synthesis of benzimidazoles. This strategy is attractive as it is more atom economical and can have more substrate scope. Shi and co-workers reported a straight forward method to construct 1*H*-benzo[*d*]imidazole using Pd-catalyzed C−H activation starting from *N*-phenylbenzimidamide (Scheme 14).[17]



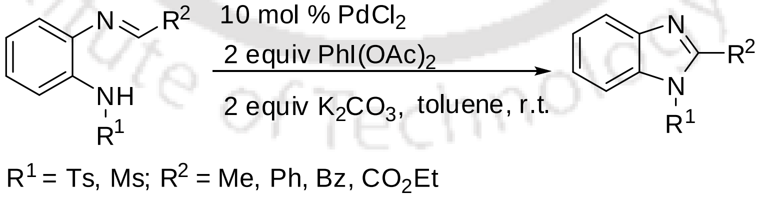
Scheme 14. Pd-Catalyzed C-H Functionalization/C-N Bond Formation

Our group reported Pd-catalyzed aerobic synthesis of 2-unsubstituted and 2-substituted *N*-aryl benzimidazoles from *N*,*N*'-bis(aryl)amidines *via* oxidative C–H amination with good substrate scope at moderate temperature (Scheme 15).[18]



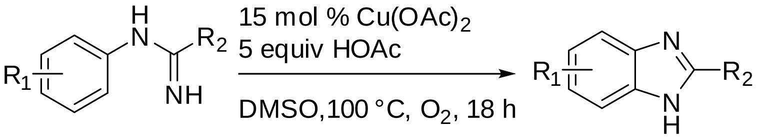
Scheme 15. Pd-Catalyzed C-H Functionalizatin/*C-N* Bond Formation

Zeng and co-workers reported a new method to construct 1,2-disubstituted benzimidazoles upon treatment with PdCl$_2$/PhI(OAc)$_2$ in the presence of K$_2$CO$_3$ at room temperature (Scheme 16).[19]



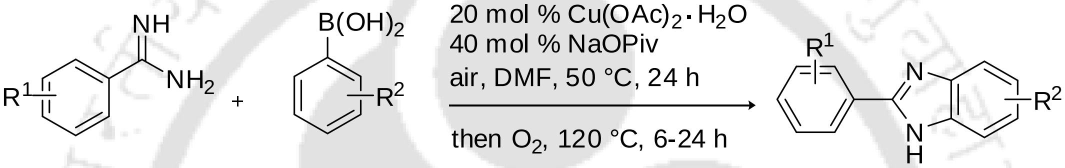
Scheme 16. Pd-Catalyzed Intramolecular C-H Functionalization/*C-N* Bond Formation

Buchwald and co-workers reported a Cu-catalyzed C-H functionalization/*C-N* bond-forming approach to provide benzimidazoles from readily available amidines at moderate temperature (Scheme 17).[6]



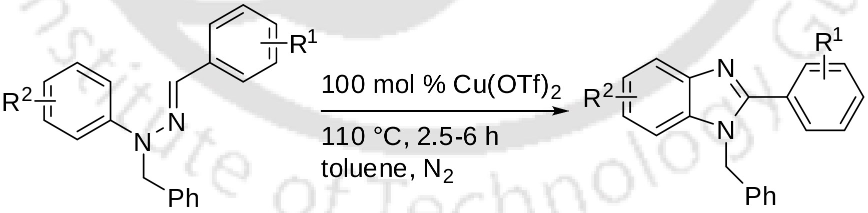
Scheme 17. Cu-Catalyzed Intramolecular C-H Functionalization/C-N Bond Formation

Zhu and co-workers reported *N*-arylation of benzamidines with aryl boronic acids in the presence of a $Cu(OAc)_2 \cdot H_2O$ and NaOPiv under aerobic conditions. Combining this step with an intramolecular direct C-H bond functionalization, catalyzed by the same catalytic system at 120 °C afford benzimidazoles (Scheme 18).[20]



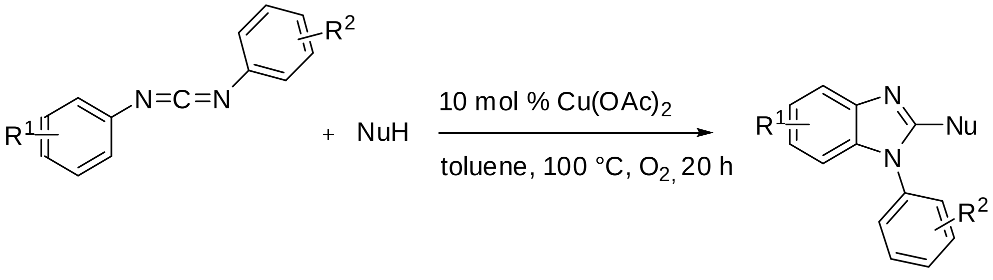
Scheme 18. Cu-Catalyzed C-H Functionalization/*C-N* Bond Formation

Efficient method for the transformation of *N*-benzyl bisarylhydrazones to functionalized 2-aryl-*N*-benzylbenzimidazoles is described. The protocol involves a Cu-mediated cascade C-H functionalization/*C-N* bond formation. Substrates having either electron-donating or withdrawing substituents undergo the cyclization to afford the target heterocycles at moderate temperature (Scheme 19).[21]



Scheme 19. Cu-Catalyzed C-H Functionalization/*C-N* Bond Formation

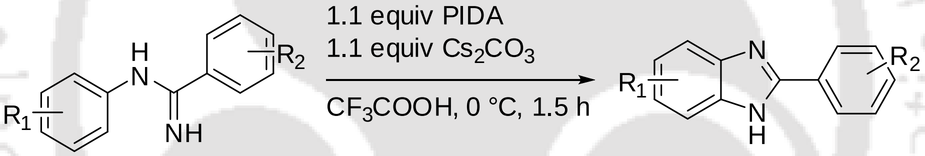
Copper-catalyzed intramolecular cyclization of amidines via C-H activation has been shown to give benzimidazoles at moderate temperature (Scheme 20).[22]



Scheme 20. Cu-Catalyzed Addition and C-H Functionalization

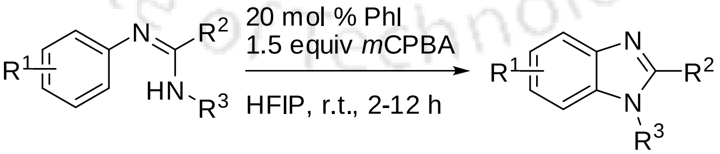
1.4 Metal-Free C-H Functionalization Methods

Few studies are focused on metal-free C-H functionalization/*C*-*N* bond formation for the synthesis of benzimidazoles. Zhu and co-workers reported the construction of benzimidazoles using PIDA-mediated intramolecular oxidative imidation of aromatic C-H bonds of *N*-arylamidines, which afford 2-alkylbenzimidazoles in good yields (Scheme 21).[23]



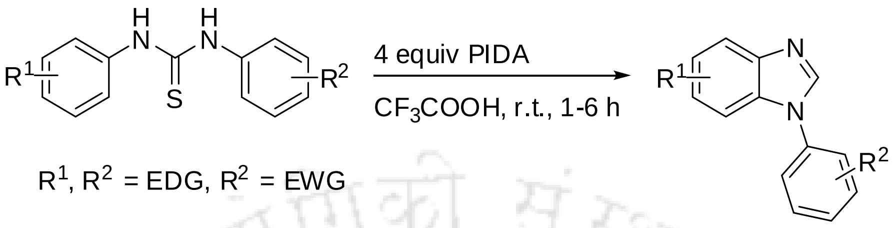
Scheme 21. PIDA-Mediated C-H Functionalization/*C*-*N* Bond Formation

Our group showed a metal-free C-H amination of *N*”-aryl-*N*’-tosyl/*N*’-methylsulfonylamidines and *N*,*N*’-bis(aryl)amidines using iodobenzene to furnish 1,2-disubstituted benzimidazoles in the presence of *m*CPBA at room temperature (Scheme 22).[24]



Scheme 22. PhI-Mediated C-H Functionalization/*C*-*N* Bond Formation

Our group also reported a metal-free protocol for the formation of *C-N* bond by aromatic C-H functionalization promoted by PIDA for the synthesis of *N*-arylated benzimidazoles from 1,3-diarylthio urea derivatives (Scheme 23).[25]



Scheme 23. PIDA-Mediated C-H Functionalization/*C-N* Bond Formation

Long and co-workers reported TEMPO-O$_2$ oxidative protocol to synthesize fused tetracyclic benzimidazoles via a metal-free oxidative C-N coupling between sp^3 C-H bond and N-H bond of readily available N-benzyl/alkyl-1,2-phenylenediamines (Scheme 24).[26]

Scheme 24. TEMPO-Catalyzed Oxidative *C-N* Bond Formation

In summary, during the past decade considerable attention has been devoted on the development of new synthetic routes for the construction of benzimidazoles. Few studies are focused on C-N cross-coupling of the aryl halides with nitrogen nucleophiles. Subsequently, efforts are made to C-H functionalization and *C-N* bond formations for the benzimidazole synthesis. This approach is more atom economical and can lead to a wide substrate scope. Although considerable effort has been made, yet effective synthetic routes for the transformation of the simple substrates into diverse benzimidazole structural scaffolds to be developed.

1.5 References

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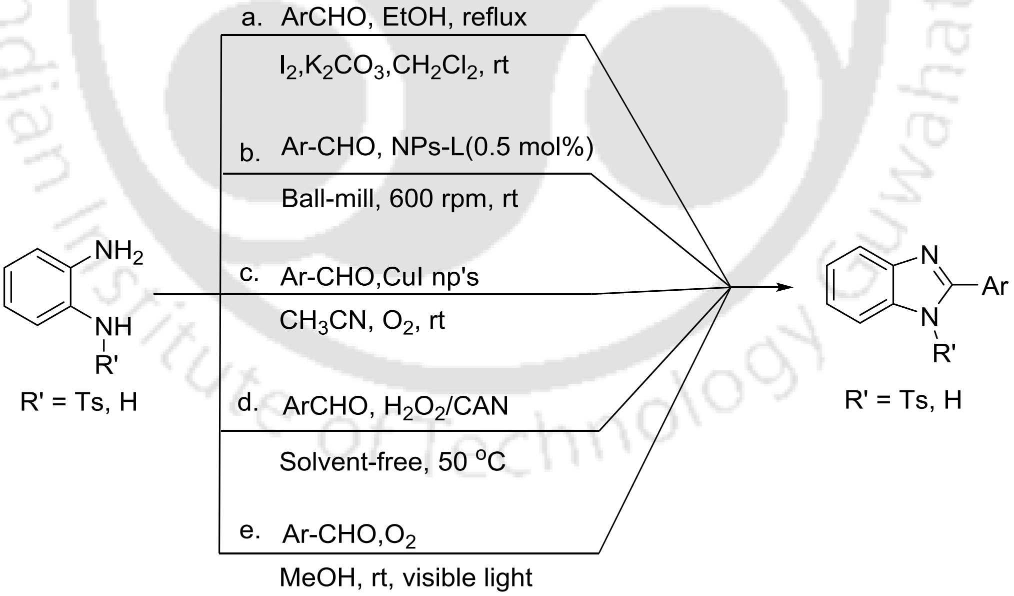
Cu-Catalyzed Oxidative Coupling of Anilines, Aldehydes and $TMSN_3$

The transformation of simple substrates into complex molecules with structural diversity remains a critical process in synthetic chemistry. Multicomponent tandem reaction provides a powerful synthetic tool to achieve this goal. In addition, transition-metal-catalyzed directed C-H functionalization affords an effective synthetic strategy for the regioselective construction of carbon-heteroatom bonds.[1] The second row transition-metals such as Ru[2], Rh[3], Pt[4,5] and Pd[6] have been considerably explored for this purpose. In contrary, few studies are focused on the Cu-based systems,[7] which are particularly attractive because of its high abundance and less toxicity. In addition, aldehydes are simple and readily available carbonyl compounds. Their utilization for the construction of *N*-heterocycles via C-H functionalization would thus be valuable.

2.1 Recent Studies on Synthesis of Benzimidazoles Using Aldehydes



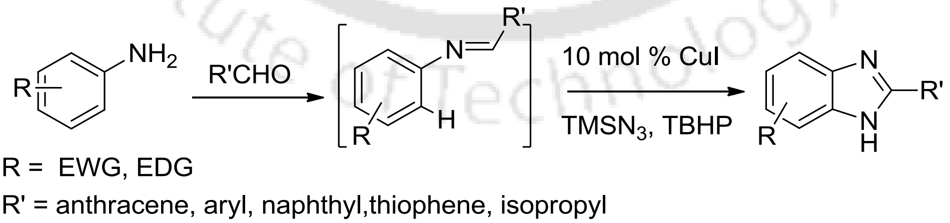
Scheme 1. Methods for Benzimidazoles Using Aldehydes

Chang and co-workers reported an intramolecular C−H amidation of imine using molecular iodine under basic conditions (Scheme 1a).[8] The required imine is readily prepared from 1,2-

diaminobenzene and aldehydes via condensation.[8] Jang group developed a solvent-free synthesis of benzimidazoles using recyclable ZnO-NPs *via* a ball-milling (Scheme 1b).[9] This synthetic approach affords an environmentally friendly conditions that scores high on the ecoscale with the low E-factor. Rawath and co-workers demonstrated a general and easy synthesis of benzimidazoles from cyclization of 1,2-diaminobenzenes with aldehydes using CuI nanoparticles as a heterogeneous catalyst (Scheme 1c).[10] The H_2O_2/CAN system has been employed as a novel, mild and efficient reagent for the preparation of benzimidazoles from 1,2-diaminobenzene and aryl aldehydes (Scheme 1d).[11] Cho group presented a green process, which uses visible light irradiation, for benzimidazole synthesis from 1,2-diaminobenzene and aldehydes in the presence of molecular oxygen as oxidant (Scheme 1e).[1] Although these methods provide the effective synthetic tool for the construction of benzimidazoles, they are often limited due to non-availability of the suitably substituted 1,2-diaminobenzenes. The development of new synthetic routes for the construction of functionalized benzimidazoles from simple substrates that can provide broad substrate scope and atom-economy would thus be valuable.

2.2 Present Study

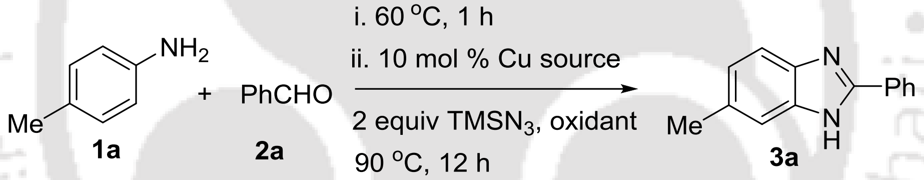
This section presents an oxidative coupling of the readily available anilines, aldehydes and $TMSN_3$ using copper-catalysis in the presence of *tert*-butyl hydroperoxide (TBHP) as an oxidant at moderate temperature (Scheme 2). The protocol affords a potential route for the construction diverse functionalized benzimidazoles.



Scheme 2. Synthesis of Benzimidazoles

The reaction was optimized with *p*-toluidine **1a** and benzaldehyde **2a** as model substrates using a Cu sources with different solvents, azides and oxidants (Table 1). The reaction took place to give benzimidazole **3a** in 60% yield when the substrates **1a** (1 equiv) and **2a** (1.2 equiv) were stirred at 60 ^{o}C for 1 h to give an imine that was reacted with CuBr (10 mol %), $TMSN_3$ (2 equiv) and TBHP (1 equiv) at 90 ^{o}C for 12 h in CH_3CN (entry 1). The use of DMSO as a solvent led to an increase the yield to 72%, whereas DMF, CH_2Cl_2, THF and toluene gave inferior results (entries 2-6). Azides such as NaN_3 and TsN_3, and oxidant, 30% H_2O_2, failed to react (entries 7-9). Subsequent screening of the Cu sources revealed that CuI exhibited superior results, giving the target heterocycle in 77% yield, while CuCl, $CuBr_2$, $CuCl_2$, $Cu(OAc)_2{\cdot}H_2O$, $Cu(OAc)_2$ and Cu_2O afforded <68% yields (entries 10-16). Lowering the amount of the Cu-source (5 mol %), TBHP (0.5 equiv) or $TMSN_3$ (1.5 equiv) led to the formation of **3a** in <61% yield (entry 17-19). Control experiment confirmed that, in the absence of either the Cu-source or TBHP, the formation of **3a** was not observed (entries 20-21).

Table 1. Optimization of the Reaction Conditions[a]



Entry	[Cu]	[N_3]	Oxidant	Solvent	Yield (%)[b]
1	CuBr	$TMSN_3$	TBHP	CH_3CN	60
2	CuBr	$TMSN_3$	TBHP	toluene	5
3	CuBr	$TMSN_3$	TBHP	CH_2Cl_2	3
4	CuBr	$TMSN_3$	TBHP	THF	3
5	CuBr	$TMSN_3$	TBHP	DMF	16
6	CuBr	$TMSN_3$	TBHP	DMSO	72
7	CuBr	TsN_3	TBHP	DMSO	n.d.

8	CuBr	NaN_3	TBHP	DMSO	n.d.
9	CuBr	$TMSN_3$	30% H_2O_2	DMSO	n.d.
10	CuCl	$TMSN_3$	TBHP	DMSO	40
11	CuI	$TMSN_3$	TBHP	DMSO	77
12	$Cu(OAc)_2{\cdot}H_2O$	$TMSN_3$	TBHP	DMSO	66
13	$CuCl_2$	$TMSN_3$	TBHP	DMSO	63
14	$CuBr_2$	$TMSN_3$	TBHP	DMSO	64
15	Cu_2O	$TMSN_3$	TBHP	DMSO	10
16	$Cu(OAc)_2$	$TMSN_3$	TBHP	DMSO	68
17	CuI	$TMSN_3$	TBHP	DMSO	56[c]
18	CuI	$TMSN_3$	TBHP	DMSO	59[d]
19	CuI	$TMSN_3$	TBHP	DMSO	61[e]
20	-	$TMSN_3$	TBHP	DMSO	n.d.
21	CuI	$TMSN_3$	-	DMSO	n.d.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), solvent (0.5 mL), 60 °C, 1 h; Cu source (10 mol %), azide (1 mmol), TBHP (0.5 mmol), 90 °C, 12 h.

[b] Isolated yield.

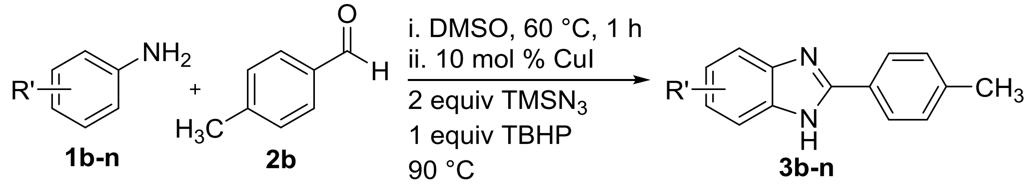
[c] 5 mol % CuI was used.

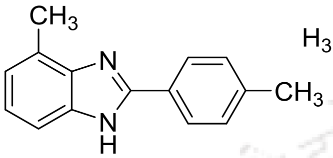
[d] 0.75 mmol $TMSN_3$ was used.

[e] 0.25 mmol TBHP was used. n.d. = not detected.

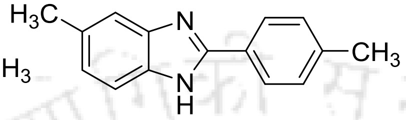
Having optimized the reaction condition, the scope of the protocol was investigated for the reaction of a series of substituted anilines and 2-aminofluorene with tolualdehyde **2b** as a representative example (Table 2). Aniline bearing electron donating and electron withdrawing substituents readily proceeded reaction, and a substituent at 2-position had little effect on the yield. Reaction of 2-methylaniline gave benzimidazole **3b** in 61% yield, while 3-methylaniline

Table 2. Reaction of Aryl Amines with Tolualdehyde[a]

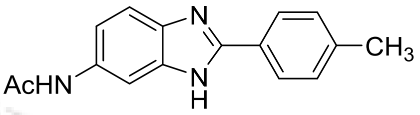




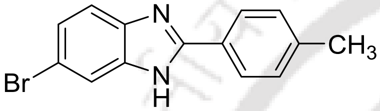
3b, 13 h, 61%



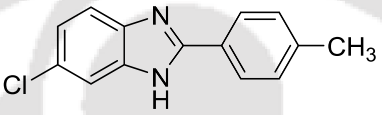
3c,12 h, 70%[c]; 14 h, 79%[d]



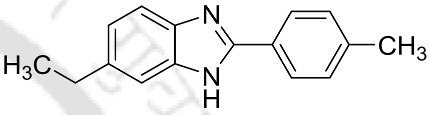
3d, 14 h, 72%



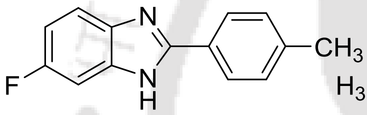
3e, 12 h, 63%



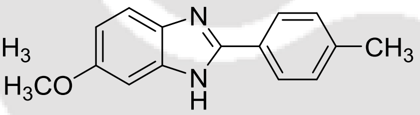
3f, 14 h, 64%



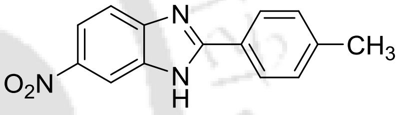
3g, 12 h, 72%



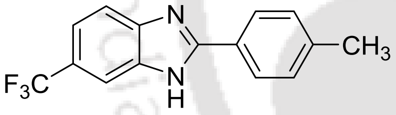
3h, 12 h, 59%



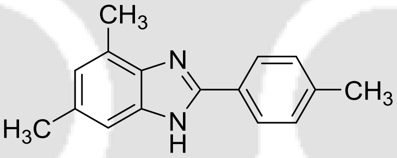
3i, 12 h, 73%[e]



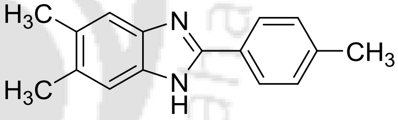
3j, 12 h, n.d.



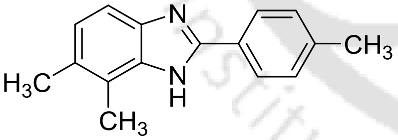
3k, 12 h, 49%



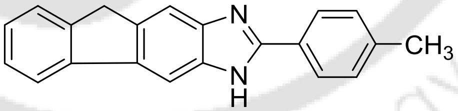
3l, 14 h, 59%



3ma, 14 h, 61%[f]



3mb, 14 h, 10%[e,f]



3n, 9 h, 70%

[a] Reaction conditions: amine **1b-n** (1 mmol), aldehyde **2b** (1.2 mmol), DMSO (1 mL), 60 °C, 1 h; CuI (10 mol %), $TMSN_3$ (2 mmol), TBHP (1 mmol) and 90 °C.

[b] Isolated yield.

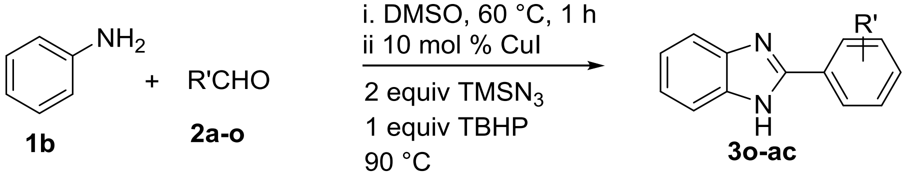
[c] 3-Methylaniline was used.

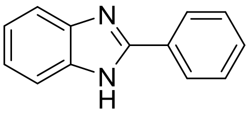
[d] 4-Methylaniline was used.

[e] Two tautomers were observed in nearly 1:1 ratio by ^1H NMR.

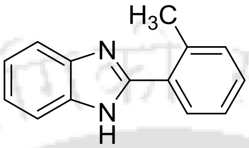
[f] Obtained as a 1:6 mixture.

Table 3. Reaction of Aniline with Various Aldehydes[a]

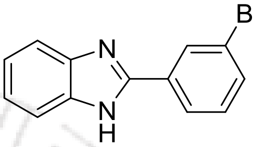




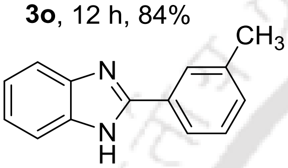
3o, 12 h, 84%



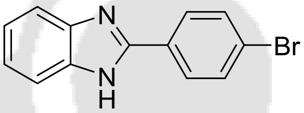
3p, 12 h, 66%



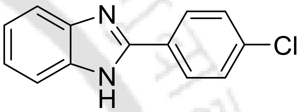
3q, 10 h, 59%



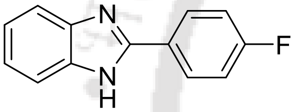
3r, 10 h, 65%



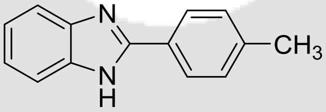
3s, 10 h, 63%



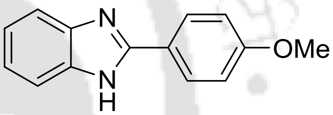
3t, 12 h, 67%



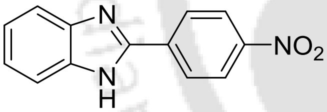
3u, 12 h, 64%



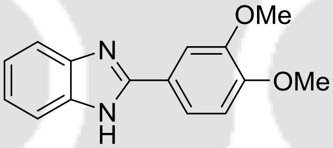
3v, 16 h, 77%



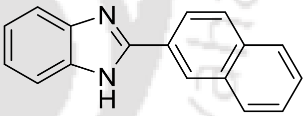
3w, 9 h, 67%



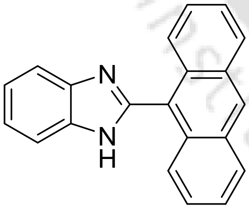
3x, 12 h, 70%



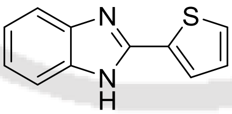
3y, 12 h, 59%



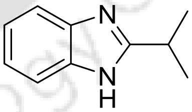
3z, 10 h, 79%



3aa, 12 h, 64%



3ab, 12 h, 68%



3ac, 14 h, 64%

[a] Reaction conditions: aniline **1b** (1 mmol), aldehyde **2a-o** (1.2 mmol), DMSO (1 mL), 60 °C, 1 h; CuI (10 mol %), $TMSN_3$ (2 mmol), TBHP (1 mmol) and 90 °C.

[b] Isolated yield.

underwent reaction to afford the desired **3c** in 70% yield. The reactions of anilines having 4-acetamide, 4-bromo, 4-chloro, 4-ethyl, 4-fluoro, 4-methyl, 4-methoxy and 4-trifluoromethyl groups produced benzimidazoles **3d-i** and **3k** in 49-73% yields. In contrast, aniline with a strong electron withdrawing group, 4-nitro, failed to react, which suggests that the electronic nature of the aryl ring is crucial for the reaction. Compound **3e** produced crystals whose structure was determined by singal crystal X-ray analysis (Figure 1). In addition, 2,4-dimethyl substtiuted anilines underwent reaction to produce benzimidzole **3l** in 59% yield, while the reaction of 3,4-dimethyl substituted aniline produced a mixture regioisomers **3ma** and **3mb** in good yields. Further, 2-aminofluorene underwent reaction to give benzimidazole **3n** in 70% yield.

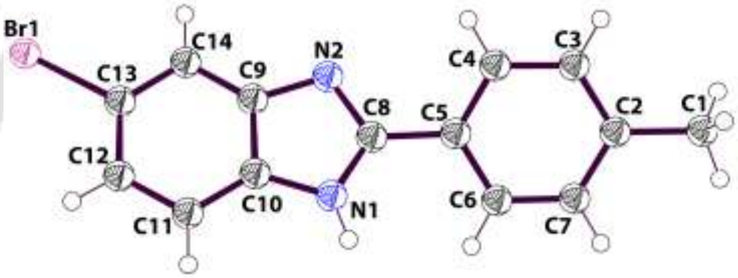
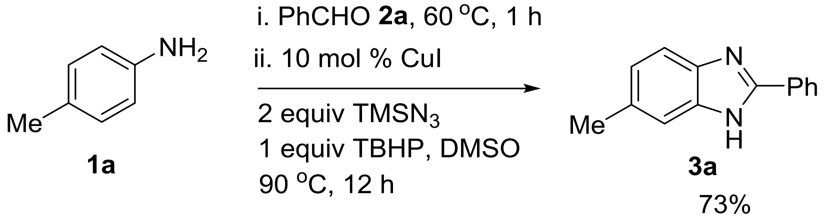
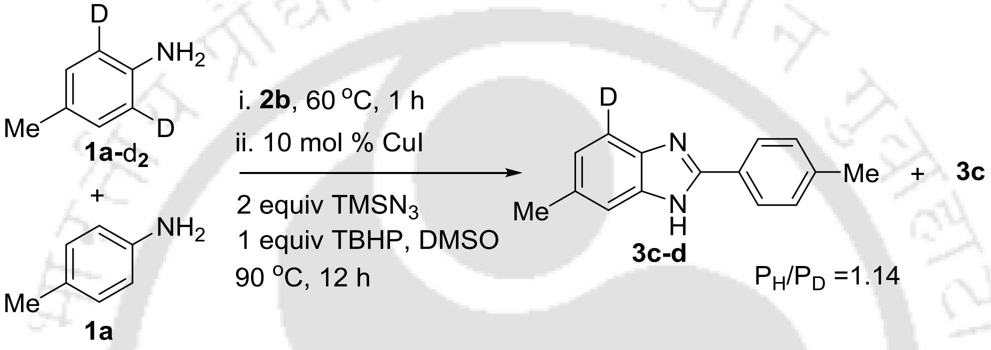


Figure 1. ORTEP diagram of **3e** with 50% ellipsoid.

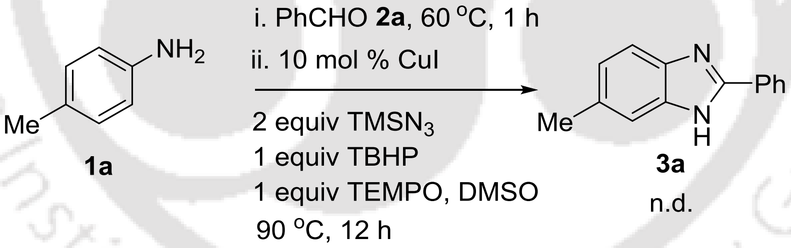
Next, we applied the protocol for the reactions of aldehydes with aniline **1b** as a standard substrate (Table 3). The reaction of benzaldehyde **1a** produced benzimidazole **3o** in 84% yield. Substituted aldehydes with electron donating and electron withdrawing groups, 2-methyl, 3-bromo, 3-methyl, 4-bromo, 4-chloro, 4-fluoro, 4-methoxy, 4-methyl and 4-nitro groups, underwent reaction to give the corresponding benzimidazoles **3p-x** in 59-77% yields. The reaction of 3,4-dimethoxybenzaldehyde gave **3y** in 59% yield, while 2-naphthaldehyde underwent reaction to furnish **3z** in 79% yield. Anthracene-9-carbaldehyde cross-coupled to provide benzimidazole **3aa** in 64% yield. The reaction of the heterocyclic aldehyde, thiophene-2-aldehyde, occurred to afford **3ab** in 68% yield. In addition, an aliphatic aldehyde, isobutyraldehyde, underwent reaction to give 2-isopropylbenzimidazole **3ac** in 64% yield. Finally, the scale up of the procedure was investigated using **1a** and **2a** as representative examples (Scheme 3). The reaction was efficient and the target product was obtained in 73% yield.



Scheme 3. Gram Scale Synthesis



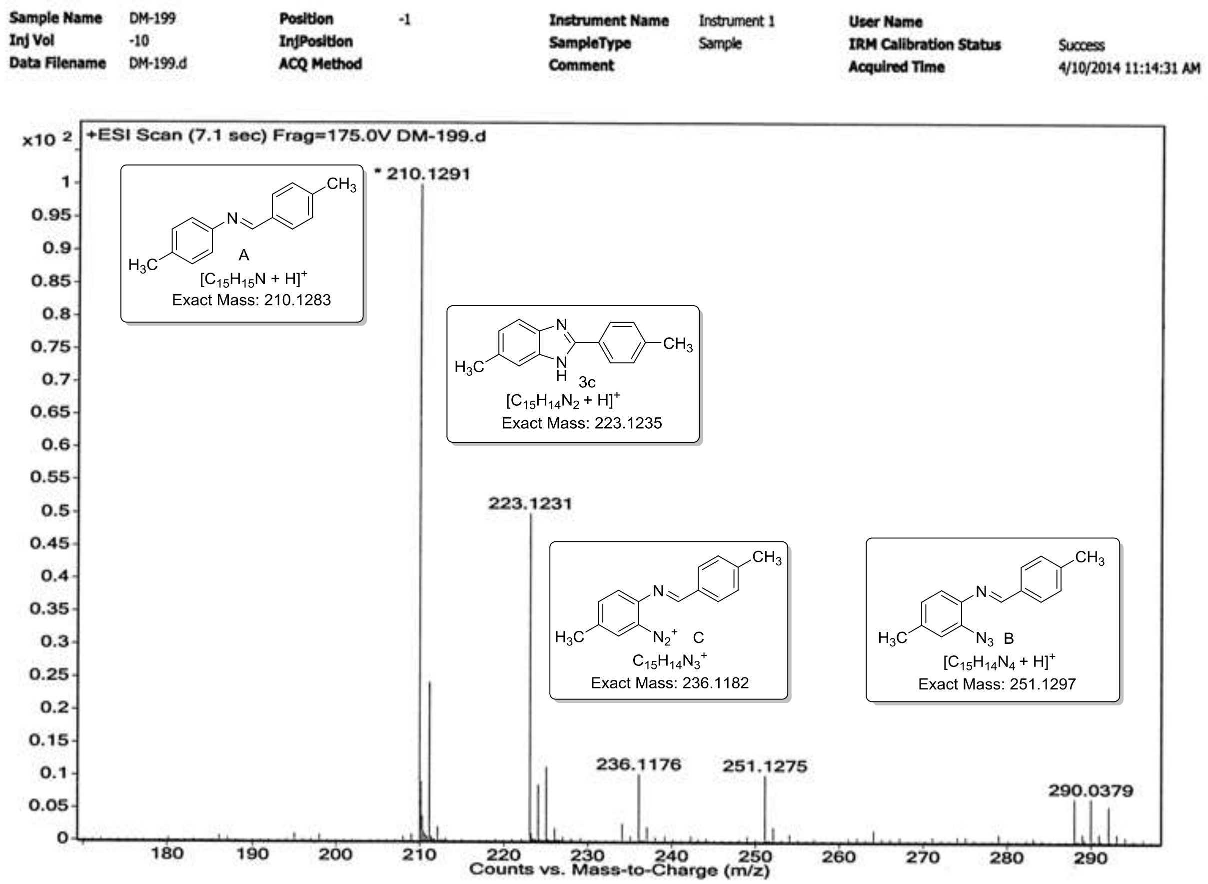
Scheme 4. Kinetic Isotope Experiment



Scheme 5. Radical Scavenger Experiment

To get insight into the reaction pathway, an intermolecular kinetic isotope experiment between equimolar amounts of **1a**-*d*$_2$ and **2b** was performed (Scheme 4). At 1 h with 23% conversion, the reaction afforded P_H/P_D = 1.14, which suggests that the C-H bond cleavage is not involved in the product determining step.[13] In addition, the radical scavenger experiment using TEMPO exhibited no reaction, which suggests that the reaction involves a radical intermediate (Scheme 5).[14] Furthermore, the ESI-MS analyses of the reaction mixture of **1a**, **2b** and TMSN$_3$ after 3 h revealed the presence of four major species **A**, **B**, **C** and **3a** (Figure

2).[15] Thus, the condensation of aldehyde with amine can give *N*-aryl imine ***a*** that may undergo chelation with CuI to afford ***b*** (Scheme 6). Oxidative addition of ***b*** with $TMSN_3$ can produce ***c*** that can react with TBHP to afford ***d***. The latter can convert into Cu(II) species ***e*** by a single electron transfer (SET).[16] Intramolecular N_3 transfer to aryl cation radical can give ***f*** that may lead to the formation of ***h*** via aryl cation ***g*** by SET. Cyclization of ***h*** may give ***i*** that can furnish the target product **3** by tautomerization to complete the catalytic cycle.



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Comment
User Name
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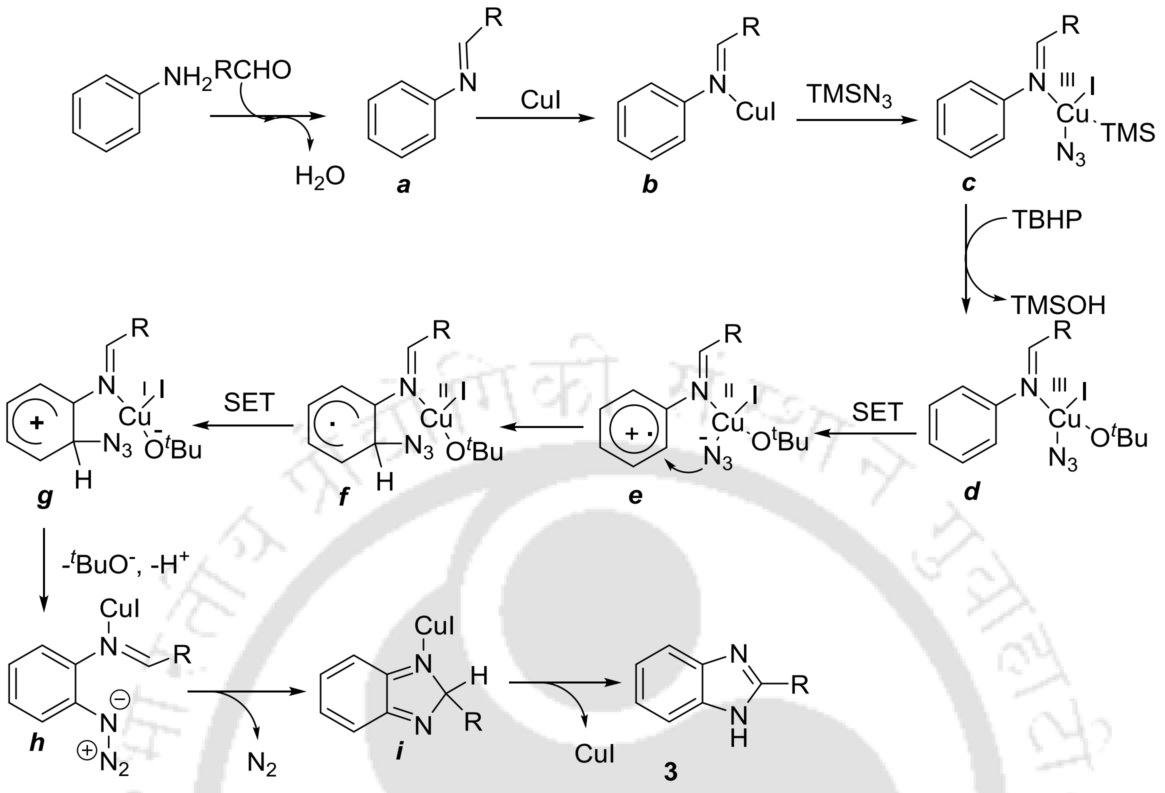
Figure 1. Major species identified using ESI-MS of the reaction mixture of **1a**, **2b** and $TMSN_3$ after 3 h.



