Chapter I

A concise explanation about the perspective towards some production of biologically significant compounds with heterocyclic moiety

I.1. Introduction:

When cyclic compounds, composed of only 'C' (carbon) atoms, within the ring, they are nominated as Carbocyclic Compounds; whereas, the compounds, accommodating minimum one hetero atom, (other than carbon atoms), inside the ring, are elected as, Heterocyclic Compounds. The most well known heteroatoms are sulphur, oxygen and nitrogen. On the other hand, heterocyclic ring holding different heteroatoms including phosphorus, tellurium and selenium, are infrequently familior. About a half of whole organic chemistry research field conducted globally is focused on chemistry of heterocycles, which is also acknowledged as the foundation of traditional organic synthetic phenomenone. Moreover, they are essential to many different procedures and industrial firms. It is commonly recognized that heterocyclic frameworks, which serve as a crucial bridge across biology and chemistry, make up over 90% in newly developed pharmaceuticals. Heterocyclic substances are largely responsible for this inventiveness and advancement of fresh scientific paradigms. **Figure I.1.** lists certain heterocyclic units with one or more heteroatoms and ring skeletons of five or six members that have been documented in the scientific literature.

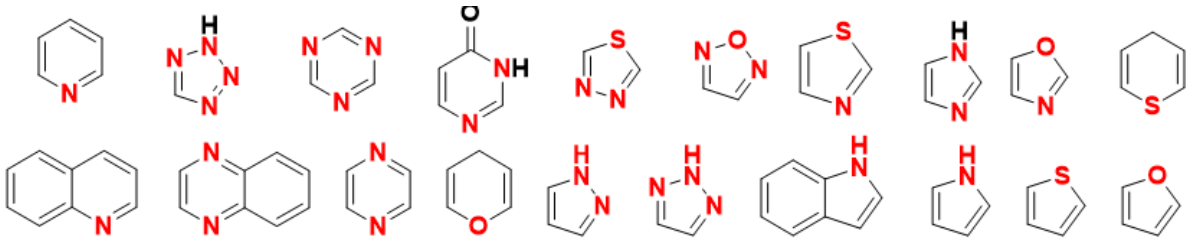


Figure I.1.: Some known five and six membered heterocyclic skeleton

Likewise, heterocyclic subunits have become extremely important for the functioning of any civilized human community in addition to being important in biology and industry. The Heterocycles make up the majority of pharmaceutical drugs that have biological consequences and resemble natural compounds. As a result, scientists are always exploring new ideas and by employing ecological models as a guide, scientists can create more effective medications, rodenticides, insecticides, and weed-killing agents. Heterocyclic substances are essential to biological functions and are necessary components of live cells. Such substances also have important and practical uses as adjusters and preservatives in a wide range of industries, such as

solvents, plastics, vulcanizing acceleration devices, reprography, makeup, and database storage. In addition, they are thought to be strong building blocks for the synthesis of naturally obtainable chemicals with biological activity such as amino acids, glycosides, organically abundant heterocyclic materials, etc. Additionally, they can be widely employed as ligands in the production of several catalysts, (composed of transition metals), which are then utilized in the manufacture of numerous organic molecules, especially compounds with heterocyclic structure.

In the pharmaceutical industry, heterocyclic analogues are widely employed as a crucial instrument in the skeletal manufacturing of many medications. An effective process for the synthesis of novel heterocyclic moieties is always important. As to an overview of the literature, over 85–95% of newly developed medications incorporate heterocyclic compounds that offer valuable scientific insights into the functioning of the biological framework. The most varied physical, chemical, and biological features can be created by combining an enormous quantity of heteroatoms, hydrogen, and carbon atoms to create substances. Over two thirds of the twenty million different chemical substances discovered by the close of the second millennium are either entirely or partly aromatic, with roughly fifty percent being heteroaromatic. Therefore, it is simple to see why the area of organic synthetic chemistry is still driven by the advancement of new techniques as well as the tactical application of established techniques for the production of more complex heterocyclic molecules. To create these heterocyclic molecules, organic chemists have worked hard to create novel, effective synthetic mechanisms.
In this **Figure I.2.**, some biologically active molecules with five and six membered heterocyclic moieties have been represented.

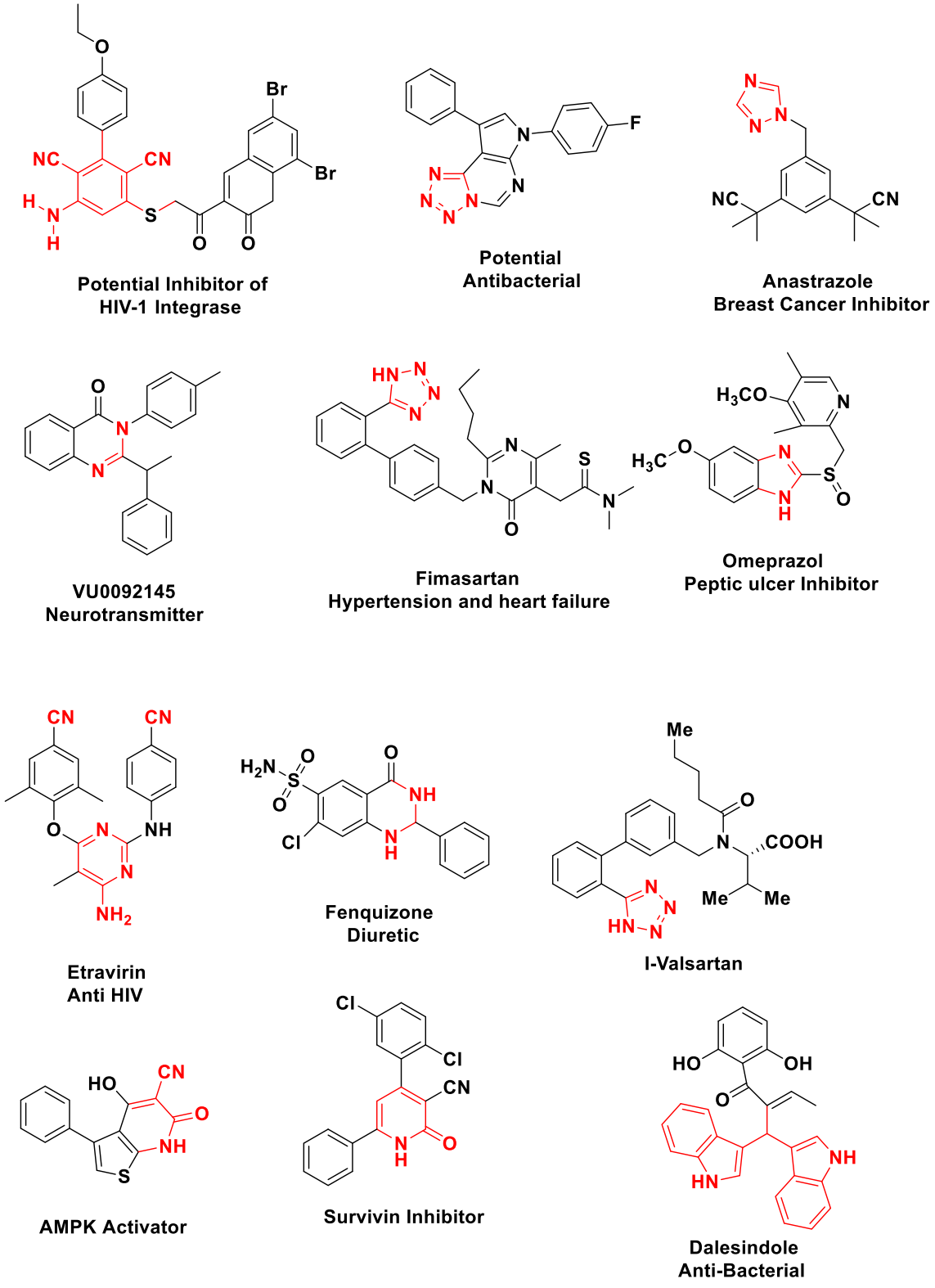
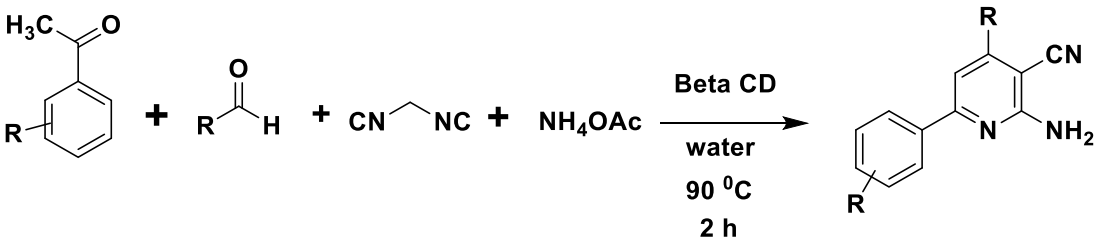


Figure I.2.: Some Biologically active molecules with five and six membered heterocyclic moieties

I.2. Methodology for the production of heterocyclic materials:

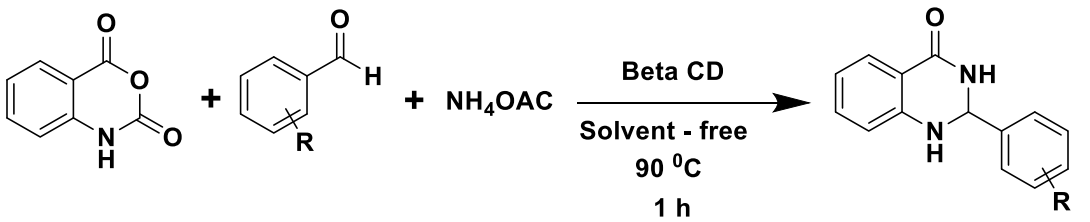
Numerous techniques for synthesizing heterocyclic substances including nitrogen, oxygen, sulfur, and selenium have been documented in the scientific community. In this part, an in-depth investigation has been conducted.

I.2.1. One - pot four - component reaction of aromatic aldehydes, acetophenone, malononitrile and ammonium acetate was carried out in a round-bottom flask to synthesize functionalized 2-amino-4, 6-diphenylnicotinonitrile by B. Mitra et al. in 2021 **(Scheme I.1.).** This reaction proceeds in presence of supramolecular recyclable β-Cyclodextrin catalyst and water solvent under 90 ^{0}C, for 2 hours. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[1]



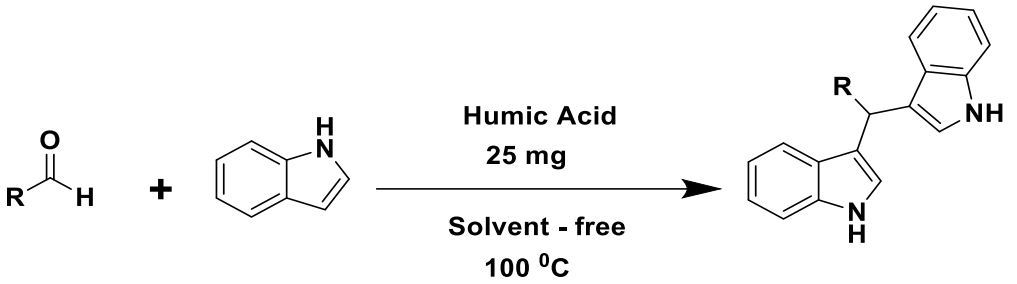
Scheme I.1. : One-pot four-component synthesis of functionalized 2-amino-4, 6-diphenylnicotinonitrile.[1]

I.2.2. One - pot three - component reaction of aromatic aldehydes, isatoic anhydride, and ammonium acetate was carried out to synthesize functionalized 2, 3-dihydroquinazolin-4(1H)-one by B. Mitra et al. in 2021 **(Scheme I.2.).** This reaction proceeds in presence of supra molecular recyclable β-Cyclodextrin catalyst under solvent – free condition at 90 ^{0}C, for 1 hour. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[1]



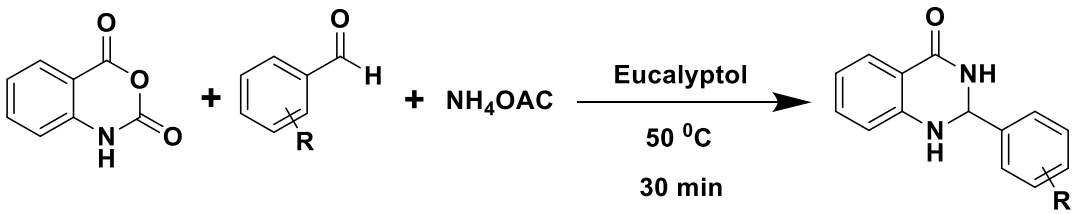
Scheme I.2. : One-pot three-component synthesis of functionalized 2, 3-dihydroquinazolin-4(1H)-one[1]

I.2.3. Two - component reaction of aromatic aldehydes and indole was carried out to synthesize some diversified bis(indolyl)methane by B. Mitra et al. in 2021 **(Scheme I.3.).** This reaction proceeds in presence of 25 gm macro sized recyclable Humic Acid catalyst under solvent – free condition at 100 ^{0}C, for 3 hours. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[2]



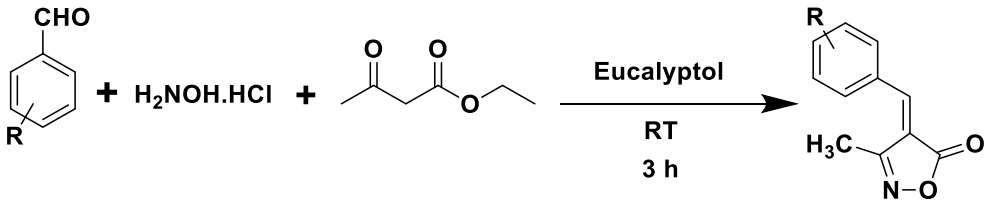
Scheme I.3. : Two - component synthesis of some diversified bis(indolyl)methane[2]

I.2.4. One - pot three - component reaction of aromatic aldehydes, isatoic anhydride, and ammonium acetate was carried out to synthesize functionalized 2, 3-dihydroquinazolin-4(1H)-one by T. Kundu et al. in 2023 **(Scheme I.4.).** This reaction was mediated through greener eucalyptol solvent under metal – free condition at 50 ^{0}C, for 30 min. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[3]



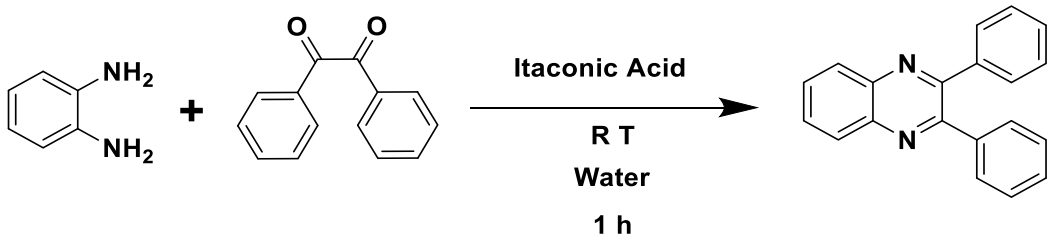
Scheme I.4. : One-pot three-component synthesis of functionalized 2, 3-dihydroquinazolin-4(1H)-one[3]

I.2.5. One - pot three - component reaction of aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride was carried out to synthesize isoxazolone derivatives by T. Kundu et al. in 2023 **(Scheme I.5.).** This reaction was mediated through greener eucalyptol solvent under metal – free condition at room temperature, for 3 hours. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[3]



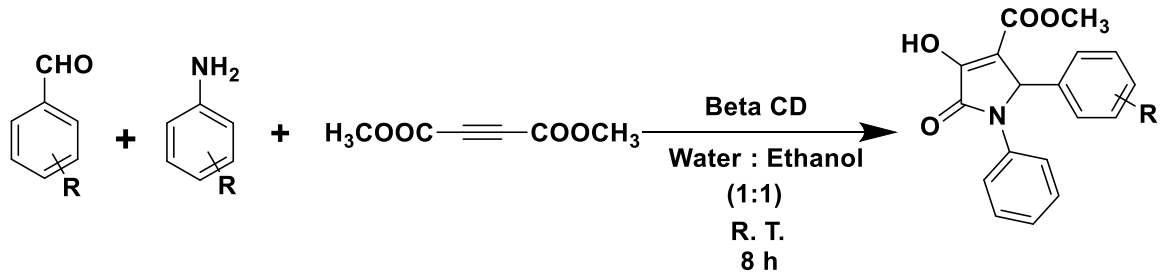
Scheme I.5. : One-pot three-component synthesis of isoxazolone derivatives[3]

I.2.6. Two - component reaction of o-phenylenediamine and benzil was carried out to synthesize some substituted quinoxaline derivatives by K. J. Tamuli et al. in 2021 **(Scheme I.6.).** This reaction proceeds in presence of cheap and biodegradable itaconic acid as a mild acid promotor under the presence of water solvent at room temperature, for 1 hour through cyclo condensation process. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[4]



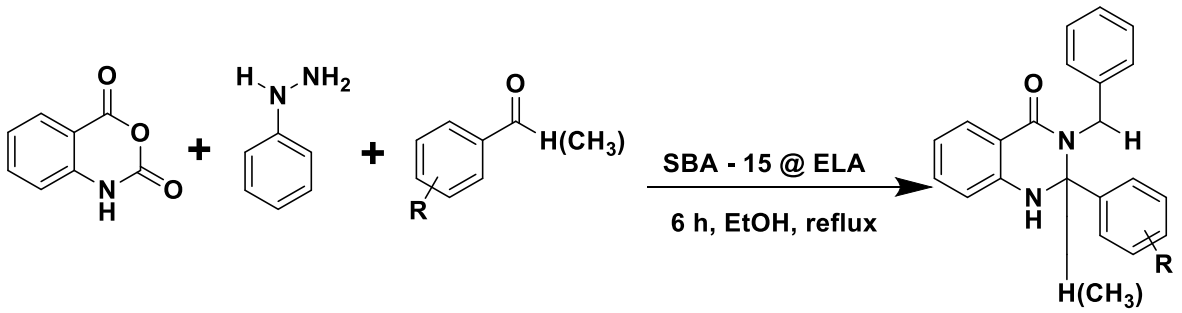
Scheme I.6. : Two - component synthesis of substituted quinoxaline derivatives[4]