Scheme 6. Proposed Reaction Pathway

In summary, Cu-catalyzed imine directed amination of *N*-aryl imines proceeds smoothly to afford substituted benzimidazoles. The use of Cu catalysts, the commercially available starting material and the broad substrate scope are significant practical advantages. The tolerance of the functional groups is a synthetically useful feature.

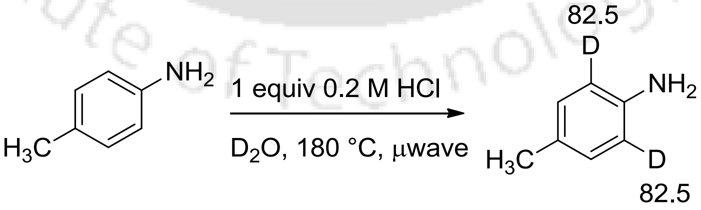
2.3. Experimental Section

2.3.1 General Information. $Cu(OAc)_2$ (99%), $CuCl_2$ (99%), CuI (98%), CuBr (97%), CuCl (90%), Cu_2O (97%), $TMSN_3$ (95%) and TBHP (98%, 5.5 M in decane) and $Cu(OAc)_2{\cdot}H_2O$ (98%) were purchased from commercial sources. Purification of the reaction products was carried out by column chromatography using silica gel (60-120 mesh). Analytical TLC was performed on silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 and 600 MHz using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as internal standard. Chemical shifts (δ) were reported in ppm and spin-spin coupling constants (J) were given in Hz. Melting points were determined using melting point apparatus and are uncorrected.IR spectra were recorded using FT-IR spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS Instrument. X-Ray data were collected with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany).

2.3.2. General Procedure for Amination of *N*-Aryl Imines. Aniline **1**(1.0 mmol) and benzaldehyde **2** (1.2 mmol) were stirred at 60 °C for 1 h in DMSO (1 mL) under air. The mixture was then cooled to room temperature and treated with CuI (10 mol %, 0.1 mmol, 19 mg), $TMSN_3$ (2 equiv, 2.0 mmol, 230 mg) and TBHP (1 equiv, 1 mmol, 181µL). The resultant mixture was stirred at 90 °C for the appropriate time (Table 1 and 2). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (2 x 5 mL). The solution was dried over Na_2SO_4, passed through a short pad of celite and evaporated on a rotary evaporator to give a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent.

2.3.3. Kinetic Isotope Studies

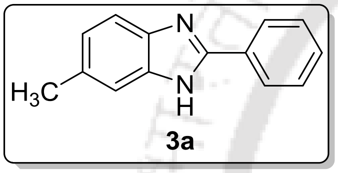
Preperation of *p*-Toluidine-d$_2$ (Scheme 7). The titled compound was perpared according to the reported procedure.[2] Deuterium incorporation (82.5%) was determined by ^{1}H NMR analysis of the mixture. Characterization data for the deuterated product: analytical TLC on silica gel, 1/4 ethyl acetate/hexane $R_f = 0.32$; pale brown solid; 185 mg, yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 3.47 (br s, 2H), 2.23 (s, 3H).



Scheme 7

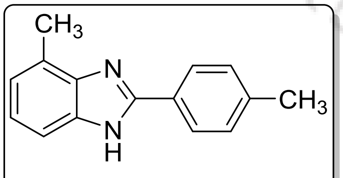
Intermolecular Kinetic Isotope Study. *p*-Toluidine **1a** (64 mg), *p*-toluidine-d$_2$ **1a-*d*$_2$** (100 mg) and *p*-tolualdehyde **2b** (1.2 equiv, 1.82 mmol, 218 mg) were stirred at 60 °C for 1 h in DMSO (1 mL) under air. The reaction mixture was then cooled to room temperature and treated with CuI (10 mol %, 0.152 mmol, 29 mg), $TMSN_3$ (2 equiv, 3.0 mmol, 350 mg) and TBHP (1 equiv, 1.52 mmol, 275 µL). The resultant mixture was stirred at 90 °C for 1 h to give 24% conversion. The resulting mixture was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (2 x 5 mL). Drying (Na_2SO_4) and passing through celite gave a clear solution, which was evaporated on a rotary evaporator to give a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent (40 mg, yield 18%). The ratio of deuterium to hydrogen was determined from the ^1H NMR relative integration values of H_a (7.47 ppm) based on H_b (7.05 ppm).

2.4. Characterization Data



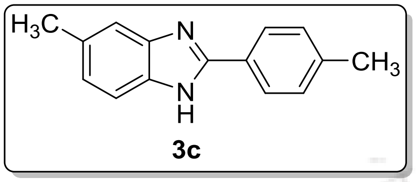
3a

6-Methyl-2-phenyl-1H-benzo[*d*]imidazole 3a. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 160 mg, yield 77%; mp 243-244 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 8.17 (d, *J* = 7.2 Hz, 2H), 7.55-7.32 (m, 5H), 7.05-7.00 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.9, 144.2, 142.0, 135.3, 133.1, 131.9, 130.7, 126.1, 123.3, 118.5, 111.1, 21.4; FT-IR (KBr) 3447, 3047, 2920, 2110, 1632, 1595, 1460, 1403, 1313, 1272, 1108, 969, 801, 699 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1073.



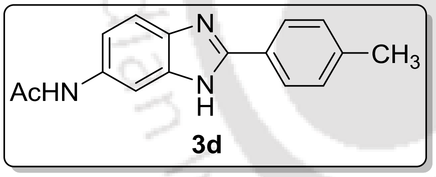
3b

4-Methyl-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3b. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 135 mg, yield 61%; ^1H NMR (600 MHz, DMSO-d_6) δ 12.74 (br s, 1H), 8.10 (s, 2H), 7.36 (d, *J* = 7.8 Hz, 3H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 6.6 Hz, 1H), 2.56 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.5, 140.5, 129.9, 127.4, 126.7, 123.6, 123.0, 21.6, 17.2; FT-IR (neat) 3402, 3029, 2917, 2115, 1620, 1504, 1485, 1439, 1373, 1285, 1117, 958, 827, 748 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1234.



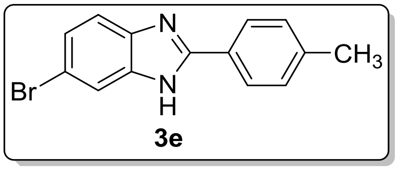
3c

5-Methyl-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3c. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.41$; white solid; 155 mg, yield 70% (using 3-methylaniline) and 175 mg, yield 79% (using 4-methyl aniline); mp 163-164 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 8.02 (s, 2H), 7.48-7.32 (m, 4H), 7.05-6.98 (m, 1H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.5, 140.3, 139.2, 138.0, 132.7, 129.9, 127.5, 126.9, 124.4, 115.2, 114.6, 21.8, 21.5; FT-IR (KBr) 3440, 2922, 2852, 1627, 1449, 1385, 1284, 1225, 1109, 1026, 922, 804, 741 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1230.



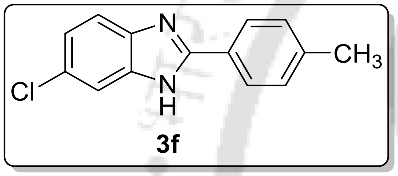
3d

***N*-(2-(*p*-tolyl)-1*H*-benzo[*d*]imidazol-6-yl)acetamide 3d.** Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.41$; pale yellow solid; 191 mg, yield 72%; mp 273-274 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (br s, 1H), 9.97 (br s, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.51 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.20 (s, 1H), 2.36 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.9, 139.3, 134.6, 129.5, 127.5, 126.1, 118.4, 114.3, 101.5, 24.0, 20.9; FT-IR (KBr) 3439, 3200, 2920, 2854, 1671, 1609, 1563, 1456, 1391, 1272, 1156, 1033, 824, 715 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}N_3OH$ 266.1293, found 266.1297.



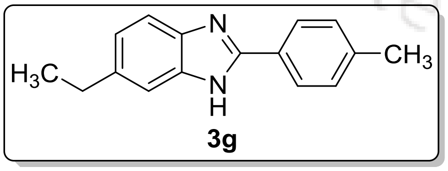
3e

6-Bromo-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3e. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 180 mg, yield 63%; mp 232-233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.77 (s, 1H), 7.52 (s, 1H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$) δ 152.0, 139.1, 128.4, 126.1, 125.7, 125.6, 123.8, 20.3; FT-IR (KBr) 3449, 3015, 2917, 2110, 1620, 1448, 1378, 1303, 1275, 1112, 1015, 911, 823, 729 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}BrN_2H$ 287.0184, found 287.0191.



3f

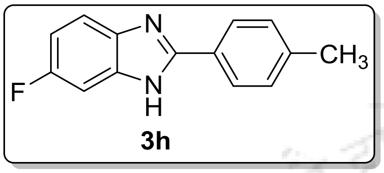
6-Chloro-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3f. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 155 mg, yield 64%; mp 234-235 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.06 (d, *J* = 7.8 Hz, 2H), 7.69-7.65 (m, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$) δ 152.1, 139.0, 128.3, 126.1, 125.9, 125.6, 121.2, 20.2; FT-IR (KBr) 3435, 2922, 2857, 2110, 1620, 1583, 1439, 1378, 1308, 1275, 1219, 1061, 963, 809, 725 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}ClN_2H$ 243.0689, found 243.0691.



3g

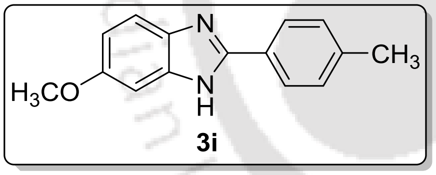
6-Ethyl-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3g. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 170 mg, yield 72%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.66 (br s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.45 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.06-7.04 (m, 1H), 2.71 (s, 2H), 2.37 (s, 3H), 1.26-1.22 (m, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 152.8, 140.2, 139.3, 129.8, 127.5, 123.3, 115.2, 113.5, 29.2, 21.4, 16.4; FT-IR (neat) 3417, 2962, 2925, 2859, 2103, 165, 1559, 1493, 1449, 1389, 1324, 1378, 1186, 1120, 1019, 965, 821, 728 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1399.



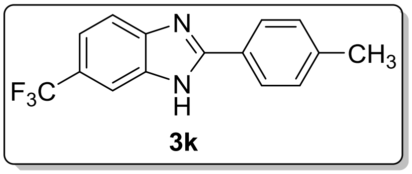
3h

6-Fluoro-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3h. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 134 mg, yield 59%; mp 231-232 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.94 (br s, 1H), 8.05 (d, *J* = 7.8 Hz, 2H), 7.63 (s, 1H), 7.50 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.04 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.4, 130.1, 127.6, 126.9, 112.3, 110.7, 110.3, 21.8; FT-IR (KBr) 3058, 2855, 2752, 2113, 1901, 1734, 1653, 1630, 1595, 1577, 1497, 1443, 1422, 1365, 1309, 1220, 1141, 1022, 824, 727 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}FN_2H$ 227.0985, found 227.0990.



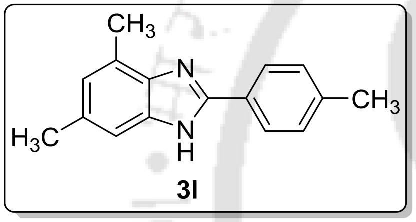
3i

6-Methoxy-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3i. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 174 mg, yield 73%; mixture of tautomers (1:1): ^1H NMR (600 MHz, DMSO-d_6) δ 12.65 (br s, 2H), 8.02 (s, 4H), 7.52 (s, 1H), 7.38 (s, 1H), 7.33 (s, 4H), 7.18 (s, 1H), 6.97 (s, 1H), 6.81 (s, 2H), 3.87 (s, 6H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 152.2, 140.3, 129.9, 127.4, 126.6, 116.2, 112.5, 97.8, 56.0, 21.6; FT-IR (neat) 3430, 2927, 2857, 2110, 1630, 1597, 1453, 1425, 1392, 1266, 1201, 1159, 1107, 1033, 949, 823, 729 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2OH$ 239.1184, found 239.1189.



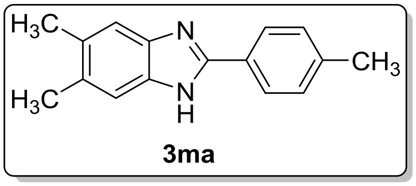
3k

2-(*p*-Tolyl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole 3k. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.31; white solid; 135 mg, yield 49%; mp 192-193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.28 (br s, 2H), 8.10 (d, *J* = 7.6 Hz, 2H), 7.84-7.81 (m, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.9, 140.2, 129.6, 126.7, 119.0; FT-IR (KBr) 3464, 3124, 2924, 1889, 1615, 1562, 1509, 1427, 1329, 1239, 1218, 1055, 1022, 936, 826, 728 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{11}N_2F_3H$ 277.0953, found 277.0961.



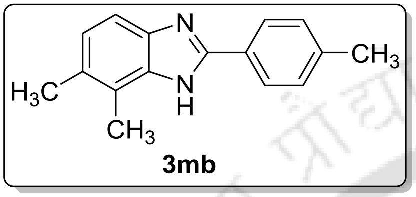
3l

4,6-Dimethyl-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3l. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 140 mg, yield 59%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.57 (br s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.15 (s, 1H), 6.81 (s, 1H), 2.52 (s, 3H), 2.38 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.4, 140.2, 132.8, 129.9, 127.6, 126.7, 125.2, 21.8, 21.6, 17.2; FT-IR (neat) 3444, 2917, 2857, 1901, 1630, 1593, 1429, 1387, 1257, 1182, 1033, 958, 827, 725 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1392.



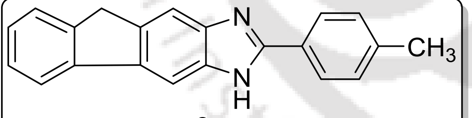
3ma

5,6-Dimethyl-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3ma. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 144 mg, yield 61%; mp 233-224 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (br s, 1H), 8.03 (d, *J* = 7.8 Hz, 2H), 7.40 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.26 (s, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 150.5, 142.5, 139.1, 133.4, 130.8, 129.4, 129.1, 127.7, 126.1, 118.8, 111.2, 20.9, 20.0 ; FT-IR (KBr) 3435, 3015, 2917, 2087, 1900, 1625, 1588, 1499, 1448, 1387, 1308, 1289, 1121, 1308, 1121, 1005, 827, 720 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1390.



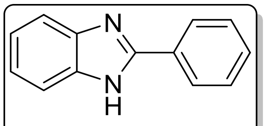
3mb

6,7-Dimethyl-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole 3mb. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.31; yellow solid; 24 mg, yield 10%; mp 190-191 °C; mixture of tautomers (1:1): ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.64 (br s, 1H), 12.30 (br s, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 7.6 Hz, 2H), 7.38-7.36 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.03-7.00 (m, 2H), 2.53 (s, 6H), 2.40 (s, 6H), 2.36 (s, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 151.3, 140.2, 132.0, 129.9, 127.5, 126.7, 126.5, 21.6, 20.6; FT-IR (KBr) 3596, 2919, 2102, 1625, 1503, 1437, 1384, 1310, 1260, 1122, 1019, 958, 827, 727 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1399.



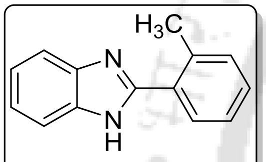
3n

2-(*p*-Tolyl)-3,9-dihydrofluoreno[2,3-d]imidazole 3n. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.41; thick brown gummy liquid; 207 mg, yield 70%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.91 (br s, 1H), 8.11 (s, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.94 (s, 1H), 7.79-7.68 (m, 1H), 7.55 (s, 1H), 7.37 (d, *J* = 7.2 Hz, 3H), 7.27 (s, 1H), 3.98 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 151.6, 142.4, 139.5, 139.4, 129.5, 127.5, 126.7, 126.4, 126.3, 125.1, 125.0, 57.9, 20.9; FT-IR (neat) 3435, 2924, 2257, 1644, 1431, 1382, 1272, 1047, 1030, 998, 826, 764 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{21}H_{16}N_2H$ 297.1392, found 297.1393.



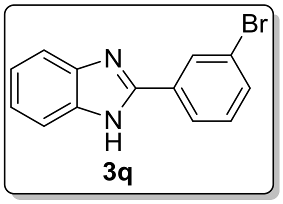
3o

2-Phenyl-1*H*-benzo[*d*]imidazole 3o. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 163 mg, yield 84%; mp 292-293 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.18 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.56-7.49 (m, 4H), 7.22-7.19 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.3, 143.8, 135.0, 130.2, 129.9, 129.0, 126.5, 122.6, 121.8, 118.2, 111.4; FT-IR (KBr) 3442, 2961, 2919, 2112, 1565, 1440, 1360, 1283, 1120, 1088, 995, 893, 743 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{10}N_2H$ 195.0922, found 195.0922.



3p

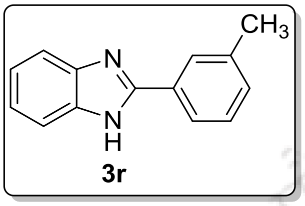
2-(*o*-Tolyl)-1*H*-benzo[*d*]imidazole 3p. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 137 mg, yield 66%; mp 223-224 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.53 (s, 1H), 7.41-7.35 (m, 3H), 7.21 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.0, 143.7, 137.0, 131.3, 130.1, 129.5, 129.4, 126.0, 122.4, 121.5, 119.0, 111.3, 21.0; FT-IR (KBr) 3440, 3048, 2973, 2721, 1938, 1619, 1597, 1448, 1406, 1369, 1275, 1229, 1047, 972, 879 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1077.



3q

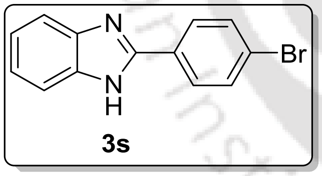
2-(3-Bromophenyl)-1*H*-benzo[*d*]imidazole 3q. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 161 mg, yield 59%; mp 223-224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (br s, 1H), 8.37 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* =

6.4 Hz, 2H), 7.56-7.50 (m, 2H), 7.25-7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 149.6, 143.7, 135.0, 132.5, 132.4, 131.1, 128.9, 125.4, 122.9, 122.3, 121.9, 119.1, 111.5; FT-IR (KBr) 3326, 3048, 2529, 2112, 1698, 1649, 1595, 1544, 1445, 1315, 1226, 1156, 970, 743 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0030.



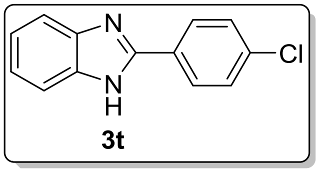
3r

2-(*m*-Tolyl)-1*H*-Benzo[*d*]imidazole 3r. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.41; white solid; 135 mg, yield 65%; mp 231-232 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.88 (br s, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.53 (d, *J* = 4.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 3.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 151.8, 144.2, 138.6, 135.4, 130.9, 130.5, 129.3, 127.4, 124.0, 122.9, 122.0, 119.2, 111.7, 21.5; FT-IR (KBr) 3439, 2920, 2859, 2114, 1685, 1554, 1443, 1308, 1239, 1122, 1039, 957, 822, 728 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{12}N_2$ H 209.1079, found 209.1088.



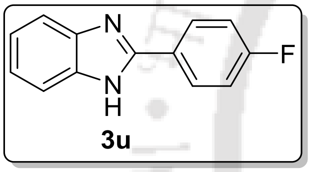
3s

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole 3s. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.41; pale yellow solid; 172 mg, yield 63%; mp 255-256 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.00 (br s, 1H), 8.13 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.66 (s, 1H), 7.55 (s, 1H), 7.22 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 150.2, 143.7, 135.1, 129.4, 129.0, 128.3, 123.4, 123.2, 122.3, 118.9, 111.7; FT-IR (KBr) 3449, 3052, 2112, 1622, 1590, 1490, 1427, 1300, 1273, 1224, 1114, 1069, 1009, 963, 828, 745 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0036.



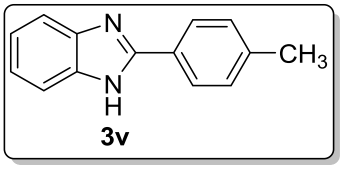
3t

2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole 3t. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 153 mg, yield 67%; mp 265-266 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.23-7.20 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.1, 143.7, 135.0, 134.4, 129.0, 128.7, 128.1, 122.7, 121.8, 118.9, 111.4; FT-IR (KBr) 3442, 2997, 2951, 2112, 1630, 1587, 1486, 1429, 1300, 1273, 1225, 1089, 1015, 965, 831, 746 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9ClN_2H$ 229.0533, found 229.0533.



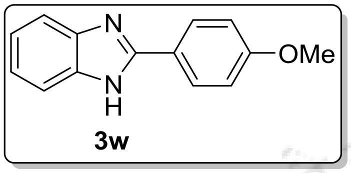
3u

2-(4-Fluorophenyl)-1*H*-benzo[*d*]imidazole 3u. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 136 mg, yield 64%; mp 240-241 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (br s, 1H), 8.23 (m, 2H), 7.66 (d, J = 6.4 Hz, 1H), 7.53 (d, J = 6.4 Hz, 1H), 7.42-7.38 (m, 2H), 7.20 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 162.3, 150.8, 144.2, 135.4, 129.2, 127.2, 123, 122.1, 119.2, 111.6, 111.7; FT-IR (KBr) 3443, 2917, 2854, 2113, 1603, 1497, 1475, 1433, 1276, 1229, 1157, 1111, 967, 838, 747 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9FN_2H$ 213.0828, found 213.0820.



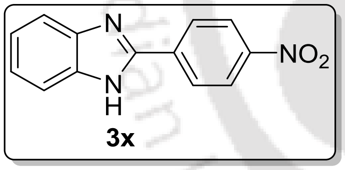
3v

2-(*p*-Tolyl)-1*H*-benzo[*d*]imidazole 3v. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 160 mg, yield 77%; mp 275-276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 8.07 (d, J = 7.2 Hz, 2H), 7.63 (s, 1H), 7.52 (s, 1H), 7.36 (d, J = 6.8 Hz, 2H), 7.19 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 151.4, 143.8, 139.6, 135.0, 129.5, 127.5, 126.4, 122.4, 121.6, 118.7, 111.2, 21.0; FT-IR (KBr) 3440, 2927, 2852, 2106, 1630, 1457, 1261, 1196, 1038, 823, 715 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1087.



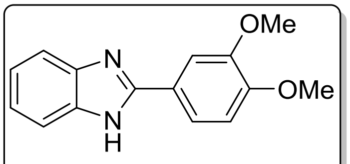
3w

2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole 3w. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 151 mg, yield 67%; mp 218-219 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.76 (br s, 1H), 8.13 (d, *J* = 7.2 Hz, 2H), 7.56 (s, 2H), 7.17-7.10 (m, 4H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 160.6, 151.4, 128.0, 122.7, 121.7, 114.4, 114.3, 111.2, 55.3; FT-IR (KBr) 3472, 2921, 2836, 2113, 1611, 1501, 1476, 1453, 1295, 1254, 1179, 1124, 1034, 965, 845, 745 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{12}N_2OH$ 225.1028, found 225.1033.



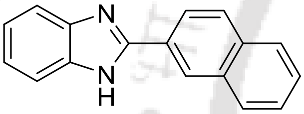
3x

2-(4-Nitrophenyl)-1*H*-benzo[*d*]imidazole 3x. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; Brown solid; 167 mg, yield 70%; mp 260-261 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.30 (br s, 1H), 8.40-8.37 (m, 4H), 7.67 (s, 2H), 7.27 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 150.0, 149.0, 147.7, 136.0, 134.5, 127.32, 127.3, 124.14, 124.1, 122.9, 114.9; FT-IR (KBr) 3451, 2661, 2110, 1667, 1603, 1516, 1433, 1340, 1290, 1101, 1008, 967, 854, 742 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9N_3O_2H$ 240.0773, found 240.0770.



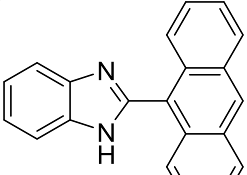
3y

2-(3,4-Dimethoxyphenyl)-1*H*-benzo[*d*]imidazole 3y. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane; R_f = 0.41; Pale Yellow solid; 150 mg, yield 59%; mp 181-182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 7.75 (s, 2H), 7.63 (s, 1H), 7.51 (s, 1H), 7.17 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.6, 150.5, 150.3, 149.0, 122.8, 122.4, 121.8, 119.5, 119.4, 111.8, 109.8, 55.6; FT-IR (KBr) 3195, 2987, 2842, 1620, 1508, 1481, 1432, 1264, 1198, 1115, 1039, 945, 847, 743 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2O_2H$ 255.1134, found 255.1140.



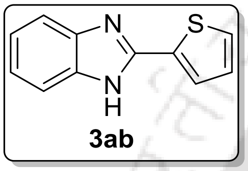
3z

2-(Naphthalen-2-yl)-1*H*-benzo[*d*]imidazole 3z. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 194 mg, yield 79%; mp 192-193 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (br s, 1H), 8.74 (s, 1H), 8.33-8.29 (m, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 6.6 Hz, 1H), 7.99 (d, *J* = 6.6 Hz, 1H), 7.71 (d, *J* = 5.4 Hz, 1H), 7.61-7.58 (m, 3H), 7.23 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$) δ 151.1, 133.1, 133.0, 132.4, 127.7, 127.6, 127.1, 126.9, 126.6, 126.1, 125.9, 125.6, 125.4, 123.3, 121.6, 114.4, 113.4; FT-IR (KBr) 3450, 3053, 2111, 1653, 1588, 1504, 1441, 1405, 1334, 1282, 1136, 1096, 982, 907, 18, 742 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{12}N_2H$ 245.1079, found 245.1091.



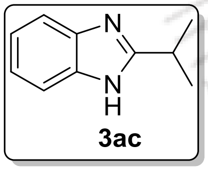
3aa

2-(Anthracen-9-yl)-1*H*-benzo[*d*]imidazole 3aa. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.71; yellow solid; 188 mg, yield 64%; mp 261-262 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.0 (br, s, 1H), 8.85 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 2H), 7.61-7.57 (m, 3H), 7.53-7.50 (m, 2H), 7.33-7.31 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.5, 130.6, 130.5, 128.8, 128.5, 126.8, 125.8, 125.64, 125.6, 122.5, 121.6, 119.1, 111.4; FT-IR (KBr) 3435, 3398, 2922, 2106, 1625, 1448, 1401, 1373, 1331, 1271, 1229, 1033, 921, 883, 790, 743 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{14}N_2$ H 295.1235, found 295.1233.



3ab

2-(Thiophen-2-yl)-1*H*-benzo[*d*]imidazole 3ab. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 136 mg, yield 68%; mp 343-344 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 7.82 (d, *J* = 3.6 Hz, 1H), 7.71 (d, *J* = 5.4 Hz, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 7.23-7.19 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 147.4, 143.9, 135.0, 134.0, 129.1, 128.7, 127.1, 123.0, 122.2, 118.9, 111.5; FT-IR (KBr) cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_8N_2SH$ 201.0486, found 201.0491.



3ac

2-Isopropyl-1*H*-benzo[*d*]imidazole 3ac. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.31; pale yellow solid; 102 mg, yield 64%; mp 232-233 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 6.98-6.92 (m, 2H), 3.04-2.99 (m, 1H), 1.27-1.20 (m, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ160.1, 121.2, 28.7, 21.3; FT-IR (KBr) 3441, 2973, 2887, 2114, 1622, 1535, 1455, 1415, 1323, 1273, 1092, 995, 750 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}N_2H$ 161.1079, found 161.1087.

Crystal Data and Structure Refinement for 3e at 296(2) K

Identification code	DM-195-2
Empirical formula	$C_{14}H_{11}BrN_2$
Formula weight	287.16
Temperature	296(2)
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.6050(3)Å α(°)= 92.198(2) b = 9.8138(3) Å β(°)= 101.769(2) c= 13.4980(4) Å γ(°)= 90.037(2)
Volume	1244.63(7)
Z	4
Density (Calculated)	1.532
Absorption coefficient	3.280
F(000)	576
Crystal size	0.30 x 0.25 x 0.21mm
Theta range for data collection	24.41^{o}
Index ranges	-11<=h<=10, -11<=k<=11, -15<=l<=15
Reflections collected	4003
Independent reflections	2726
Completeness to theta=24.41^{o}	97.9%
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restains/parameter	2726/0/309
Goodness-of-fit on F^2	1.046
Final R indices [I>2 sigma (I)]	R_1= 0.0472 wR_2=0.1486
R indices all data	R_1= 0.0772 wR_2= 0.1669

2.5. References

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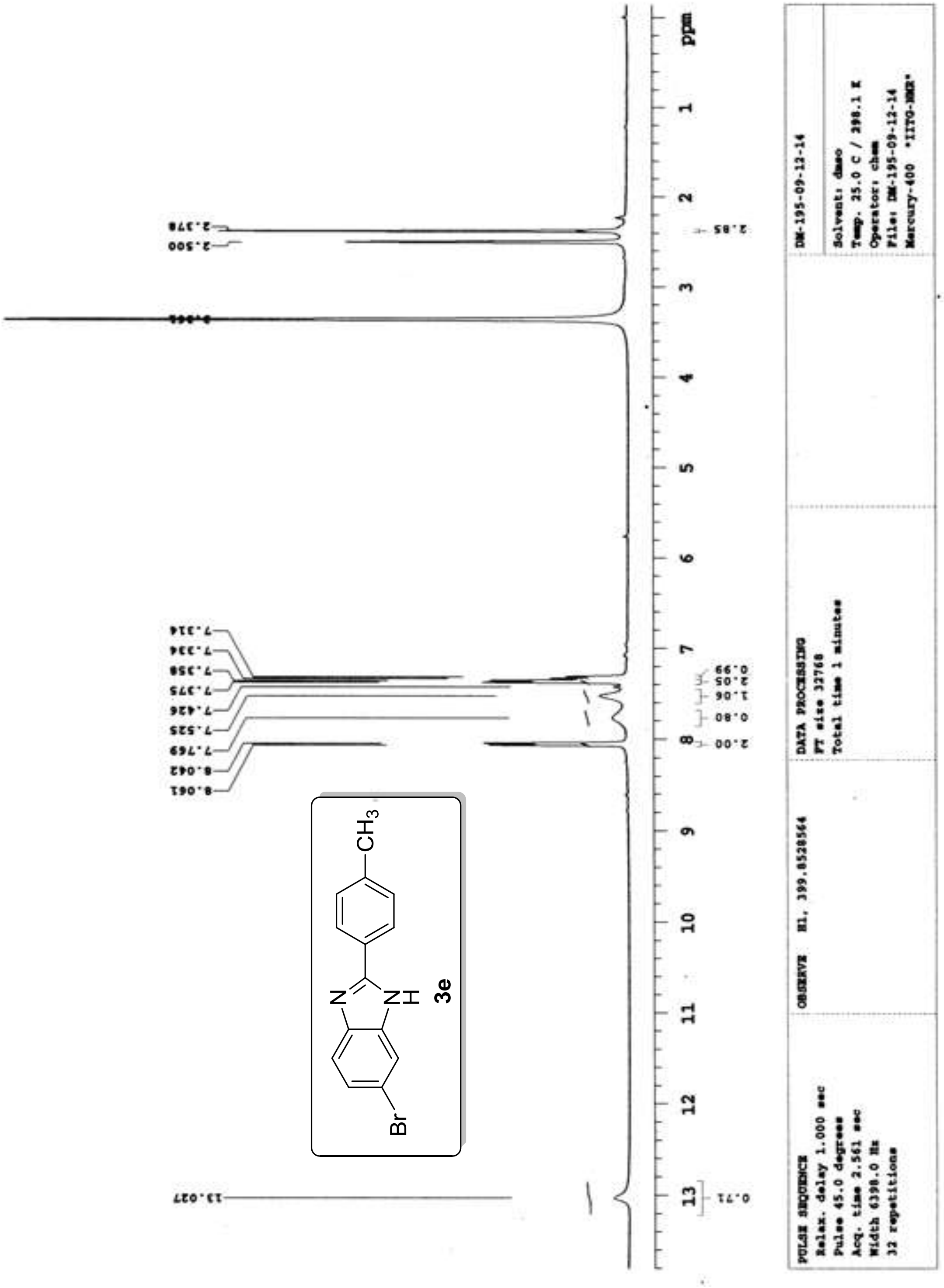

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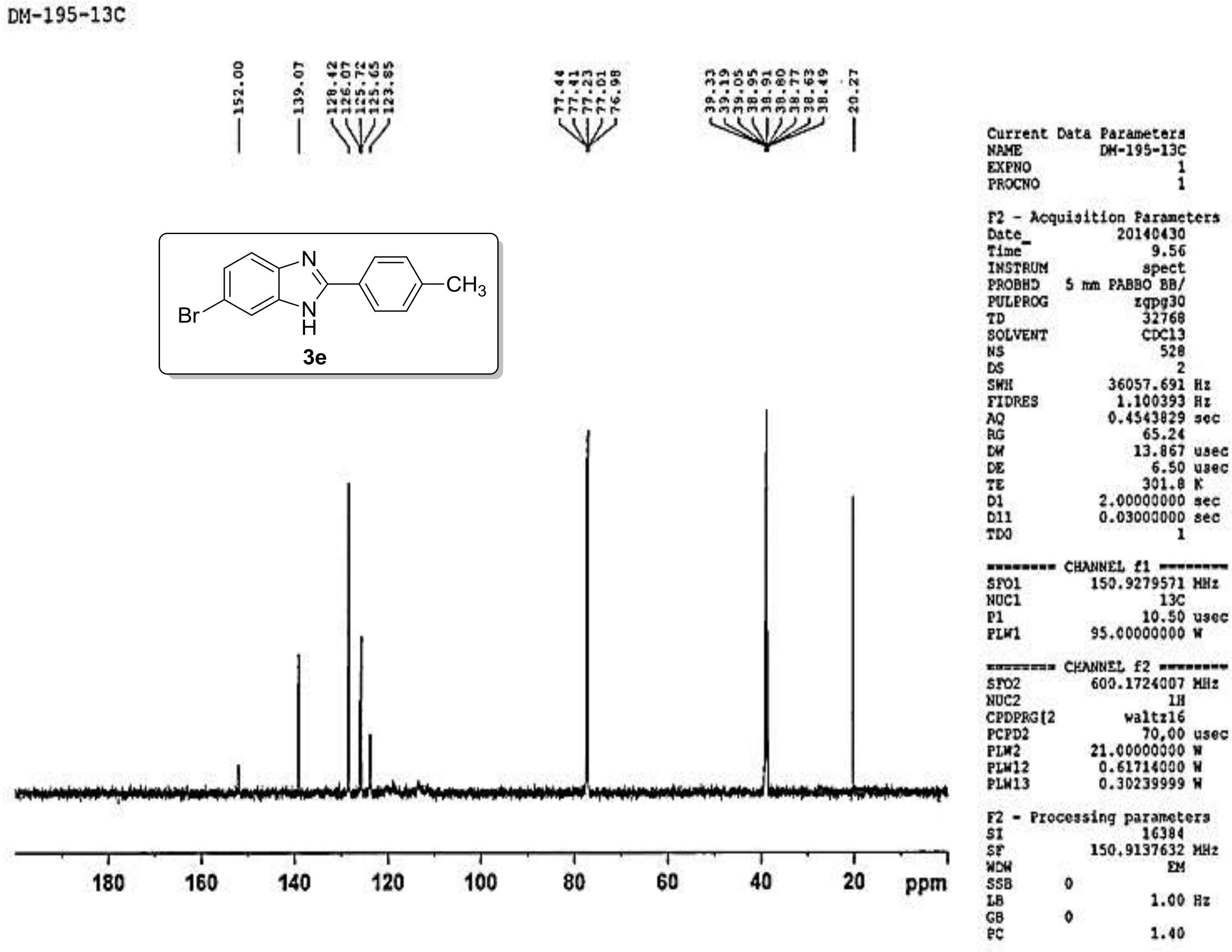