I.2.7. One - pot three - component reaction of aromatic aldehydes, aniline, and dimethylacetylenedicarboxylate was carried out to synthesize methyl 2-aryl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate derivatives by S. Paul et al. in 2023 **(Scheme I.7.).** This reaction was mediated through greener supra molecular β-Cyclodextrin catalyst under metal – free condition, in presence of 1:1 water – ethanol solvent at room temperature, for 8 hours. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[5]



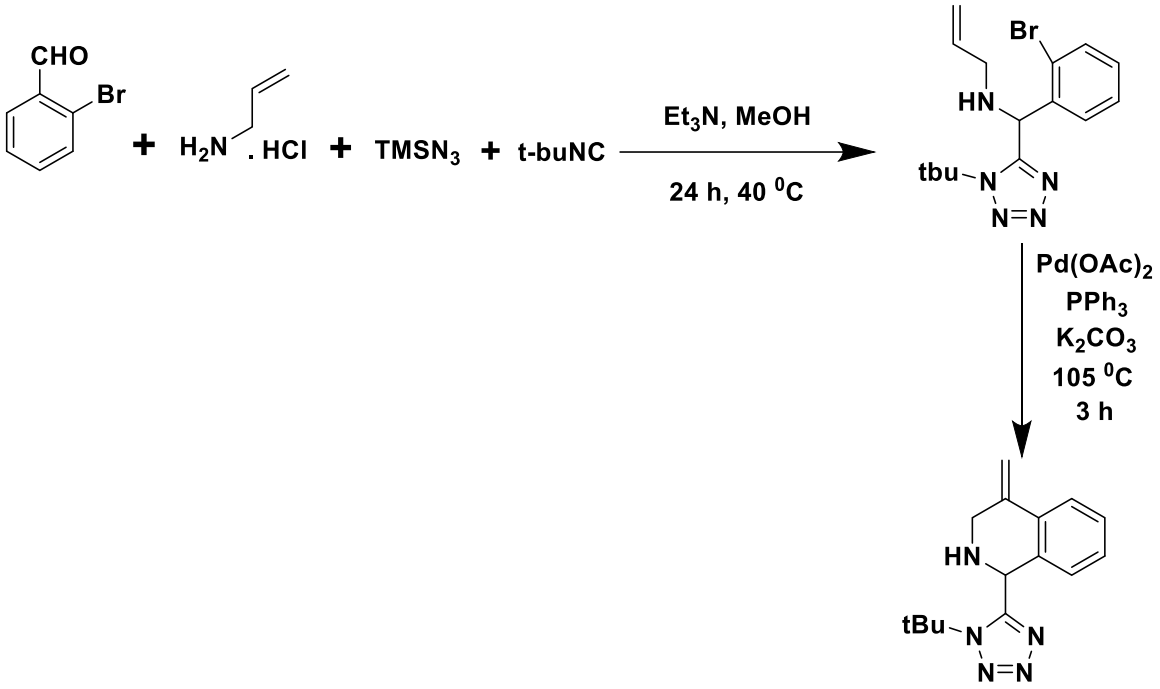
Scheme I.7. : One-pot three-component synthesis of 2-aryl-4-hydroxy-5-oxo-1-phenyl-2, 5-dihydro-1H-pyrrole-3-carboxylate derivatives[5]

I.2.8. One - pot three - component reaction of isatoic anhydride, phenyl hydrazine, and aromatic aldehydes or acetophenone derivatives was carried out to synthesize 4-oxo-dihydroquinazolinone derivatives by N. M. Yazdi et al. in 2024 **(Scheme I.8.).** This reaction was mediated through SBA-15@ELA nano catalyst under reflux condition, in presence of ethanol solvent for 6 hours. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[6]



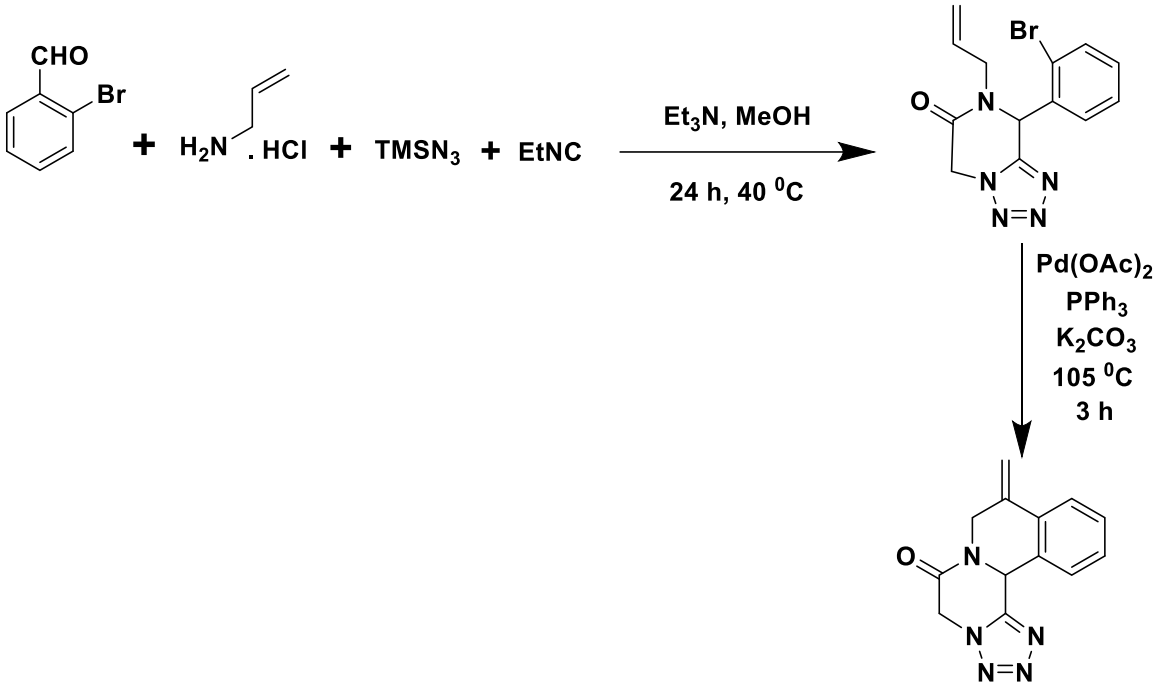
Scheme I.8. : One-pot three-component synthesis of 4-oxo-dihydroquinazolinone derivatives[6]

I.2.9. One - pot four – component Ugi reaction followed by intra molecular Heck reaction of 2-bromobenzaldehyde, allylamine hydrochloride, trimethylsilyl azide and *tert*-butyl isocyanide derivatives was carried out to synthesize functionalized tetrazolyl-1,2,3,4-tetrahydroisoquinolines by J. Niu et al. in 2024 **(Scheme I.9.).** This Ugi reaction was mediated through Et_3N in 5 mL MeOH, at 40 ^{0}C, for 24 hours and Heck reaction was carried out by dissolving in MeCN solvent, $Pd(OAc)_2$ catalyst, PPh_3 and K_2CO_3 reagent for 3 hours at 105 °C under N_2 atmosphere. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[7]



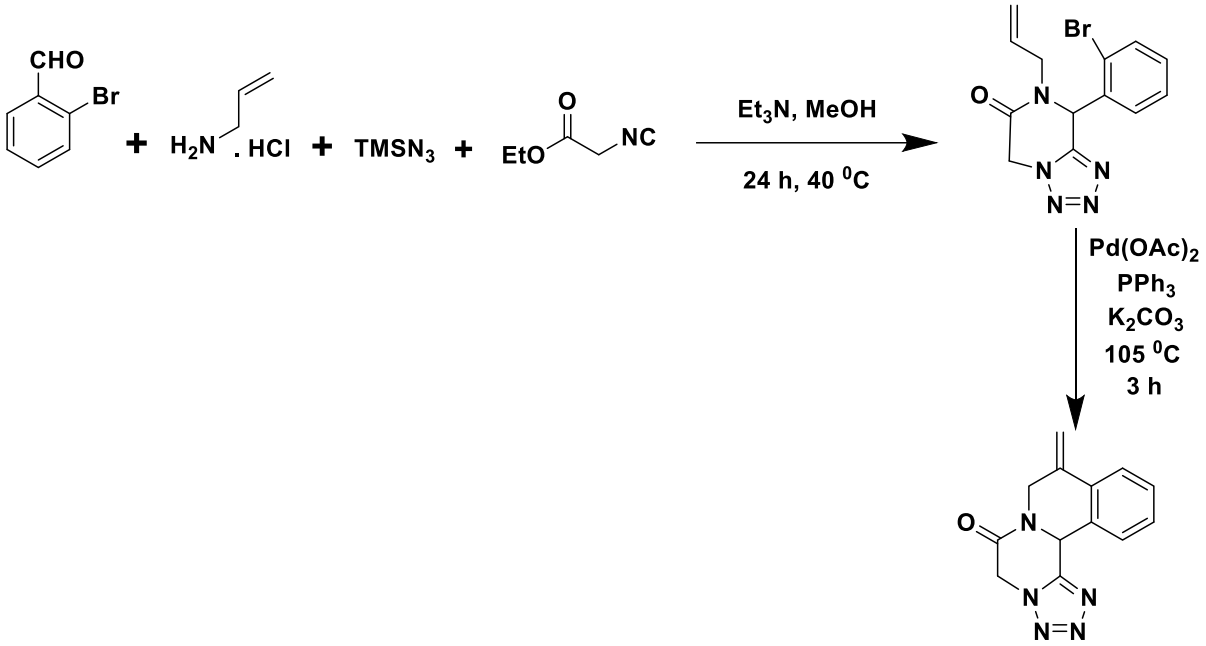
Scheme I.9. : One-pot four-component synthesis of functionalized tetrazolyl-1, 2, 3, 4-tetrahydroisoquinolines[7]

I.2.10. One - pot four – component Ugi reaction of 2-bromobenzaldehyde, allylamine hydrochloride, trimethylsilyl azide and Ethyl isocyanide derivatives was carried out to synthesize tetrazolo[1,5-*a*]pyrazin-6(5*H*)-one derivatives, followed by intra molecular Heck reaction to synthesis functionalized tetracyclic tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones by J. Niu et al. in 2024 **(Scheme I.10.).** This Ugi reaction was mediated through Et_3N in 5 mL MeOH, at 40 ^0C, for 24 hours and Heck reaction was carried out by dissolving in MeCN solvent, $Pd(OAc)_2$ catalyst, PPh_3 and K_2CO_3 reagents for 3 hours at 105 °C under N_2 atmosphere. The structures of the prepared products were characterized through their FT - IR, ^1H NMR, ^{13}C NMR spectra and elemental analysis.[7]



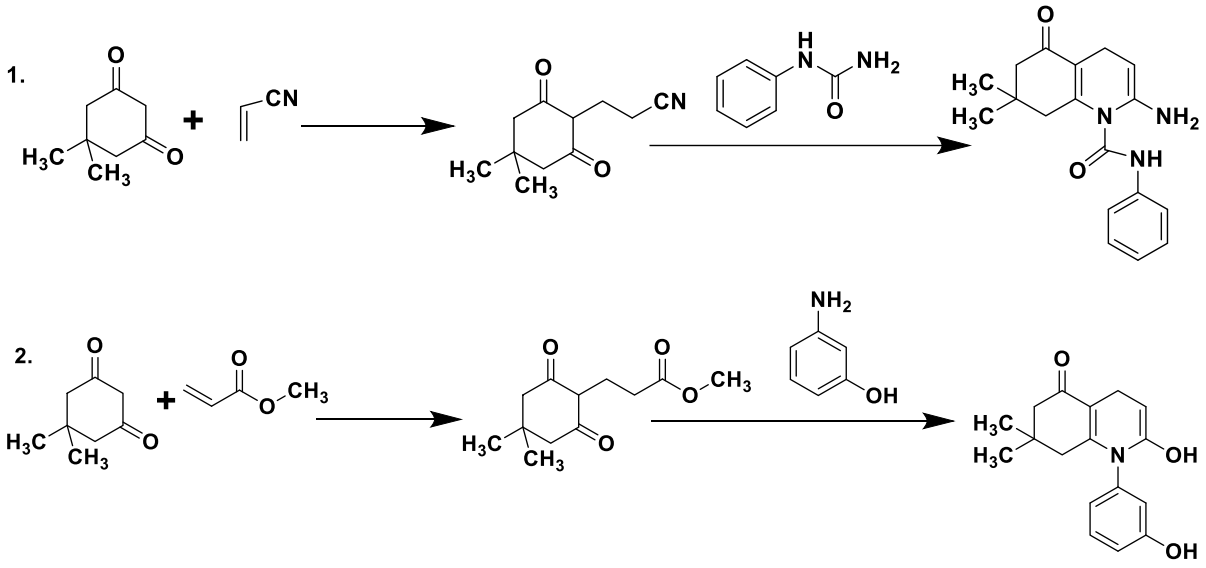
Scheme I.10. : One-pot four-component synthesis of functionalized tetracyclic tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones[7]

I.2.11. One - pot four – component Ugi reaction followed by intra molecular Heck reaction of 2-bromobenzaldehyde, allylamine hydrochloride, trimethylsilyl azide and Ethyl 2 - isocyanate derivatives was carried out to synthesize functionalized tetrazolo[1,5-*a*]pyrazin-6(5*H*)-one derivatives, by J. Niu et al. in 2024 **(Scheme I.11.).** This Ugi reaction was mediated through Et_3N in 5 mL MeOH, at 40 ^{0}C, for 24 hours and Heck reaction was carried out by dissolving in MeCN solvent, $Pd(OAc)_2$ catalyst, PPh_3 and K_2CO_3 reagents for 3 hours at 105 °C under N_2 atmosphere. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[7]

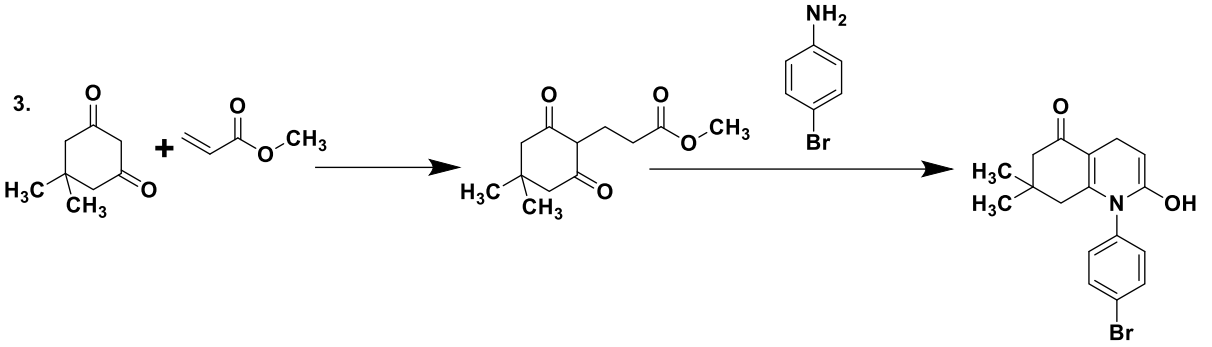


Scheme I.11. : One-pot four-component synthesis of functionalized tetracyclic tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones[7]

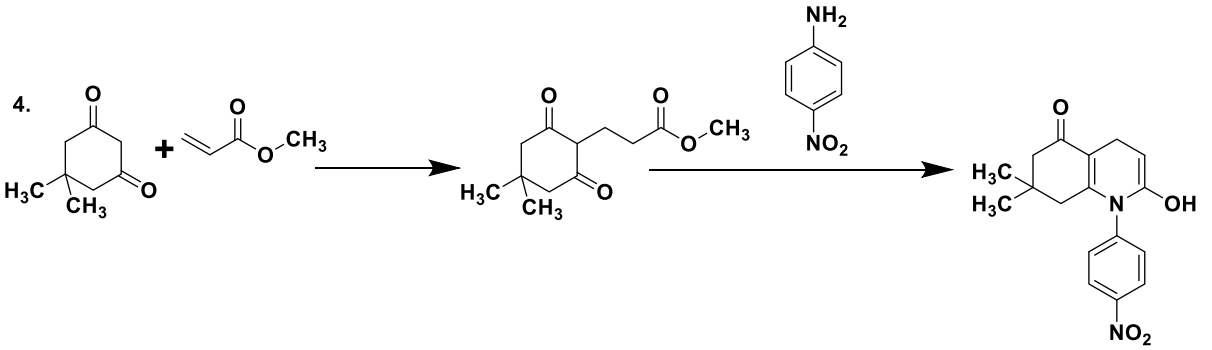
I.2.12. A number of one - pot synthesis of heterocyclic dihydroquinoline analogues, incorporating quinoline and pyrimidine fused rings in condensation reaction using nanocrystalline-TiO_2 on dodecyl-sulfated silica support (NCTDSS) catalyst, under reflux condition was done by S. M. Hughighi et al. in 2022 **(Scheme I.12.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[8]



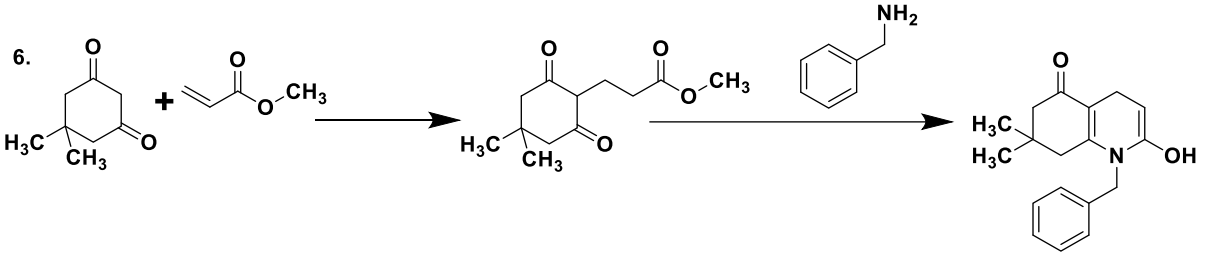
3.