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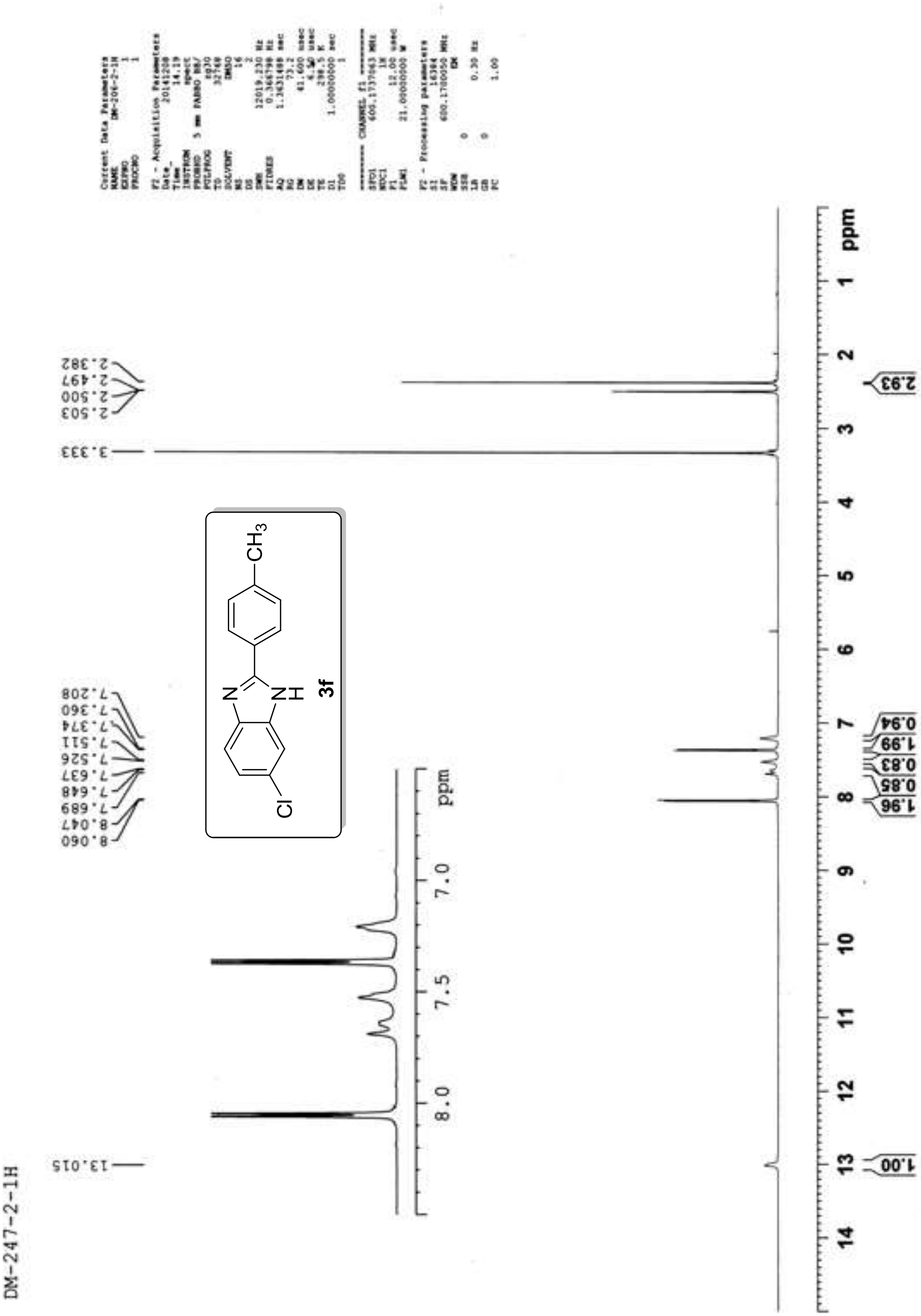
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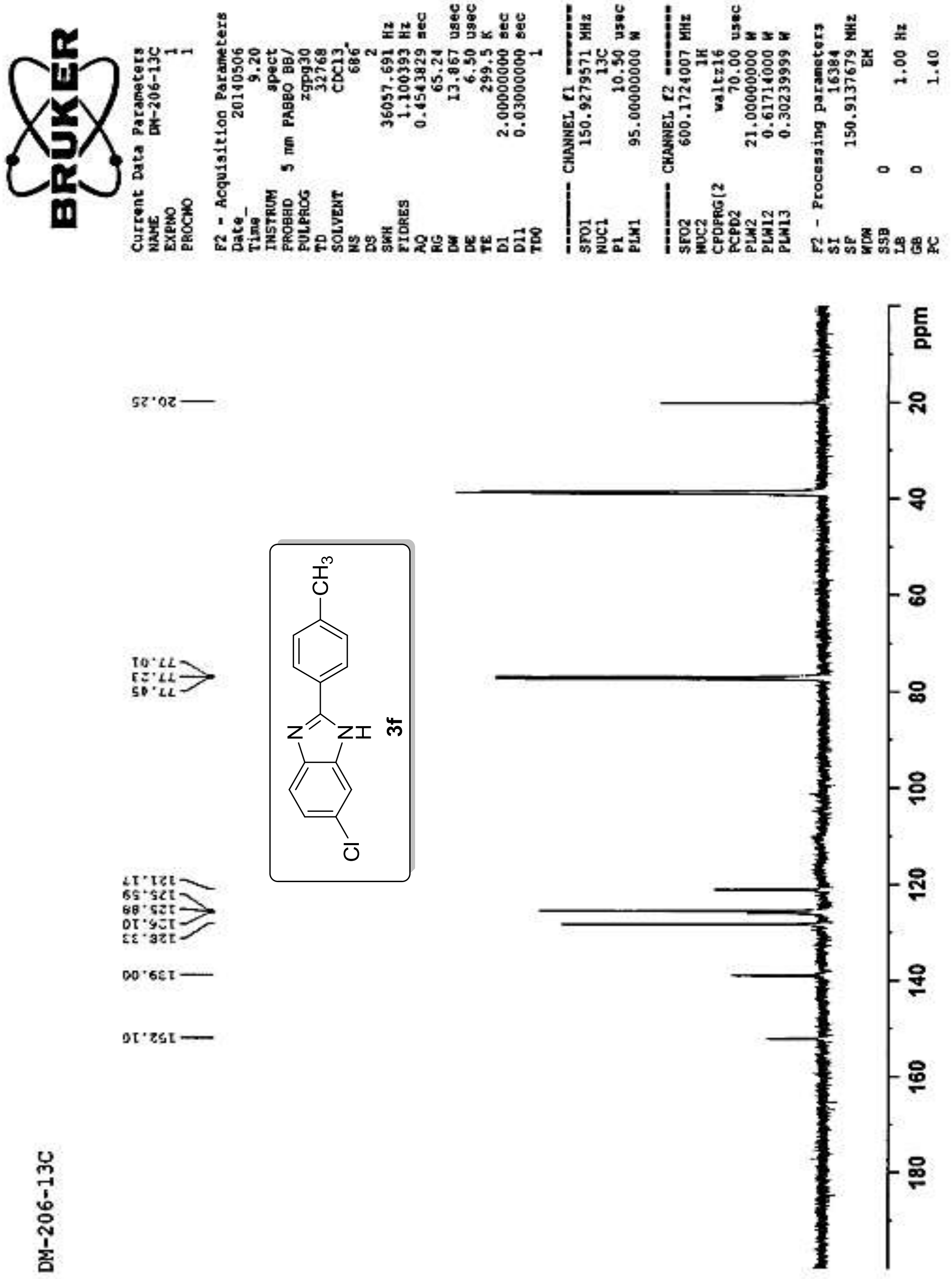
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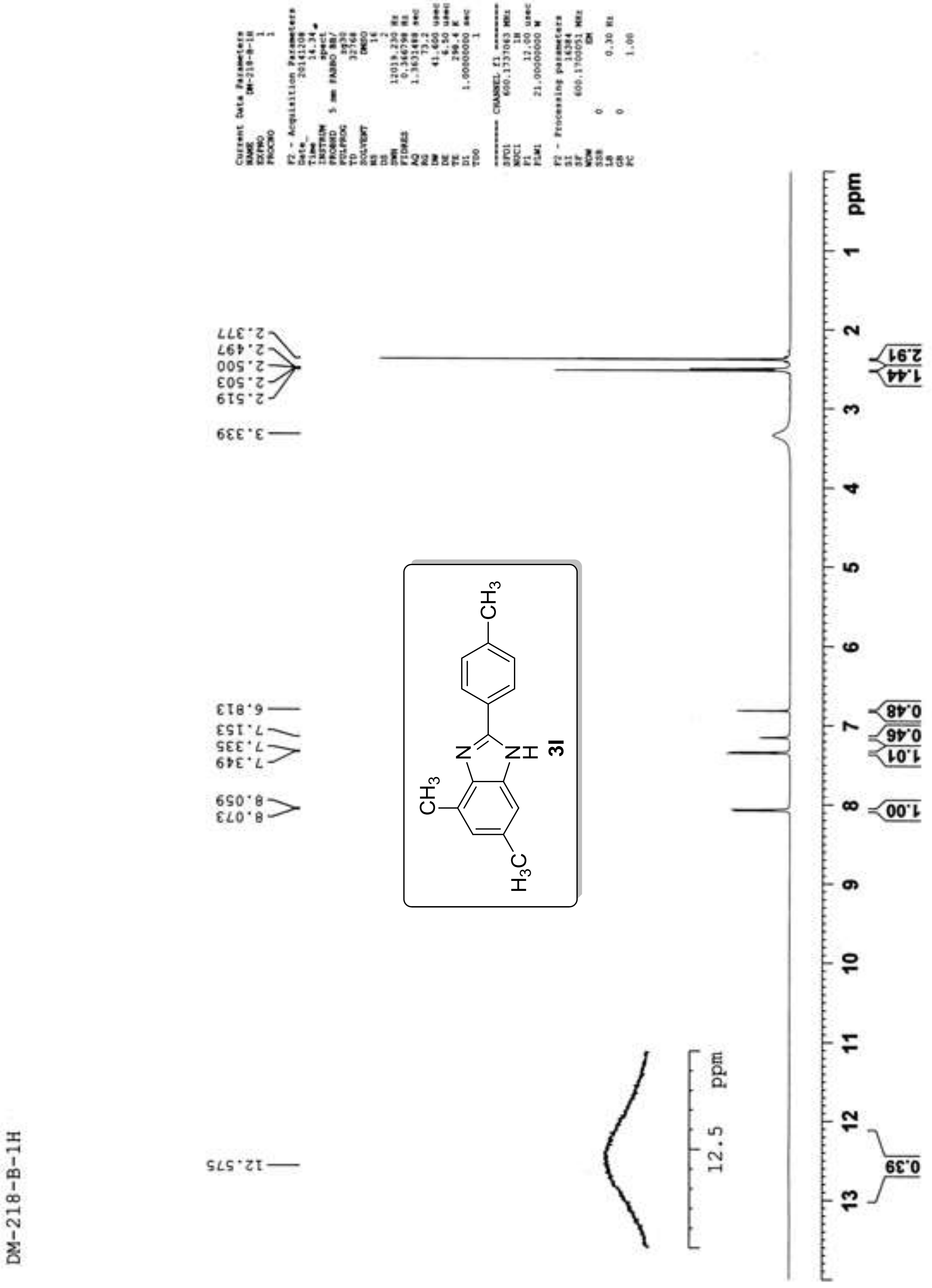
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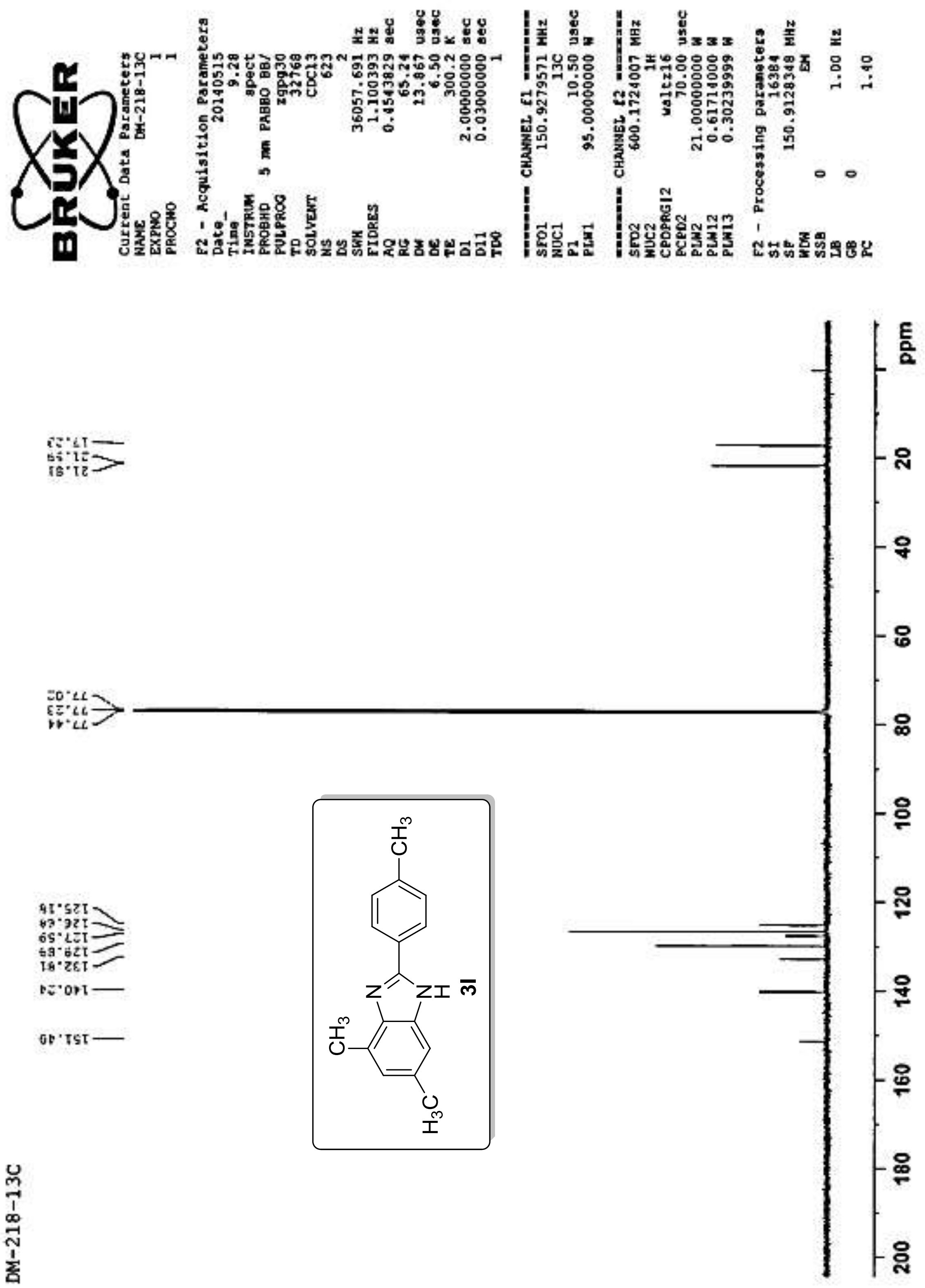

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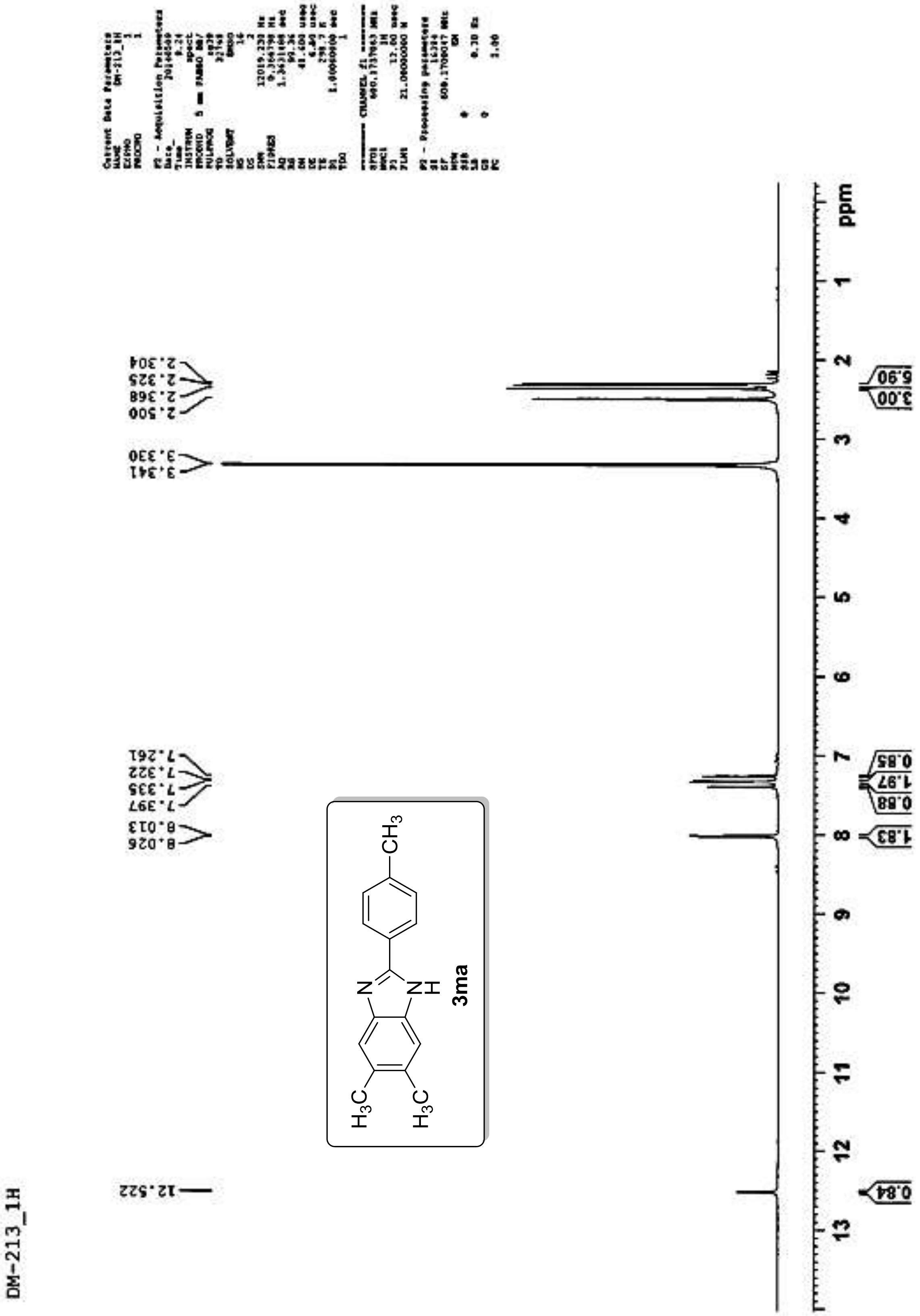
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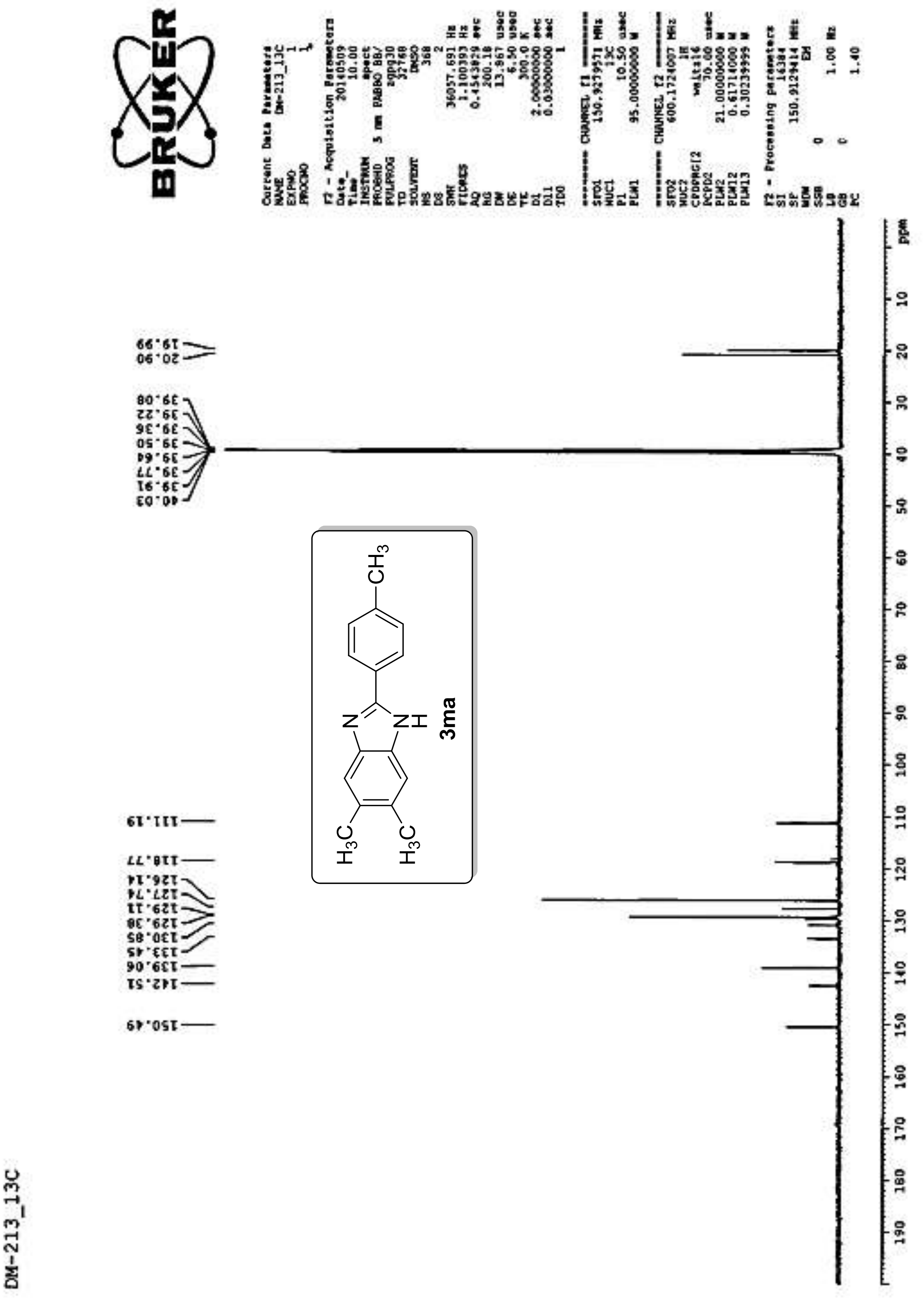
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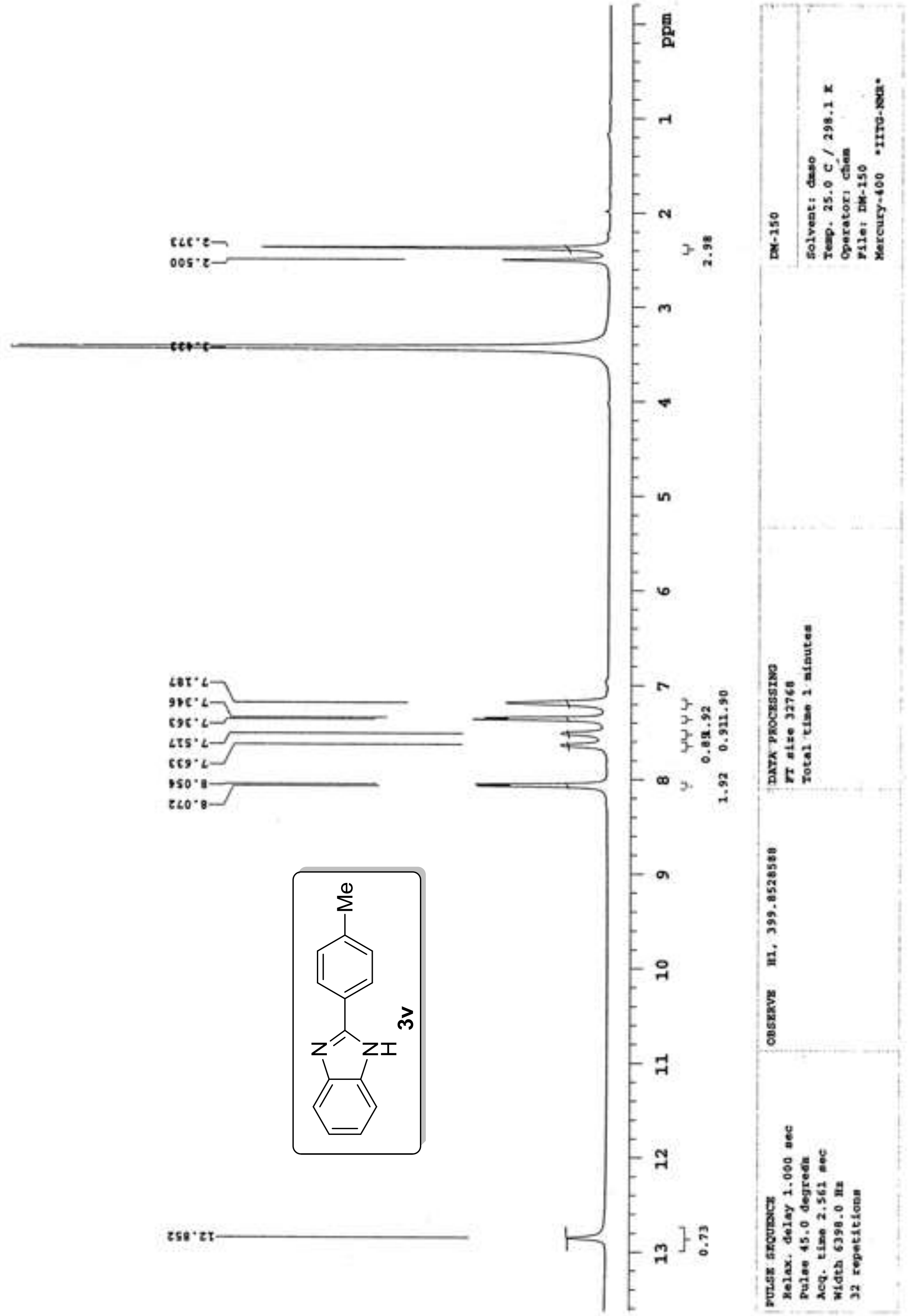
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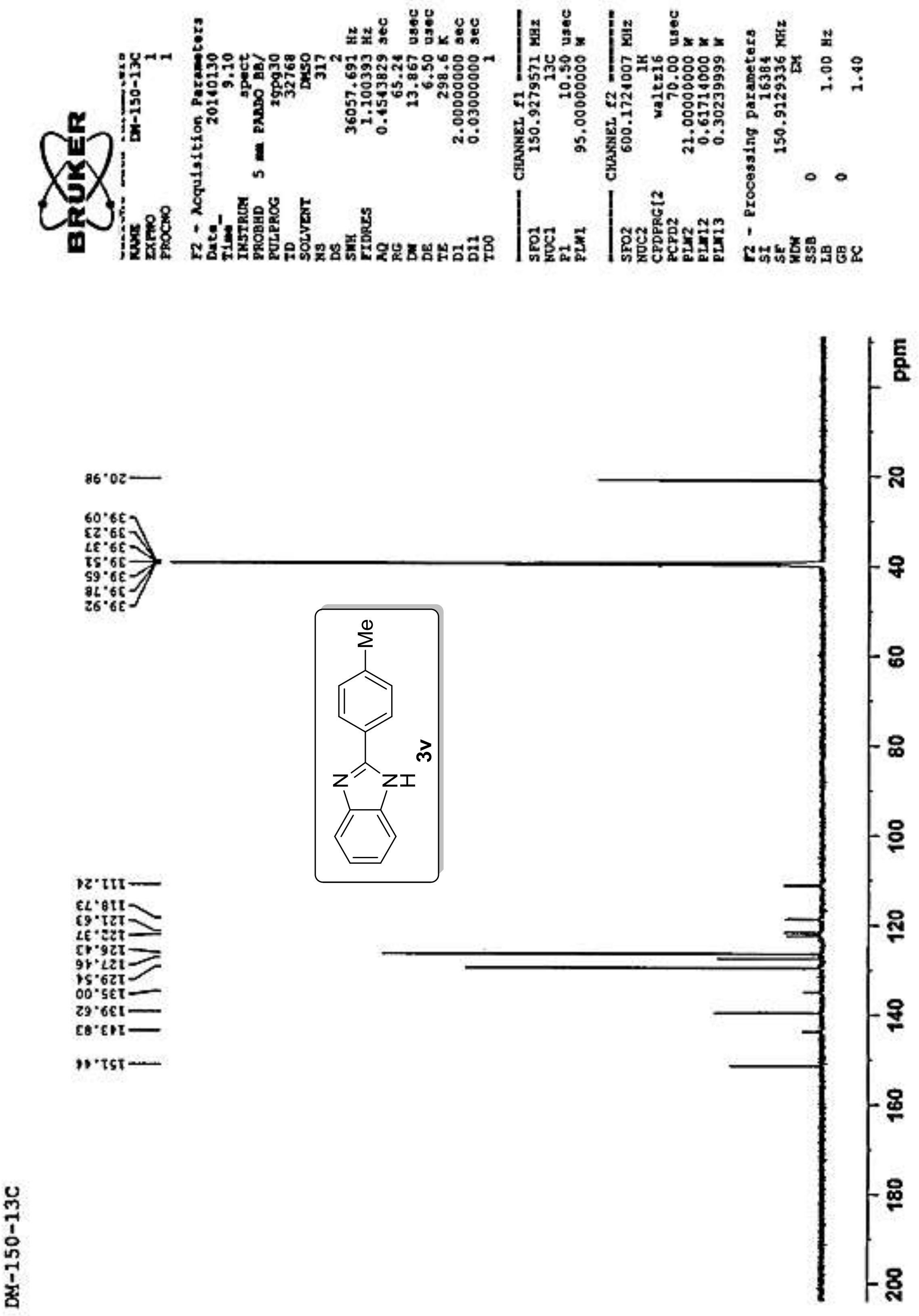
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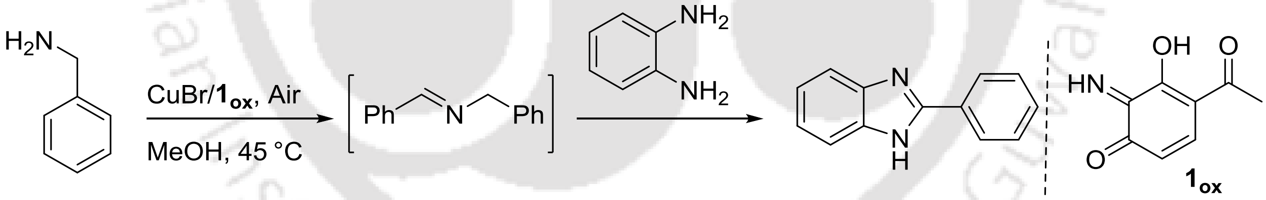
Cu-Catalyzed Oxidative Coupling of Anilines, Benzylamine and NaN_3

Recent advances in transition-metal-catalyzed C-H functionalization using directing groups have led to the development of effective methods for the regioselective carbon-carbon and carbon-heteroatom bonds formation.[1] Among them, the C-N bond formation[2] has attracted considerable attention due to the presence of this moiety in numerous compounds that are of biological, medicinal and material interests.[3] More recently, *ortho*-selective C-H azidation of arene has been accomplished using $-NH_2$[4] and imine[5] as the directing groups. In addition, benzylamine and benzyl alcohols are readily available simple substrates and find broad utilities in synthetic chemistry. Exploration of benzylamine and benzyl alcohols for the construction *N*-nitrogen containing heterocycles would thus be valuable.

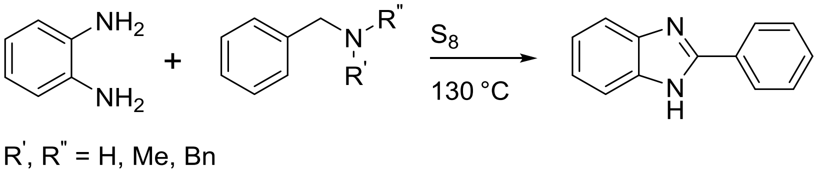
3.1 Recent Methods for the Synthesis of Benzimidazoles Using Benzylamine

Largeron described a bioinspired catalytic oxidative coupling of activated and non-activated primary amine with 1,2-diaminobenzenes under air to give 1,2-disubstituted benzimidazoles through oxidation and nucleophilic addition reactions (Scheme 1).[6]



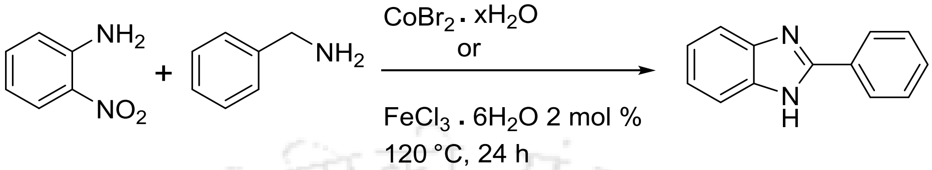
Scheme 1. Cu-Catalyzed Synthesis of Benzimidazoles

Nguyen and co-workers reported a solvent and catalyst-free synthesis of benzimidazoles from alkyl amine and 1,2-diaminobenzene using elemental sulfur as an oxidant (Scheme 2).[7]



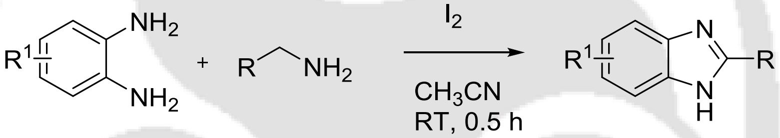
Scheme 2. Metal-Free Synthesis of Benzimidaozoles

The construction of functionalized 2-aryl benzimidazoles has been shown using a solvent-free Co- or Fe-catalyzed redox condensation of 2-nitroanilines with benzylamine (Scheme 3).[8] This cascade reaction includes benzylamine oxidation, nitro reduction, condensation and aromatization.



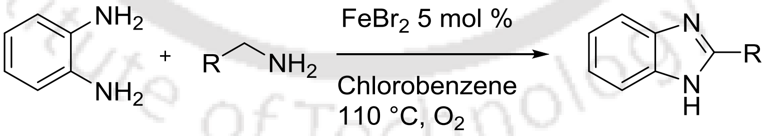
Scheme 3. Co-Catalyzed Synthesis of Benzimidazoles.

Narender and co-workers developed a simple protocol for the iodine-mediated synthesis of benzimidazole from readily available 1,2-diaminobenzene with benzylamine (Scheme 4).[9] This method involves a metal-free *C−N* bond formation at ambient temperature to produce the product in good yield.



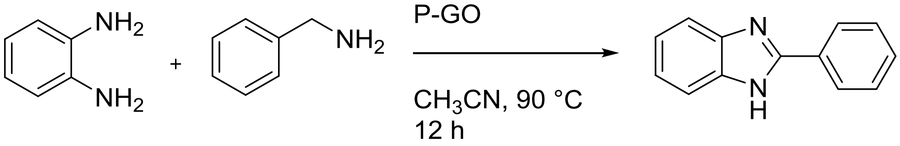
Scheme 4. Iodine-Mediated Synthesis of Benzimidazoles

Gopalaiah and co-workers reported Fe-catalyzed oxidative coupling of benzylamine with 1,2-diaminobenzene to give 2-aryl benzimidazoles using molecular oxygen as a sole oxidant (Scheme 5).[10]



Scheme 5. Fe-Catalyzed Synthesis of Benzimdazoles

Loh and co-workers showed a porous graphene oxide as a metal-free catalyst in the presence of air for oxidative coupling of primary amines. They explored carbon-carbon and carbon-heteroatom bond formation strategy to functionalize primary amines in tandem to produce a series of 2-aryl benzimidazoles (Scheme 6).[11]

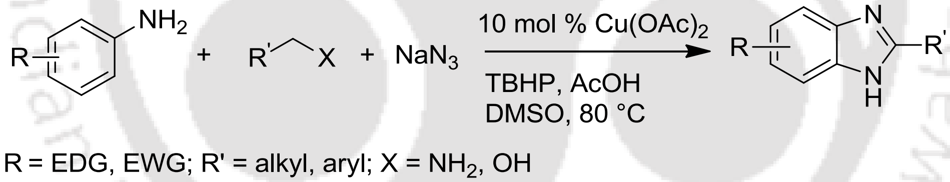


Scheme 6. Graphene Oxide Mediated Synthesis of Benzimdazoles

Development of C-H functionalization strategy for the construction of benzimidazoles using benzylamine will be more atom economical that can lead to broad substrate scope and structural diversity.

3.2 Present Study

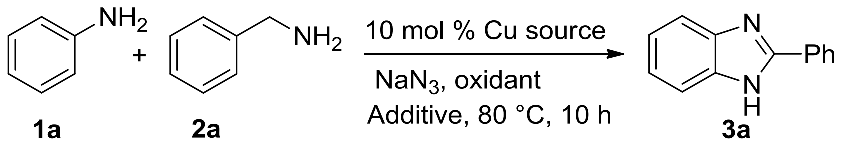
This sections describes a Cu-catalyzed oxidative cross-coupling of anilines¸ benzylamine and NaN_3 to afford benzimidazoles *via* a domino transimination, *ortho* selective amination and cyclization sequence. The utilization of the simple substrates and the broad substrate scope are the significant practical advantages. These reaction conditions can be utilized for the coupling benzyl alcohol in moderate yield.



Scheme 7. Cu-Catalyzed Synthesis of Benzimidazoles

The reaction was optimized using aniline **1a** and benzylamine **2a** as the model substrates with NaN_3 employing different Cu-sources, oxidants and solvents (Table 1). The oxidative cross-coupling occurred to afford benzimidazole **3a** in a trace amount when the substrates **1a** and **2a** were stirred at 80 ^{o}C for 10 h with 10 mol % CuI, 3 equiv NaN_3 and 2 equiv TBHP in DMSO (entry 1). The use of CH_3COOH as an additive led an increase in the yield to 44%,

Table 1. Optimization of the Reaction Conditions[a]



Entry	Cu source	Additive	Solvent	**3a** (%)[b]
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2	CuI	CH_3COOH	DMSO	44
3	CuI	$(CH_3)_3CCOOH$	DMSO	trace
4	CuI	CF_3COOH	DMSO	trace
5	CuBr	CH_3COOH	DMSO	31
6	CuCl	CH_3COOH	DMSO	50
7	$CuCl_2$	CH_3COOH	DMSO	60
8	$Cu(OAc)_2$	CH_3COOH	DMSO	82
9	$CuSO_4{\cdot}5H_2O$	CH_3COOH	DMSO	trace
10[c]	$Cu(OAc)_2$	CH_3COOH	DMSO	trace
11	$Cu(OAc)_2$	CH_3COOH	DMF	56
12	$Cu(OAc)_2$	CH_3COOH	toluene	24
13	$Cu(OAc)_2$	CH_3COOH	1,4-dioxane	43
14	$Cu(OAc)_2$	CH_3COOH	CH_3CN	46
15[d]	$Cu(OAc)_2$	CH_3COOH	DMSO	38
16[e]	$Cu(OAc)_2$	CH_3COOH	DMSO	35
17	-	CH_3COOH	DMSO	n.d.
18[f]	$Cu(OAc)_2$	CH_3COOH	DMSO	n.d.

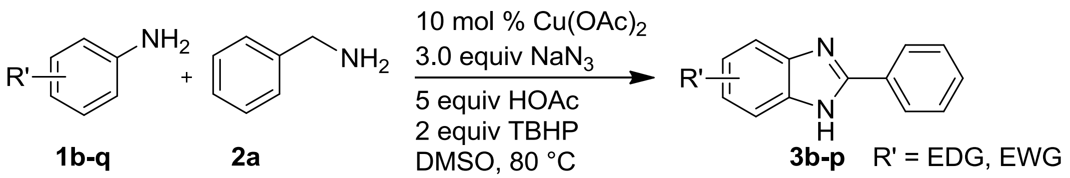
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), [Cu] (10 mol %), NaN_3 (1.5 mmol), TBHP (1 mmol), AcOH (2.5 mmol), solvent (0.5 mL), 80 °C, 10 h.

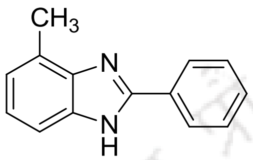
[b] Determined by 600 MHz ^1H NMR.

[c] Using air, 30% H_2O_2 or DTBP. [d] $Cu(OAc)_2$ (5 mol %).