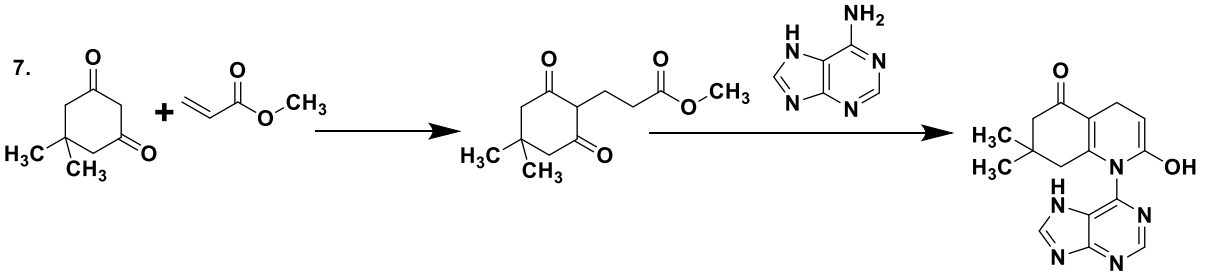
4.



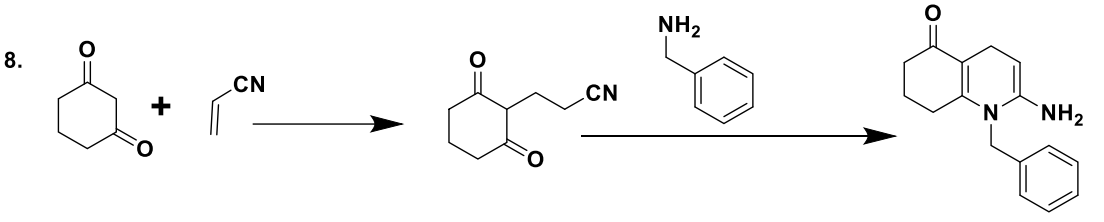
6.



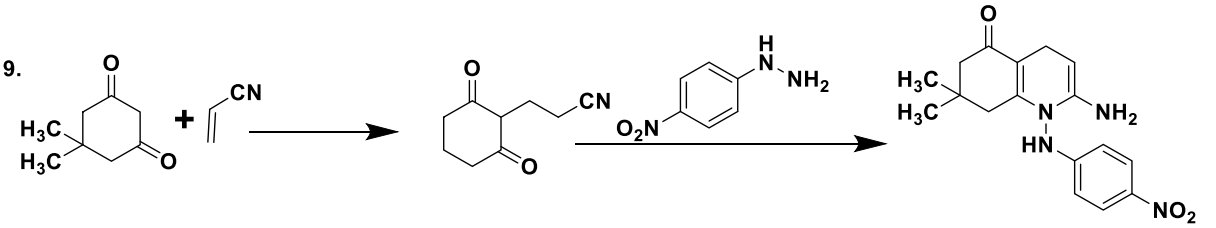
7.



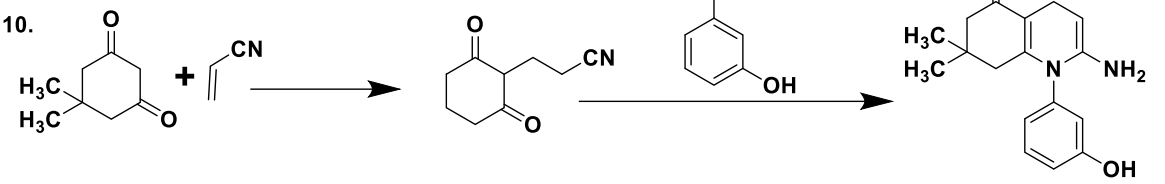
8.



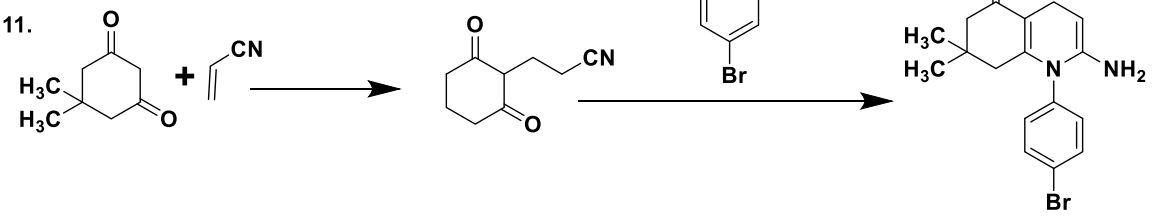
9.



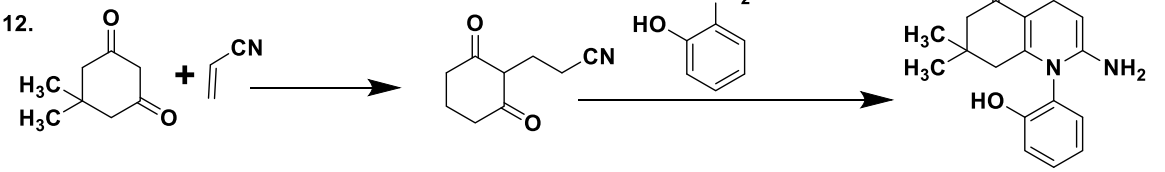
10.



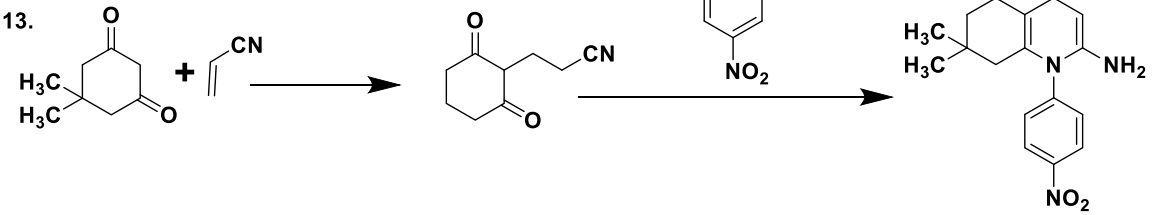
11.



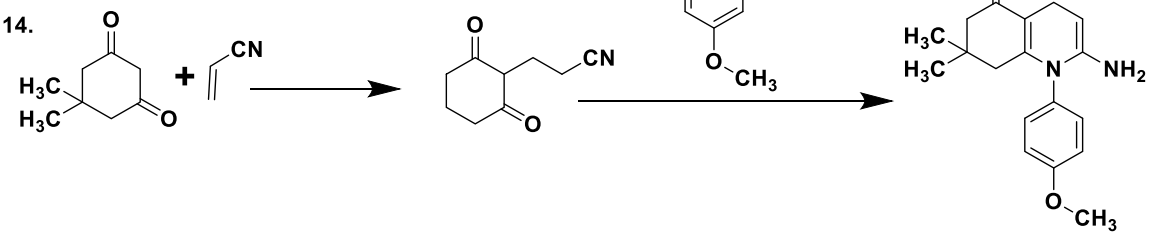
12.

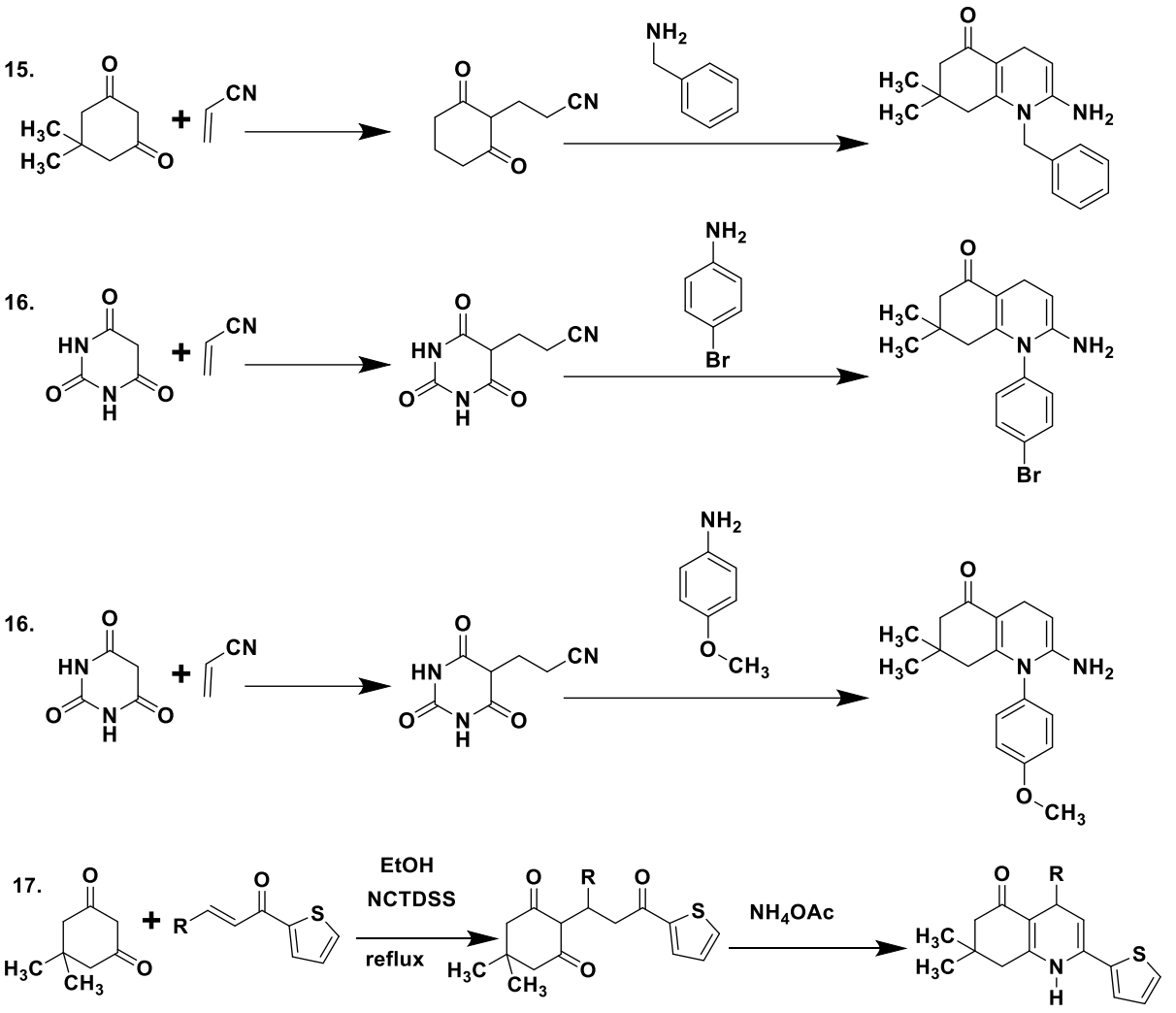


13.



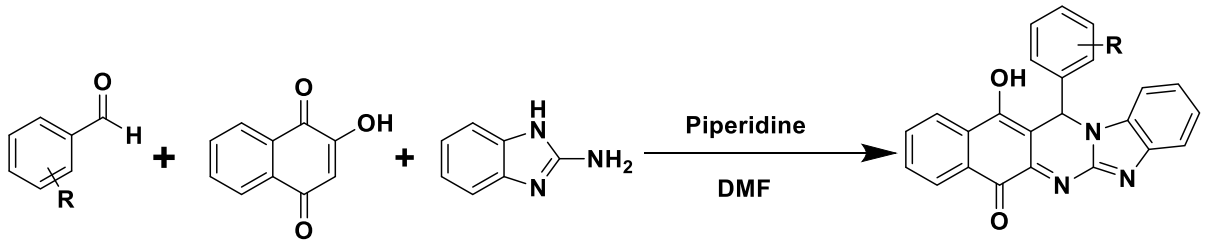
14.





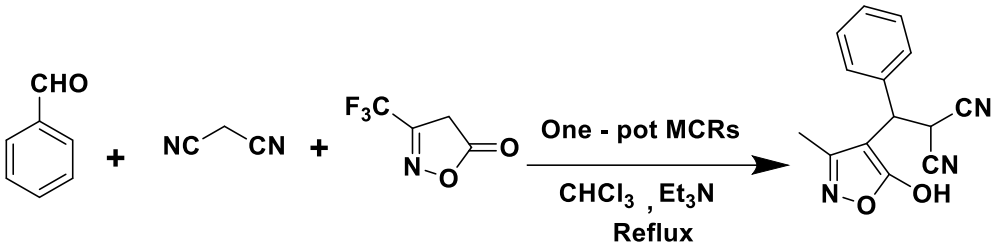
Scheme I.12. : A number of one - pot synthesis of heterocyclic dihydroquinoline analogues[8]

I.2.13.. Domino, cost effective, one - pot three – component reaction of 2-hydroxy-1,4-naphthoquinone, aromatic aldehydes, and 2-aminobenzimidazole was carried out to synthesize functionalized novel benzo[g]benzo[4,5]imidazo[2,1-b]quinazoline derivatives, by M. A. Sarhadi et al. in 2024 **(Scheme I.13.).** This reaction was mediated through piperidine in DMF solvent. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[9]



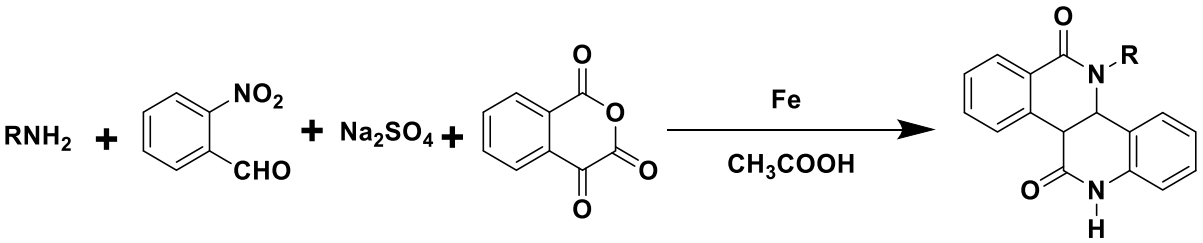
Scheme I.13. : One-pot three-component synthesis of functionalized novel benzo[g]benzo[4,5]imidazo[2,1-b]quinazoline derivatives[9]

I.2.14. One - pot three – component reaction of 3-(trifluoromethyl)isoxazol-5(4H)-one, malononitrile and aldehydes was carried out to synthesize functionalized trifluoromethylated isoxazolone-tethered trisubstituted methane derivatives, by Y. Zhang et al. in 2023 **(Scheme I.14.).** This reaction was mediated through catalytic amount of triethylamine. The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[10]



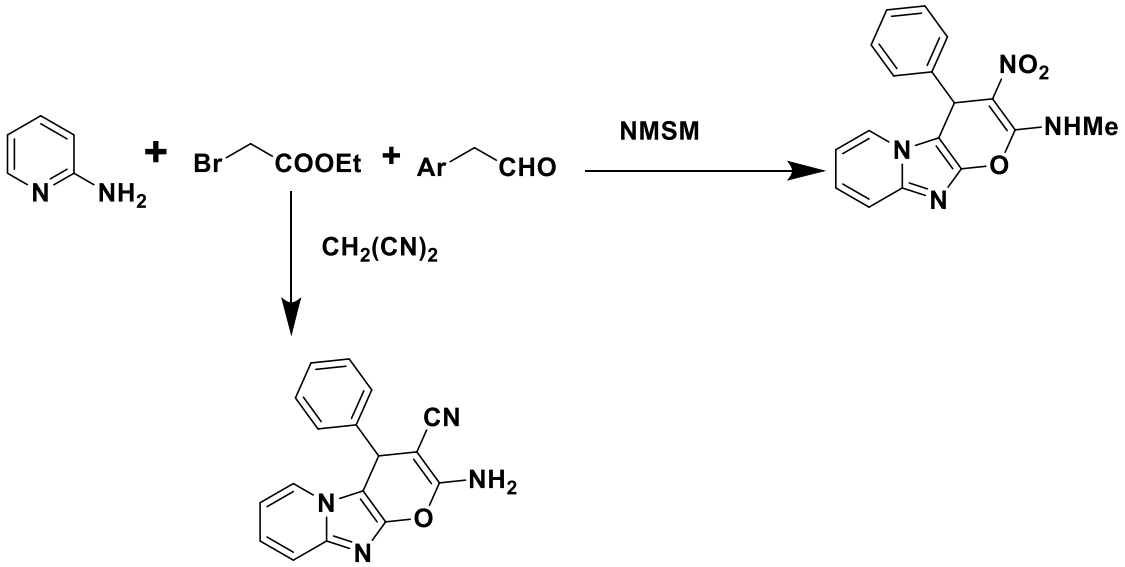
Scheme I.14. : One-pot three-component synthesis of functionalized trifluoromethylated isoxazolone-tethered trisubstituted methane derivatives[10]

I.2.15. One - pot multi – component sequential reaction of 2-nitrobenzaldehyde, aliphatic/aromatic amines, and homophthalic anhydride was carried out for telescopic synthesis of a nitrogen-fused heterocycle dihydrodibenzonapthyridinedione via imine formation, then the Castagnoli-Cushman reaction followed by nitro-reduction and intramolecular lactamization, by S.S. Deshmukh et al. in 2024 **(Scheme I.15.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[11]



Scheme I.15. : One - pot multi – component synthesis of nitrogen-fused heterocycle dihydrodibenzonapthyridinedione[11]

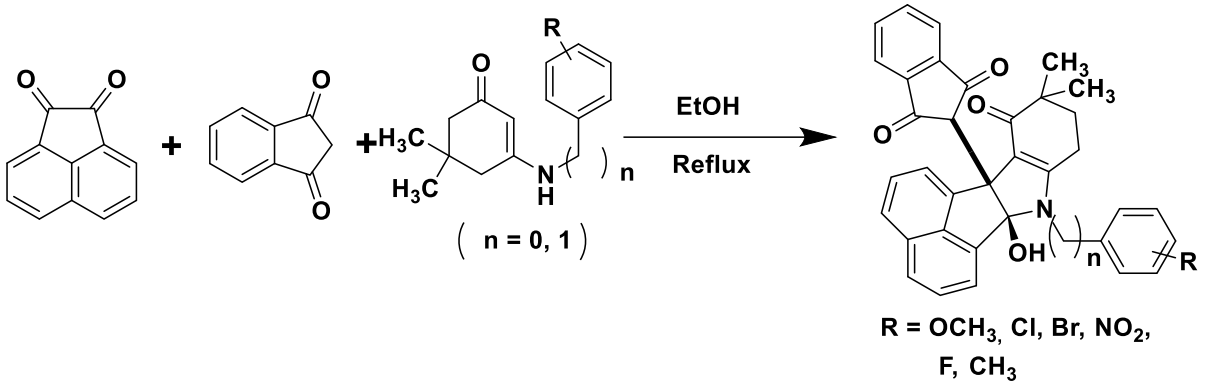
I.2.16. One - pot multi – component sequential reaction of 2-aminopyridine, ethyl 2-bromoacetate, ethanol and substituted benzaldehyde, followed by NMSM or malononitrile was carried out for synthesis of novel N-methyl-3-nitro-4-aryl-4H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridine-2-amine and 2-amino-4-aryl-4H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridine-3-carbonitrile respectively by R. Vediyappan et al. in 2023 **(Scheme I.16.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[12]



Scheme I.16. : One - pot multi – component synthesis of novel N-methyl-3-nitro-4-aryl-4H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridine-2-amine and 2-amino-4-aryl-4H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridine-3-carbonitrile[12]

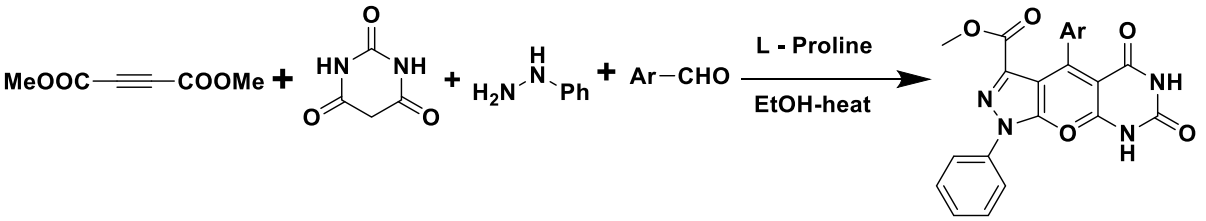
I.2.17. One - pot four – component reaction of dimedone, arylamines, acenaphthoquinone, and 1,3-indondione was carried out for synthesis of acenaphtho[1,2-b]indolindenedione derivatives

and acenaphtho[1,2-b]indolone derivatives by Z. Amiri et al. in 2023 **(Scheme I.17.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[13]



Scheme I.17. : One - pot four – component synthesis of acenaphtho[1,2-b]indolindenedione derivatives and acenaphtho[1,2-b]indolone derivatives[13]

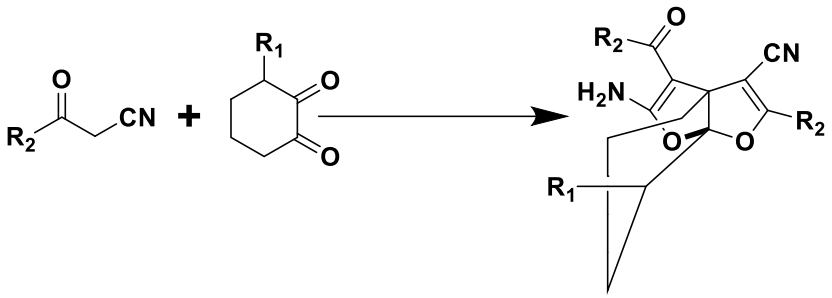
I.2.18. One - pot four – component L – Proline mediated condensation reaction of dimethyl but-2-ynedioate, Phenyl hydrazine, barbituric acid and aromatic aldehyde under Ethanol solvent was carried out for synthesis of methyl 4-(4-chlorophenyl)-5,7-dioxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo [4′,3′:5,6] pyrano[2,3-d] pyrimidine-3-carboxylate derivatives by M. B. Yadav et al. in 2021 **(Scheme I.18.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[14]



Scheme I.18. : One - pot four – component synthesis of methyl 4-(4-chlorophenyl)-5,7-dioxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo [4′,3′:5,6] pyrano[2,3-d] pyrimidine-3-carboxylate derivatives[14]

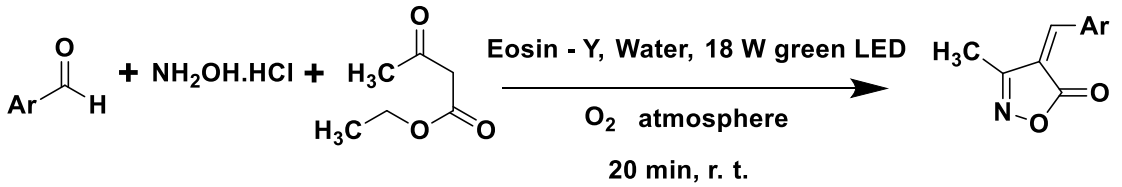
I.2.19. One – pot straightforward two – component effective base-catalyzed Knoevenagel, Michael and intramolecular/Paal-Knorr cyclization strategic reaction of cyclic α-diketones and α-cyanoketones was carried out for synthesis of heterocyclic [4.3.3] tetrahydro epoxyetheno

benzo-furan propellanes (TEBFs) by M. B. Yadav et al. in 2022 **(Scheme I.19.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[15]



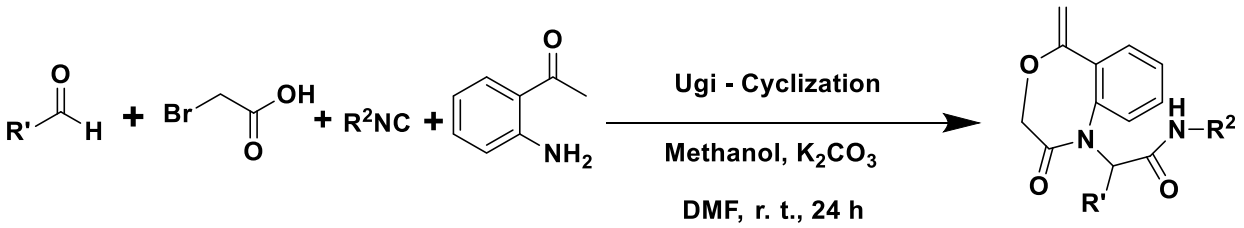
Scheme I.19. : One - pot four – component synthesis of heterocyclic [4.3.3] tetrahydro epoxyetheno benzo-furan propellanes (TEBFs)[15]

I.2.20. An eco-friendly green and metal-free visible light mediated, water solvent oriented one – pot three – component effective eosin-Y catalyzed reaction of aryl aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride was carried out for synthesis of biologically potent 4-benzylidene-3-methylisoxazol-5(4H)-one by R. Kumar et al. in 2023 **(Scheme I.20.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[16]



Scheme I.20. : One - pot four – component synthesis of biologically potent 4-benzylidene-3-methylisoxazol-5(4H)-one[16]

I.2.21. An user-friendly, one – pot four – component effective base catalyzed Ugi - cyclization reaction of 2′-aminoacetophenone, aldehydes, bromoacetic acid, and isocyanides was carried out for synthesis of biologically potent 2-oxo-benzo[1,4]oxazepines by M. Mirfattahi et al. in 2024 **(Scheme I.21.).** The structures of the prepared products were characterized through their FT - IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.[17]



Scheme I.21. : One - pot four – component synthesis of biologically potent biologically potent 2-oxo-benzo[1,4]oxazepines[17]

I.3. Conclusion:

Thus, we can observe that several synthetic techniques are being developed to synthesize heterocyclic molecules with biological potency. It is evident from the analysis above that there is still much room for the development of novel response techniques in this area.

I.4. References:

References are displayed in **BIBLIOGRAPHY** under General Introductory part of **Chapter I,** that is, **A concise explanation about the perspective towards some production of biologically significant compounds with heterocyclic moiety** (pp. 197 - 198**).**

Section A

Humic Acid: A Rarely Explored, Robust, Green Catalyst for Solvent-Free Synthesis of 4*H*-Benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate and Benzo[*d*]thiazole

I.A.1. Introduction:

In the past several decades, research practices in chemistry are constantly evolving through overcoming the rigidities such as, fixed reaction patterns, systematic approaches inside the confines of a laboratory. In order to make any system sustainable, attempts should be made to keep the laboratory experimental conditions in accordance with the environment, surrounding us. Therefore, any alteration, innovation or discovery, made in the system must be handled with great care and consideration to ensure its suitability to the surroundings. The continuous environmental degradations and its already visible devastating impacts have made the researchers and scientists to be focused on to the suitability of their research like never before. As a consequence, like any other procedures, organic synthesis must look at the sustainability aspect through the application of innovative and greener protocols that avoid the use of hazardous solvents, toxic chemicals, poisonous catalysts, and harsh reaction conditions. Use of such substances can result in massive environmental pollution and damage to the nature, during the synthesis of chemical components, particularly organic molecules. For that reason, organic synthetic methodologies must attempt to replace the traditional solvents and catalysts (wherever possible) with appropriate alternatives. The need to keep the drug industry flourishing through maintaining the sustainable protocols makes it worthwhile to pursue chemical synthesis.

Solvent-free protocols are greener and one of the best solutions to these environmental issues, since they can eliminate most of the flaws like pyrophoric property of harmful and hazardous solvents with high volatility and poor recovery. There are ample scopes in future, for further more detailed inspection of the solvent-free pathway, basically, as a part for synthesizing of organic molecules through greener methodology. Due to such factors, solvent-free pathways of organic synthesis have become very much popular in recent years. The aim of this initiative is to enhance earthly consciousness above a number of hazardous chemicals and substitution of harmful solvents and substituting them using greener products to progress towards green chemistry [1–9].

Generally, high molecular weight materials are very much useful for organic synthesis because of their low toxicity, ease of separation, easy recovery and reusability. Among them humic acid is very rarely used, non toxic, easily accessible, inexpensive, environmentally benign, high molecular weight polymer with extraordinary catalytic activity. Humic acid is derived primarily from biodegradation of dead and decreased organic materials and obtained mostly in

peat, soil, coal, upland streams, dejected lakes and well water. It's interesting and essential catalytic activity is exhibited owing to the presence of wide range of most ample functional groups, e.g. carboxyl (-COOH) and phenolic hydroxyl (=CH-OH) group in its structure. However, a careful review of the literature reveals that, only a few articles have reported the application of catalyst. Therefore, there is an enormous scope of further detailed exploration of its catalytic venture in multidirectional protocols of biosynthesis. Low catalyst loading, outstanding yield and significant functional group toleration are some of the extraordinary characteristics of humic acid in its catalytic approach. Another important convenience about humic acid is its renewability. Structure of humic acid is given below **(Figure I.A.1.)** [10–12].

The previously reported humic acid mediated solvent-free production of multiple collection of functionalized bis(indolyl)methanes, bis(pyrazolyl)methanes, bis-coumarins and bis-lawsones by the reaction of vast range of aldehydes with Indole, 3-methyl-1-phenyl pyrazolone, 4-hydroxy coumarin and 2-hydroxy naphthalene-1,4-dione respectively [10]. Another previously reported humic acid catalyzed reaction was one pot, three components, water mediated preparation of 5-substituted 1*H*-tetrazoles, from a number of aldehydes, hydroxylamine hydrochloride in presence of sodium azide [11]. Again, humic acid was used as a support of Pd/Ni bimetallic catalyst for Heck coupling reaction, in one of the previous studies [12].

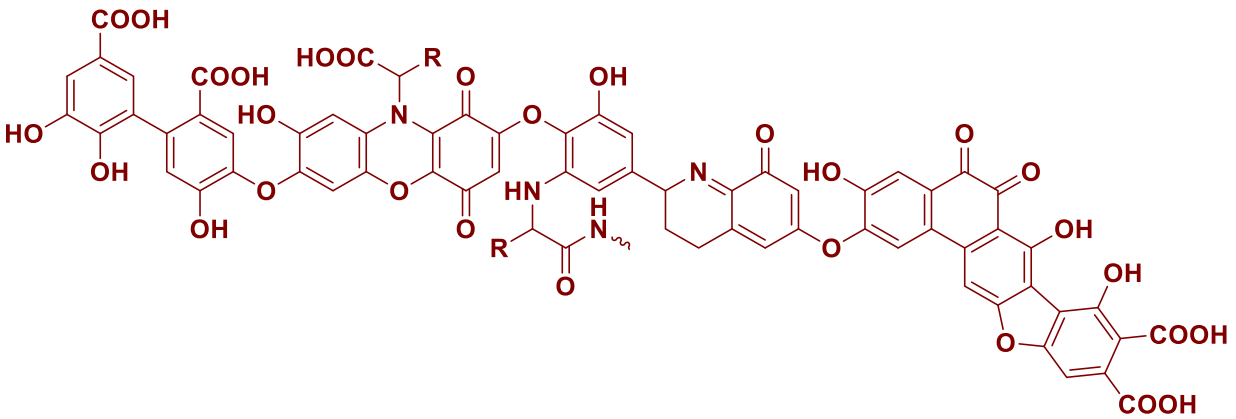


Figure I.A.1.: Structure of Humic Acid

4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine is a very essential compound under the highly important branch of fused heterocycles, with a vast pharmacological [13], pharmaceutical [14] and industrial [14] properties. It consists of a large number of biological activities, such as, antibacterial [14], anti-tumor [14], anti-inflammatory [14], antiviral [14], anticonvulsant [14],

anticancer [14], antifungal [14] or fungicidal [15], anti allergic [15], antimicrobial [15], anti mycobacterial [15], anti proliferative [15], anticoagulant [16], anti herbicidal [16], anti tuberculosis [17] – etc. It can be used as a salient synthon to design various modern medicinal drugs [18] for synthesizing a number of biologically active compounds [19] and natural products[5]. It's a remarkable optical liquid [8] with electronic properties [8] and used as dyes[20] and fluorescent [12] materials. This compound is so much useful for constructing medicines, associated with human and cattle contagious disorder such as, AIDS, hepatitis B and C, tuberculosis and bovine viral diarrhea, drug resistant cancers i.e. leukemia, carcinoma, melanoma and multi drug resistant tumors, which has no definite remedy or effective availability of vaccines till date [11].

It is very well known fact, that, heterocyclic and polycyclic compounds, containing nitrogen, sulfur and oxygen (N, S, and O respectively) are very much flexible and necessary framework for designing a variety of drugs [21]. Some basic skeletal structures of such bioactive drugs are represented below **(Figure I.A.2.).** Benzothiazole and its derivatives, the important part of heterocyclic [13] and polycyclic compounds [13], represent a number of biological [22], medicinal [23], pharmacological [14], pharmaceutical [24] significances like analgesic [15], anti epilepsy [25], anti lateral sclerosis [17], anti hypertensive [15], anti HIV [15], antiulcer [15], anti diabetic [26], anti Parkinson [27], antithrombotic [15], antihistamine [28], antiemetic [20], anti anxiety [29], anti stress [30], anti glutamate [19], anti parasitic [18], anti helminthic [31] – etc. They are used in auto immune diseases [17]. Benzothiazoles are extensive important class of pervasive heterocyclic moieties [32] and exist as molecules or molecular framework in many bioactive natural products [24], e.g. Vitamin B_{12} [12]. They have huge applications in material sciences [24] or material chemistry [24] as the primary components of materials with optical or electronic belongings [33] and also used as ligands of transition metals and intermediates of organic reactions [34]. They play an important role as ligands in asymmetric transformations [26]. It has great application prospect in synthesis of variety of agrochemical compounds [26]. They are pharmacophores and applied in variety of modern drug discovery and development like Omeprazol (proton-pump deterrence), Condesartan and Telmisartan (AT1 receptor nemesis), Mebendazole (drug to prevent parasitic worm infection), Dabigatran (direct thrombin inhibitor), Flunoxaprofen (NSAID) and Riluzole (sodium channel barricade and drug to fend off amyotrophic lateral sclerosis) – etc [27]. Benzothiazole derivatives are also present in Fanetizole

(anti-inflammatory agent), UDP-galacto-pyranose mutase inhibitor, κ and μ narcotic receptor and small molecular somatostatic receptor subtype 5 (SST5R) antagonists – etc [35]. It can act as efficient enzyme inhibitor, e.g. it is very popular inhibitor of Chemokin receptor ($CXCR_3$) [36], Lymphocyte Tyrosine kinase (LCK) [28], Glycinamide Ribonucleotide Transformylase (GARTfase) [37], Topo isomerase-1[15], Aldol reductase [38], HIV reverse transcriptase [15] - etc. Some derivatives of benzothiazole behave as plant growth regulators [39], photosensitizes, LTD_4 receptors [18], potent cataionic Trypsin receptor [30] and chemosensor[40] for a range of analytes. They are actively used in corrosion science [41]. These compounds are especially found in the moieties, which can conduct the life cycles in various cells [28]. They act a very significant role in metabolic process, taking place in living organisms [20]. They have vast industrial significances [6]. In industry, they are used as antioxidants [13], vulcanization accelerators [18], dopants in light emitting organic electroluminescent devices, i.e. nonlinear optical luminescent [13]. They can exhibit florescent properties [13] and so, they are used in designing sensor molecules of specific categories [13]. They can form the compounds with cytotoxic activities [15] and imaging agent for Ca^{2+} channel antagonist [13].