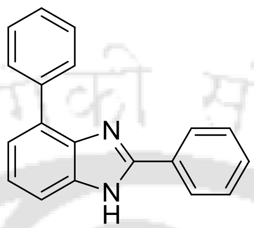
[e] AcOH (5 mmol). [f] No TBHP. n.d. = not detected.

Table 2. Reaction of Substituted Anilines with Benzylamine[a]

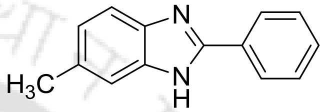




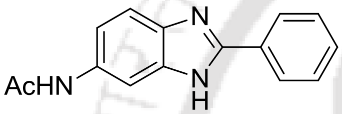
3b, 13 h, 66%



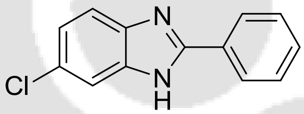
3c, 12 h, 52%



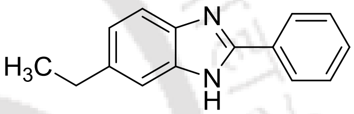
3d,10 h, 79%



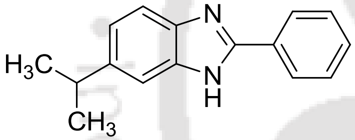
3e, 12 h, 68%



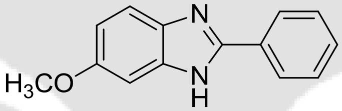
3f, 15 h, 54%



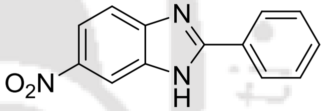
3g, 8 h, 73%



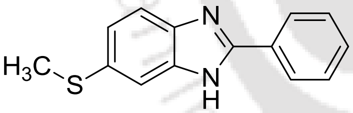
3h, 8 h, 72%



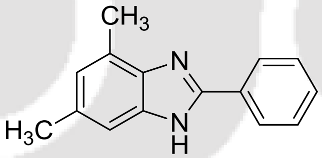
3i, 8 h, 63%



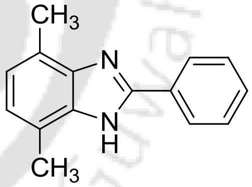
3j, 12 h, n.d.



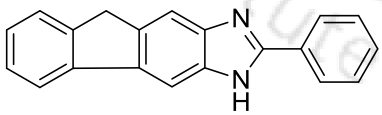
3k, 12 h, 66%



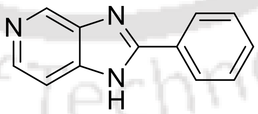
3l, 10 h, 62%[b]; 12 h, 70%[c]



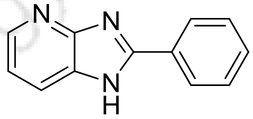
3m, 12 h, 53%



3n, 15 h, 68%



3o, 16 h, n.d.



3p, 16 h, n.d.

[a] Reaction conditions: amine **1b-q** (1 mmol), benzylamine **2a** (1.2 mmol), Cu(OAc)$_2$ (10 mol %), NaN$_3$ (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C.

[b] 3,5-Dimethylaniline used.

[c] 2,4-Dimethylaniline used.

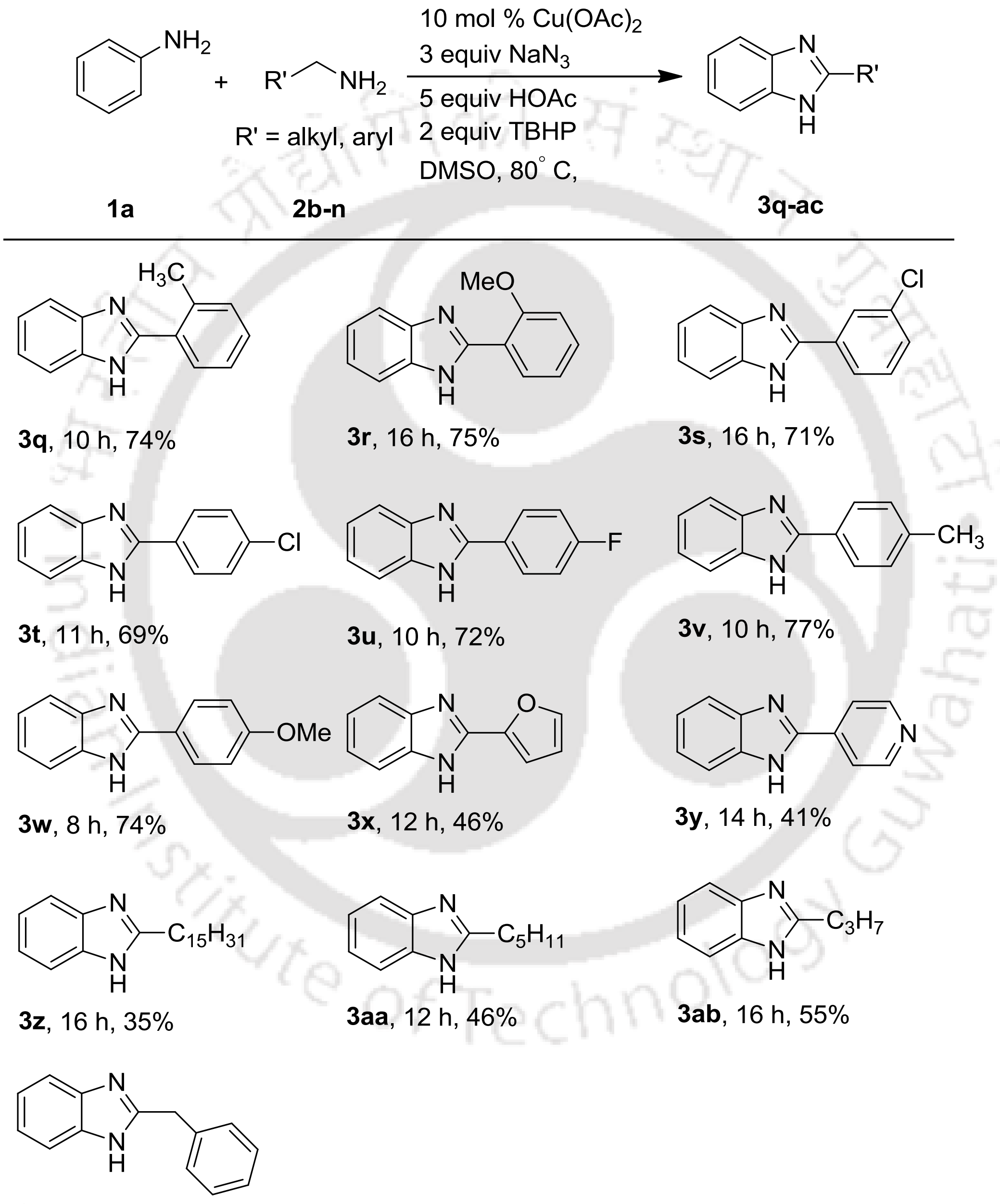
whereas CF_3COOH and $(CH_3)_3CCOOH$ produced inferior results (entries 2-4). Subsequent screening of the copper sources led to further increase in the yield to 82% using $Cu(OAc)_2$, whereas CuBr, CuCl and $CuCl_2$ showed moderate catalytic activities (entries 5-8). In contrast, $CuSO_4 \cdot 5H_2O$ afforded **3a** in a trace amount (entry 9). Similar results were observed using air, 30% H_2O_2 and DTBP as the oxidants (entries 10). DMSO was found to be the solvent of choice, whereas DMF, toluene, 1,4-dioxane and CH_3CN furnished **3a** in moderate yields (entries 11-14). Varying the amount of the catalyst (5 mol %) or additive (10 equiv) led to drop the yield to <38% (entries 15-16). Control experiments confirmed that without the Cu catalyst or TBHP, the formation of **3a** was not observed (entries 17-18).

Having the optimal the reaction conditions, the oxidative coupling of substituted anilines **1b-q** was next explored using **2a** as a standard substrate (Table 2). Anilines **1b** and **1c** with methyl and phenyl groups at the 2-position underwent reaction to give benzimidazoles **3b** and **3c** in 66 and 52% yields, respectively. Similarly, anilines **1d-i** bearing acetamide, chloro, ethyl, isopropyl, methoxy and methyl groups at the 4-position furnished the corresponding benzimidazoles **3d-i** in 54-79% yields, whereas aniline **1j** with strong electron withdrawing nitro group failed to react and the formation of benzimidazole **3j** was not observed. However, the reaction of aniline **1k** with 4-thiomethyl group produced benzimidazole **3k** in 66% yield, while anilines **1l-n** with methyl groups at 2,4-, 3,5- and 2,5-positions gave benzimidazoles **3l-m** in 53-70% yields. Similar result was observed with 2-aminofluorene **1o** affording **3n** in 68% yield. In contrast, the reaction of heterocyclic amines such as 2-aminopyridine **1p** and 3-aminopyridine **1q** failed to produce the target benzimidazoles **3o-p** and the starting materials were remained intact.

Next, the reaction of primary alkyl amines was explored with aniline as the standard substrate (Table 3). Benzylamines **2b-c** bearing substitution at the 2-position with methyl and methoxy groups underwent reaction to furnish benzimidazoles **3q** and **3r** in 74 and 75% yields, respectively. Similar result was observed with benzylamine **2d** bearing 3-chloro group affording **3s** in 71% yield. The reaction of benzylamines **2e-h** bearing substitution at 4-position with chloro, fluoro, methoxy and methyl groups produced benzimidazoles **3t-w** in 69-77% yields. Heterocyclic substrates such as furfurylamine **2i** and 4-picolylamine **2j** underwent reaction to give benzimidazoles **3x** and **3y** in 46 and 41% yields, respectively.

Furthermore, amines such as butylamine **2k**, hexylamine **2l**, hexadecane-1-amine **2m** and 2-phenyl ethanamine **2n** could be cross-coupled to afford 2-alkyl benzimidazoles **3z-ac** in 35-55% yields.

Table 3. Reaction of Alkyl Amines with Aniline^{a,b}



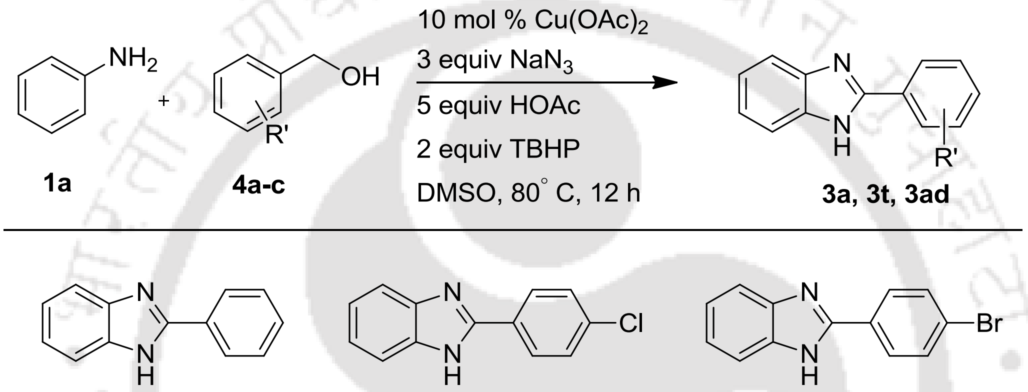
3q, 10 h, 74%
3r, 16 h, 75%
3s, 16 h, 71%
3t, 11 h, 69%
3u, 10 h, 72%
3v, 10 h, 77%
3w, 8 h, 74%
3x, 12 h, 46%
3y, 14 h, 41%
3z, 16 h, 35%
3aa, 12 h, 46%
3ab, 16 h, 55%
3ac, 15 h, 48%

[a] Reaction conditions: aniline**1a** (1 mmol), alkyl amines **2b-n** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), NaN_3 (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C.

[b] Isolated yield.

The reaction conditions are compatible for the reaction of analogue benzyl alcohols (Table 4). For examples, benzyl alcohol **4a** underwent reaction to furnish benzimidazole **3a** in 45% yield. Increase in the quantity of benzyl alcohol **4a** from 1.2 to 3 equiv led to an improvement in the yield to 61%. Similar results were observed with benzyl alcohol bearing bromo and chloro groups at the 4-position affording benzimidazoles **3t** and **3ad** in moderate yields.

Table 4. Reaction of Aniline with Benzyl Alcohols[a]



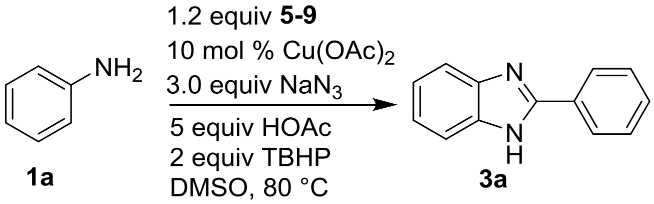
3a, 12 h, 45%, 61%[b] **3t**,12 h, 39%, 54%[b] **3ad,** 12 h, 35%, 62%[b]

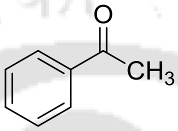
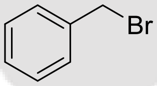
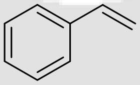
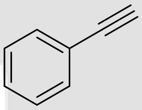
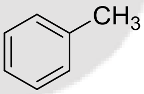
[a] Reaction conditions: aniline **1a** (1 mmol), benzyl alcohol **4a-c** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), NaN_3 (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C.

[b] Alcohol **4a-c** (3 mmol) used.

Finally, the utility of the protocol was investigated for the reaction of aldehyde precursors **5-9** (Table 5). The reaction of acetophenone **5** and styrene **7** exhibited no benzimidazole formation, whereas benzyl bromide **6** and phenylacetylene **8** and toluene **9** underwent reaction to produce the corresponding benzimidazoles in 5-30% yields. These results suggest that broad range of substrates can be cross-coupled in moderate to good yields. To understand the reaction pathway, the intermolecular kinetic isotope experiment was performed between **1d** and **1d-d$_2$** and P_H/P_D was found to be 1.0 (23% conv., 2.5 h), which suggests that the C-H bond cleavage may not be involved in the product-determining step (Scheme 8).[12] Further, the radical scavenger experiment using TEMPO exhibited no benzimidazole formation, which suggests that a radical intermediate may be involved (Scheme 9).[13] In addition, the

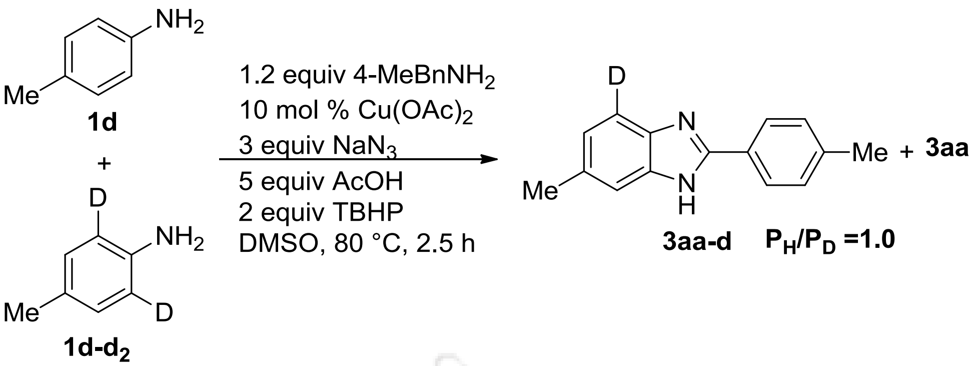
Table 5. Reaction of Aldehyde Precursors with Aniline[a]



Entry	Aldehyde Precursor	**3a** (%)[b]
1	 **5**	n.d.
2	 **6**	9
3	 **7**	n.d.
4	 **8**	30
5	 **9**	5

[a]Reaction conditions: aniline**1a** (1 mmol), aldehyde precursor **5-10** (1.2 mmol), Cu(OAc)$_2$ (10 mol %), NaN$_3$ (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 ^{o}C.

[b]Isoalted yield.



Scheme 8. Kinetic Isotope Experiment

Scheme 9. Radical Scavenger Experiment

ESI-MS analysis of the reaction mixture of **1a** and **2a** revealed the presence of three major species, **A**, **B** and benzimidazole **3a** (Figure 1). Formation of **A** suggests that the oxidative coupling of benzylamine may be involved via *sp*^{3} C-H functionalization,[14] while the intermediate **B** reveals the involvement of transimination[15] of **A** with aniline followed by imine directed[2d] *ortho* selective *sp*^{2} C-H azidation. The subsequent Cu(OAc)$_2$ catalyzed reduction of –N$_3$ may produce –NH$_2$ under heating.[16] The absence of the peaks corresponding to 2-azidoaniline or 2-aminoaniline suggests that the reaction may not involve -NH$_2$ as the directing group for the azidation.[2a] Thus, the Cu(II)-catalyzed oxidative coupling of alkyl amine can give imine ***a***, which can undergo transimination with aniline to form ***b***. Coordination[17] of ***b*** with Cu(OAc)$_2$ can furnish ***c***, which may subsequently combine with *in situ* generated N$_3$ radical from HN$_3$ and TBHP to form the intermediate ***d***. A single electron transfer[18] (SET) from the aryl ring to the metal center may lead to the formation of ***e***, which can convert into ***f*** by azido transfer into the aryl ring.[18] The latter may convert into ***g*** via SET process, that could be reduced to ***h*** under heating in the presence of Cu(OAc)$_2$.[16] Oxidative cyclization of ***h*** can produce ***i*** that can aromatize to afford **3** and Cu(II) to complete the catalytic cycle (Scheme 10). The role of AcOH is to generate HN_3 from NaN_3. Furthermore, the intermediate ***b***, prepared from aniline and benzaldehyde, underwent reaction to produce benzimidazole **3a** in 77% yield (Scheme 11). These results clearly suggest that the reaction may proceed via the intermediate ***b*** using imine as the directing group.

Sample Name	DM-349-5H	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	DM-349-5H.d	**ACQ Method**		**Comment**		**Acquired Time**	11/24/2015 10:57:12 AM

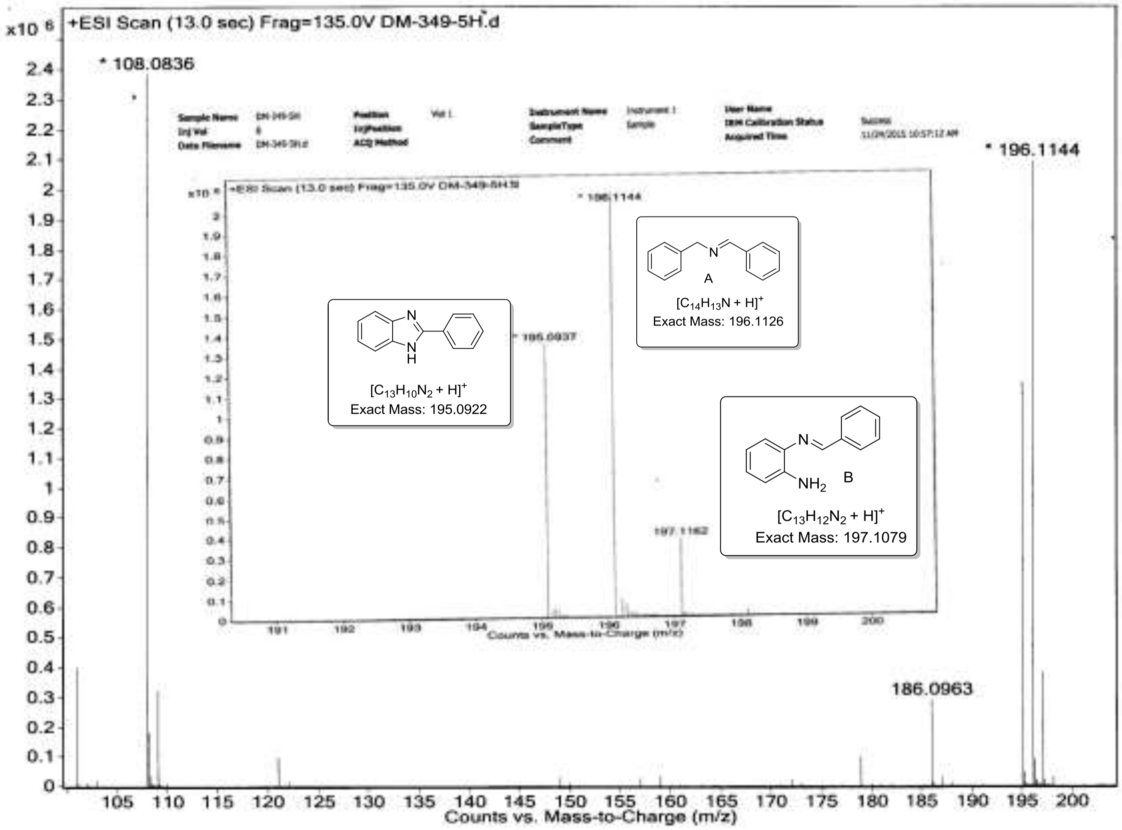
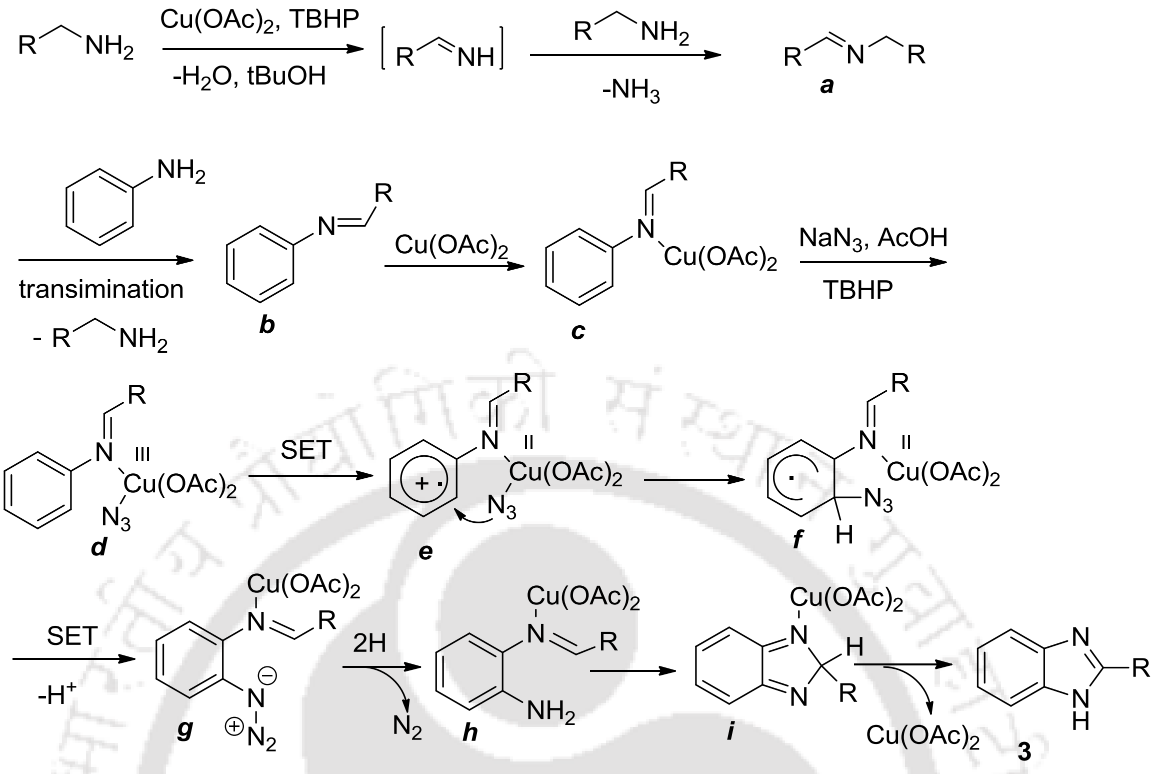
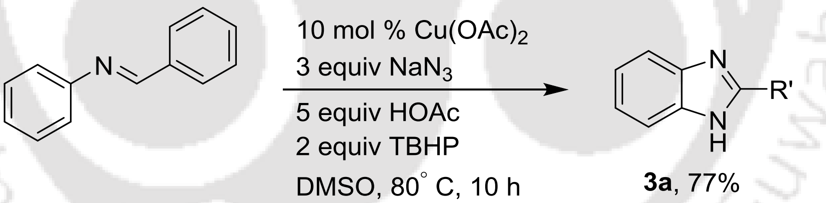


Figure 1. Major Species Identified using ESI-MS of the Reaction **1a** and **2a** after 5 h.



Scheme 10. Proposed Reaction Pathway



Scheme 11. Control Experiment

In summary, Cu-catalyzed oxidative cross-coupling of anilines, alkyl amines and NaN_3 in the presence of TBHP has been demonstrated to produce substituted benzimidazoles. These reaction conditions can be extended to the reaction of benzyl alcohols in place of benzylamines to produce the target products. Mechanistic investigation suggests that reaction may involve a SET process. The broad substrate scope, use of simple substrates and structural diversity are the important practical advantages.

3.3. Experimental Section

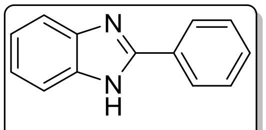
3.3.1. General Information: See section 2.3.1 (page-21) for general information. NaN_3 (99%), AcOH and benzylamine were purchased from commercial sources.

3.3.2. General Procedure for the Synthesis of Benzimidazoles. To a stirred solution of aniline **1** (1.0 mmol), $Cu(OAc)_2$ (10 mol %, 0.1 mmol, 18 mg), NaN_3 (3 equiv, 3.0 mmol, 195 mg), AcOH (5 equiv, 5.0 mmol, 300 mg) and TBHP (2 equiv, 2 mmol, 360 µL) in DMSO (1 mL) was added alkyl amine **2** or alcohol **4** (1.2 mmol), and the resultant mixture was stirred at 80 °C for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and treated with saturated $NaHCO_3$ (5 mL). The solution was then extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford analytically pure products.

3.3.3. Kinetic Isotope Study

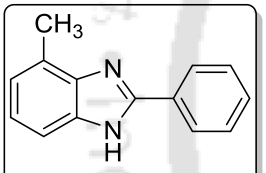
To a stirred solution of *p*-toluidine **1d** (0.18 mmol, 20 mg), *p*-toluidine **1d-d₂**[12b] (0.32 mmol, 35 mg), $Cu(OAc)_2$ (10 mol %, 0.05 mmol, 9 mg), NaN_3 (3 equiv, 1.5 mmol, 97 mg), AcOH (5 equiv, 2.5 mmol, 150 mg) and TBHP (2 equiv, 1 mmol, 90 µL) in DMSO (0.5 mL) was added 4-$MeBnNH_2$ **2j** (1.2 equiv, 0.6 mmol, 73 mg), and the resultant mixture was stirred at 80 ^{o}C. After 2.5 h, the reaction mixture was cooled to room temperature and treated with saturated $NaHCO_3$ (3 mL). The mixture was then extracted with ethyl acetate (3 x 5 mL) and washed with brine (2 x 3 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford a mixture of **3ae-d** and **3ae** as a white solid in 19% (21 mg) yield. The ratio of deuterium to hydrogen was determined by the ^{1}H NMR relative integration values of H_a (7.95 ppm) based on H_b (7.51 ppm).

3.4. Characterization Data



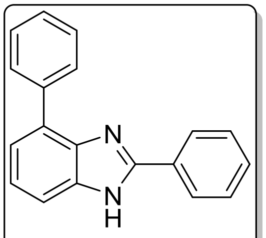
3a

2-Phenyl-1*H*-benzo[*d*]imidazole 3a. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.41$; white solid; 137 mg, yield 70%; mp 290-291 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.19 (d, $J = 7.8$ Hz, 2H), 7.67 (s, 1H), 7.56-7.48 (m, 4H), 7.20 (s, 2H); ^{13}C {^1H} NMR (150 MHz, DMSO-d_6) δ 151.2, 143.8, 135.0, 130.1, 129.8, 128.9, 126.4, 122.5, 121.6, 118.9, 111.3; FT-IR (KBr) 3436, 3048, 2962, 2922, 2114, 1623, 1591, 1462, 1411, 1374, 1276, 1120, 1029, 971, 744,703 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{13}H_{10}N_2H$ 195.0922, found 195.0913.



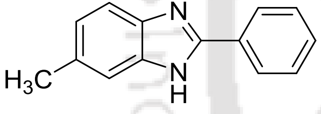
3b

4-Methyl-2-phenyl-1*H*-benzo[*d*]imidazole 3b. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.42$; white solid; 137 mg, yield 66%; mp 247-248 °C; mixture of tautomers (1.2:1): ^1H NMR (600 MHz, DMSO-d_6) δ 12.83 (br s, 1H), 12.57 (br s, 1H), 8.26-8.18 (m, 4H), 7.55-7.49 (m, 7H), 7.35 (d, $J = 7.2$ Hz, 1H), 7.11-7.07 (m, 2H), 6.99 (s, 2H) 2.59 (s, 3H), 2.57 (s, 3H); ^{13}C {^1H} NMR (150 MHz, $CDCl_3$) δ 151.2, 150.4, 143.5, 143.2, 134.7, 134.5, 130.3, 129.74, 129.7, 128.9, 128.8, 128.4, 126.7, 126.5, 126.4, 123.1, 122.5, 121.9, 121.8, 121.3, 116.3, 108.8, 17.2, 16.7; FT-IR (neat) 3435, 3051, 2921, 2854, 2717, 2115, 1619, 1537, 1481, 1458, 1371, 1287, 785, 746, 703 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2H$ 209.1078, found 209.1057.



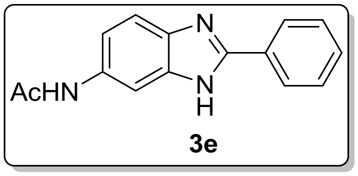
3c

2,4-Diphenyl-1*H*-benzo[*d*]imidazole 3c. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; white solid; 141 mg, yield 52%; mp 256-257 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (br s, 1H), 8.21-8.16 (m, 4H), 7.59-7.50 (m, 6H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.2, 141.3, 138.3, 135.8, 130.6, 130.1, 129.8, 128.9, 128.8, 128.5, 128.2, 127.0, 126.5, 122.9, 120.5, 110.6; FT-IR (neat) 3435, 3057, 2921, 2851, 2114, 1617, 1457, 1415, 1390, 1316, 1244, 1112, 1027, 750, 697 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{19}H_{14}N_2H$ 271.1235, found 271.1229.



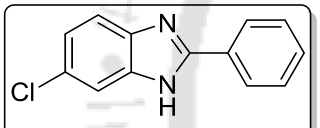
3d

6-Methyl-2-phenyl-1*H*-benzo[*d*]imidazole 3d. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; white solid; 164 mg, yield 79%; mp 246-247 °C; mixture of tautomers (1:1.3):^{1}H NMR (600 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 12.74 (br s, 1H), 8.16 (d, *J* = 7.8 Hz, 4H), 7.55-7.52 (m, 5H), 7.48-7.45 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 150.8, 142.0, 131.8, 130.3, 129.6, 128.9, 126.3, 123.9, 123.3, 118.5, 111.0, 21.3; FT-IR (KBr) 3435, 3047, 2921, 2856, 2110, 1631, 1595, 1463, 1401, 1308, 1276, 1112, 972, 804, 702, 689 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2H$ 209.1078, found 209.1071.



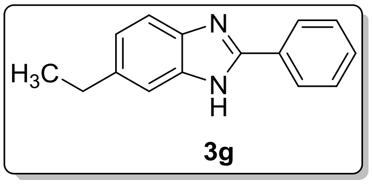
3e

N-(2-Phenyl-1*H*-benzo[*d*]imidazol-6-yl)acetamide 3e. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 171 mg, yield 68%; mp 262-263 °C; mixture of tautomers (1:2.1): ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 12.79 (br s, 1H), 10.03 (br s, 1H), 9.93 (br s, 1H), 8.16-8.13 (m, 4H), 8.02 (s, 1H), 7.58-7.52 (m, 5H), 7.47-7.45 (m, 2H), 7.39-7.37 (m, 2H), 7.21-7.19 (m, 2H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 168.1, 168.0, 151.7, 151.0, 143.9, 140.0, 135.1, 134.9, 131.3, 130.2, 129.6, 129.0, 126.4, 126.2, 118.7, 115.8, 114.5, 110.9, 109.3, 101.5, 24.1; FT-IR (KBr) 3436, 2957, 2922, 2851, 2130, 1643, 1497, 1463, 1313, 1259, 1178, 1025, 994, 822, 694 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{15}H_{13}N_3OH$ 252.1137, found 252.1146.



3f

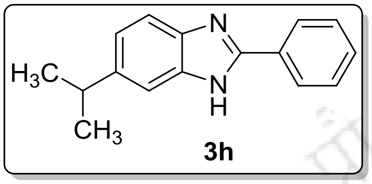
6-Chloro-2-phenyl-1*H*-benzo[*d*]imidazole 3f. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.48; white solid; 123 mg yield 54%; mp 200-201 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.12 (br s, 1H), 8.17 (d, *J* = 7.8 Hz, 2H), 7.69-7.50 (m, 5H), 7.23 (d, *J* = 7.8 Hz, 1H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 152.7, 130.2, 129.7, 129.0, 126.6, 126.5, 122.4; FT-IR (KBr) 3444, 2920, 2119, 1624, 1584, 1462, 1450, 1438, 1384, 1275, 1107, 1062, 808, 692 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{13}H_9ClN_2H$229.0532, found 229.0512.



3g

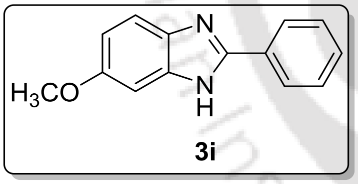
6-Ethyl-2-phenyl-1*H*-benzo[*d*]imidazole 3g. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; brown liquid; 162 mg, yield 73%; ^{1}H NMR (400 MHz, DMSO-d_6)

δ 12.82 (br s, 1H), 8.20 (d, *J* = 8.4 Hz, 2H), 7.57-7.47 (m, 3H), 7.46-7.41 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 130.4, 129.7, 128.9, 126.3, 28.5, 16.4; FT-IR (neat) 3390, 3064, 2963, 2928, 2106, 1628, 1595, 1453, 1431, 1405, 1374, 1280, 1055, 814, 776, 692 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1235.



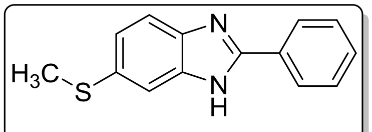
3h

6-Isopropyl-2-phenyl-1*H*-benzo[*d*]imidazole 3h. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; liquid; 170 mg, yield 72%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 8.20 (s, 2H), 7.59-7.52 (m, 3H), 7.47-7.36 (m, 2H), 7.09 (s, 1H), 2.99 (s, 1H), 1.26 (d, *J* = 7.2 Hz, 6H); tautomers (1:1): ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.0, 143.2, 142.3, 135.2, 130.4, 129.6, 128.9, 126.3, 121.6, 120.7, 118.6, 115.8, 110.9, 108.3, 33.7, 24.4; FT-IR (neat) 3400, 3067, 2959, 2927, 2256, 2104, 1628, 1541, 1463, 1431, 1364, 1288, 1047, 815, 776 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1393.



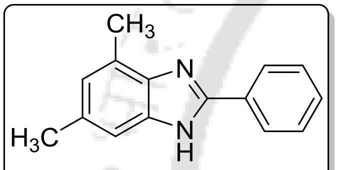
3i

6-Methoxy-2-phenyl-1*H*-benzo[*d*]imidazole 3i. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; liquid; 141 mg, yield 63%; tautomers (1:1): ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.82 (br s, 2H), 8.18-8.17 (m, 4H), 7.57-7.52 (m, 6H), 7.46-7.44 (m, 2H), 7.31-7.20 (m, 1H), 7.04 (s, 1H), 6.86 (s, 2H), 3.81 (s, 6H); tautomers (1:1): ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.1, 150.5, 138.4, 130.4, 129.5, 128.9, 128.3, 127.3, 126.7, 126.2, 119.4, 112.3, 111.6, 111.2, 101.4, 94.5, 55.5; FT-IR (neat) 3414, 2924, 2854, 2255, 1631, 1594, 1539, 1490, 1455, 1434, 1159, 1117, 1026, 823, 778 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2OH$ 225.1028, found 225.1031.



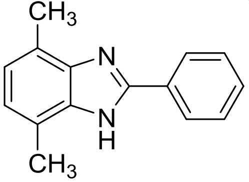
3k

6-(Methylthio)-2-phenyl-1*H*-benzo[*d*]imidazole 3k. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.31; liquid; 158 mg, yield 66%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.19 (d, *J* = 7.8 Hz, 2H), 7.55-7.53 (m, 3H), 7.49-7.46 (m, 2H), 7.17 (d, *J* = 4.8 Hz, 1H), 2.52 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 151.4, 130.0, 129.9, 129.0, 126.5, 122.9, 121.9, 119.2, 117.2, 111.9, 109.4, 16.5; FT-IR (KBr) 3400, 2920, 2856, 2255, 2126, 1624, 1582, 1537, 1463, 1441, 1422, 1278, 1025, 1004, 806, 777 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2SH$ 241.0799, found 241.0796.



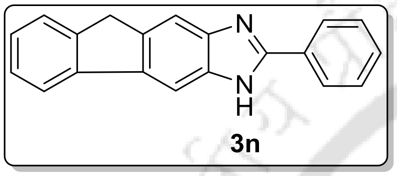
3l

4,6-Dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole 3l. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 138 mg, yield 62% (3,5-diMe aniline) and 155 mg, 70% (2,4-diMe aniline); mp 190-191 °C; tautomers (1:0.6); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.67 (br s, 1H), 12.46 (br s, 1H), 8.23 (d, *J* =7.8 Hz, 2H), 8.16 (d, *J* = 7.2 Hz, 2H), 7.54-7.45 (m, 6H), 7.26 (s, 1H), 7.12 (s, 1H), 6.83-6.82 (m, 2H) 2.54-2.50 (m, 6H), 2.50-2.37 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 151.0, 149.9, 143.9, 141.4, 134.8, 132.7, 131.7, 130.6, 130.5, 129.6, 129.4, 128.9, 128.8, 127.8, 126.6, 126.2, 124.7, 123.6, 120.7, 116.0, 108.5, 21.4, 21.2, 17.1, 16.6; FT-IR (neat) 3456, 3146, 2922, 2853, 2108, 1683, 1627, 1456, 1406, 1332, 1254, 1031, 838, 701, 682 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1231.



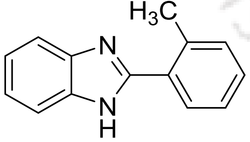
3m

4,7-Dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole 3m. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.41; white solid; 118 mg, yield 53%; mp 231-232 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.63 (br s, 1H), 8.37-8.35 (m, 2H), 7.68-7.60 (m, 3H), 7.02-7.00 (m, 2H), 2.68-2.62 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, CDCl$_3$) δ 150.4, 134.2, 130.5, 129.6, 128.8, 126.7, 125.5, 123.0, 121.9, 118.5, 112.8, 17.0, 16.5; FT-IR (neat) 3435, 2922, 2852, 2108, 1625, 1457, 1410, 1313, 1264, 1029, 963, 705 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1241.



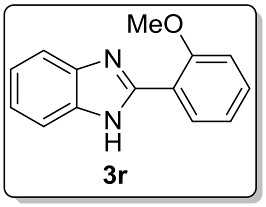
3n

2-Phenyl-3, 9-dihydrofluoreno[2,3-*d*]imidazole 3n. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.45; white solid; 192 mg, yield 68%; mixture of tautomers (1:1); ^{1}H NMR (600 MHz, CDCl$_3$) δ 13.05 (br s, 1H), 12.97 (br s, 1H), 8.24-8.20 (m, 4H), 7.96-7.87 (m, 2H), 7.77-7.69 (m, 2H), 7.64-7.48 (m, 10H), 7.39-7.36 (m, 2H), 7.28-7.26 (m, 2H), 4.15-4.11 (m, 1H), 3.99 (s, 1H); ^{13}C {^{1}H} NMR (150 MHz, CDCl$_3$) δ 151.5, 130.2 129.7, 128.9, 126.7, 126.5, 126.3, 125.0, 115.1; FT-IR (neat) 3433, 2922, 1629, 1457, 1433, 1403, 1311, 1107, 962, 854, 768, 725, 751, 698 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{20}H_{14}N_2H$ 283.1235, found 283.1235.



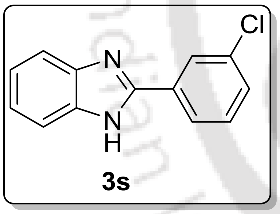
3q

2-(*o*-Tolyl)-1*H*-benzo[*d*]imidazole 3q. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.41; white solid; 154 mg, yield 74%; mp 223-224 °C; ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 12.63 (br s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.54 (s, 1H), 7.41-7.35 (m, 3H), 7.21 (s, 2H), 2.61 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d$_6$) δ 151.9, 143.6, 137.0, 134.3, 131.3, 130.1, 129.4, 129.3, 126.0, 122.3, 121.4, 118.9, 111.3, 21.0; FT-IR (KBr) 3435, 3052, 2959, 2786, 2111, 1620, 1542, 1454, 1409, 1367, 1216, 1092, 900, 765, 746, 733 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1085.



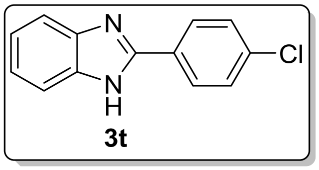
3r

2-(2-Methoxyphenyl)-1*H*-benzo[*d*]imidazole 3r. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 168 mg, yield 75%; mp 236-237 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 8.33 (d, *J* = 7.2 Hz, 1H), 7.65-7.60 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 2H) 7.13 (t, *J* = 7.2 Hz, 1H), 4.02 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 156.8, 149.0, 142.8, 134.8, 131.2, 129.8, 122.1, 121.6, 120.9, 118.5, 118.1, 112.1, 55.7; FT-IR (KBr) 3436, 3007, 2964, 2111, 1604, 1584, 1474, 1435, 1373, 1281, 1244, 1089, 1022, 966, 746 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2OH$ 225.1027, found 225.1027.



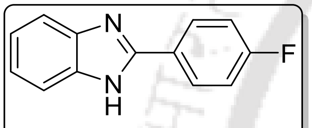
3s

2-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazole 3s. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 162 mg, yield 71%; mp 239-240 °C;^{1}H NMR (600 MHz, DMSO-d_6) δ 13.06 (br s, 1H), 8.23-8.22 (m, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.60-7.54 (m, 3H), 7.26-7.20 (m, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 149.8, 143.7, 135.0, 133.8, 132.2, 130.9, 129.5, 126.1, 125.0, 122.9, 122.0, 119.1, 111.6; FT-IR (KBr) 3434, 3045, 2964, 2877, 2788, 2113, 1602, 1591, 1541, 1442, 1403, 1285, 1229, 1079, 998, 925, 743 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{13}H_9ClN_2$ H 229.0533, found 229.0518.



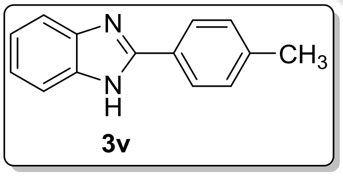
3t

2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole 3t. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 157 mg, yield 69%; mp 266-267 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.0 (br s, 1H), 8.19 (d, *J* = 7.2 Hz, 2H), 7.63-7.56 (m, 4H), 7.21 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 150.2, 134.5, 129.0, 128.1, 122.3, 118.9, 111.5; FT-IR (KBr) 3445, 2996, 2957, 2116, 1635, 1583, 1482, 1421, 1323, 1256, 1234, 1095, 1025, 966, 835, 757 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{13}H_9ClN_2H$ 229.0532, found 229.0529.



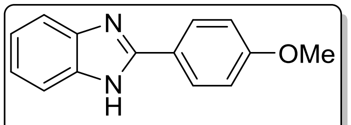
3u

2-(4-Fluorophenyl)-1*H*-benzo[*d*]imidazole 3u. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; yellow solid; 153 mg, yield 72%; mp 239-240 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.22 (s, 2H), 7.65 (s, 1H), 7.53 (s, 1H), 7.40 (s, 2H), 7.20 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 164.0 (d, *J* = 247.0 Hz,), 150.5, 143.8, 135.1, 128.8 (d, *J* = 7.5 Hz), 126.9, 122.6, 121.8, 118.9, 116.2 (d, 22.5 Hz), 111.4; FT-IR (KBr) 3435, 3052, 2960, 2854, 2116, 1603, 1497, 1475, 1433, 1276, 1228, 1156, 1110, 837, 747 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{13}H_9FN_2H$ 213.0828, found 213.0821.



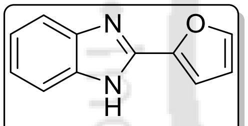
3v

2-(*p*-Tolyl)-1*H*-benzo[*d*]imidazole 3v. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 160 mg, yield 77%; mp 275-276 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 8.08 (d, *J* = 9 Hz, 2H), 7.65-7.63 (m, 1H), 7.52 (s, 1H), 7.36 (d, *J* = 9 Hz, 2H), 7.20-7.17 (m, 2H), 2.38 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 151.4, 143.9, 139.6, 135.0, 129.5, 127.5, 126.4, 122.4, 121.6, 118.7, 111.2, 21.0; FT-IR (KBr) 3435, 3053, 2961, 2919, 2855, 2115, 1621, 1588, 1448, 1430, 1226, 1122, 1042, 821, 747 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1065.



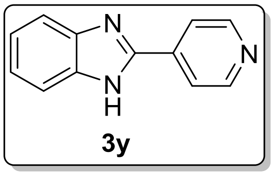
3w

2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole 3w. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 166 mg, yield 74%; mp 217-218 °C; ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 12.75 (br s, 1H), 8.12 (s, 2H), 7.62 (s, 1H), 7.49 (s, 1H), 7.17-7.11 (m, 4H), 3.84 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d$_6$) δ 160.6, 151.4, 143.9, 135.0, 128.1, 122.7, 122.1, 121.5, 118.5, 114.4, 111.0, 55.3; FT-IR (KBr) 3472, 3054, 2923, 2855, 2113, 1611, 1500, 1476, 1453, 1295, 1254, 1179, 1124, 1033, 965, 845, 745 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2OH$ 225.1027, found 225.1026.



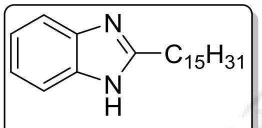
3x

2-(Furan-2-yl)-1*H*-benzo[*d*]imidazole 3x. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; white solid; 85 mg, yield 46%; mp 284-285 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.94 (br s, 1H), 7.95 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.20-7.19 (m, 3H), 6.73 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 145.6, 144.7, 143.7, 134.2, 122.7, 121.8, 118.8, 112.4, 111.4, 110.5; FT-IR (KBr) 3434, 3059, 2924, 2853, 2663, 1630, 1525, 1443, 1416, 1364, 1278, 1234, 1014, 979, 906, 883, 738, 589 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{11}H_8N_2OH$ 185.0715, found 185.0715.



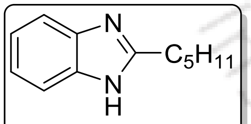
3y

2-(Pyridin-4-yl)-1*H*-benzo[*d*]imidazole 3y. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.20; pale yellow solid; 80 mg, yield 41%; mp 220-221 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.27 (br s, 1H), 8.76 (s, 2H), 8.10 (s, 2H), 7.74 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.30-7.25 (m, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 150.5, 149.8, 148.8, 143.6, 137.1, 135.0, 123.6, 122.3, 120.3, 119.5, 111.8; FT-IR (KBr) 3418, 2925, 2255, 2128, 1646, 1609, 1433, 1384, 1317, 1234, 1048, 1025, 1001, 765 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{12}H_9N_3H$ 196.0875, found 196.0875.



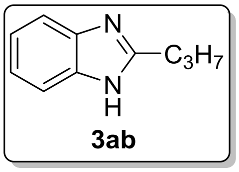
3z

2-Pentadecyl-1*H*-benzo[*d*]imidazole 3z. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; white solid; 115 mg, yield 35%; mp 91-92 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.14 (br s, 1H), 7.44 (s, 2H), 7.09 (s, 2H), 2.77 (s, 2H), 1.74 (s, 2H), 1.22 (s, 24H) 0.84 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 31.3, 29.0, 28.9, 28.73, 28.7, 28.5, 27.6, 22.1, 14.0; FT-IR (KBr) 3435, 3089, 2954, 2920, 2849, 2101, 1625, 1541, 1470, 1458, 1206, 1155, 753, 744 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{22}H_{36}N_2H$ 329.2956, found 329.2936.



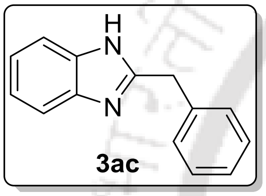
3aa

2-Pentyl-1*H*-benzo[*d*]imidazole 3aa. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane; R_f = 0.35; brown solid; 86 mg, yield 46%; mp 140-141 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 7.44 (s, 2H), 7.10-7.09 (m, 2H), 2.79 (t, J = 7.2 Hz, 2H), 1.77-1.74 (m, 2H), 1.32-1.30 (m, 4H), 0.87-0.84 (m, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 155.3, 121.1, 30.9, 28.5, 27.3, 21.9, 13.9; FT-IR (KBr) 3390, 3050, 2951, 2924, 2852, 2773, 2257, 2128, 1647, 1537, 1447, 1418, 1233, 1024, 998, 766 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{12}H_{16}N_2H$ 189.1392, found 189.1394.



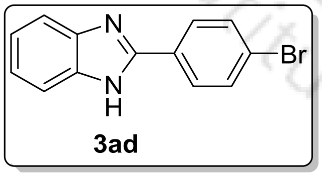
3ab

2-Propyl-1*H*-benzo[*d*]imidazole 3ab. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; brown solid; 88 mg, yield 55%; mp 230-231 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.15 (br s, 1H), 7.45 (s, 2H), 7.10 (s, 2H), 2.78 (t, J = 7.2 Hz, 2H), 1.80-1.76 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 155.0, 121.1, 30.5, 21.0, 13.7; FT-IR (KBr) 3434, 2257, 2129, 1646, 1047, 1025, 996, 827, 766, 688 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{10}H_{12}N_2H$ 161.1079, found 161.1078.



3ac

2-Benzyl-1*H*-benzo[*d*]imidazole 3ac. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 100 mg, yield 48%; mp 221-222 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.29 (br s, 1H), 7.46 (s, 2H), 7.34-7.30 (m, 4H), 7.24-7.21 (m, 1H), 7.13-7.10 (m, 2H), 4.16 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 153.3, 137.4, 128.5, 128.2, 126.3, 121.1, 34.7; FT-IR (KBr) 3436, 3049, 2923, 2683, 1623, 1536, 1493, 1456, 1426, 1270, 1222, 1147, 1024, 748, 722 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{14}H_{12}N_2H$ 209.1078, found 209.1071.



3ad

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole 3ad. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 95 mg, yield 35%; mp 260-261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.13-8.08 (m, 2H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.23-7.19 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.0, 143.5, 134.8, 131.8, 129.2, 128.1, 123.0, 122.6, 121.6, 118.7, 111.2; FT-IR (KBr) 3435, 3056, 2120, 1619, 1584, 1485, 1423, 1297, 1270, 1221, 1197, 1064, 1005, 960, 820, 742 cm^{-1}. HRMS (ESI) m/z: [M+H] calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0028.

3.5. References

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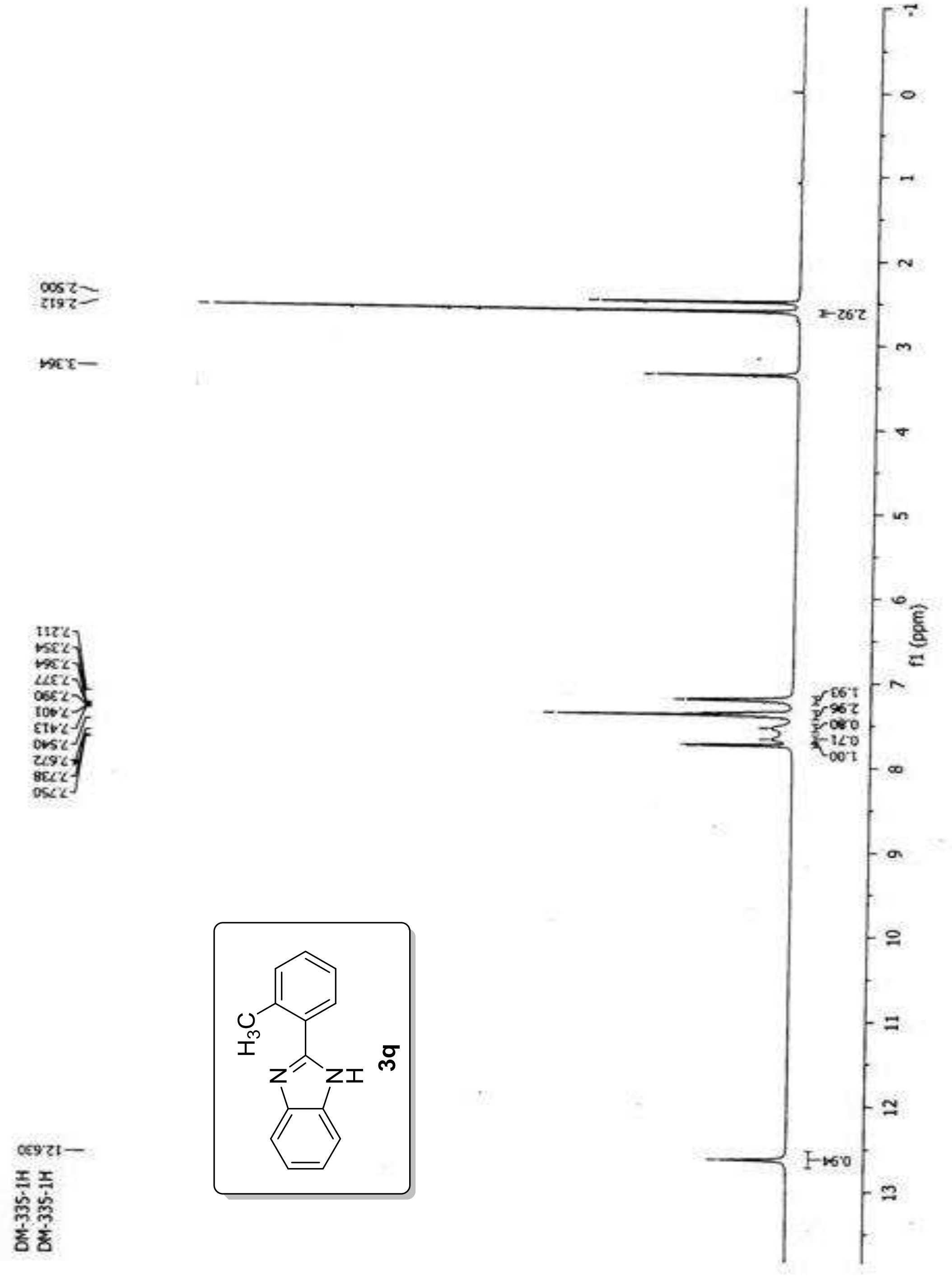
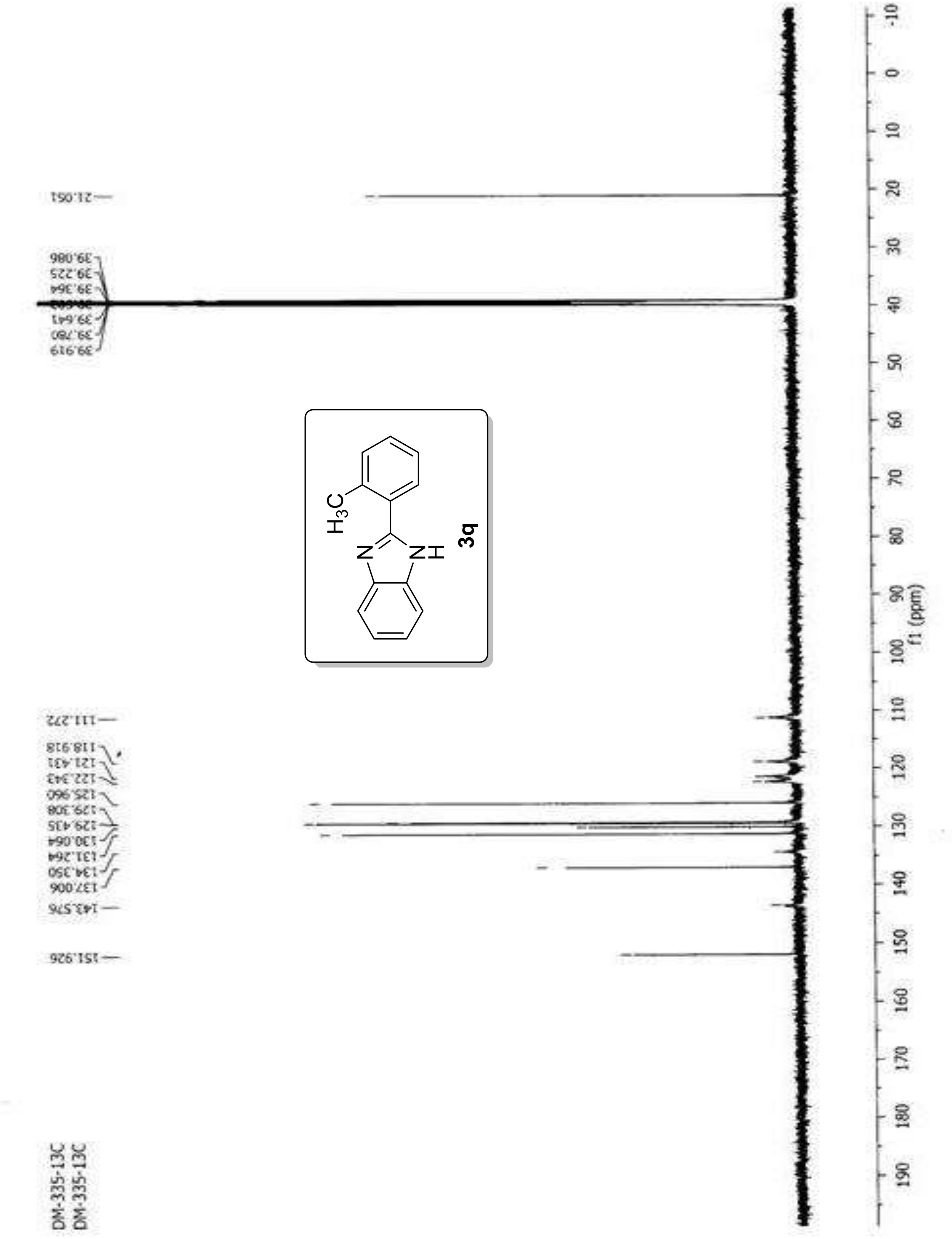
3.6. Selected NMR (^{1}H and ^{13}C) Spectra

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111.272
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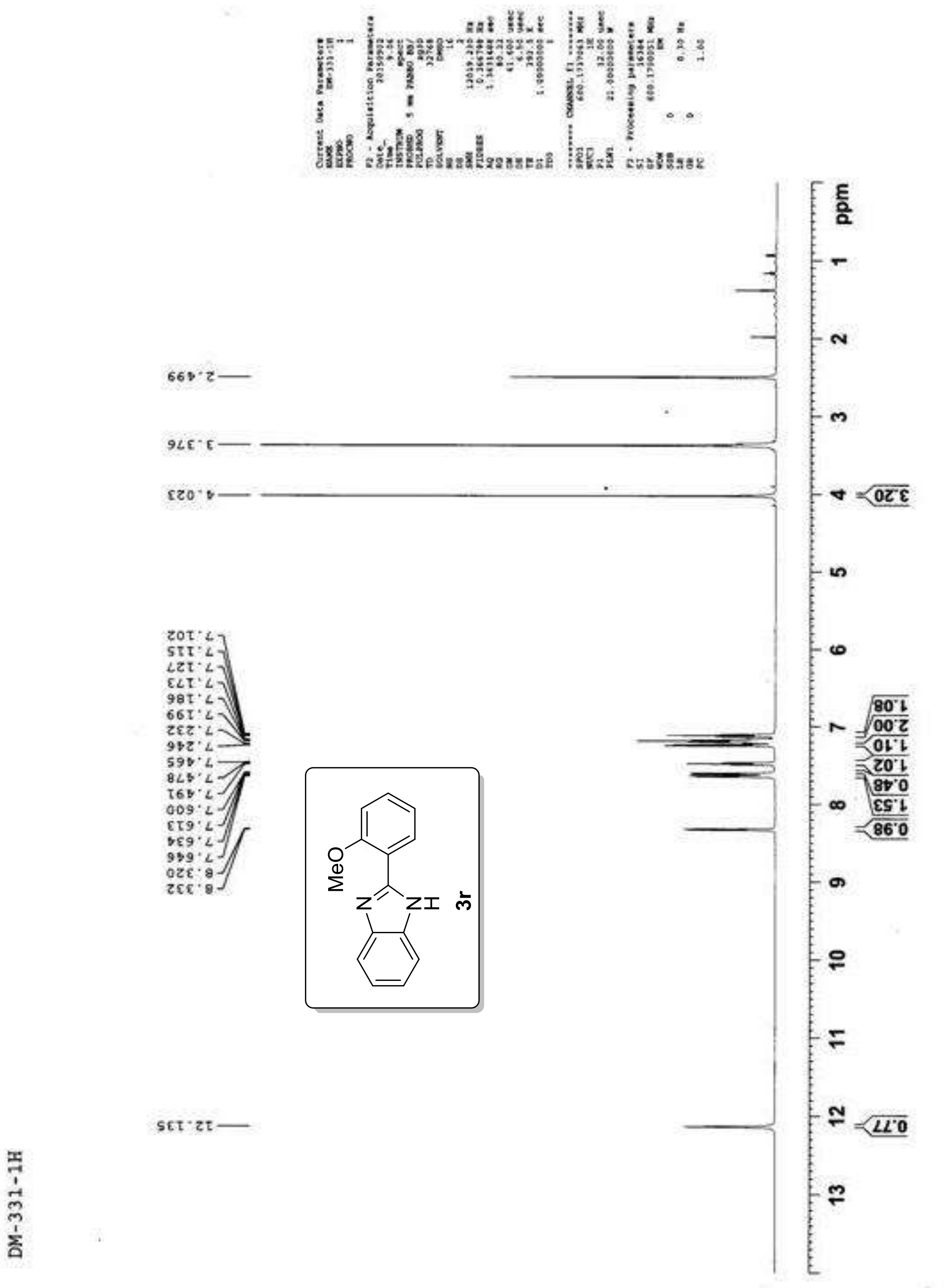
125.960
129.308
129.435
130.064
131.264
134.350
137.006
143.576
151.926
DM-335-13C
DM-335-13C
H$_3$C
N
NH
3q
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)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7.246
7.232
7.199
7.186
7.133
7.127
7.115
7.102
4.023
3.376
2.499
MeO
N
NH
3r
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
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2.00
1.10
1.02
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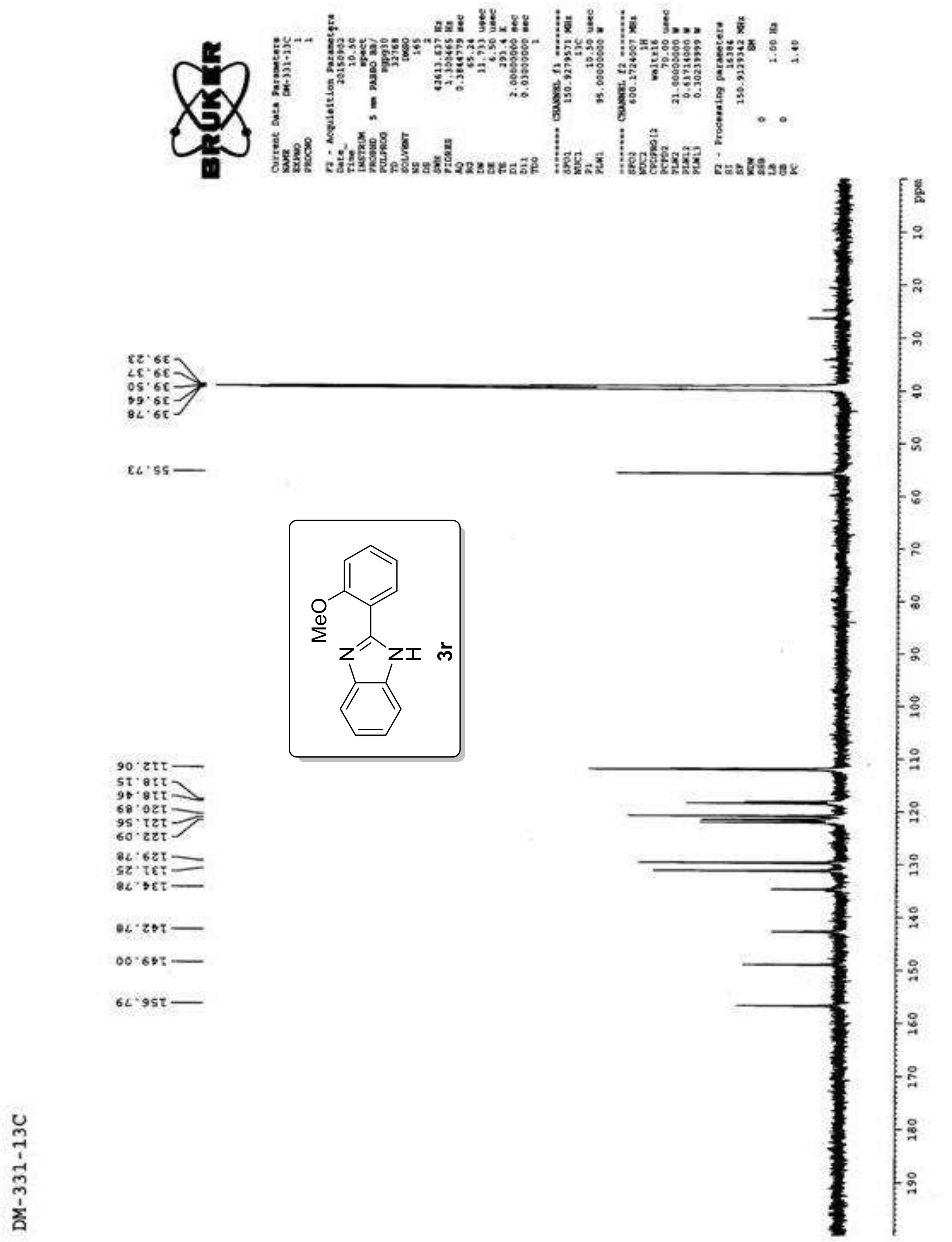
1.53
0.98
0.77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55.73
39.78
39.64
39.50
39.37
39.23
MeO
N
NH
3r
Current Data Parameters
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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
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Time 10.30
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 165
DS 2
SWH 42613.637 Hz
FIDRES 1.300465 Hz
AQ 0.3844779 sec
RG 65.24
DW 11.733 usec
DE 6.50 usec
TE 293.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
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SFO1 150.9279571 MHz
NUC1 13C
P1 10.30 usec
PLW1 95.00000000 W
======== CHANNEL f2 ========
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30233999 W
F2 - Processing parameters
SI 16384
SF 150.9129342 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
190
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150
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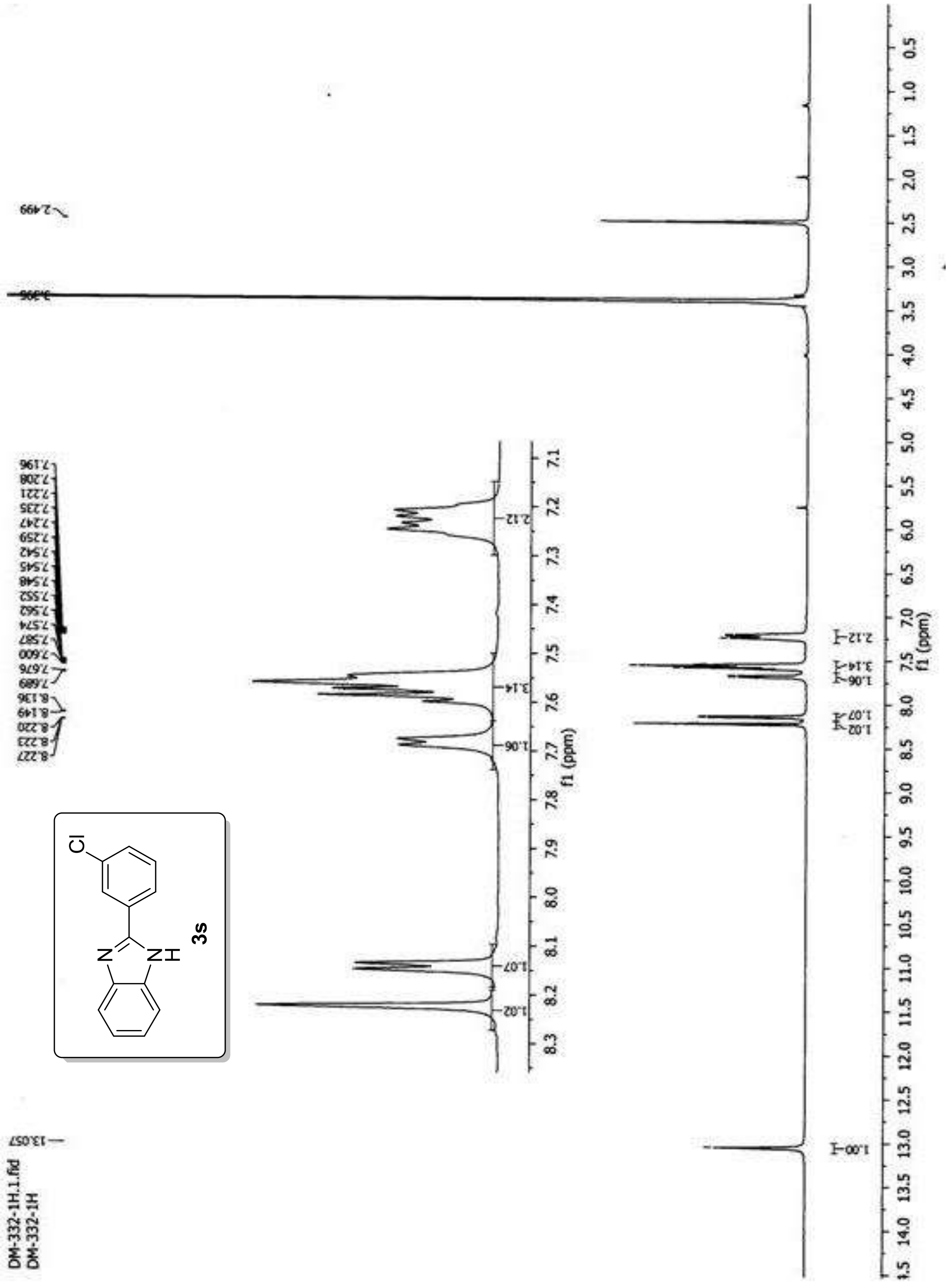
40
30
20
10
ppm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7.548
7.545
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7.235
7.221
7.208
7.196
3.396
2.499
3s
Cl
N
NH
1.00
1.02
1.07
1.06
3.14
2.12
f1 (ppm)
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
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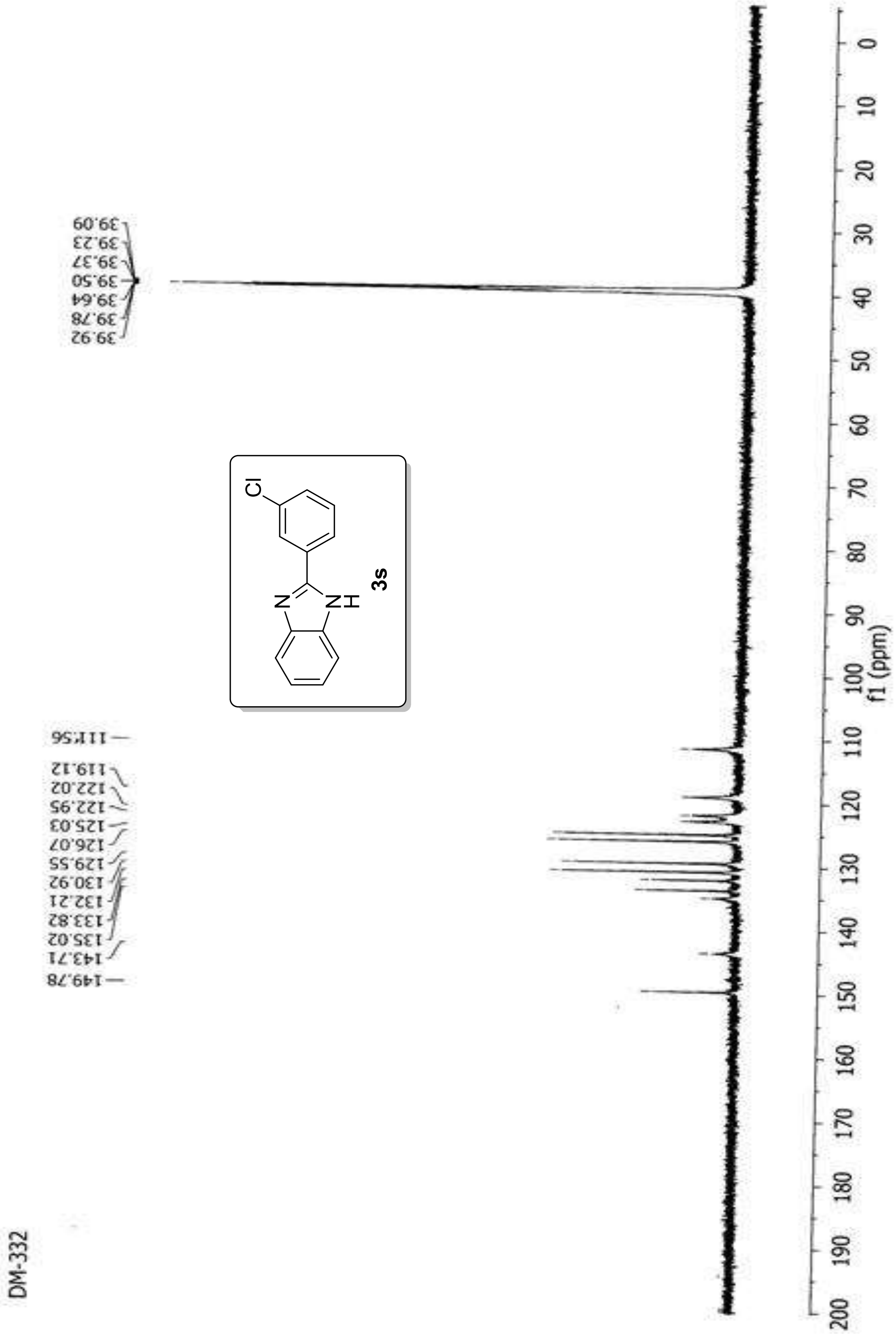
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119.12
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39.50
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39.23
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Cl
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NH
3s
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190
180
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50
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30
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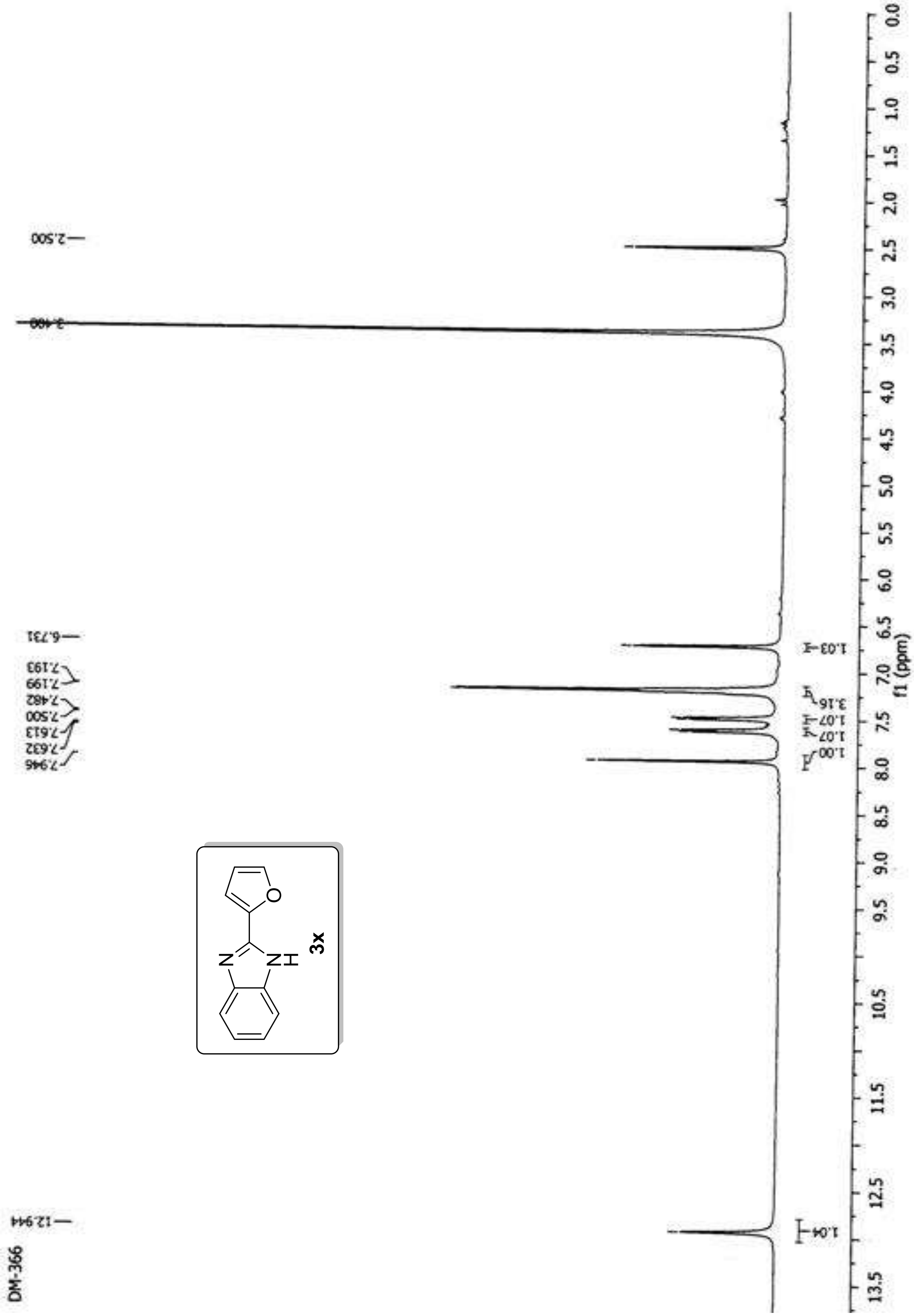
f1 (ppm)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1.03
3.16
1.07
1.07
1.00
1.04
NH
N
O
3x
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
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9.0
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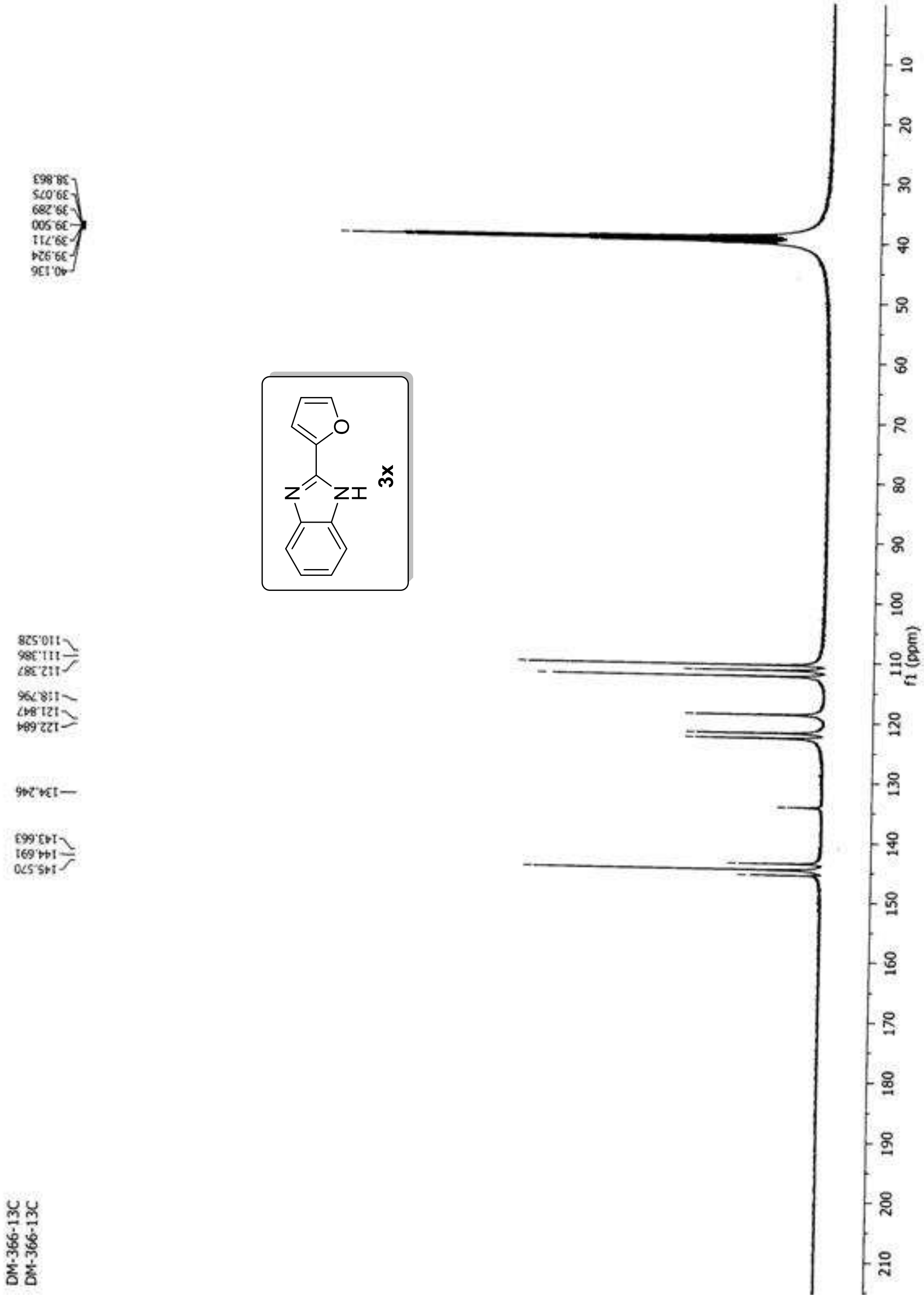
11.5
12.5
13.5
f1 (ppm)