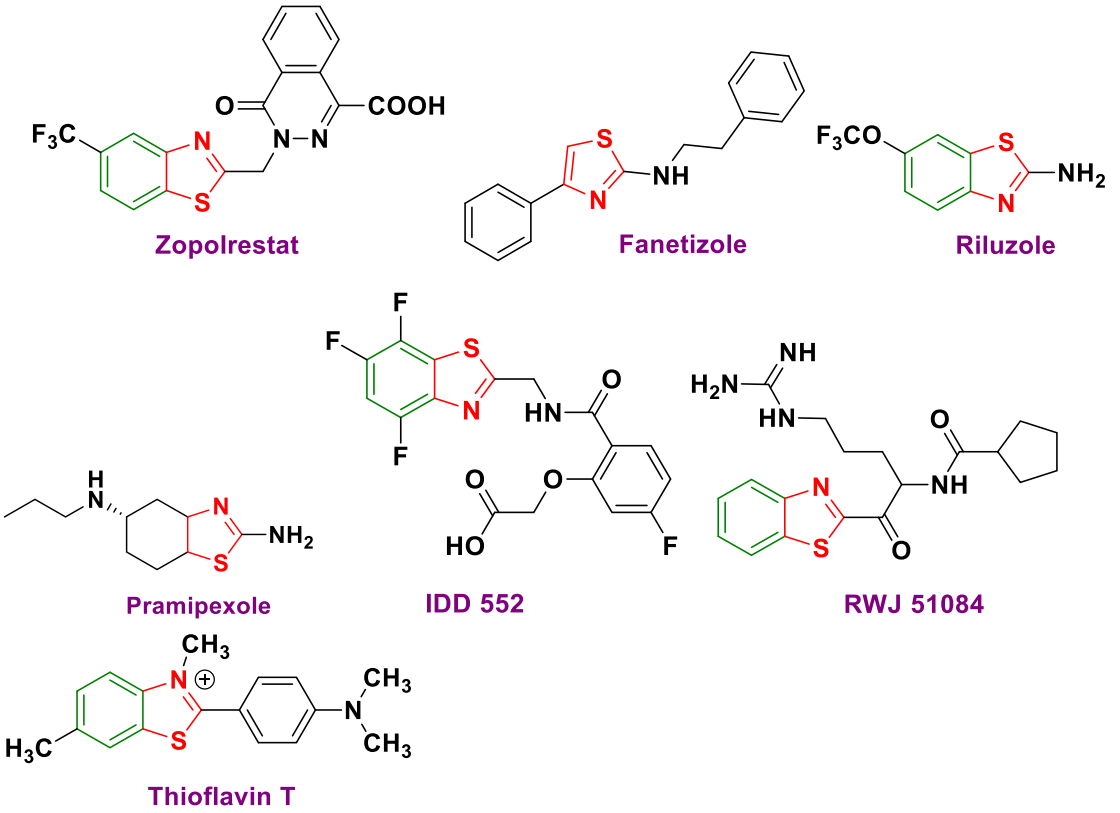


Figure I.A.2.: Some examples of biologically active drugs

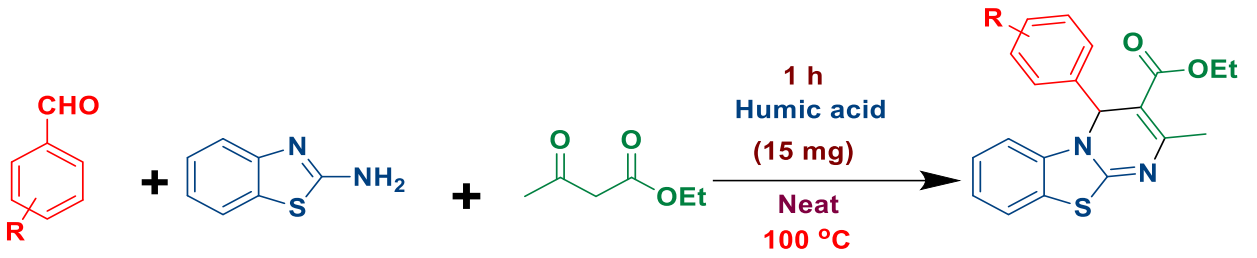
4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate was synthesized previously by using the catalysts like; magnetic nano catalyst (nano – kaoline or hydrated aluminium silicate Al_2O_3, $2SiO_2$, $2H_2O$)/Ti^{4+}/Fe_3O_4 [14], nano-Co-[4-chlorophenyl-salsylaldimine-pyranopyridine dione]Cl_2 or nano-Schiff base complex [42], DBU and CPB (cetyl pyridinium bromide) [15], phosphorus containing ionic liquids [13], Fe_3O_4@nano-cellulose/Cu(II) [43], Fe_3O_4@SiO_2-$TiCl_3$ nano particles [44], nano cellulose/BF_3/Fe_3O_4 [17], nano-$TiCl_2$/cellulose [16], L-proline [45], Lewis acid, covalently grafted over sulfonic acid functionalized carbon@titania composites [46], ager [47], ammonium chloride [19], microwave over *p*-TSA clay [48], MgO or 12-tungstophosphoric acid [49], chitosan [50], phosphoric acid supported on alumina (H_3PO_4-Al_2O_3) [51], Mg-Al-CO_3 and Ca-Al-CO_3 hydrotalcite [52], TBAHS [53] – etc.

Benzo[*d*]thiazole was synthesized previously by using the catalysts like; amino quinolate B,B-diphenyl complex as the photocatalyst [54], enzyme like Trypsin, Lipase, Bovin – etc.[22], H_2SO_4, HCl, H_3PO_4, HF – etc. traditional acid catalysts [23], Bronstead acid surfactant combined ionic liquids [32], I_2 in TBHP (Tert butyl hydroperoxide) [55], Cu(II)-Glycerol/MCM-41 (nanocatalyst) [20, 84], mesoporous titania - alumina mixed oxide [56], magnetic Co-doped $NiFe_2O_4$ [36], nano composite, mesoporous silica supported samarium [57], Ag_2O (in microwave) [58], epichlorohydrin cross linked β-cyclodextrin (β-CD polymer) [59], YCl_3 [60], UIO-66-NH_2 derived Bronstead acid catalyst [61], nano sealed UIO-66-NH-RSO_3H catalyst [53], ZnO nano particles [62], iron catalyst [37], ruthenium silicate zeolite [21], vanadium and molybdenum Schiff base complexes [28], flurescein (photocatalyst i.e. visible light in presence of O_2) [33], fluorinated phosphoric acid [34], camphore sulfonic acid [29], hydrotalcite, visible LED light in photosensitizer [63], laccase/DDQ [64], NH_2-MIL-125(Ti) metal-organic framework [65], tin modified mono ammonium phosphate fertilizer ($SnCl_2$ in MAP) or SnP_2O_7 in EtOH [66], hybrid crystal $H_3N(CH_2)_4NH_3SiF_6$ (monoalkyl ammonium hexafluorosilicate) [31], $NiFe_{2-x}Eu_XO$ nano structured catalyst [67], TiO_2 nano particle in H_2O_2(in P_{25} nanoparticles) [27], mesoporous poly(melamine-formaldehyde) [38], water(H_2O) [68], magnetic nano particles supported tungsto silicic acid [69], iron phthalocyanine [35], NaY zeolite functionalized by sulfamic acid/$Cu(OAC)_2$ or NaY zeolite-$NHSO_3H$/$Cu(OAC)_2$ as hybrid catalyst [25], oxalic acid: L-proline [40], solid acid supported on magnetic nano particles (solid acid catalyst [Fe_3O_4@SiO_2@$(CH_2)_3$NPC-SO_3H]Cl) [70], MIL-101(Fe)hexagonal microspindle [18], functionalized magnetic core shell nano particles, containing I_3^-, i.e. [Fe_3O_4@SiO_2@$(CH_2)_3NMe_3^+$]I_3^- [71], chitosan-SO_3H [72],

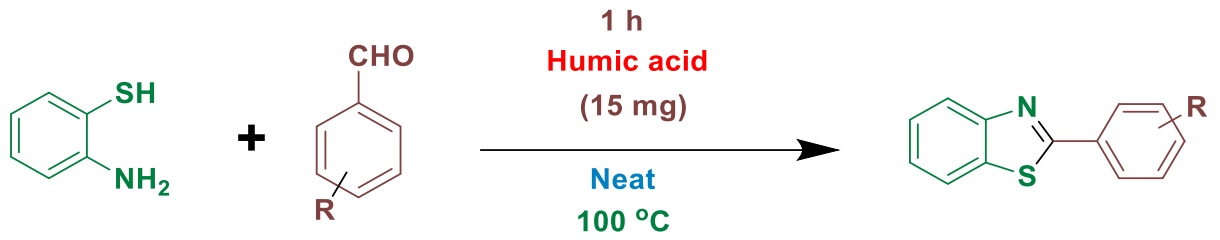
$H_3N(CH_2)_5NH_3BiCl_5$ [73], copper containing nano silica thioalated dendritic material [41, 85], two dimensional Bi_2WO_6 nano sheets as a sturdy catalyst (towards photocatalyzation) [39], phosphoric acid supported on alumina (H_3PO_4/Al_2O_3) [51], CuI [74], $VOSO_4$ catalyst in ethanol [75], calcinized egg shell [26], copper(II)-diaminosarcophagine functionalized SBA-15 [30], proline-based ionic liquid catalyst [76], nano-titania-supported sulfonic acid catalyst (n-TSA) [77], tBuONa [78], visible light photo catalyst [79], i.e. CdSe nano composites, made by monmorillonitrile (MMT) [71], SiO_2-HNO_3 [80], Ag_2O_3/Celite [81], $Fe_3O_4/SiO_2/(CH_2)_3NMe_3^+ Br^-$ core shell nano particles [82], $CuFe_2O_4$ nano particle catalyst [83] – etc.

Metal catalysts are very much expensive, hazardous, dangerous, poisonous, fatal, toxic, and huge time consuming to be prepared. Ionic liquids are also very much expensive, auto toxic, especially for human and aquatic organisms. Moreover, Ionic liquids have their limited solubility and they cannot be removed by distillation. Therefore, we have chosen humic acid since; it is much superior in its catalytic approach with respect to the other mentioned catalysts. This makes the overall methodology of those reactions is superior in greener and environmentally more sustainable approach with respect to their previous studies.

The discussion, presented in the previous paragraphs, indicates the points of interests to synthesize compounds, containing benzothiazole moieties with a large no. of conveniences. The target compounds in this experiment, were functionalized 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine along with its derivatives in addition to functionalized benzo[*d*]thiazole and its derivatives. The present study utilized humic acid as significant greener catalyst and used some greener pathway like, solvent-free methodology **(Schemes I.A.1., I.A.2.). Scheme I.A.1.** represented here, the reaction of benzaldehyde, 2-aminobenzothiazole and ethylacetoacetate; along with the formation of functionalized 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine; on the other hand, Scheme 2 represented below, the reaction of benzaldehyde and 2-aminothiophenol; along with the formation of functionalized benzo[*d*]thiazole; in presence of humic acid catalyst, under absolute solvent – free condition.



Scheme I.A.1. : Humic acid mediated synthesis of functionalized 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine



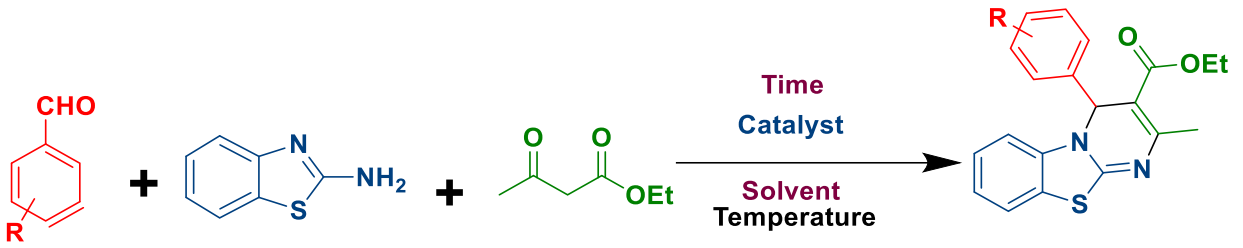
Scheme I.A.2. : Humic acid mediated synthesis of functionalized benzo[*d*]thiazole

I.A.2. Result and Discussion:

Catalyst, solvent and temperature are important driving components of any chemical reactions. So, it is necessary to maintain properly, the extent of catalyst, solvent and temperature throughout the target synthetic procedure. 1 mmol of benzaldehyde, 1 mmol of 2-aminobenzothiazole and 1 mmol of ethylacetoacetate were taken as reactants to undergo model reaction **(Scheme I.A.1.).** We started our optimization technique (Optimization procedure of **Scheme I.A.1.**, has been represented in Table I.A.1., below, in details), at first, with solvent, in presence of 30 mg of catalyst and next, it was observed that, refluxing with water, methanol and ethanol, the yield of the product was extensively low (Table I.A.1., entry 1, 2, 3). After that, by refluxing for 6 h continuously, the yield of the product was 50% with DMF (Table I.A.1., entry 4). When we carried out the same reaction, under neat condition, at 100 °C, with same amount of catalyst, then the yield of the product was enhanced up to 95% (Table I.A.1., entry 5). Then we started the optimization of catalyst by lowering the quantity as, 25 mg, 15 mg, 10 mg and 5 mg (Table I.A.1., entry 6, 7, 8, 9). As a result, we observed that, 15 mg of catalyst was enough to carry out this pathway and the yield of the product was 92% (Table I.A.1., entry 7). On the other hand, the

reaction could never be undergone in devoid of catalyst (Table I.A.1., entry 10). After that, by lowering the temperature up to room temperature, the yield of the product was reduced gradually (Table I.A.1., entry 11, 12, 13). Next, we kept track of the required time, for proceeding of the reaction and we found that, 1 h is sufficient for obtaining the maximum amount of product, under the indistinguishable reaction condition (Table I.A.1., entry 15).

Table I.A.1.: Optimization of reaction condition **(Scheme I.A.1.)**[a]



Entry	Solvent	Catalyst loading (mg)	Temperature (°C)	Time (h)	Yield(%)[b]
1.	Water	30	reflux	6	trace
2.	Methanol	30	reflux	6	30
3.	Ethanol	30	reflux	6	42
4.	DMF	30	reflux	6	50
5.	Neat	30	100	6	95
6.	Neat	25	100	6	94
7.	Neat	15	100	6	92
8.	Neat	10	100	6	49
9.	Neat	5	100	6	43
10.	Neat	Nil	100	6	-
11.	Neat	15	70	6	77
12.	Neat	15	50	6	65
13.	Neat	15	rt	6	trace
14.	Neat	15	100	3	92
15.	**Neat**	**15**	**100**	**1**	**92**

The **bold** part signifies the optimized conditions;

[a]Reaction of benzaldehyde (1 mmol), 2-aminobenzothiazole (1 mmol) and ethylacetoacetate (1 mmol);

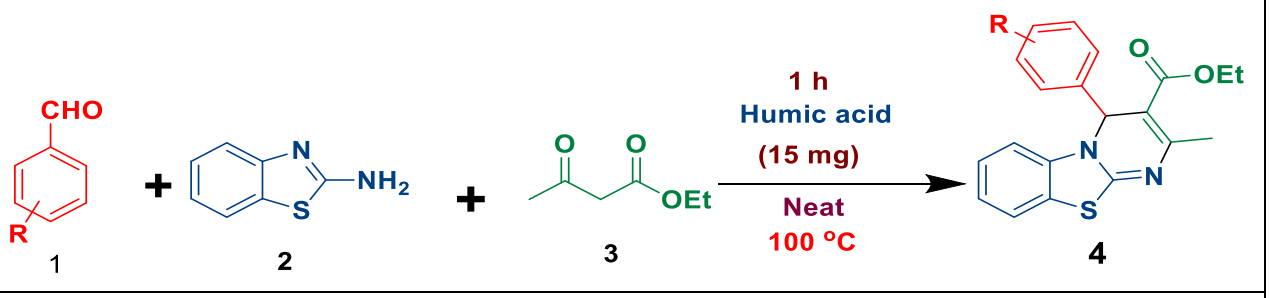
[b]Isolated yield was extracted through column chromatography.

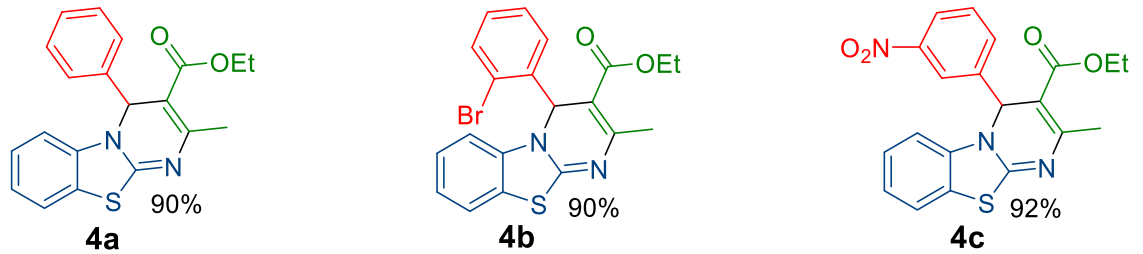
To perform in detailed study of our schemes, functionalized aldehydes were treated with 2-aminobenzothiazole and ethylacetoacetate **(Scheme I.A.1.)** under optimized condition and a variety of a number of 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate derivatives were constructed. The resulted compounds have been listed below in Table I.A.2.