3x

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DM-366-13C
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144.691
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39.924
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39.500
39.289
39.075
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f1 (ppm)
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150
140
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100
90
80
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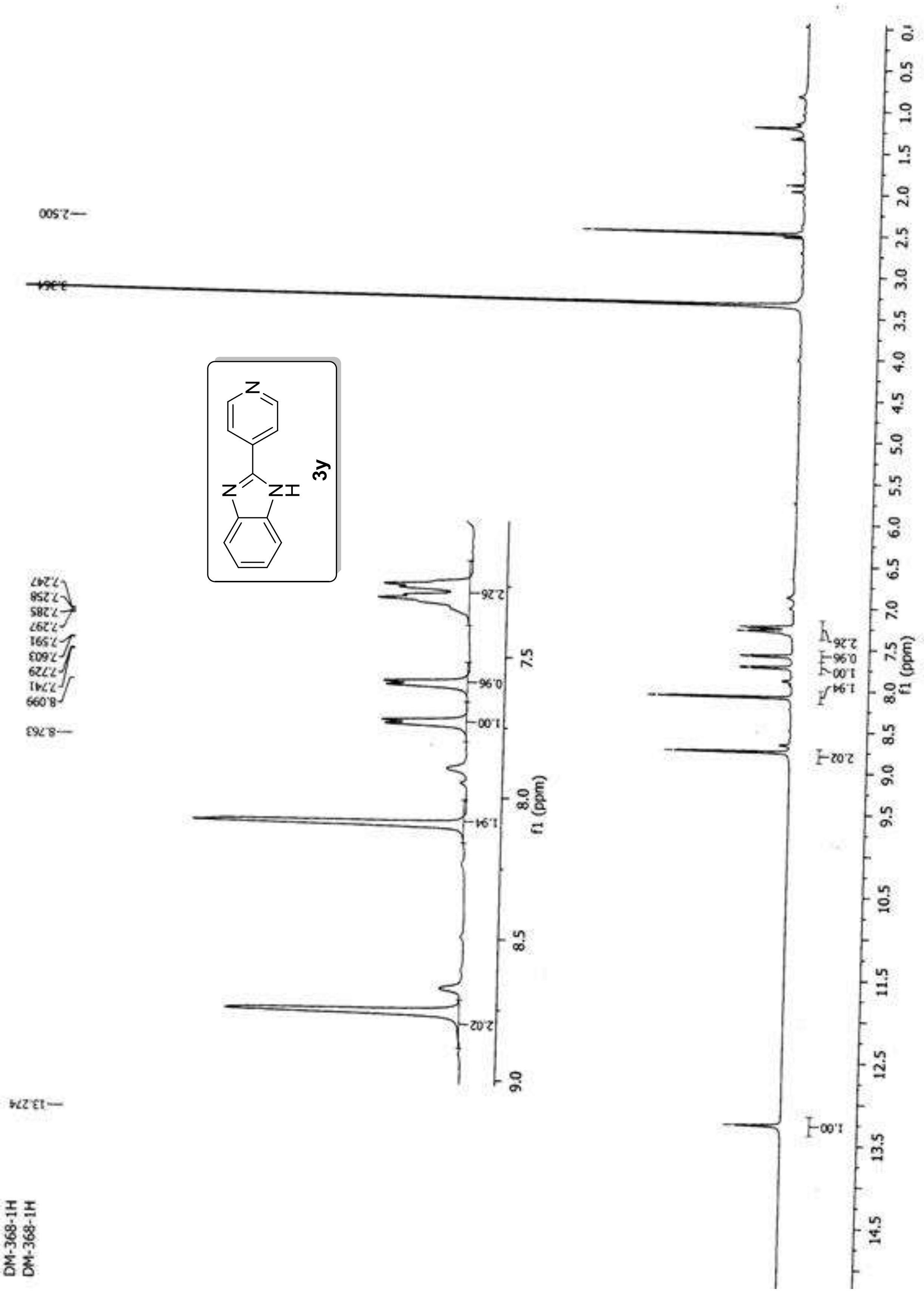
10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7.247
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3y
NH
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N
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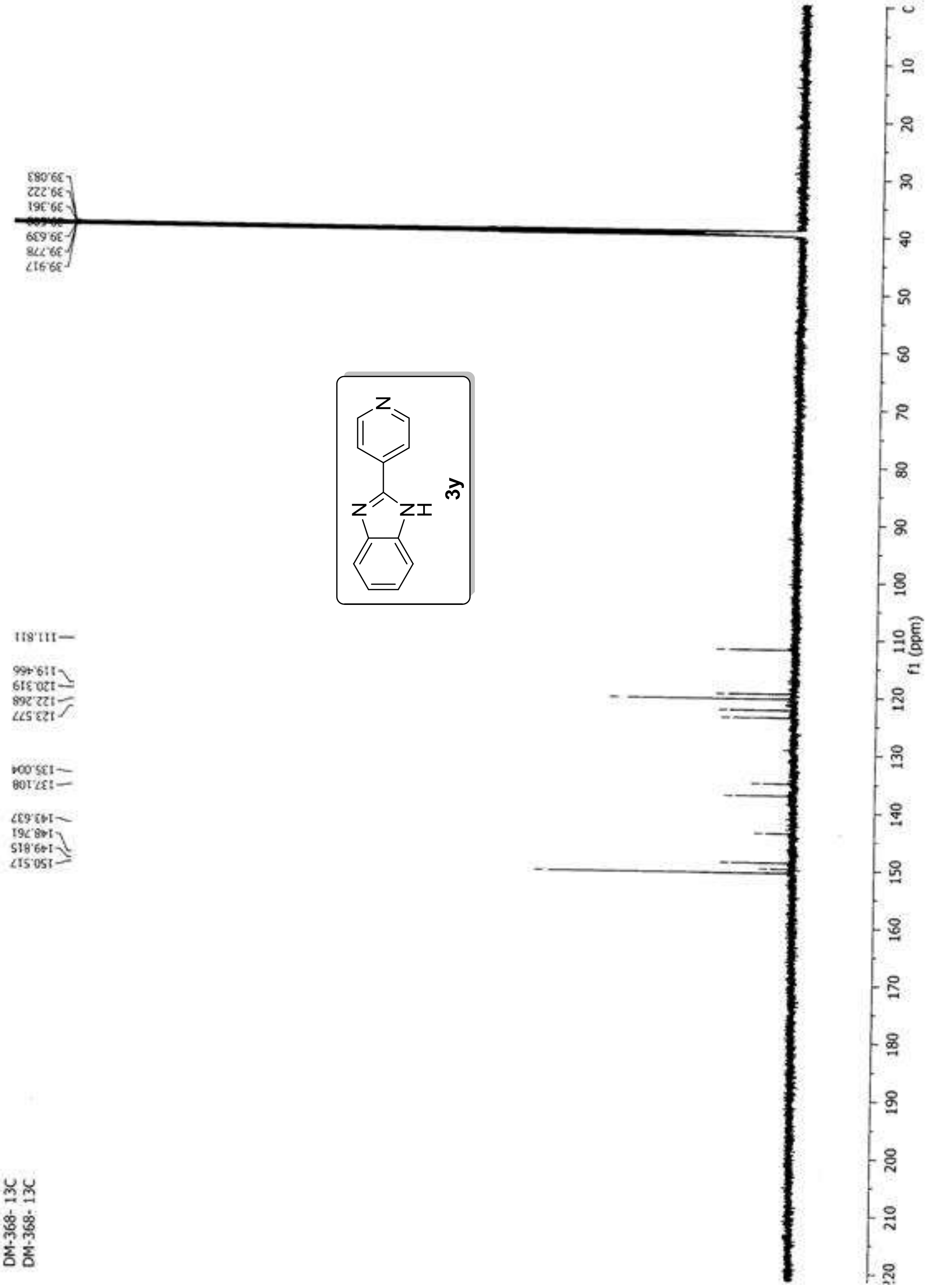
0.96
2.26
1.00
f1 (ppm)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DM-368- 13C
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149.815
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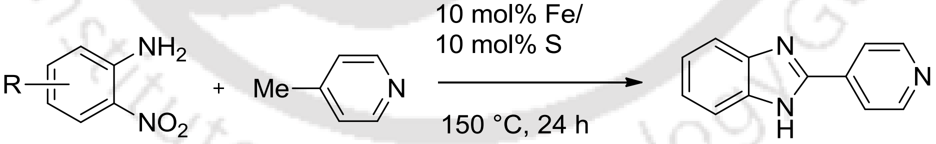
N
N
NH
3y
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

Cu-Catalyzed Oxidative Coupling of Anilines, Methyl Arenes and $TMSN_3$

Functionalization of C-H bond is a fundamental and important process in both academia and industries. They provide efficient synthetic tool for rapid generation of complex molecules from simple substrates. However, the selectivity is major issue in these reaction when the substrate has more than one C-H bond with similar reactivity. Recently, the directed C-H functionalization has emerged as an effective synthetic route for the selective carbon-heteroatom bond formation. Both the reaction of sp^3 and sp^2 C-H bonds are investigated mainly using Ru, Rh and Pd-based catalytic systems. Subsequently efforts have been made on the use of copper based systems. In addition, methyl arenes are simple and readily available hydrocarbons, whose regioselective functionalization would thus be valuable. The functionalization of the sp^3 C-H bond for the construction of C-C bonds has considerably studied. In contrast, the sp^3 C-H functionalization and C-N bond are limited that can find broad utilities for the construction medicinally important structural scaffolds.

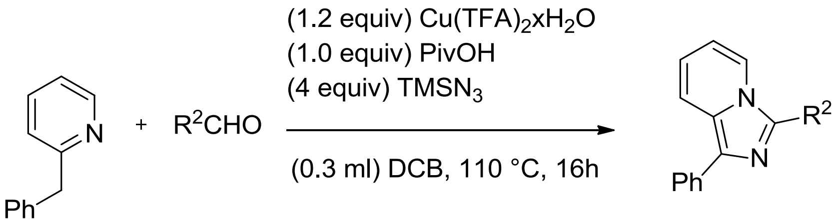
4.1. C-H Functionalization and C-N Bond Formation of Methyl Arenes

Iron sulfide generated *in situ* from elemental sulfur and iron is found to efficiently catalyze a redox/condensation cascade reaction of 2-aminonitrobenzene with 4-methylpyridine (Scheme 1).[1] This method represents a straightforward approach to 2-hetaryl benzimidazole synthesis



Scheme 1. Fe/S-Catalyzed Synthesis of 2-Pyridyl Benzimidazoles

The construction of imidazopyridines is reported via a three-component reaction of benzylpyridines, aldehydes and $TMSN_3$ at moderate temperature (Scheme 2).[2] Cu-promoted amination of the benzylic C(sp^3)–H bond is a key step of this multiple C–N bond-forming sequence.

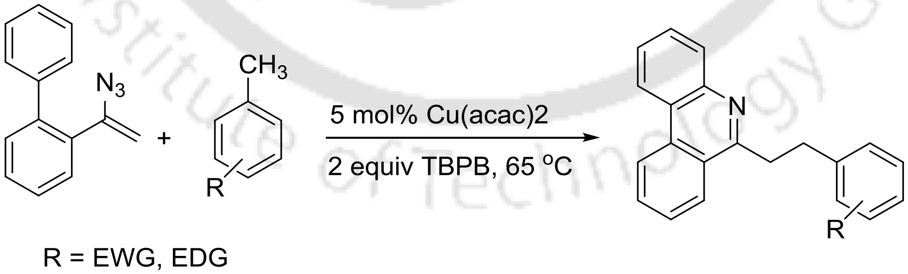


Scheme 2. Copper-Catalyzed Synthesis of Imidazopyridines

Li and co-workers showed DTBT-mediated synthesis of quinazolinones *via* C(sp^3)−H activation followed by C−N bond formation at moderate temperature (Scheme 3).[3]

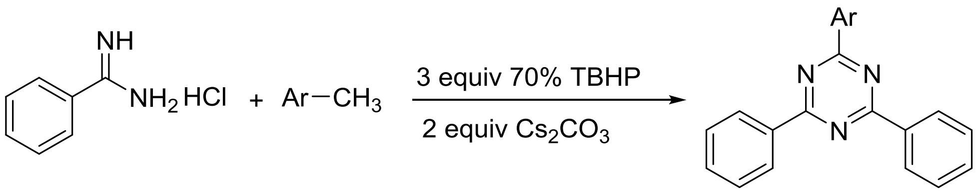
Scheme 3. Peroxide-Mediated Synthesis of Quinazolinones

Guao and co-workers reported a tandem synthesis of phenanthridines *via* an oxidative radical cyclization of vinyl azides with methyl arenes (Scheme 4).[4] These reaction conditions can be extended to the reaction of the substrates containing unactivated C(sp^3)-H bonds such as ethers and alkanes.



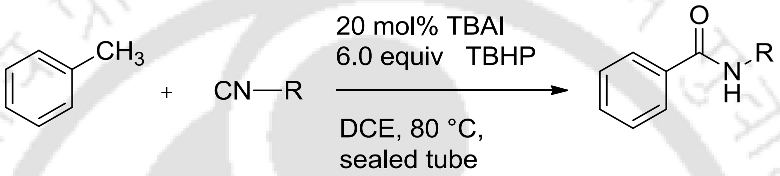
Scheme 4. Cu-Catalyzed Synthesis of Phenanthridines

TBHP mediated oxidative coupling of amidines with methyl arene is reported to produce 1,3,5-triazines (Scheme 5).[5] Methyl arene is used as effective aldehyde precursors in the tandem oxidation-imination-cyclization transformation.



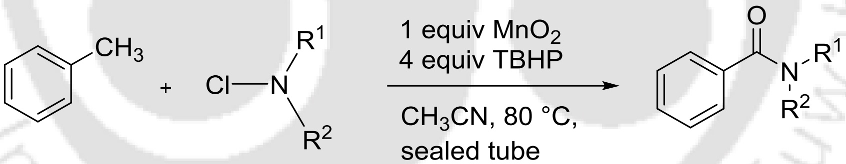
Scheme 5. TBHP-Mediated Synthesis of 1,3,5-Trizines

Li and co-workers reported the oxidative coupling of isocyanide with toluene using tetrabutylammonium iodide (TBAI) to produce amides at moderate temperature (Scheme 6).[6]



Scheme 6. TBAI-Mediated Synthesis of Amides

Mn-mediated synthesis of amides from methyl arenes and *N*-chloroamines is reported in the presence of TBHP at moderate temperature (Scheme 7).[7]

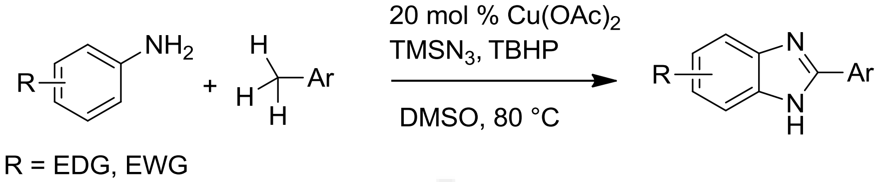


Scheme 7. Mn-Mediated Synthesis of Amides

Development of effective synthetic methods for the tandem C-H functionalization and C-N formation for methyl arenes that can lead to diverse functionalized heterocycles would thus be valuable.

4.1. Present Study

This section focuses on Cu-catalysed cross-coupling of anilines, methyl arene and $TMSN_3$ in the presence of TBHP at moderate temperature to produce 2-aryl benzimidazoles via a tandem C(sp^3/sp^2)-H functionalization and *C-N* bonds formations. The selectivity and multiple C-H functionalization of the simple substrates are the significant practical features.

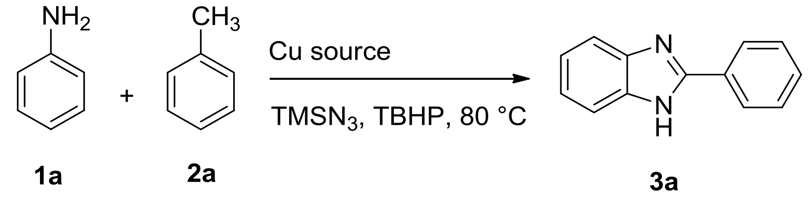


Scheme 8. Cu-Catalyzed Tandem C-H Functionalization and C-N Bond Formation

First, the reaction was optimized using aniline **1a** and toluene **2b** as the model substrates employing different Cu sources, solvents and azides (Table 1). Gratifyingly, the oxidative cross-coupling occurred to afford 2-aryl benzimidazole **3a** in 69% conversion when the substrates **1a** and **2a** were reacted with 20 mol % $Cu(OAc)_2$, 2 equiv $TMSN_3$ and 3 equiv of TBHP at 80 °C in toluene (entry 1). Subsequent screening of the solvents led to an increase in the conversion to 84% using DMSO, while CH_3CN produced 45% conversion (entries 2-3). In contrast, DMF and THF were not effective (entries 4-5). In a set of Cu sources investigated, CuBr, CuCl, Cu(OAc), CuI, $CuCl_2$, $CuSO_4 \cdot 5H_2O$, $Cu(OAc)_2 \bullet H_2O$ and $Cu(OAc)_2$, the latter gave the best results (entries 6-12). $TMSN_3$ was found to be superior to NaN_3/AcOH (entry 13). Decreasing the amount of the Cu source (10 mol %), TBHP (1.5 equiv) or toluene (5 equiv) led the formation of **3a** in <61% conversion (entries 14-16). Peroxides such as 30% H_2O_2 and di-*tert*-butyl peroxide (DTBP) were not effective and the formation of the target heterocycles was not observed (entries 17-18). Control experiments confirmed that the absence of the Cu source or TBHP showed no reaction (entries 19-20).

Having optimized the reaction conditions, the scope of the procedure was studied for the reaction of a series of substituted anilines **1b-m** with mesitylene **2b** as a representative example (Scheme 2). Aniline bearing substitution at the 2-position with methyl group cross-coupled to furnish benzimidazole **3b** in 77% yield. The reaction of anilines **1c-h** having substitution at the 4-position with bromo, chloro, fluoro, methoxy, methyl and methylthioether functional groups afforded the corresponding benzimidazoles **3c-h** in 63-76% yields. It is noteworthy that the thioether was intact and no oxidation was observed. Aniline **1j** having 4-trifluoromethyl group underwent reaction to produce benzimidazole **3j** in

Table 1. Optimization of the Reaction Conditions[a]



Entry	Cu source	Oxidant	Solvent	**3a** (%)[b]
1	$Cu(OAc)_2$	TBHP	Toluene	69
2	$Cu(OAc)_2$	TBHP	DMSO	84(77)[c]
3	$Cu(OAc)_2$	TBHP	CH_3CN	45
4	$Cu(OAc)_2$	TBHP	THF	n.d.
5	$Cu(OAc)_2$	TBHP	DMF	n.d.
6[d]	$Cu(OAc)_2$	TBHP	DMSO	62
7	CuBr	TBHP	DMSO	79
8	CuCl	TBHP	DMSO	73
9	CuOAc	TBHP	DMSO	72
10	CuI	TBHP	DMSO	75
11	$CuCl_2$	TBHP	DMSO	79
12	$Cu(OAc)_2{\cdot}H_2O$	TBHP	DMSO	65
13	$CuSO_4{\cdot}5H_2O$	TBHP	DMSO	trace
14[e]	$Cu(OAc)_2$	TBHP	DMSO	trace
15[f]	$Cu(OAc)_2$	TBHP	DMSO	61
16[g]	$Cu(OAc)_2$	TBHP	DMSO	43
17	$Cu(OAc)_2$	30%H_2O_2	DMSO	n.d.
18	$Cu(OAc)_2$	DTBP	DMSO	trace
19[h]	-	TBHP	DMSO	n.d.
20[i]	$Cu(OAc)_2$	-	DMSO	n.d.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (5.0 mmol), [Cu] (20 mol %), $TMSN_3$ (1.0 mmol), TBHP (1.5 mmol), solvent (0.5 mL), 80 °C, 12 h.

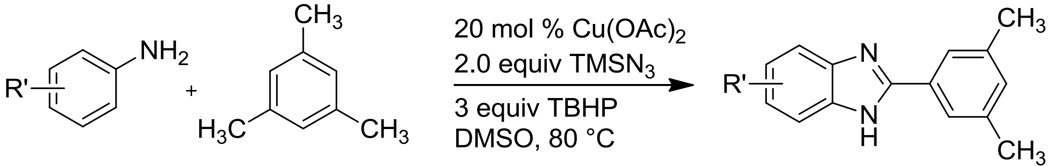
[b] Determined by 600 MHz ^1H NMR. [c] Isolated yield.

[d] Toluene (2.5 mmol) was used.

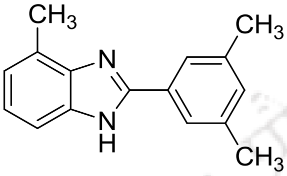
[e] NaN_3 (1.0 mmol) and AcOH (2.5 mmol) were used. [f] $Cu(OAc)_2$ (10 mol %) was used.

[g] TBHP (0.75 mmol) was used. [h] No $Cu(OAc)_2$. [i] No TBHP.

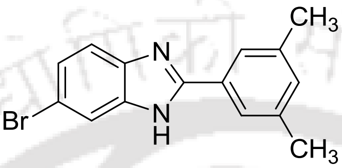
Table 2. Reaction of Substituted Anilines with Mesitylene[a,b]



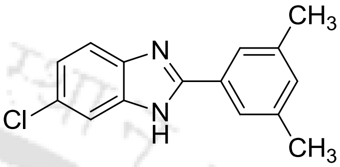
1b-m **2b** **3b-m** R' = EDG, EWG



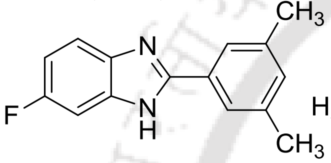
3b, 12 h, 77%



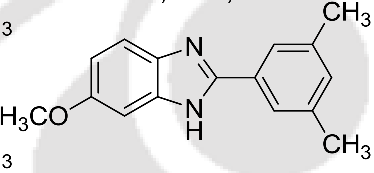
3c, 12 h, 72%



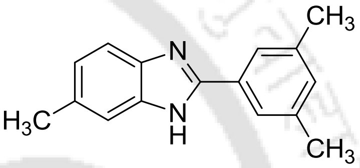
3d, 14 h, 67%



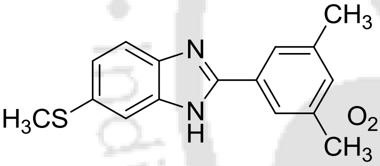
3e, 14 h, 63%



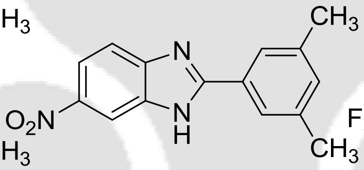
3f, 12 h, 69%



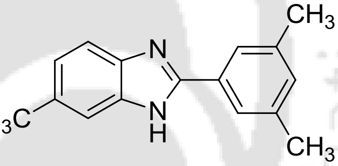
3g,14 h, 76%



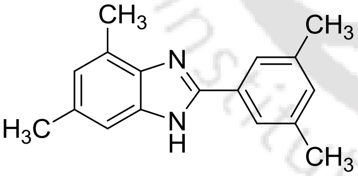
3h, 14 h, 65%



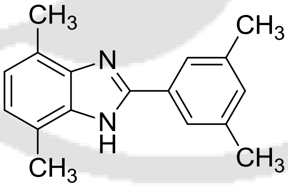
3i, 12 h, n.d.



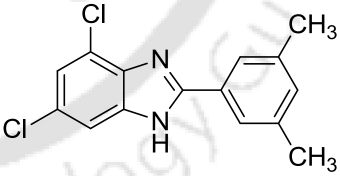
3j, 18 h, 62%



3k, 14 h, 71%



3l, 14 h, 64%

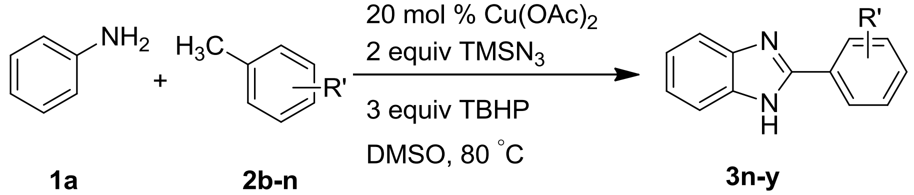


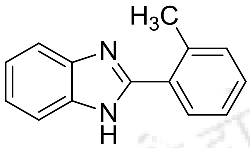
3m, 16 h, n.d.

[a] Reaction conditions: aniline **1b-m** (1 mmol), mesitylene **2b** (10 mmol), Cu(OAc)2 (20 mol %), TMSN3 (2 mmol), TBHP (3 mmol), DMSO (1 mL), 80 °C.

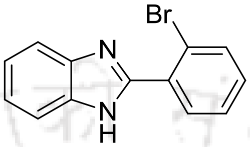
[b] Isolated yield.

Table 3. Reaction of Substituted toluenes with Aniline^a

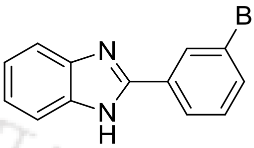




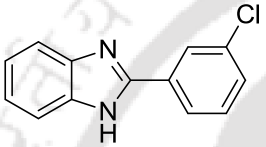
3n, 14 h, 62%



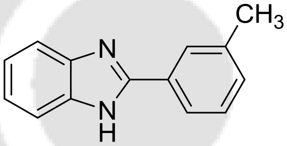
3o, 23 h, n.d.



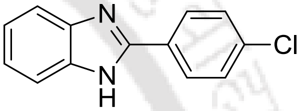
3p, 22 h, 52%



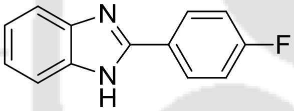
3q, 21 h, 57%



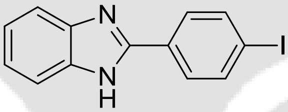
3r, 14 h, 68%



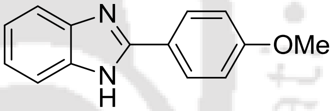
3s, 21 h, 57%



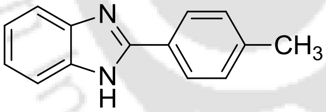
3t, 19 h, 48%



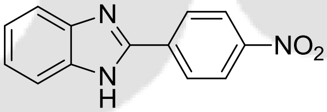
3u, 23 h, 51%



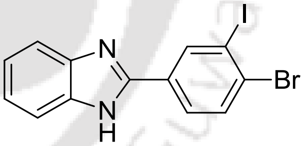
3v, 23 h, 69%



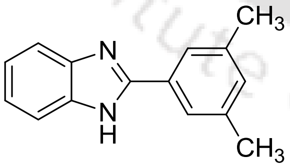
3w, 14 h, 67%



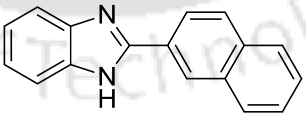
3x, 25 h, 56%



3y, 24 h, 43%



3z, 14 h, 68%

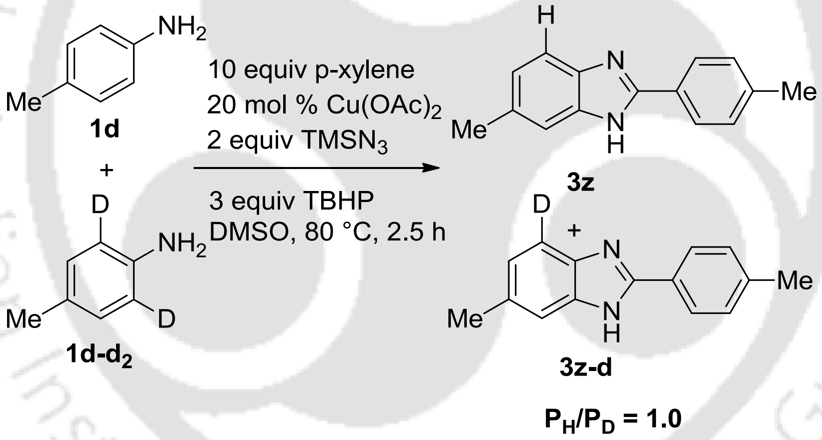


3za, 16 h, 70%

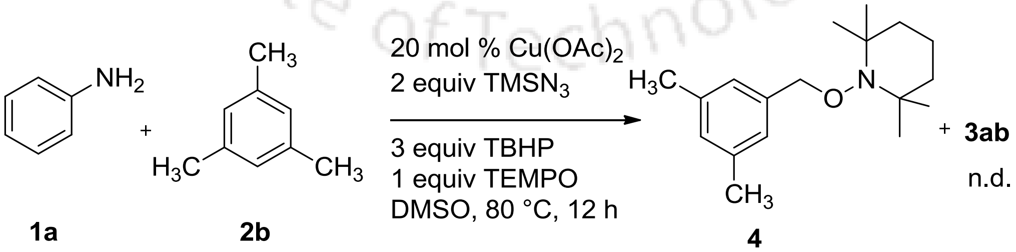
^{a}Reaction conditions: aniline**1a** (1 mmol), Substituted toluenes **2b-n** (10 mmol), $Cu(OAc)_2$ (20 mol %), $TMSN_3$ (2 mmol), TBHP (3 mmol), DMSO (1 mL), 80 °C.

^{b}Isolated yield.

in 62% yield. The reaction 2,4-dimethylaniline and 3,5-dimethylaniline underwent reaction to produce benzimidazoles **3k** and **3l** in 71 and 64% yield. In contrast, 2,4-dichloroaniline was a unsuccessful substrate and the formation of **3m** was not observed. However, the reaction of toluene **2d-f** bearing substitution at the 3-position with bromo, chloro and methyl groups afforded the corresponding benzimidazoles **3p-r** in 52-68% yields. Similar results observed with the substrates **2g**-l bearing the substitution at the 4-position with chloro, fluoro, iodo, methoxy, methyl and nitro groups, giving the heterocycles **3s-x** in 48-69% yields. In addition, toluene bearing substitutions at the 3 and 4-positions with iodo and bromo groups underwent reaction to furnish benzimidazole **3y** in 43% yield, whereas the reaction of mesitylene produced **3z** in 68% yield. Further, 2-methylnaphthalene underwent reaction to give the target heterocycle **3za** in 70% yield. Interestingly, the reactive iodo group was intact and no amination was observed.



Scheme 9. Kinetic Isotope Experiment



Scheme 10. Radical Scavenger Experiment

Sample Name	DM-442	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	DM-442.d	**ACQ Method**		**Comment**		**Acquired Time**	2/9/2017 2:55:06 PM

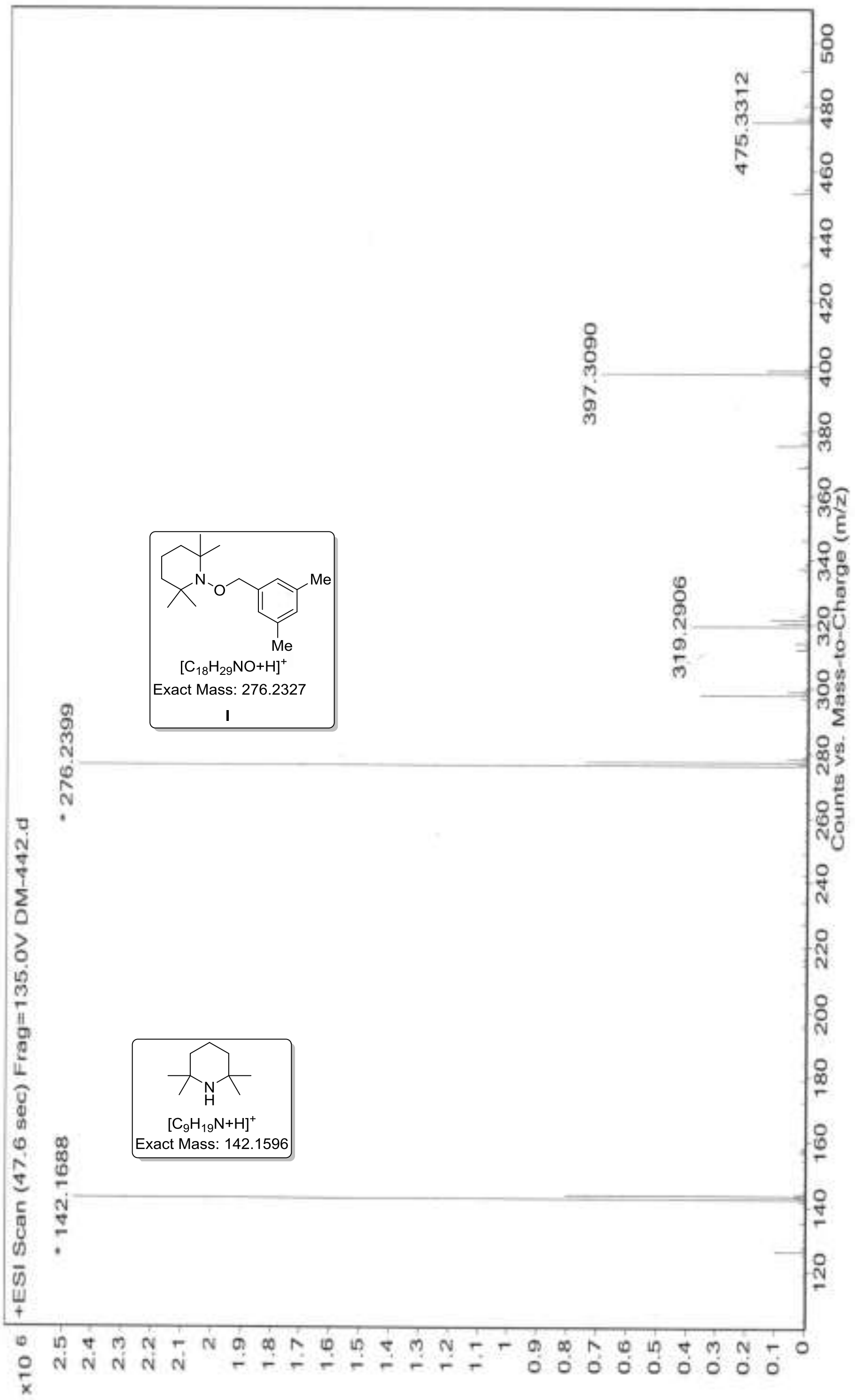


Figure 1. ESI-MS of the Radical Scavenger Experiment Having **4**.

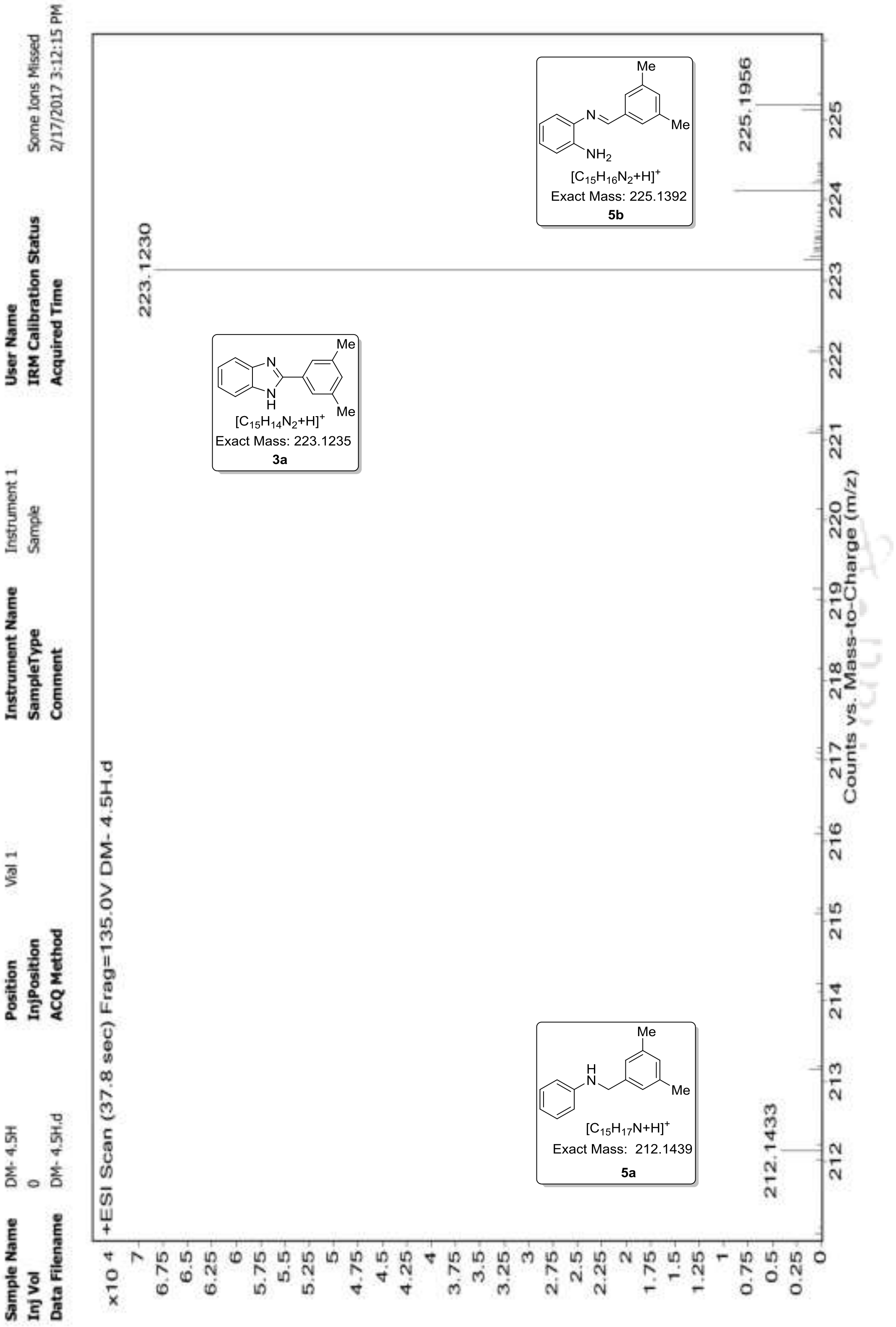
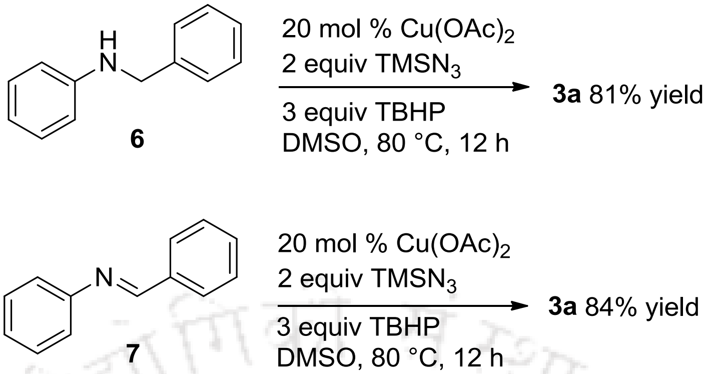


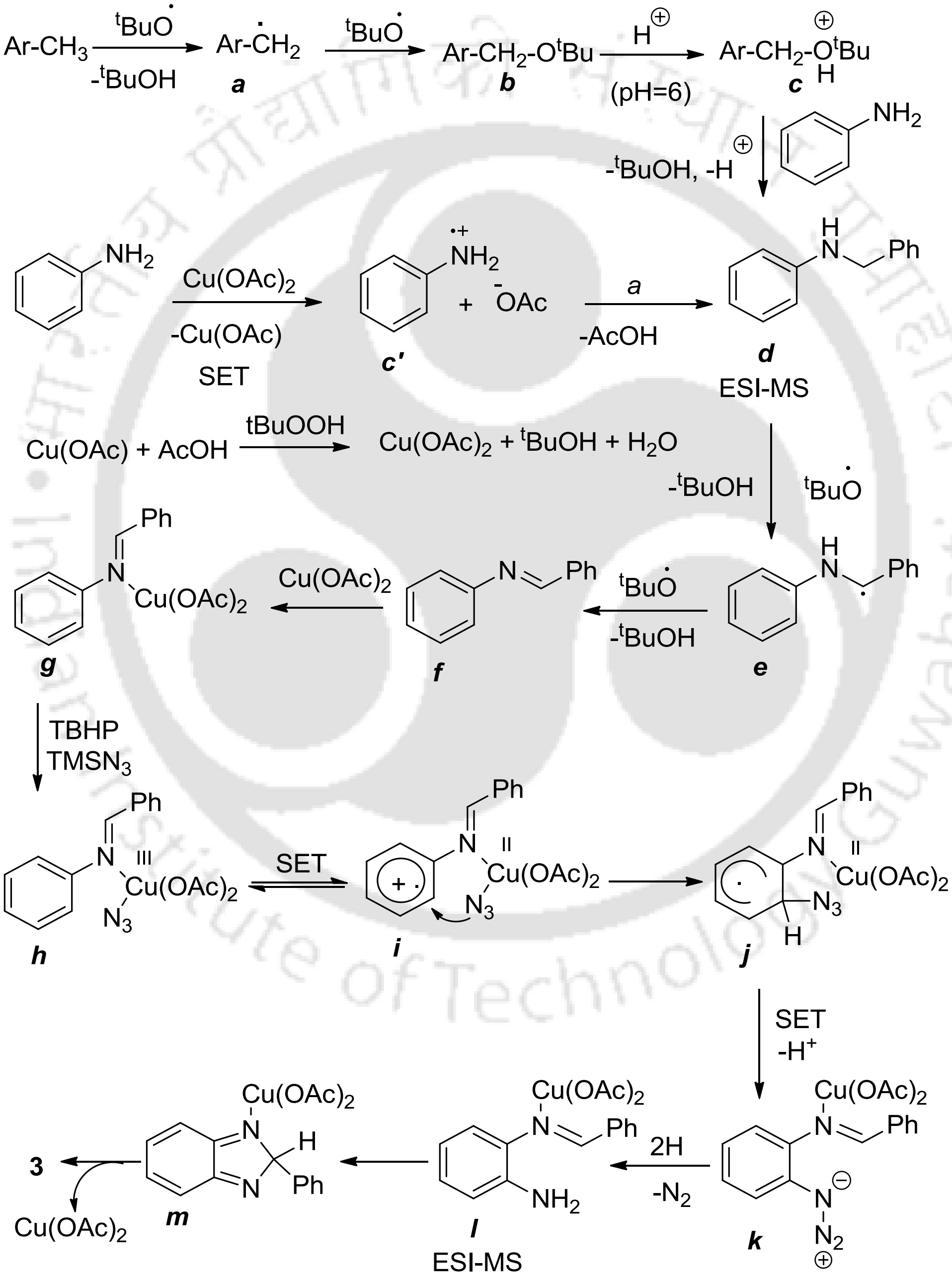
Figure 1. ESI-MS of the Reaction Mixture of **1a** and **2b** after 6 h.



Scheme 11. Control experiments

To get insight into the mechanism, an intermolecular kinetic isotope experiment was performed employing **1d** and **1d-d$_2$** as the examples.[8] The observed P_H/P_D = 1.0 (23% conversion, 2.5 h) suggests that the product determining step may not involve the azidation of the aryl C(sp^2)-H bond (Scheme 9).[9] The radical scavenger experiment using TEMPO revealed the formation of **4**, which suggests that the reaction may involve a radical pathway (Scheme 10 and Figure 1).[10] In addition, the ESI-MS analysis of the reaction mixture of **1a** and **2b** revealed the formation a three major species **5a**, **5b** and **3ab** (Figure 2).[11] These results suggest that the reaction may involve a selective direct amination of methyl arene C(sp^3)-H bond with aniline N-H bond to give **5a**,[12] which can lead to a tandem oxidation to imine[13] followed by *ortho*-selective C-H azidation[14] and conversion to amine[15] to furnish **5b.** Intramolecular cyclization of **5b** can produce **3ab**. The absence of the formation of 2-azidoaniline in the ESI-MS suggests that the reaction may not involve a NH_2 directed *ortho*-azidation. Further, the reaction of *N*-benzylaniline **6** and imine **7** with $TMSN_3$ afforded benzimidazole **3a** in 81 and 84% yield, respectively (Scheme 11). Thus, copper(II) with TBHP can produce tBuO· radical, which can react with methyl arene C-(sp^3)-H bond to give the benzyl radical ***a*** (Scheme 12). The latter with tBuO· radical can provide benzyl t-butyl ether ***b***.[3] Since the reaction medium is acidic (pH= 6), protonation of ***b*** can give ***c***, which can lead to nucleophilic substitution with aniline to provide *N*-benzylaniline ***d***. Alternatively, aniline can oxidize to cation radical ***c'*** *via* a single electron transfer (SET), which can react with benzyl radical to produce ***d***.[16] The reduced Cu(OAc) can be converted to $Cu(OAc)_2$ with

AcOH and TBHP. Oxidation of ***d*** can give the imine ***f*** that can chelate with $Cu(OAc)_2$ to yield ***g***. TBHP with $TMSN_3$ can produce $N_{3\cdot}$ radical that can react with *f* to afford the Cu(III) species ***h***, which can give the Cu(II)) species ***i*** via SET.[17] Transfer of N_3^- to aryl ring may lead to the generation of a radical intermediate ***j***, which can lead to SET to yield to ***k***. Cu(II) assisted transformation of azide to amine followed by an intramolecular cyclization can produce the target heterocycle **3** and Cu(II) species to complete the catalytic cycle.



Scheme 12. Proposed Reaction Pathway

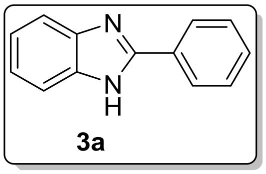
In summary, Cu-catalyzed tandem oxidative C-H functionalization and *C-N* bonds formation of anilines, methyl arene and $TMSN_3$ has been accomplished in the presence of TBHP at moderate temperature. The selectivity, multiple C-H functionalization and *C-N* bonds formations and their application for the construction of medicinally important benzimidazoles are important practical features.

4.2. Experimental Section

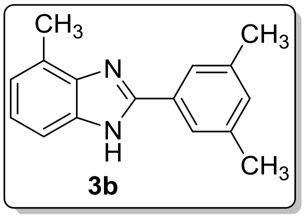
4.2.1. General Information: See section 2.3.1 (page-21) for general information. All methyl arenes were purchased from commercial suppliers and used as received.

4.2.2. General Procedure for the Oxidative Coupling of Methyl Arenes, Anilines and $TMSN_3$. To a stirred solution of aniline **1** (1 mmol), $Cu(OAc)_2$ (20 mol %, 0.2 mmol, 36 mg), $TMSN_3$ (2 equiv, 2.0 mmol, 230 mg) and TBHP (3 equiv, 3 mmol, 544 µL) in DMSO (1 mL) was added methyl arene **2** (10 mmol), and the resultant mixture was heated at 80 °C for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. The reaction mixture was then cooled to room temperature and stirred with saturated Na_2SO_3 (1 mL) for 1 h and extracted with ethyl acetate (3 x 10 mL). The combined organic solution was washed with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford analytically pure products.

4.3. Characterization Data

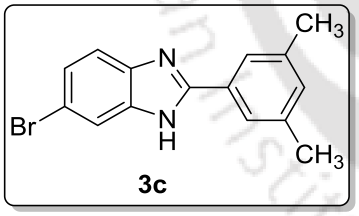

3a

2-Phenyl-1*H*-benzo[d]imidazole 3a. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.40$; white solid; 75 mg, yield 77%; mp 310-320 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.91 (br s, 1H), 8.19 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.56-7.48 (m, 4H), 7.22-7.19 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.2, 143.8, 135.0, 130.1, 129.8, 128.9, 126.4, 122.5, 121.6, 118.9, 111.3; FT-IR (KBr) 3442, 3047, 2960, 2923, 1747, 1590, 1476, 1462, 1444, 1373, 1226, 1187, 1119, 1004, 744,739 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{10}N_2H$ 195.0922, found 195.0922.



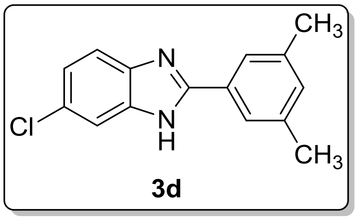
3b

2-(3,5-Dimethylphenyl)-4-methyl-1*H*-benzo[d]imidazole 3b. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 91 mg, yield 77%; mp 230-240 °C. mixture of tautomers (1.2:1): ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.73 (br s, 1H), 12.47 (br s, 1H), 7.87 (s, 2H), 7.80 (s, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.12-7.07 (m, 4H), 6.99-6.97 (m, 2H), 2.57 (s, 3H), 2.56 (s, 3H), 2.38 (s, 12H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.3, 150.5, 137.9, 137.8, 134.4, 131.0, 130.1, 128.2, 124.4, 124.1, 122.9, 122.2, 121.6, 121.5, 116.1, 108.6, 20.8, 17.0, 16.6; FT-IR (neat) 3420, 2925, 2854, 2256, 2129, 1650, 1465, 1047, 1025, 999, 827, 765, 632 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1391.



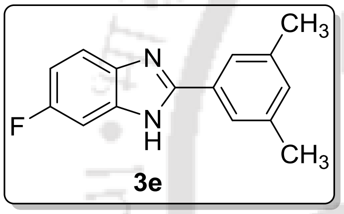
3c

6-Bromo-2-(3,5-dimethylphenyl)-1*H*-benzo[d]imidazole 3c. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.54; white solid; 108 mg, yield 72%; mp 250-260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H), 7.79 (s, 2H), 7.67-7.49 (m, 2H), 7.33 (s, 1H), 7.14 (s, 1H), 2.36 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.9, 152.5, 145.3, 142.9, 138.1, 134.1, 131.6, 129.5, 125.0, 124.6, 124.4, 121.1, 120.4, 113.9, 113.0, 20.9; FT-IR (KBr) 3437, 2922, 2853, 2113, 1724, 1604, 1540, 1464, 1414, 1396, 1363, 1241, 1018, 917, 858, 800 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}BrN_2H$ 301.0340, found 301.0341.



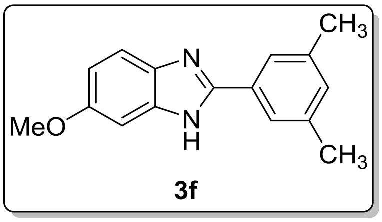
3d

6-Chloro-2-(3,5-dimethylphenyl)-1*H*-benzo[d]imidazole 3d. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.55$; white solid; 86 mg, yield 67%; mp 252-262 °C. ^{1}H NMR (600 MHz, $CDCl_3$+DMSO-d_6) δ 13.02 (br s, 1H), 7.79 (s, 2H), 7.68-7.63 (m, 1H), 7.53 (s, 1H), 7.21 (d, *J* = 5.4 Hz, 1H), 7.14 (s, 1H), 2.37 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.9, 137.9, 131.3, 129.2, 127.0, 124.2, 124.1, 122.1, 20.8; FT-IR (KBr) 3435, 2954, 2920, 2635, 2114, 1601, 1583, 1542, 1465, 1416, 1397, 1364, 1284, 1019, 927, 802 cm^{-1}.HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}ClN_2H$ 257.0846, found 257.0843.



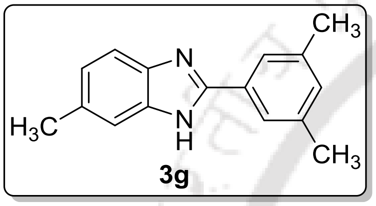
3e

2-(3,5-Dimethylphenyl)-6-fluoro-1*H*-benzo[d]imidazole 3e. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.51$; White solid; 76 mg, yield 63%; mp 242-252 °C.mixture of tautomers (1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.0 (br s, 1H), 7.79 (d, *J* = 6.6 Hz, 2H), 7.64 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.51 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 8.4, 1.8 Hz, 1H), 7. 14 (d, *J* = 5.4 Hz, 2H), 7.08-7.01 (m, 2H), 2.36 (s, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.0 ($^1J_{C,F}$ = 234.0 Hz), 154.2, 140.0, 133.2, 129.8, 125.2, 112.0 ($^2J_{C,F}$ = 24.0 Hz), 21.9; FT-IR (neat) 3437, 2957, 2921, 2853, 2113, 1632, 1604, 1487, 1468, 1357, 1263, 1109, 1018, 834, 800, 730 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}FN_2H$ 241.1141, found 241.1141.



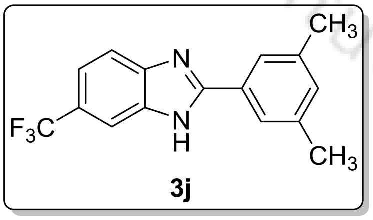
3f

2-(3,5-Dimethylphenyl)-6-methoxy-1*H*-benzo[d]imidazole 3f. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.32; liquid; 87 mg, yield 69%. mixture of tautomers (1.6:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.66 (br s, 1H), 11.96 (br s, 1H), 7.75 (s, 2H), 7.46 (s, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 6.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.80 (s, 3H), 2.36 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 175.3, 157.1, 152.4, 139.9, 132.8, 130.1, 124.9, 113.3, 56.6, 22.1, 21.9; FT-IR (neat) 3434, 2925, 2966, 2854, 2254, 2127, 1650, 1464, 1367, 1236, 1049, 1026, 1004, 825, 764 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2OH$ 253.1341, found 253.1345.



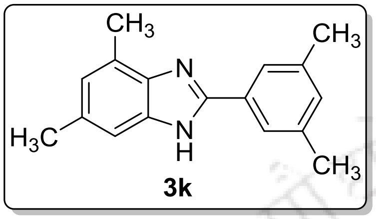
3g

2-(3,5-Dimethylphenyl)-6-methyl-1*H*-benzo[d]imidazole 3g. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; white solid; 90 mg, yield 76%; mp 225-235 °C. mixture of tautomers (1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.69 (br s, 1H), 12.66 (br s, 1H), 7.78 (s, 4H), 7.50 (d, *J* = 6.6 Hz, 1H), 7.42-7.38 (m, 2H), 7.29 (s, 1H), 7.10 (s, 2H), 7.00 (s, 2H), 2.42 (s, 6H), 2.36 (s, 12H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 146.0, 137.9, 130.9, 130.1, 124.0, 123.1, 123.0, 118.4, 118.2, 110.9, 21.2, 20.9; FT-IR (KBr) 3432, 2919, 2858, 2109, 1631, 1605 1539, 1467, 1389, 1318, 1284, 1271, 1230, 1122, 854, 798 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2SH$ 269.1112, found 269.1112.



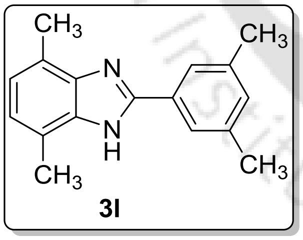
3j

2-(3,5-Dimethylphenyl)-6-(trifluoromethyl)-1*H*-benzo[d]imidazole 3j. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; liquid; 90 mg, yield 62%. mixture of tautomers (1:1): ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.27 (br s, 1H), 13.26 (br s, 1H), 7.99 (s, 1H), 7.83-7.80 (s, 6H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53-7.51 (m, 2H), 7.18 (s, 2H), 2.38 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.4, 153.9, 146.2, 143.2, 138.2, 137.4, 136.9, 132.0, 131.9, 129.3, 128.0, 124.5, 124.2, 122.8, 122.6, 122.4, 119.4, 119.0, 118.4, 116.0, 112.2, 108.7, 20.9; FT-IR (neat) 3420, 2922, 2853, 2808, 2648, 1631, 1606, 1544, 1463, 1422, 1333, 1249, 1156, 1120, 1065, 857 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}F_3N_2H$ 291.1109, found 291.1106.



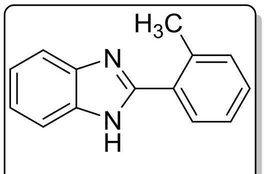
3k

2-(3,5-Dimethylphenyl)-4,6-dimethyl-1*H*-benzo[d]imidazole 3k. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.46; white solid; 89 mg, yield 71%; mp 232-238 °C. mixture of tautomers (1:0.6); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.56 (br s, 1H), 12.30 (br s, 1H), 7.85 (s, 2H), 7.77 (s, 2H), 7.23 (s, 1H), 7.10 (d, *J* = 6.0 Hz, 3H), 6.82 (d, *J* = 8.4 Hz, 2H), 2.52-2.50(m, 6H), 2.38-2.37 (m, 18H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.0, 148.5, 141.3, 137.8, 137.7, 131.4, 130.9, 130.8, 130.3, 127.7, 124.5, 124.3, 123.9, 123.4, 115.8, 108.3, 21.3, 20.9, 17.0, 16.5; FT-IR (neat) 3434, 2918, 2858, 2111, 1606, 1531, 1464, 1393, 1363, 1324, 1275, 1086, 854, 839 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_2H$ 251.1548, found 251.1550.



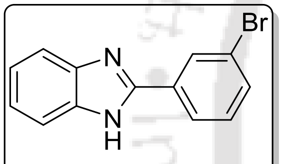
3l

2-(3,5-Dimethylphenyl)-4,7-dimethyl-1*H*-benzo[d]imidazole 3l. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; white solid; 80 mg, yield 64%; mp 276-280 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.40 (br s, 1H), 7.85 (s, 2H), 7.09 (s, 1H), 6.84 (s, 2H), 2.50-2.48 (m, 6H), 2.36 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.1, 138.4, 137.5, 131.5, 130.4, 126.5, 124.8, 122.9, 21.3, 17.1; FT-IR (neat) 3434, 2856, 2106, 1606, 1540, 1457, 1410, 1377, 1362, 1325, 1279, 1098, 1017, 854, 805, 733 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_2H$ 251.1548, found 251.1537.



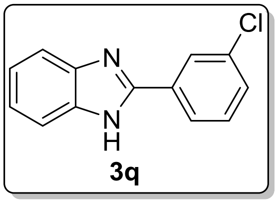
3n

2-(o-Tolyl)-1*H*-benzo[d]imidazole 3n. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; white solid; 65 mg, yield 62%; mp 224-230 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 12.64 (br s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.40-7.36 (m, 3H), 7.23-7.19 (m, 2H) 2.61 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 151.3, 138.2, 130.5, 130.1, 128.9, 127.0, 123.6, 122.1, 21.1; FT-IR (KBr) 3431, 3049, 2959, 2923, 1541, 1490, 1463, 1448, 1406, 1369, 1314, 1275, 1098, 750,742 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1084.



3p

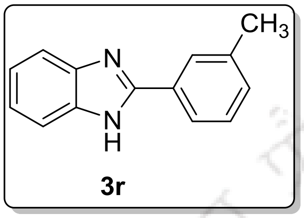
2-(3-Bromophenyl)-1*H*-benzo[d]imidazole 3p. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; White solid; 71 mg, yield 52%; mp 240-246 °C.^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.06 (br s, 1H), 8.37 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.70-7.67 (m, 2H), 7.56-7.51 (m, 2H), 7.25-7.21 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 149.6, 143.6, 135.0, 132.5, 132.4, 131.2, 128.9, 125.4, 123.0, 122.3, 122.0, 119.1, 111.5; FT-IR (KBr) 3437, 3065, 3043, 2958, 2921, 2113, 1622, 1590, 1565, 1440, 1400, 1361, 1283, 1120, 1072, 974, 680 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0034.



3q

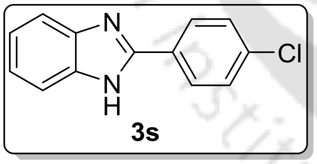
2-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazole 3q. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; white solid; 65 mg, yield 57%; mp 232-240 °C. ^{1}H NMR (400

MHz, DMSO-d_6) δ 13.06 (br s, 1H), 8.22 (s, 1H), 8.15 (d, *J* = 6.8 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.61-7.54 (m, 3H), 7.26-7.19 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.8, 143.6, 135.0, 133.8, 132.2, 131.0, 129.6, 126.0, 125.1, 123.0, 122.0, 119.1, 111.6; FT-IR (KBr) 3442, 3068, 3045, 1962, 2921, 1602, 1571, 1489, 1465, 1442, 1316, 1080, 1010,894, 744 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9ClN_2$ H 229.0533, found 229.0542.



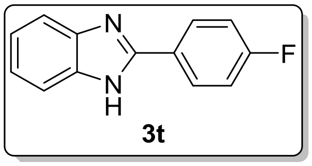
3r

2-(m-Tolyl)-1*H*-benzo[d]imidazole 3r. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; white solid; 71 mg, yield 68%; mp 221-228 °C.^{1}H NMR (600 MHz, DMSO-d_6) δ 12.86 (br s, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.58 (s, 2H), 7.44 (t, *J* = 7.2 Hz, 1H) 7.31 (d, *J* = 7.2 Hz, 1H), 7.20-7.19 (m, 2H) 2.41 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.9, 143.7, 137.0, 134.4, 131.3, 130.1, 129.4, 129.3, 126.0, 122.4, 121.4, 118.9, 111.3, 21.0; FT-IR (KBr) 3435, 3051, 2922, 2853, 1610, 1590, 1538, 1488, 1446, 1400, 1359, 1313, 1274, 1226, 794, 742 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1082.



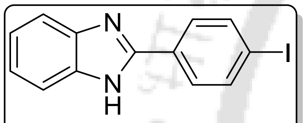
3s

2-(4-Chlorophenyl)-1*H*-benzo[d]imidazole 3s. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; White solid; 65 mg, yield 57%; mp 282-290 °C.^{1}H NMR (600 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 3H), 7.55 (s, 1H), 7.22 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.2, 143.7, 134.6, 129.1, 129.0, 128.2, 122.8, 121.9, 119.0, 111.5; FT-IR (KBr) 3439, 3052, 2922, 2851, 2115, 1622, 1602, 1586, 1448, 1429, 1273, 1225, 1089, 831, 746 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9ClN_2H$ 229.0533, found 229.0535.



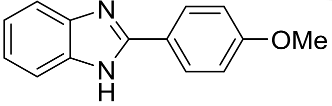
3t

2-(4-Fluorophenyl)-1_H_-benzo[d]imidazole 3t. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; yellow solid; 136 mg, yield 64%; mp 241−242 °C.^{1}H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.22 (m, 2H), 7.66 (m, 1H), 7.53 (m, 1H), 7.40 (m, 2H), 7.20 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.1 ($^1J_{C\text{-}F}$ = 248.5 Hz), 150.4, 143.8, 135.0, 128.7 ($^3J_{C\text{-}F}$ = 8.2 Hz), 126.8, 122.6, 121.7, 118.8, 116.0 ($^3J_{C\text{-}F}$ = 21.7 Hz), 111.3; FT-IR (KBr) 3443, 3053, 2917, 2853, 2113, 1603, 1497, 1476, 1452, 1433, 1397, 1276, 1229, 1157, 1111, 967, 838 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9FN_2H$ 213.0828, found 213.0821.



3u

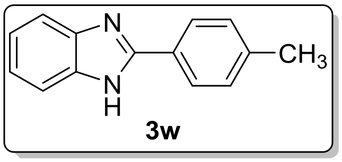
2-(4-Iodophenyl)-1_H_-benzo[d]imidazole 3u. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid ; 82 mg, yield 51%; mp 276-282 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 7.96-7.92 (m, 4H), 7.67 (d, _J_ = 7.8 Hz, 1H), 7.53 (d, _J_ = 7.8 Hz, 1H), 7.24-7.19 (m, 2H).^{13}C NMR (150 MHz, $CDCl_3$+DMSO-d_6) δ 160.9, 150.5, 137.9, 129.8, 128.4, 96.8; FT-IR (KBr) 3428, 2958, 2925, 2854, 2256, 2128, 1647, 1464, 1048, 1025, 999, 826, 765 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_9IN_2H$ 320.9889, found 320.9889.



3v

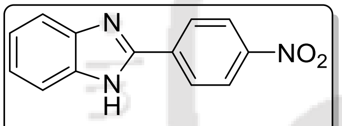
2-(4-Methoxyphenyl)-1_H_-benzo[d]imidazole 3v. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; white solid; 77 mg, yield 69%; mp 220-223 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.73 (br s, 1H), 8.12 (d, _J_ = 8.4 Hz, 2H), 7.62 (d, _J_ = 7.2 Hz, 1H), 7.49 (d, _J_ = 7.2 Hz, 1H), 7.18-7.15 (m, 2H), 7.12 (d, _J_ = 8.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.6, 151.3, 128.0, 122.7, 122.0, 121.4, 118.5, 114.3, 111.0, 55.3; FT-

IR (KBr) 3430, 3054, 2923, 2854, 1611, 1499, 1476, 1453, 1435, 1294, 1254, 1232, 1033, 965, 745 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{12}N_2OH$ 225.1028, found 225.1025.



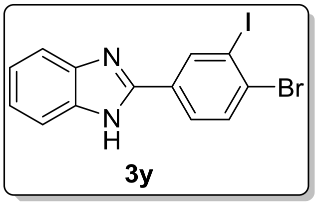
3w

2-(p-Tolyl)-1*H*-benzo[d]imidazole 3w. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 70 mg, yield 67%; mp 248-252 °C.^{1}H NMR (600 MHz, DMSO-d_6) δ 12.84 (br s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H),7.51 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.20-7.17 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.5, 139.8, 129.7, 127.4, 126.5, 122.2, 115.1, 21.1; FT-IR (KBr) 3432, 3052, 2919, 2854, 1621, 1588, 1500, 1475, 1448, 1430, 1398, 1317, 1274, 1122, 821, 747 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1085.



3x

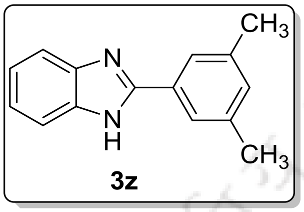
2-(4-Nitrophenyl)-1*H*-benzo[d]imidazole 3x. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane; R_f = 0.35; White solid; 67 mg, yield 56%; mp 264-268 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.31 (br s, 1H), 8.41 (s, 4H), 7.71 (s, 1H), 7.62 (s, 1H), 7.27 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.2, 148.1, 136.1, 127.6, 124.5, 123.9, 122.7, 119.6, 112.1; FT-IR (KBr) 3430, 2658, 2115, 1658, 1610, 1520, 1435, 1343, 1296, 1115, 1010, 962, 844, 736 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9N_3O_2H$ 240.0773, found 240.0779.



3y

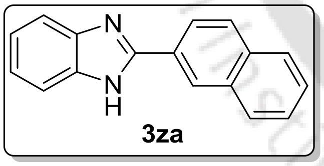
2-(4-Bromo-3-iodophenyl)-1*H*-benzo[d]imidazole 3y. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; White solid; 86 mg, yield 43%; mp 282-288 °C. ^{1}H NMR

(600 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.72 (d, J = 1.8 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.26-7.20 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.7, 137.4, 133.2, 130.7, 130.4, 127.6, 123.1, 122.0, 120.8, 119.1, 111.5, 102.7;FT-IR (KBr) 3436, 2924, 2853, 1622, 1423, 1316, 1279, 1227, 1107, 1009, 968, 821, 740 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_8BrIN_2H$ 398.8994, found 398.8994.



3z

2-(3,5-Dimethylphenyl)-1*H*-benzo[d]imidazole 3z. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; white solid; 75 mg, yield 68%; mp 256-260 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 7.81 (s, 2H), 7.63 (s, 1H), 7.51 (s, 1H), 7.19 (s, 2H), 7.12 (s, 1H), 2.37 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.4, 143.8, 138.0, 134.9, 131.2, 130.0, 124.2, 122.3, 121.5, 118.7, 111.2, 20.9; FT-IR (KBr) 3435, 3051, 2962, 2918, 2855, 1605, 1535, 1465, 1446, 1405, 1361, 1323, 1272, 1020, 912, 741 cm^{-1}. HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1231



3za

2-(Naphthalen-2-yl)-1*H*-benzo[d]imidazole 3za. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; yellow solid; 94 mg, yield 79%; mp 190−191 °C. mixture of tautomers (1.5:1): ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.13 (br s, 2H), 8.76 (m, 1H), 8.73 (m, 1H), 8.35-8.30 (m, 2H), 8.08-8.05 (m, 3H), 7.97 (m, 3H), 7.65-7.59 (m, 8H), 7.24 (m, 3H), 7.00-6.99 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.3, 133.5, 133.4, 132.8, 132.7, 128.6, 128.5, 128.48, 128.4, 127.8, 127.6, 127.3, 127.2, 127.1, 127.0, 126.9, 125.9, 125.8, 124.0, 123.9, 122.2; FT-IR (KBr) 3451, 3055, 2110, 1654, 1590, 1546, 1504, 1482, 1405, 1335, 1282, 1138, 1093, 1009, 939, 818 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}N_2H$ 245.1079, found 245.1105.