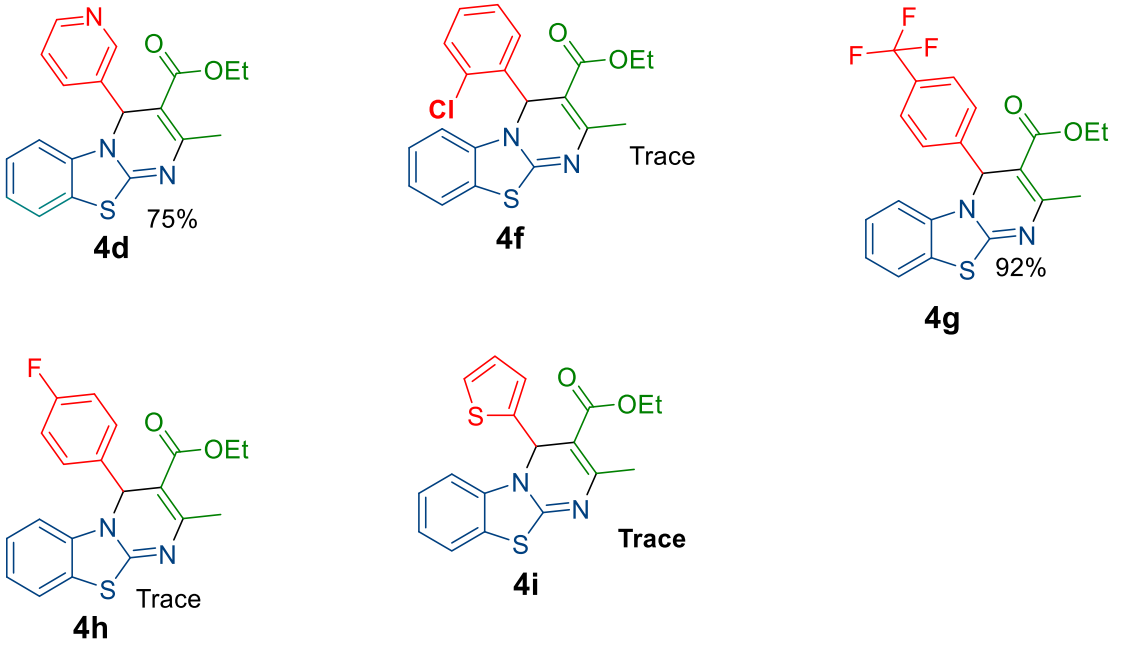
It was observed that, when electron withdrawing groups, especially nitro and trifluoromethyl were present in aldehyde, the product yield was very good (Table I.A.2., entry 4c, 4g respectively). But it was observed that, when aldehyde contained heterocyclic moiety, like thiophene, the product yield was not good (Table I.A.2., entry 4i). However, aldehyde with heterocyclic moiety, like pyridine, produced the products with medium yield (Table I.A.2., entry 4d). On the other hand, electron withdrawing groups like bromo, at ortho position, gave good yield (Table I.A.2., entry 4b). On the contrary, electron withdrawing group chloro at ortho position and that of fluoro at para position, gave poor yield of the product (Table I.A.2., entry 4f, 4h respectively).

Table I.A.2.: Structural Representation of some synthesized compounds through the reaction pathway, mentioned in Scheme I.A.1.[a]

[a]**Table I.A.2.:** Synthesis of functionalized thiazolo[3,2-*a*]pyrimidine derivatives **(Scheme I.A.1.)**





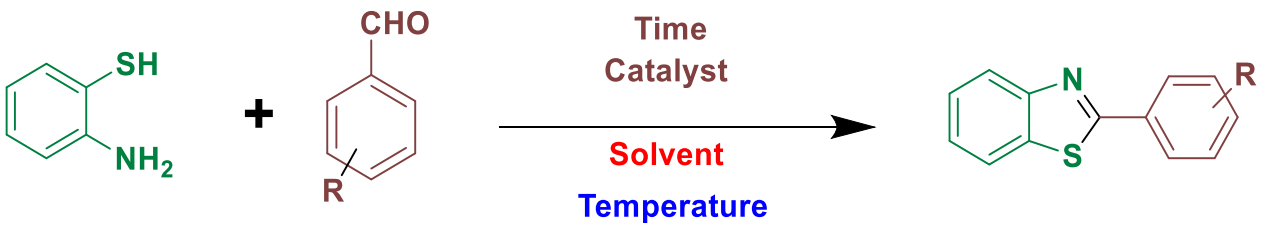


[a]Reaction of aldehydes (1 mmol), 2-aminobenzothiazole (1 mmol), ethylacetoacetate (1 mmol) and humic acid (15 mg), under solvent-free condition for 1 h.

In **Scheme I.A.2.**, we took 1 mmol of 2-aminothiophenol and 1 mmol of benzaldehyde as reactants to undergo model reaction **(Scheme I.A.1.).** In the screening method of this reaction, (Optimization procedure of **Scheme I.A.2.**, has been represented in Table I.A.3., below, in details), at first we choose solvent, in presence of 30 mg of catalyst, refluxing with water, DMF, methanol and ethanol the yield of the product was very low (Table I.A.3., entry 1, 2, 3, 4). By maintaining of 100 ºC temperature continuously for 4 h, the yields of the product were 50% and 32% with PEG-200 and DMSO respectively (Table I.A.3., entry 5, 6).When we underwent the same reaction in neat condition, at 100 ºC, with same amount of catalyst, then the yield of the product was enhanced up to 98% (Table I.A.3., entry 7). Then we initiated the optimization of catalyst, by reducing the amount of catalyst (Table I.A.3., entry 8, 9, 10, 11). Thus, it was observed that, 15 mg of catalyst was enough to carry out this procedure and the yield of the product was 97% (Table I.A.3., entry 9). On the other hand, the reaction could never be feasible to perform in devoid of catalyst (Table I.A.3., entry 12). After that, by lowering the temperature, the yield of the product was reduced frequently (Table I.A.3., entry 13, 14, 15). Next, we kept an eye on the required time for proceeding of the reaction and we discovered that, 1 h is sufficient for

gaining the maximum amount of product, under exactly the same reaction condition (Table I.A.3., entry 17).

Table I.A.3.: Optimization of reaction condition **(Scheme I.A.2.)**[a]



Entry	Solvent	Catalyst loading (mg)	Temperature (°C)	Time (h)	Yield(%)[b]
1.	Water	30	reflux	4	-
2.	DMF	30	reflux	4	42
3.	Methanol	30	reflux	4	trace
4.	Ethanol	30	reflux	4	30
5.	PEG-200	30	100	4	50
6.	DMSO	30	reflux	4	32
7.	Neat	30	100	4	98
8.	Neat	25	100	4	98
9.	Neat	15	100	4	97
10.	Neat	10	100	4	88
11.	Neat	5	100	4	82
12.	Neat	Nil	100	4	-
13.	Neat	15	70	4	87
14.	Neat	15	50	4	81
15.	Neat	15	rt	4	Trace
16.	Neat	15	100	2	97
17.	**Neat**	**15**	**100**	**1**	**97**

The **bold** part signifies the optimized conditions;

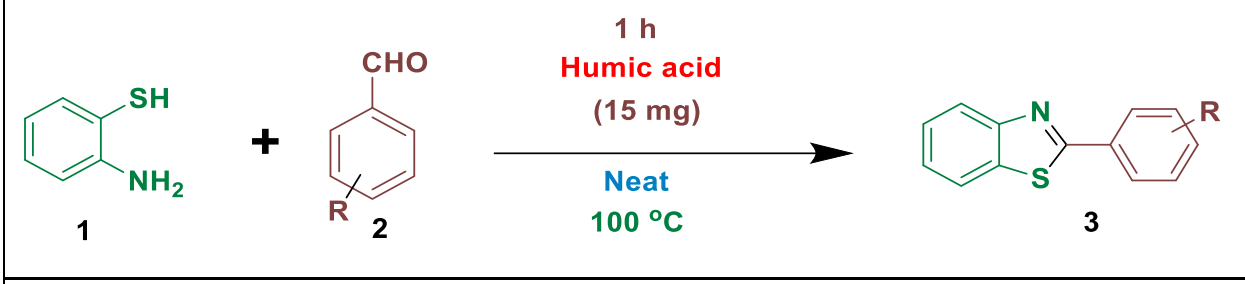
[a]Reaction of benzaldehyde (1 mmol) and 2-aminothiophenol (1 mmol);

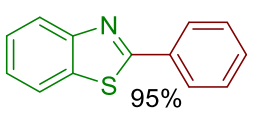
[b]Isolated yield was extracted through column chromatography.

To go through the detailed study of Scheme I.A.2., functionalized aldehydes were treated with 2-aminothiophenol (Scheme I.A.2.) under optimized condition and a variety of a number of benzo[*d*]thiazole derivatives were prepared. The resulted compounds have been listed below in Table-4. From this table, it was observed that, when electron withdrawing groups i.e. nitro at meta position, fluoro, chloro, trifluoromethyl and biphenyl at para position, were present in aldehyde, the product yield was excellent (Table I.A.4., entry 3b, 3k, 3m, 3h, 3l respectively). But it was also observed that, when an aldehyde contained electron withdrawing group i.e. fluoro at meta position, the yield was medium (Table I.A.4., entry 3i). When an aldehyde contained heterocyclic moieties like thiophene and furan, the product yield was medium to good (Table I.A.4., entry 3d, 3f respectively). Aldehyde, containing electron donating N, N dimethyl and methoxy groups, at para position, produced medium to good yield (Table I.A.4., entry 3e, 3o respectively). Vaniline and Salicylaldehyde gave very good yield (Table I.A.4., entry 3c, 3j respectively). Also, 2 naphthaldehyde produced a very good yield (Table I.A.4., entry 3n).

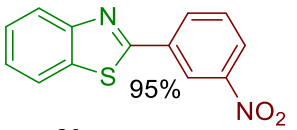
Table I.A.4.: Structural Representation of some synthesized compounds through the reaction pathway, mentioned in Scheme I.A.2. [a]

[a]**Table I.A.4. :** Synthesis of functionalized benzo[*d*]thiazole derivatives **(Scheme I.A.2.)**

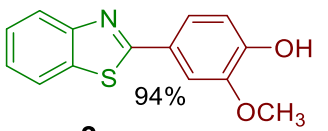




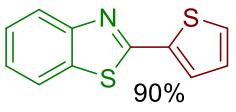
3a



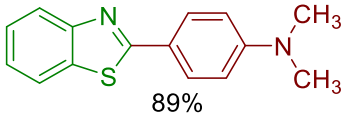
3b



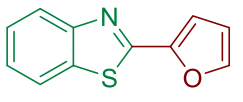
3c



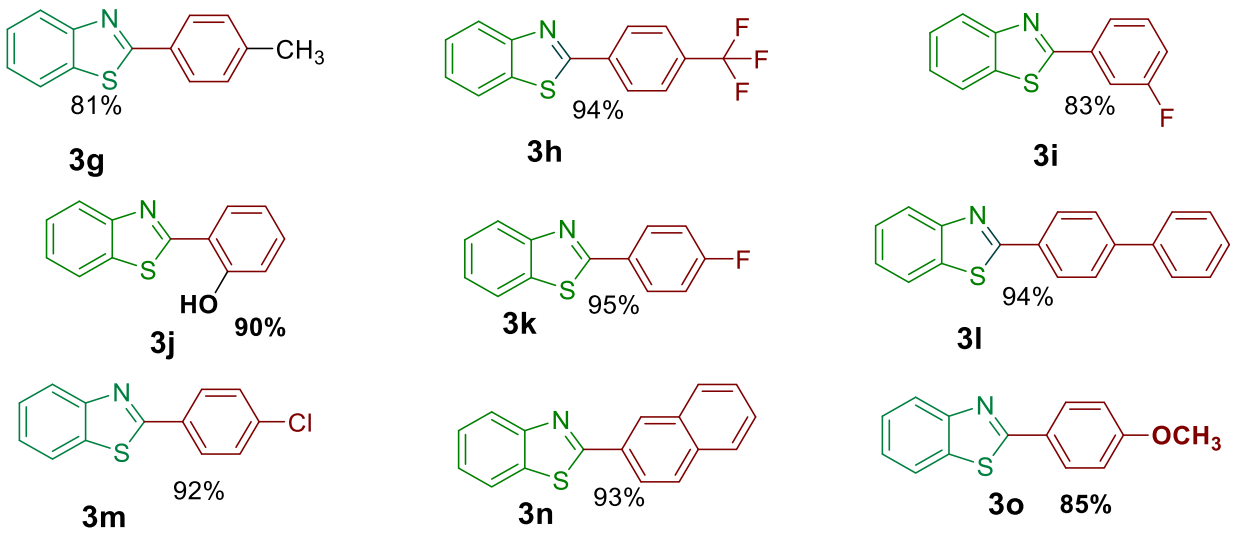
3d



3e



3f **85%**



[a]Reaction of aldehydes (1mmol), 2-amino-thiophenol (1 mmol) and humic acid (15 mg) under solvent-free condition for 1 h.

I.A.3. Reusability Experiment:

Renewability of humic acid was confirmed through a model reaction, with benzaldehyde (5 mmol) and 2-aminothiophenol (5 mmol) in presence of 75 mg humic acid, under optimized reaction condition. After finishing of the first run, ethyl acetate (4 ml) was added to the reaction mixture. Catalyst was taken back smoothly from the reaction mixture by easy filtration procedure. Then the recovered catalyst was washed with ethyl acetate (3×4 ml) and next it was dried before being handed down for the next run. The filtrate of reaction mixture was shifted to another container and this method was done for two times repetitively. The catalyst was then washed with ethyl acetate again and after that, it was dried for affording the black coloured humic acid, which was used in the next run, with its dryness. Recuperation of humic acid was slightly lower than the amount used in the first run. However, the recuperated catalyst was used continuously for 4 runs with almost similar affinity and there was no noteworthy degradation in the transformation. This Recyclability test of humic acid catalyst has been represented in **Figure I.A.3.** below, through bar diagram. It signifies that, humic acid can expose its catalytic activity up to five successive runs without any considerable reduction in it and in lowering of the yield of the product.

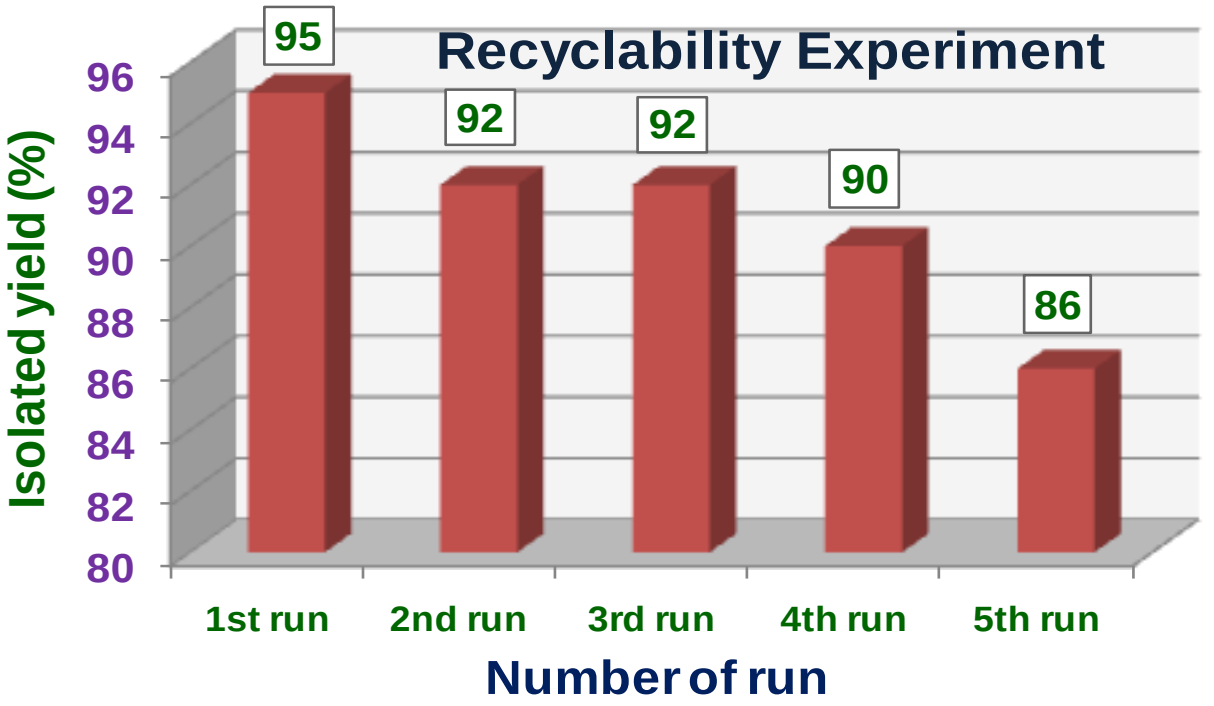


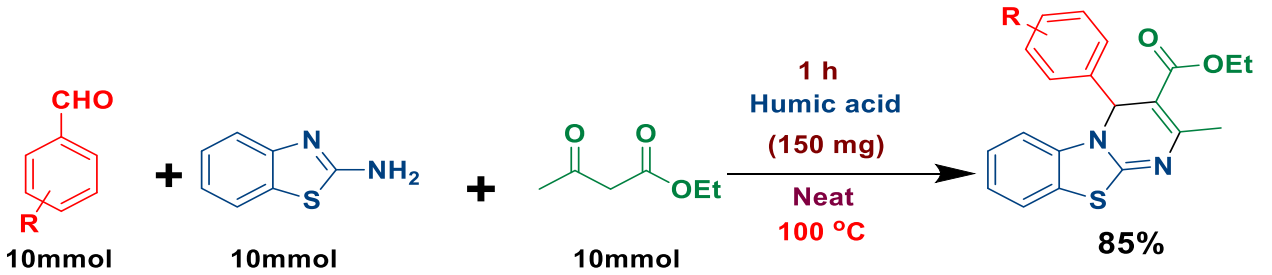
Figure I.A.3.: Reusability of Humic Acid catalyst

I.A.4. Gram - Scale Reaction:

The application of this methodology was examined in large scale, through carrying out the reactions in **gram-scale** (10 mmol scale) procedure. These also produced good yield, like the yield obtained in small scale reaction techniques. This Gram – Scale Reaction technique has been represented below, schematically, through **Figure I.A.4.**

Scale-up experiments:

Scheme I.A.1. :



Scheme I.A.2.:

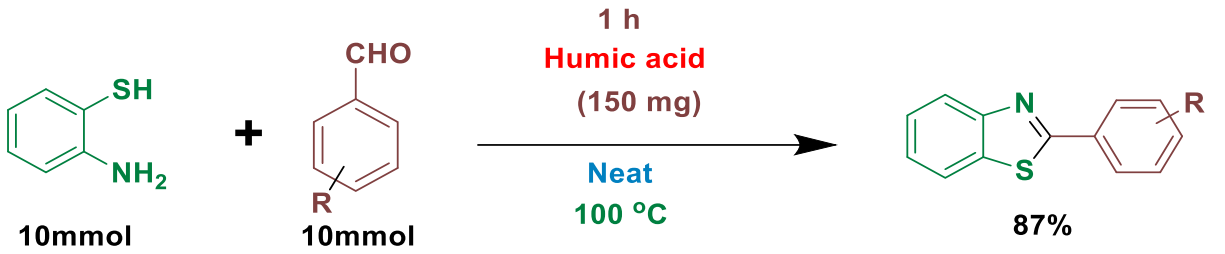
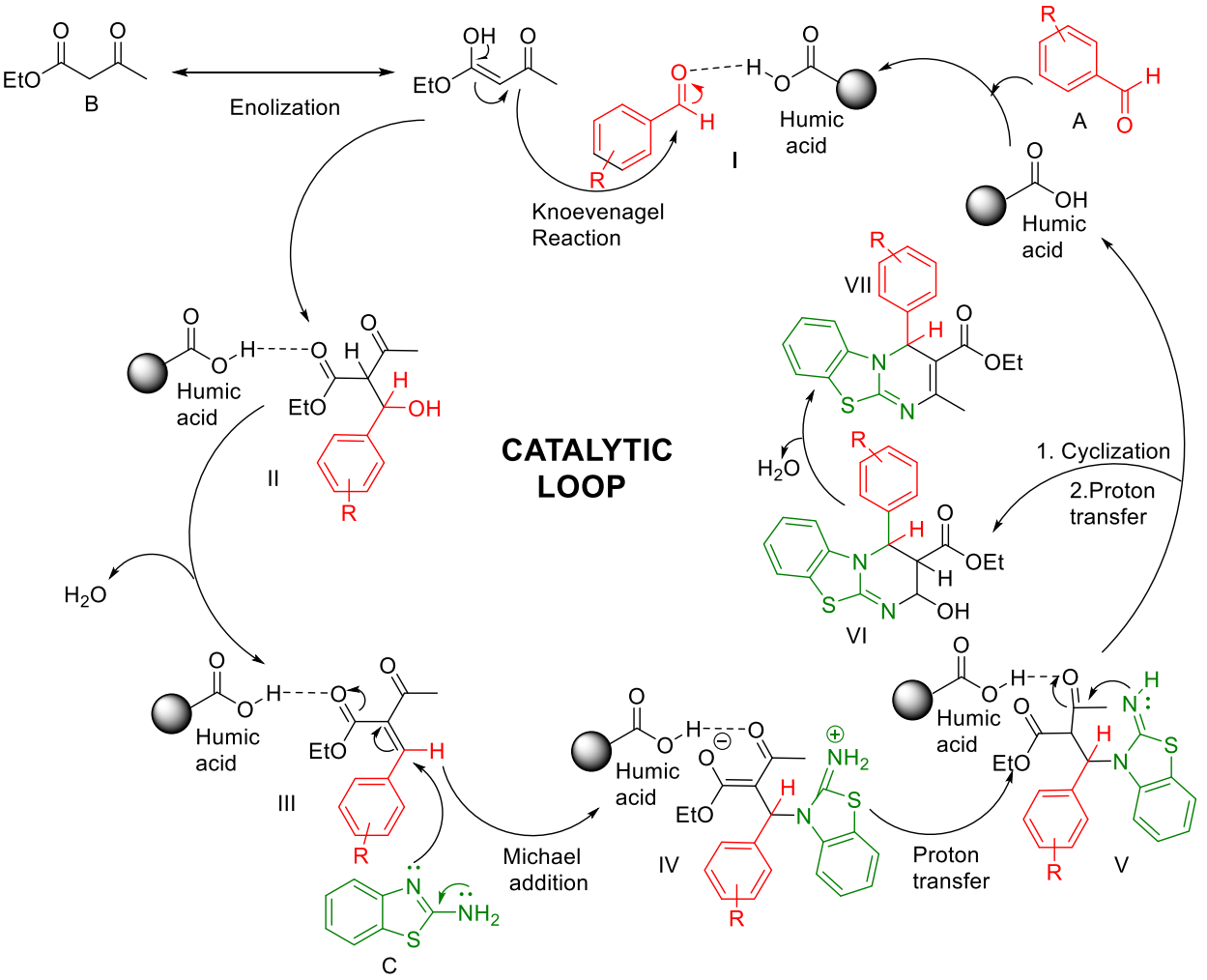


Figure I.A.4.: Gram – Scale Reaction

I.A.5. Plausible Mechanism for the Synthesis of 4H-benzo[4,5]thiazolo[3,2-a]pyridine-3-carboxylate and benzo[d]thiazole:

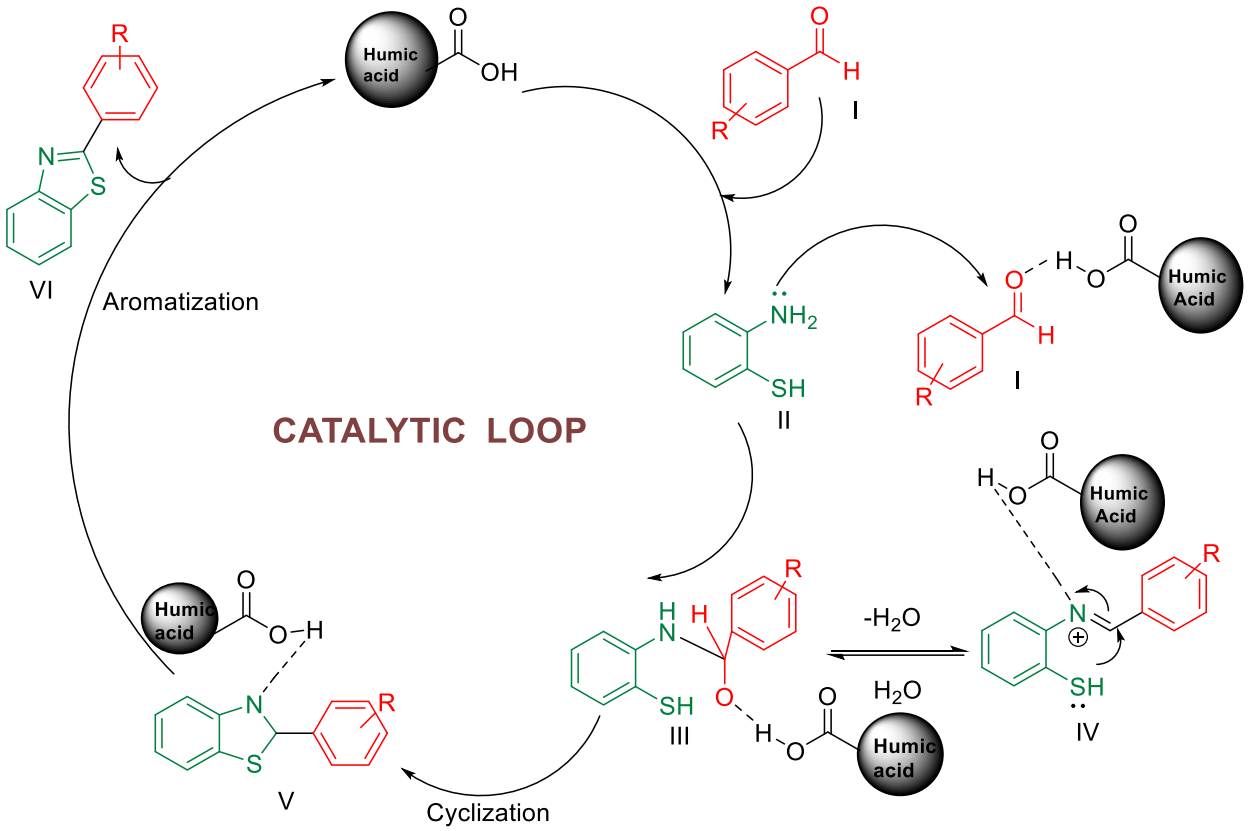
From the literature survey we have prepared the plausible mechanism for the synthesis of 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate, which is designed in **Scheme I.A.3.** At first, the catalyst activates the aldehyde (A), through its acidic part (-COOH) to enhance the electrophilicity of the carbonyl group so that it can help the nucleophilic attack by enolised form of ethylacetoacetate (B), by simple nucleophilic addition pathway and the intermediate (II) is formed. Humic acid activates further, the carbonyl carbon of –COOEt in intermediate (II). Then after water elimination we get the intermediate (III), into which, the nucleophilic centre of 2-aminobenzohiazole (C) attacks through Michael addition pathway i.e. at the 4 position. Thus we get the intermediate (IV) in which carbonyl carbon is activated again by humic acid catalyst. After that, through proton transfer, we get the intermediate (V), which then undergoes cyclization, followed by proton transfer process. Thus, we get the compound (VI), which forms the final product 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (VII), by elimination of water and after that, the humic acid catalyst is restored. This reaction mechanism and pathway have been diagrammatically represented through the following **Scheme I.A.3.**



Scheme I.A.3. : Plausible mechanistic pathway for synthesis of 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

From the surveying of literature, we have designed the plausible mechanism for the synthesis of benzo[*d*]thiazole, which is represented in **Scheme I.A.4.** At first, the catalyst activates the aldehyde (I) through its acidic part (-COOH), to increase the electrophilic nature of carbonyl group and so, it helps the nucleophilic attack by $–NH_2$ group of 2-aminothiophenol (II) by simple nucleophilic addition pathway and intermediate (III) is formed. This is transformed into intermediate (IV), by the loss of a water molecule. The enamine intermediate (IV) is activated again by the catalyst. Then nucleophilic attack occurs by –SH group of the same compound, followed by cyclization and aromatization. Through the formation of intermediate (V), the expected product benzo[*d*]thiazole (VI) is formed. After that the humic acid catalyst is restored.

This reaction mechanism and pathway have been diagrammatically represented through the following **Scheme I.A.4.**



Scheme I.A.4.: Plausible mechanistic pathway for synthesis of benzo[*d*]thiazole

I.A.6. Conclusion:

In conclusion, we have represented an environment friendly and feasible technique for synthesizing a number of functionalized 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate and benzo[*d*]thiazole derivatives under the absence of any solvent, taking humic acid as catalyst to activate carbonyl oxygen of respective aldehydes and ester for enhancing the electrophilicity of carbonyl carbon, followed by nucleophilic addition onto that position. The overall mechanism proceeds through Cascade reaction, involving a well known Knoevenagel and Michael Addition pathway. Since, no metal was used here, so, the overall method was maintained as greener synthetic one. Again, the solvent-free condition, contributes a huge environmental sustainability to the protocol. Humic acid catalyst can be regained through easy filtration procedure and its recovery factor can proceed up to fifth run in devoid of any characteristic deviation of its extent of

activity. So, the basic uniqueness and creativity manifestation of this methodology, is, the utilization of environmentally benign, easily accessible and low priced humic acid catalyst, instead of any toxic, fatal, dangerous, exhaustive, hazardous and expensive metal catalyst. This methodology proposed in the present study can be considered as a part of the consistent effort of the scientists and researchers by creating a significant evolution within the chemical world of medicines, synthetic pathways of natural products and drug industries, in future endeavors.

I.A.7. Experimental Section:

I. General Information:

All the compounds were acquired from commercial suppliers and used without further purification. All the products were purified by column chromatography on silica gels (60−120 Mesh, SRL, India). For TLC, Merck plates coated with silica gel 60, F254 were utilized. ^{1}H NMR,^{19} F and ^{13}C NMR were recorded using 400 MHz, 376 MHz and 100 MHz, respectively, on Bruker AV 400 NMR spectrometer using TMS as internal standard. Splitting manners of protons were explained as s (singlet), d (doublet), t (triplet) and m (multiplet).

II. General procedure for the synthesis of 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine:

A mixture of 2-aminobenzothiazol (1 mmol), benzaldehyde (1 mmol), ethylacetoacetate (1 mmol) and humic acid (15 mg) was blended at 100 °C for 1 h in open air in a reaction vessel (50 mL) using a magnetic stirring bar. The reaction progress was kept track of using TLC with a mixture of ethyl acetate and petroleum ether as the eluent medium. After finishing of the reaction, the mixture was annihilated to room temperature and ethyl acetate (5 mL) was added to the reaction mixture and the catalyst was separated by easy filtration and was extracted with ethyl acetate twice (2×20 ml). Amalgamated extracts were cleaned with distilled water, dried over anhydrous Na_2SO_4 and concentrated. The primitive product was decontaminated by passing through a column packed with silica gel (eluent: ethyl acetate–petroleum ether). The products obtained were known compounds and were recognized by their color, melting point and NMR spectroscopy.

III. General procedure for the synthesis of benzo[*d*]thiazole:

A mixture of 2-aminothiophenol (1 mmol) benzaldehyde (1 mmol) and humic acid (15 mg) was blended at 100 ºC for 1 h in open air in a reaction vessel (50 mL) using a magnetic stirring bar. The reaction progress was kept an eye on using TLC with a mixture of ethyl acetate and petroleum ether as the eluent medium. After finishing of the reaction, the mixture was annihilated to room temperature and ethyl acetate (5 mL) was added to the reaction mixture and the catalyst was separated by smooth filtration tecnique and was extracted with ethyl acetate twice (2×20 ml). Amalgamated extracts were washed with purified water, dried over anhydrous Na_2SO_4 and concentrated. The primitive product was decontaminated by passing through a column packed with silica gel (eluent: ethyl acetate–petroleum ether). The products obtained were known compounds and were recognized by their color, melting point and NMR spectroscopy.

IV. Spectroscopic data and Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of various benzo[*d*]thiazole and 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine derivatives :

2-Phenylbenzo[*d*]thiazole (Figure I.A.5.)

M.P.: 111 -113 ºC; grey solid; yield : 93%; **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.371 – 7.411 (m, 2H), 7.479 – 7.520 (m, 3H), 7.909 (d, *J* = 8 Hz, 1H), 8.078 – 8.113 (m, 3H) **(Figure I.A.6.).** **^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):** 116.685, 121.642, 123.250, 125.219, 126.346, 127.105, 127.585, 128.629, 129.047, 130.998, 133.628, 135.074, 154.148, 168.120**(Figure I.A.7.).**