4.5. References

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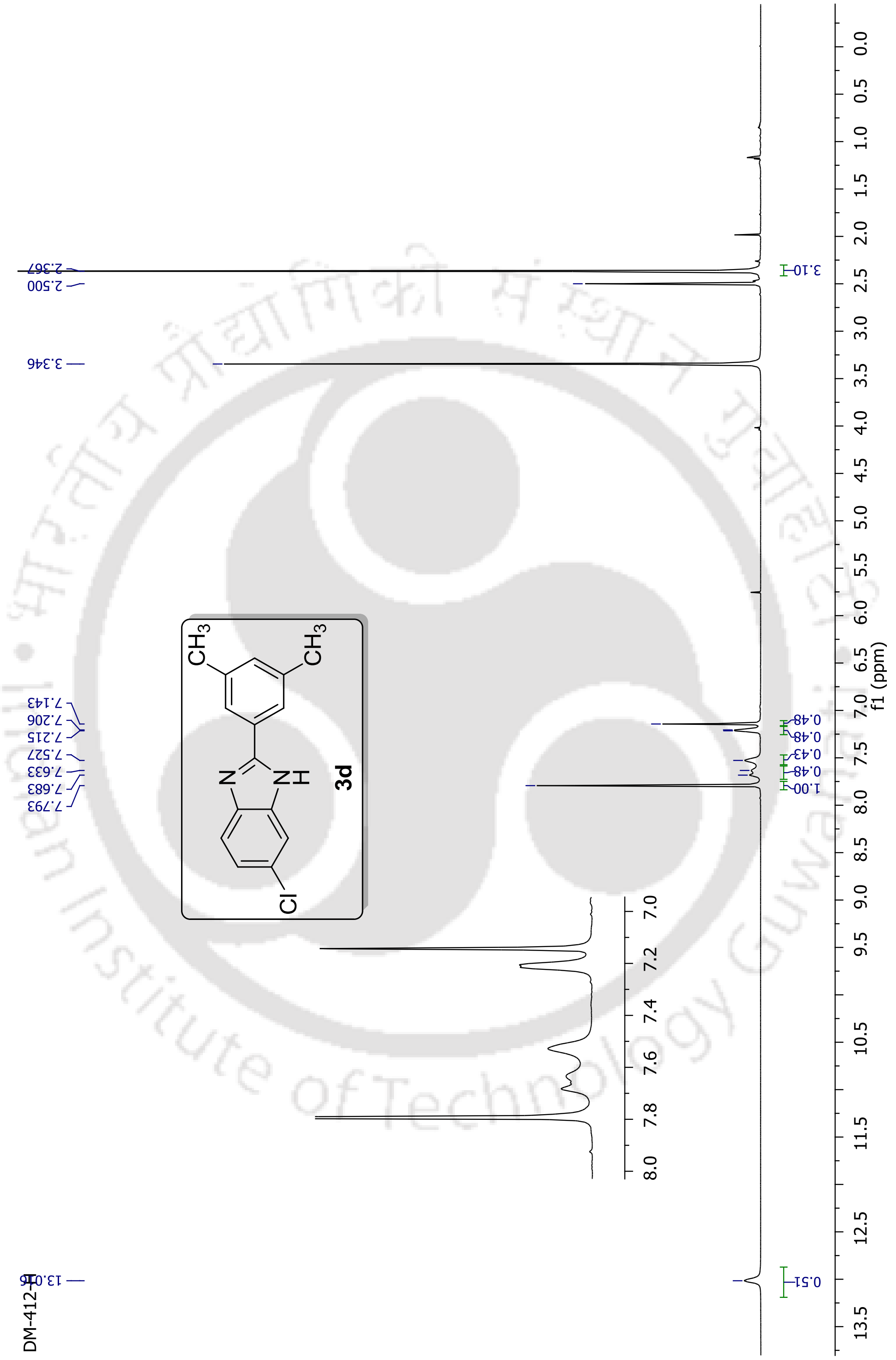
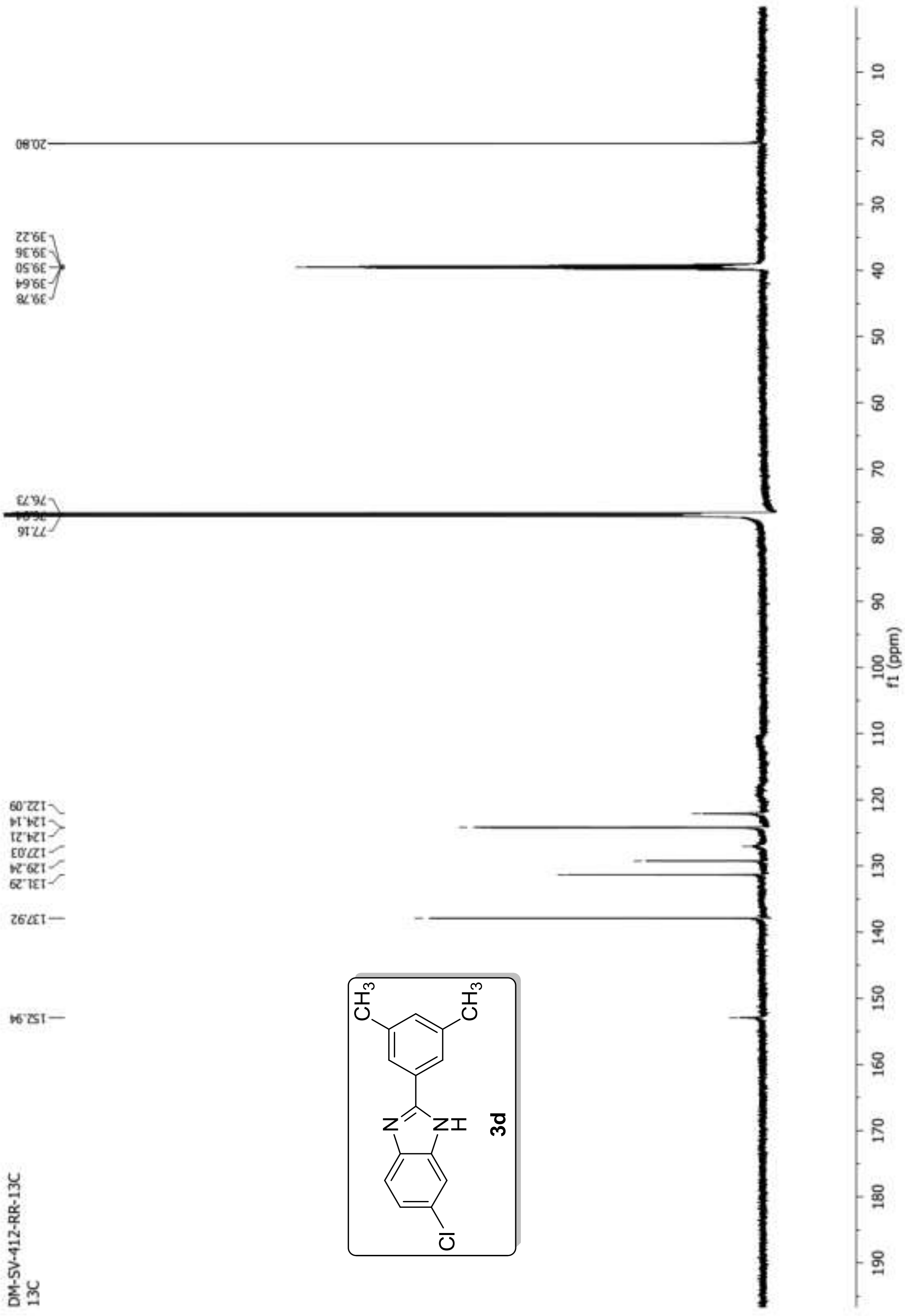
4.6. Selected NMR (^{1}H and ^{13}C) Spectra

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39.36
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39.64
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76.73
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122.09
124.14
124.21
127.03
129.24
131.29
137.92
152.94
CH3
CH3
N
NH
Cl
10
20
30
40
50
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70
80
90
100
110
120
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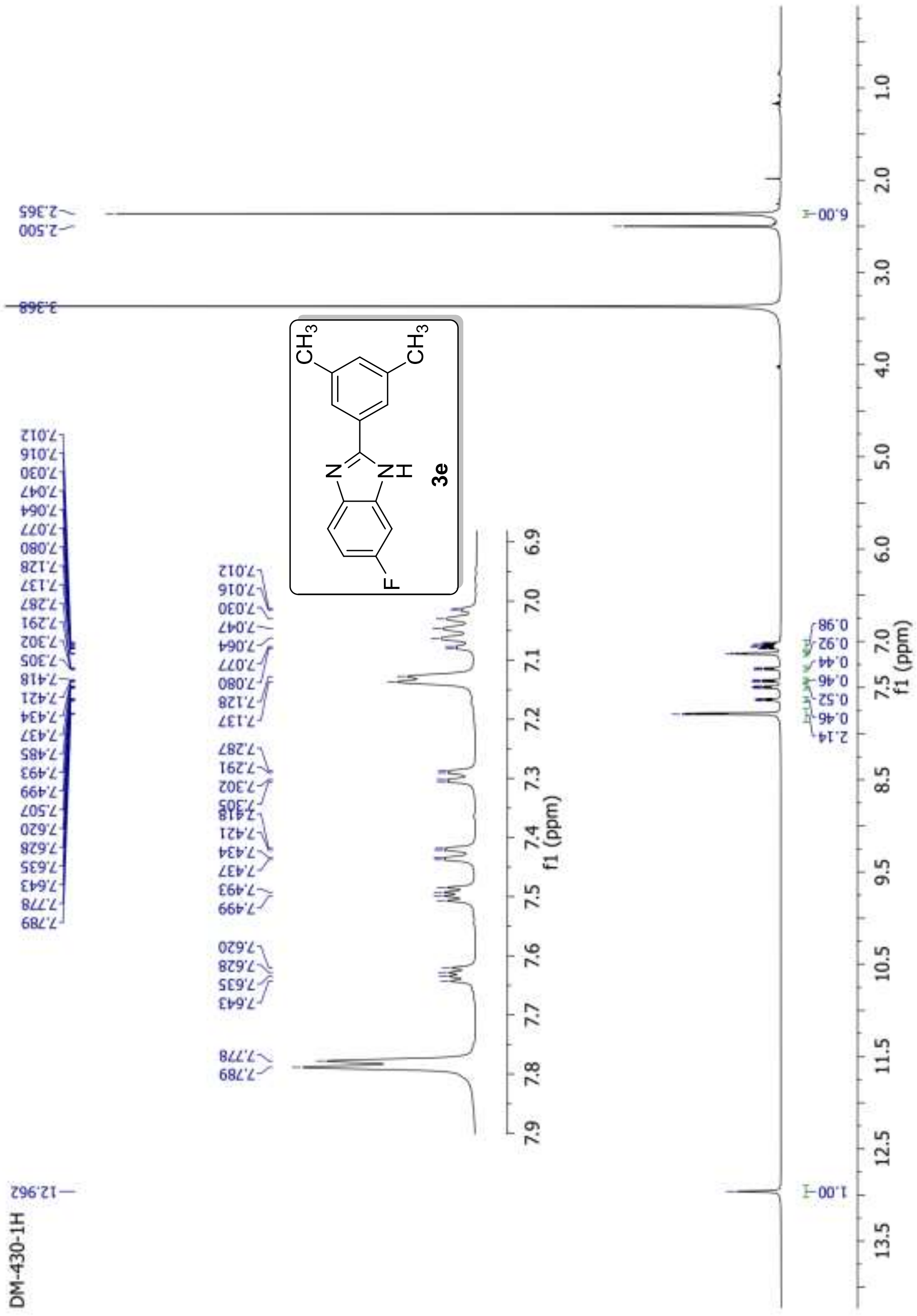
150
160
170
180
190
f1 (ppm)

3d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7.620
7.507
7.499
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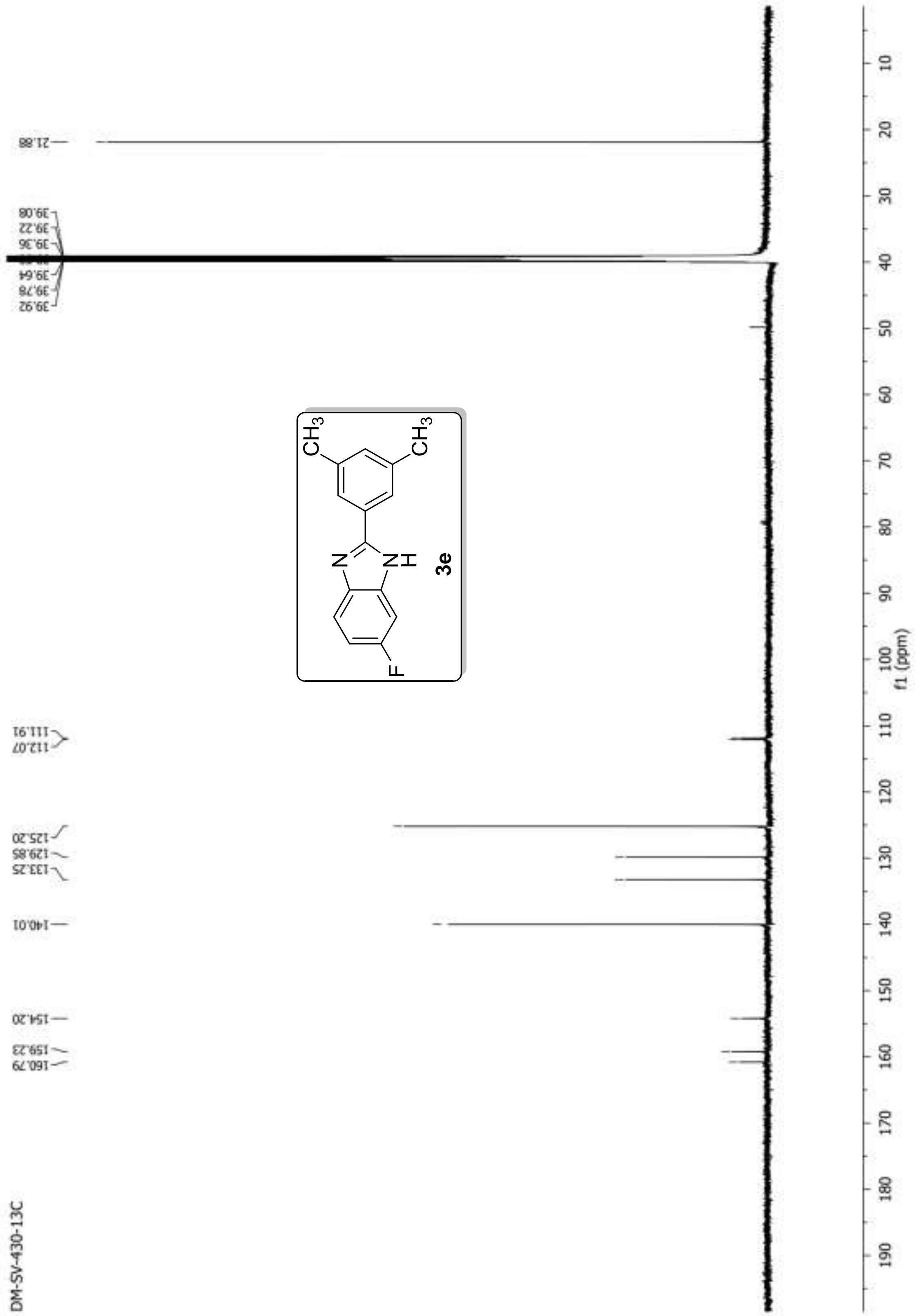
7.485
7.437
7.434
7.421
7.418
7.305
7.302
7.291
7.287
7.137
7.128
7.080
7.077
7.064
7.047
7.030
7.016
7.012
3.368
2.500
2.365
CH3
CH3
N
NH
F
3e
6.00
0.98
0.92
0.44
0.46
0.52
0.46
2.14
1.00
f1 (ppm)
1.0 2.0 3.0 4.0 5.0 6.0 7.0 7.5 8.5 9.5 10.5 11.5 12.5 13.5
6.9 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9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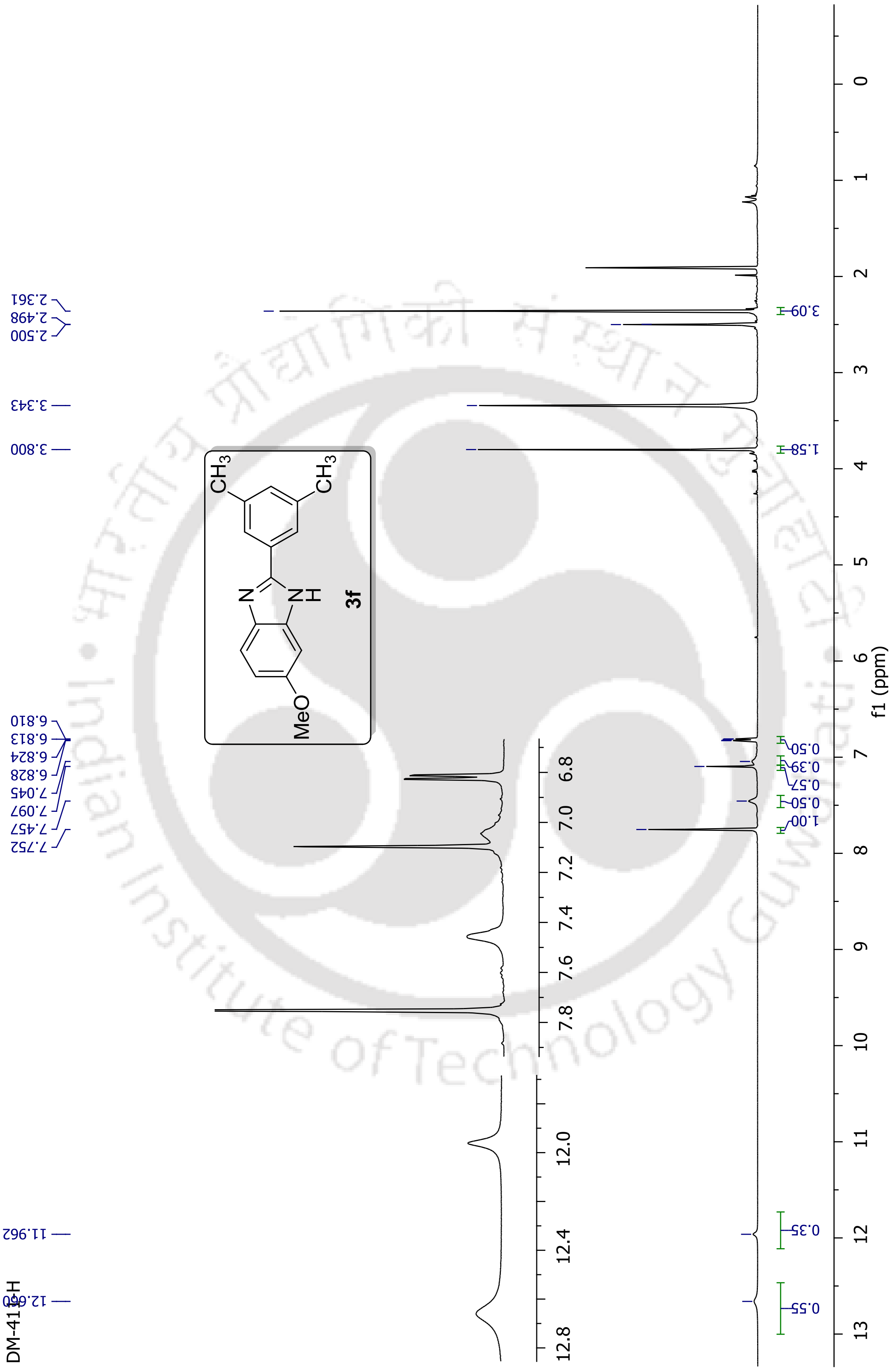
39.22
39.36
39.64
39.78
39.92
111.91
112.07
125.20
129.85
133.25
140.01
154.20
159.23
160.79
CH3
CH3
N
NH
F
3e
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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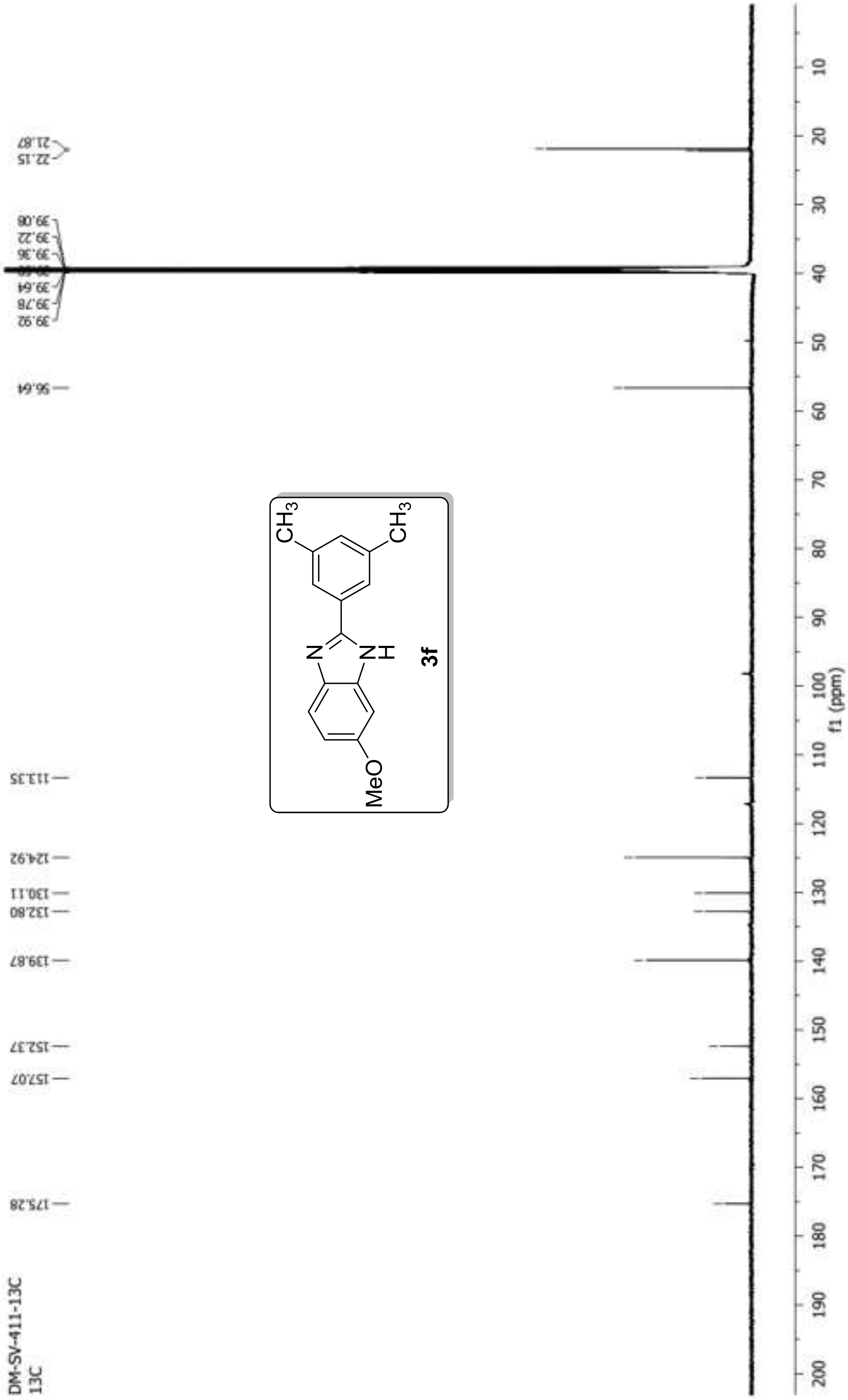
6.824
6.813
6.810
3.800
3.343
2.500
2.498
2.361
CH3
CH3
N
NH
MeO
3f
3.09
1.58
0.50
0.39
0.57
0.50
1.00
0.35
0.55
6.8
7.0
7.2
7.4
7.6
7.8
12.0
12.4
12.8
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)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39.22
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39.92
56.64
113.35
124.92
130.11
132.80
139.87
152.37
157.07
175.28
MeO
N
NH
CH3
CH3
3f
f1 (ppm)
10
20
30
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50
60
70
80
90
100
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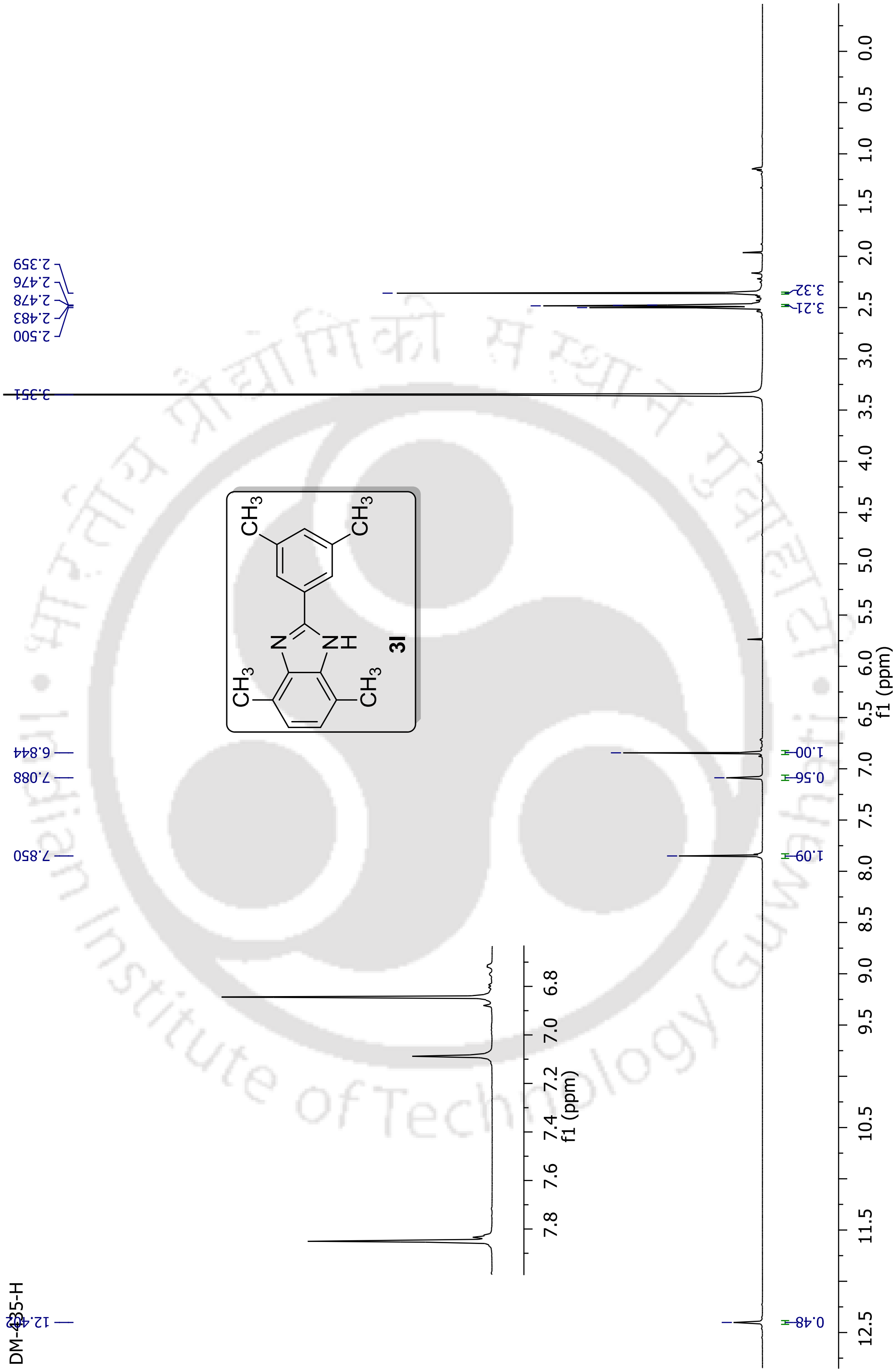
140
150
160
170
180
190
200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2.476
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0.48
1.09
0.56
1.00
3.21
3.32
CH3
CH3
N
NH
CH3
CH3
3l
f1 (ppm)
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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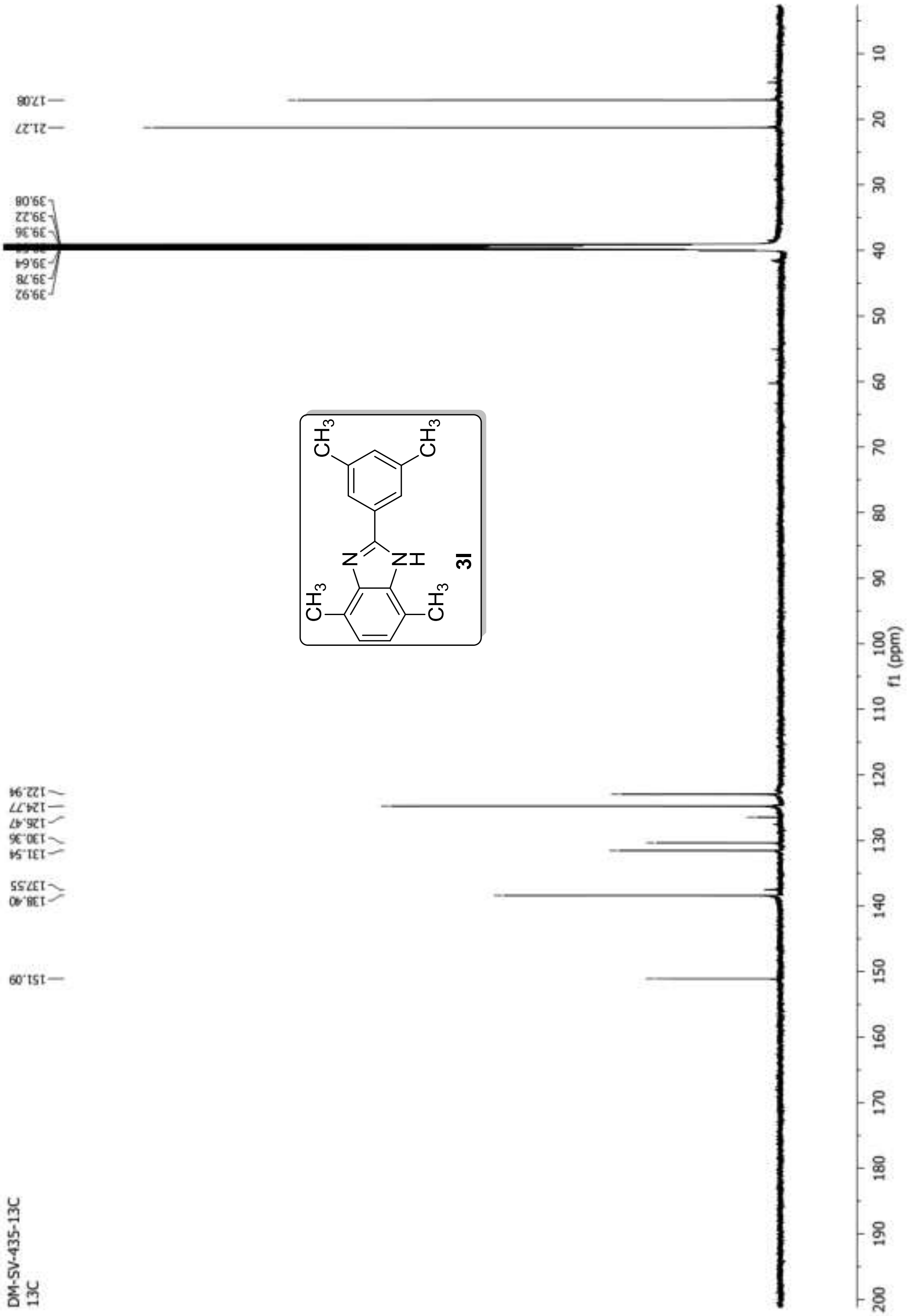
7.6
7.4
7.2
7.0
6.8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CH3
CH3
N
NH
3l
f1 (ppm)
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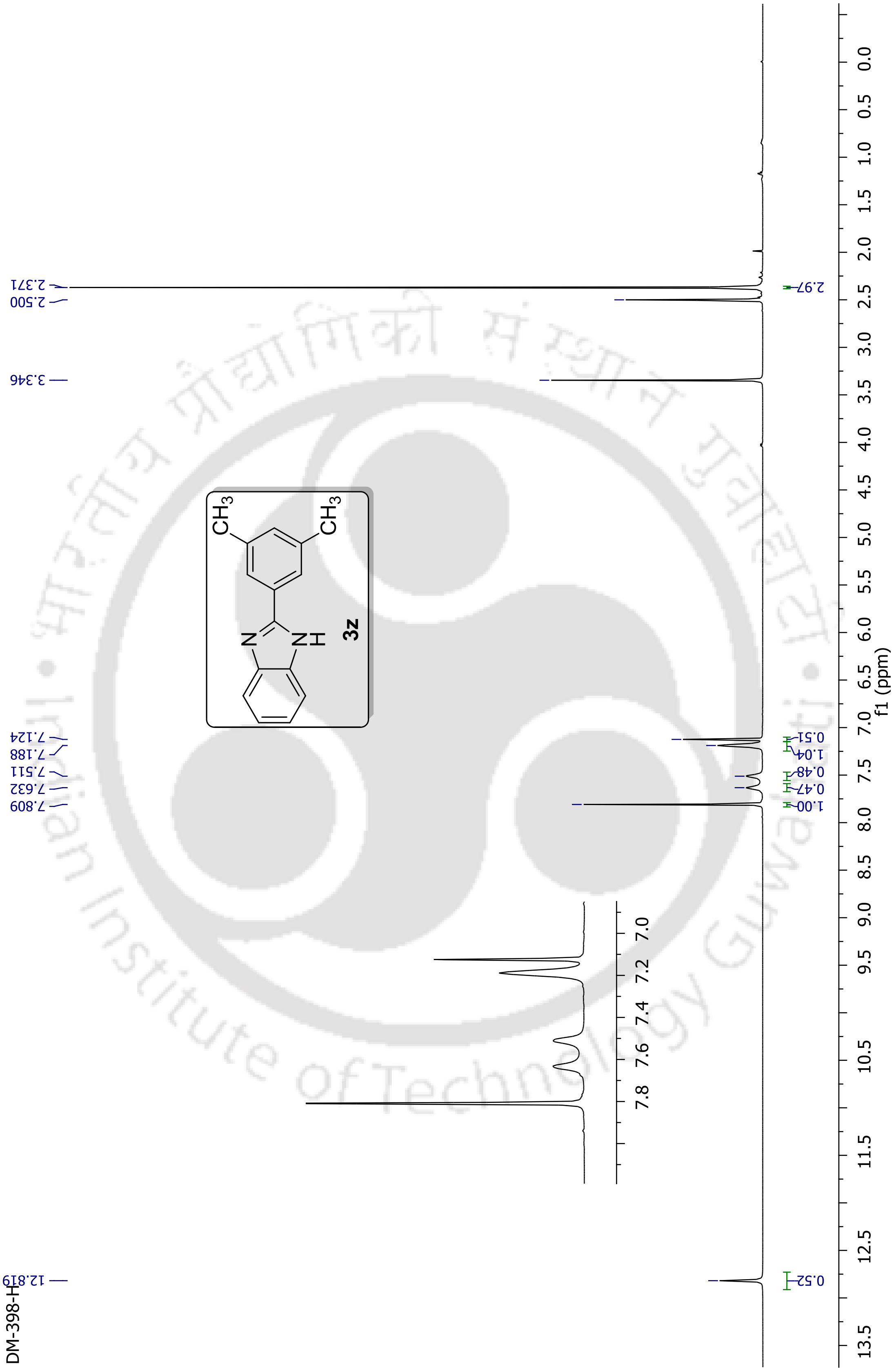
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0.47
1.00
0.52
CH$_3$
CH$_3$
N
NH
3z
7.0
7.2
7.4
7.6
7.8
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
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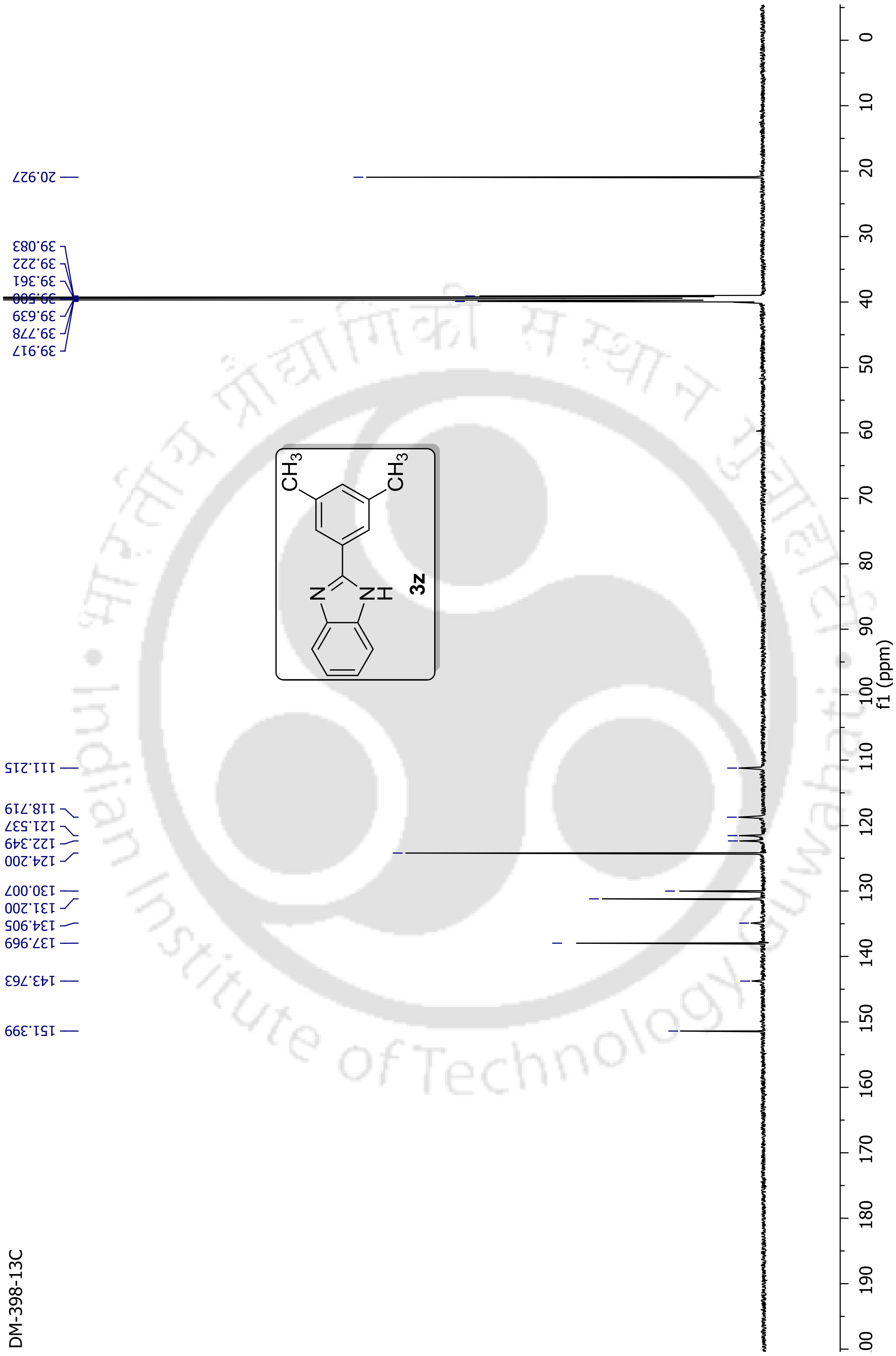
11.5
12.5
13.5
f1 (ppm)


20.927
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124.200
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131.200
134.905
137.969
143.763
151.399
DM-398-13C
CH3
CH3
N
NH
3z
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

Summary and Outlook

Benzimidazoles are previlaged structural scaffolds due to their interesting biological and medicinal properties. Benzimidazoles also find broad utilities in material chemistry. The development of experimentally simple and efficient synthetic methods using the readily available simple substrates is thus important in synthetic organic chemistry.

The chapter one covers the recent developments in the construction of benzimdiazoles. Considerable progress has been made using cross-coupling and C-H functionalization strategies. These approaches are attractive as they are effective at moderate temperarture with greater atom economy and broad substrate scope.

The chapter two describes the Cu-catalyzed oxidative three component coupling of anilines, aldehydes and $TMSN_3$ in the presence of TBHP at moderate temperature. The reaction of a series of anilines and aromatic as well as aliphatic aldehydes with $TMSN_3$ has been demonstrated. The reaction is quite general and the target products could be obtained in good yields. The mechanistic aspects has been demonstrated using kinetic isotope and radical scavanger studies.

The chapter three focuses on Cu-catalyzed oxidative three component coupling of anilines, benzylamines and NaN_3 in the presence of TBHP at moderate temeprature. The reaction of wide range of anilines and benzylamines with NaN_3 is demonstrated. The reaction involves a tandem transamination, C-H functionazation and C-N bond formation to produce the target products in good yields. The mechanistic investigation has been presented based on kinetic isotope and mass analysis of the intermediates.

The chapter four deals with the copper-catalyzed oxidative three component coupling of anilines, methyl arenes and $TMSN_3$ in the presence of TBHP to yield benzimidazoles. This reaction involves a multiples C-H functionalization and *C-N* bond formation. The reaction of a series of anilines and methyl arenes are demonstrated. The mechanistic investigation suggest that the reaction involves the formation of *N*-benzylamine followed oxidation to imine, *ortho*-selective azidation and intramolecular cyclization.

These studies provide an potenital synthetic tool to accomplish benzimidazoles with broad substrate scope and functinal group diversity from the simple substrate at moderate temperature. This study will open new avenue for the further development of regioslective multiple C-H functionalization of simple substrates to produce diverse nitrogen containing heterocycles.