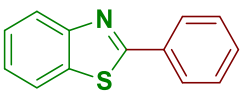


Figure I.A.5. Structure of 2-Phenylbenzo[*d*]thiazole

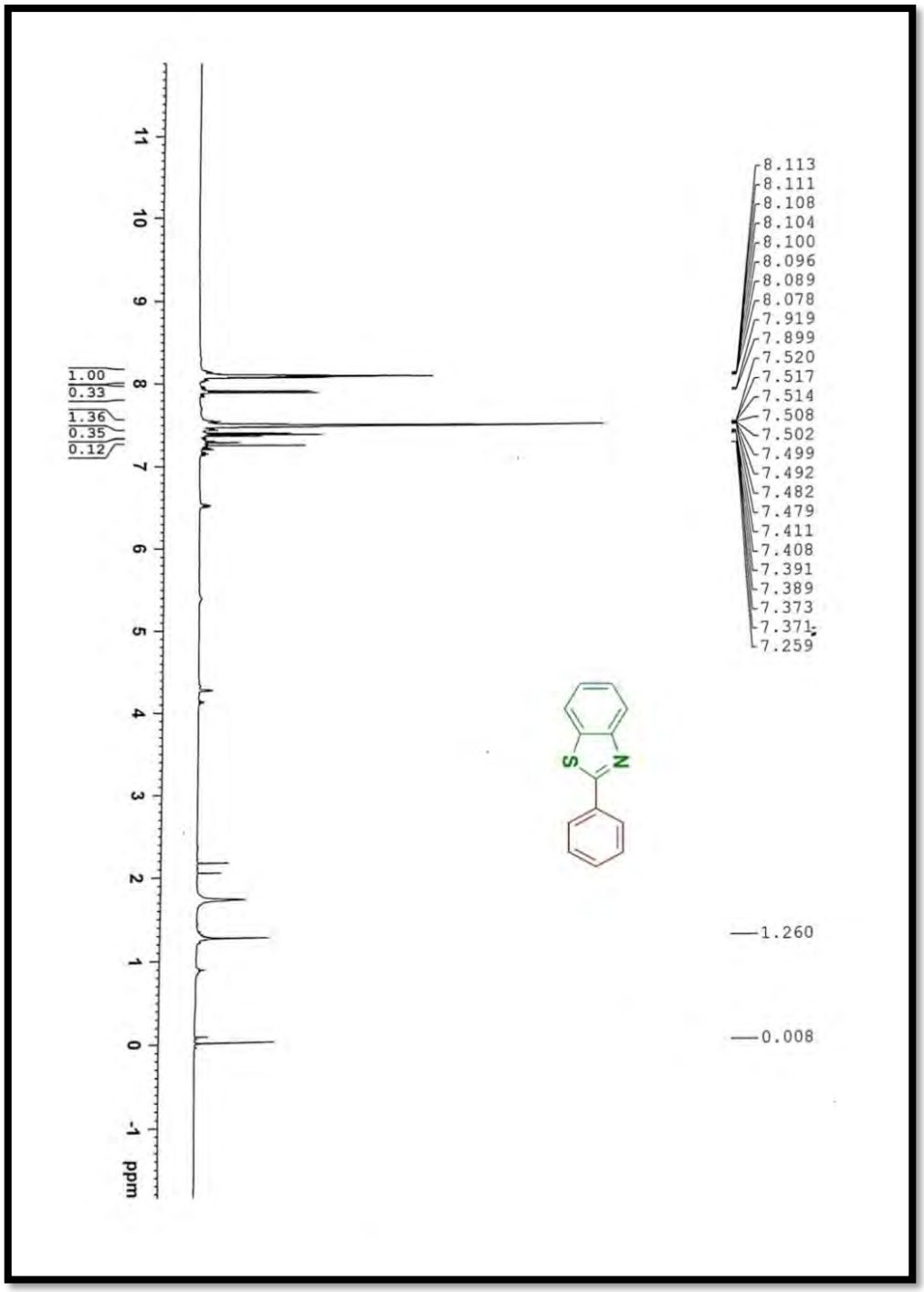


Figure I.A.6. ^{1}H Spectroscopical representation of 2-Phenylbenzo[*d*]thiazole

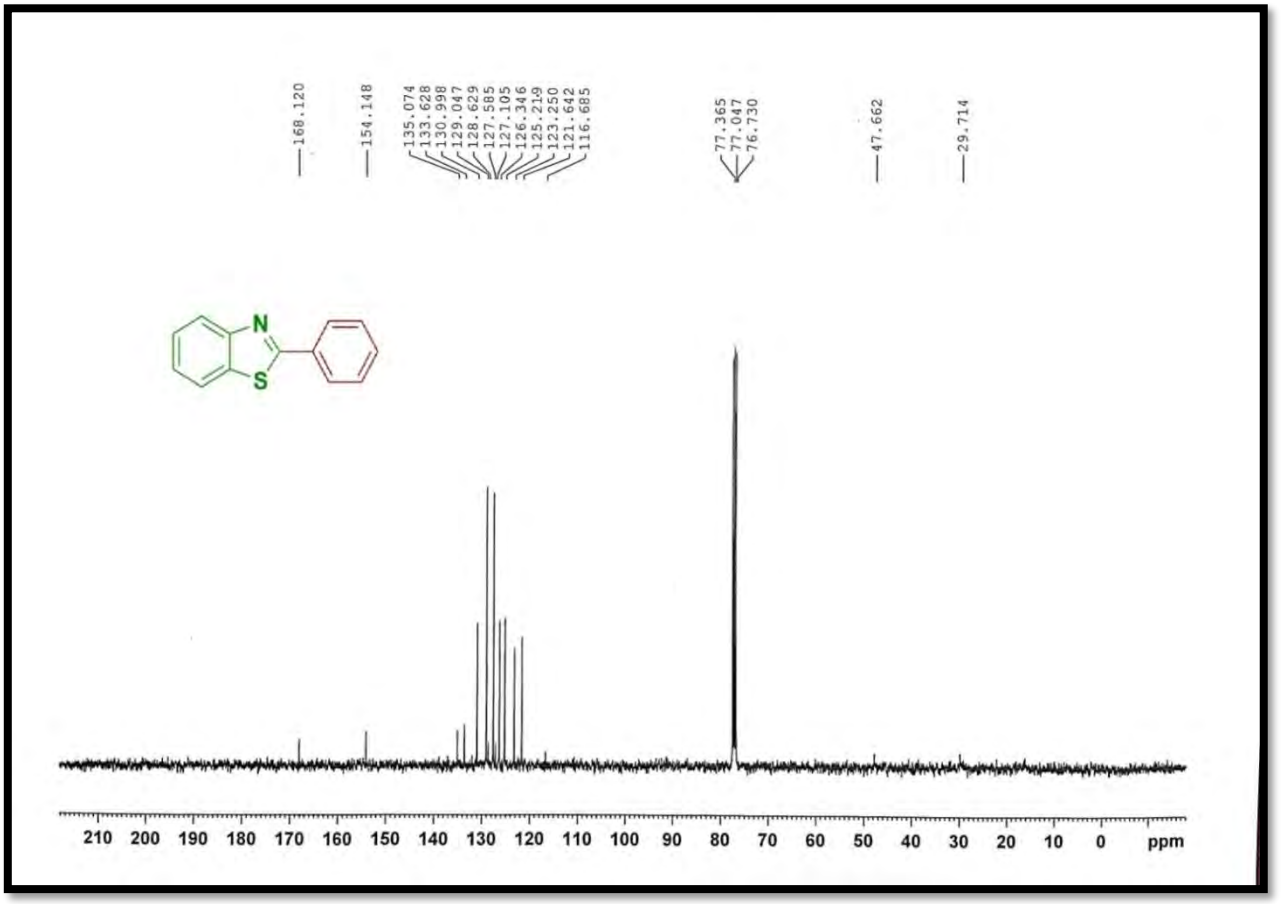


Figure I.A.7. ^{13}C Spectroscopical representation of 2-Phenylbenzo[*d*]thiazole

2-(3-Nitrophenyl)benzo[*d*]thiazole (Figure I.A.8.)

M.P. : 182.2 – 183.5 ºC; off – white solid, yield : 95%; **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.456 -7.476 (m, 1H), 7.551 (d, *J* = 0.8 Hz, 1H), 7.694 (t, *J* = 8 Hz, 1H), 7.954 (d, *J* = 8 Hz, 1H), 8.120 (d, *J* = 8 Hz, 1H), 8.325 (s, 1H), 8.424 (d, *J* = 8 Hz, 1H), 8.935 (m, 1H) **(Figure I.A.9.).**

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 121.840, 122.348, 123.761, 125.189, 126.041, 126.842, 130.113, 133.004, 135.187, 135.309, 148.773, 153.954, 164.899 **(Figure I.A.10.).**

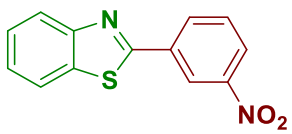


Figure I.A.8. Structure of 2-(3-Nitrophenyl)benzo[*d*]thiazole

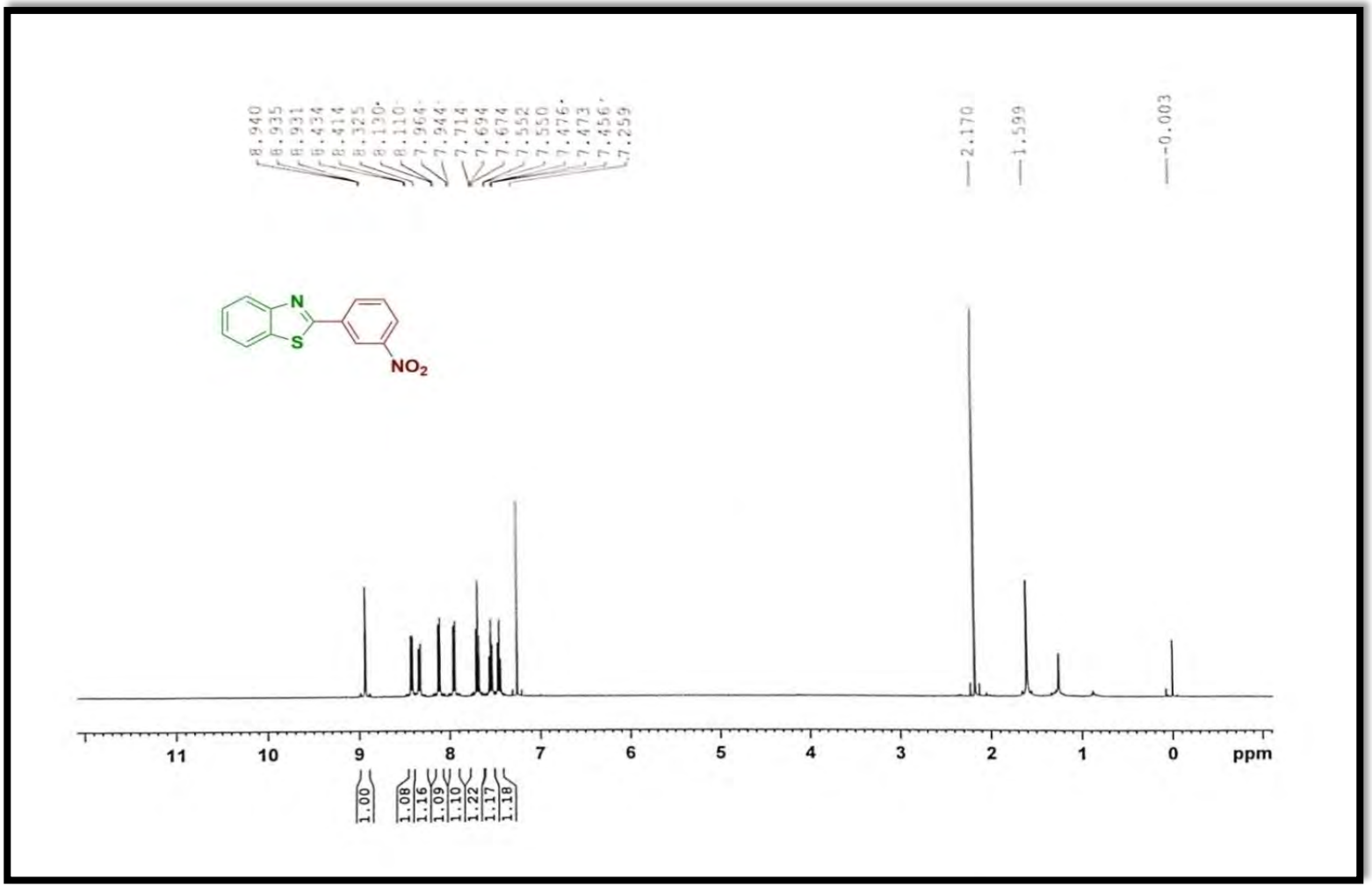


Figure I.A.9. ^{1}H Spectroscopical representation of 2-(3-Nitrophenyl)benzo[*d*]thiazole

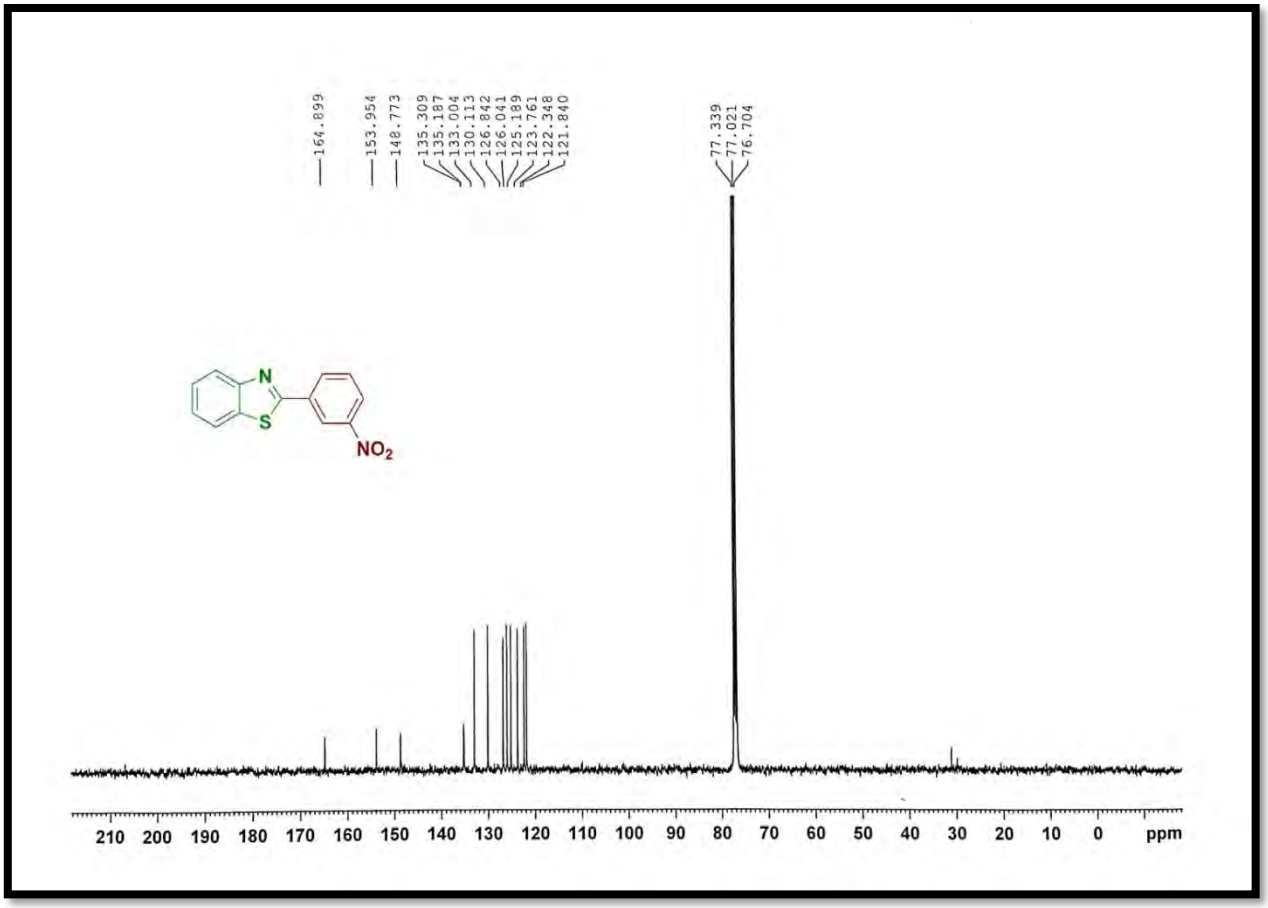


Figure I.A.10. ^{13}C Spectroscopical representation of 2-(3-Nitrophenyl)benzo[*d*]thiazole

2-(Thiophen-2-yl)benzo[*d*]thiazole (Figure I.A.11.)

M.P. : 99 °C; white solid; yield : 90%; **^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm):** 7.142 (dd, *J* = 4 Hz; *J* = 4.8 Hz, 1H), 7.348 – 7.389 (m, 1H), 7.454 – 7.515 (m, 2H), 7.657 – 7.669 (m, 1H), 7.853 (d, *J* = 8 Hz, 1H), 8.03 (d, *J* = 8 Hz, 1H) **(Figure I.A.12.).**

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 121.642, 123.250, 125.219, 126.346, 127.105, 127.585, 128.629, 129.047, 130.998, 133.628, 135.074, 154.148, 168.120 **(Figure I.A.13.).**

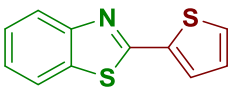


Figure I.A.11. Structure of 2-(Thiophen-2-yl)benzo[*d*]thiazole

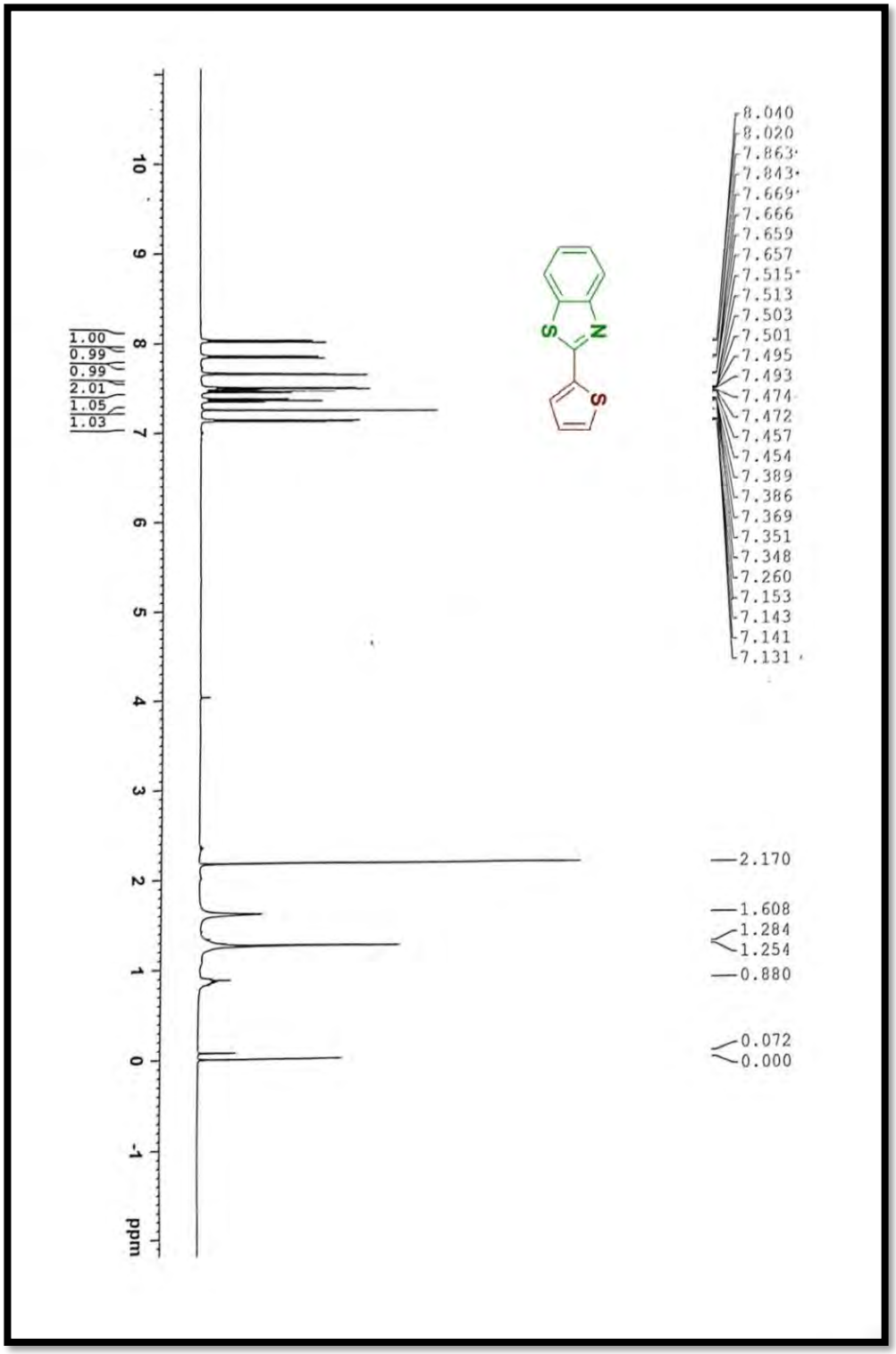


Figure I.A.12. ^{1}H Spectroscopical representation of 2-(Thiophen-2-yl)benzo[*d*]thiazole

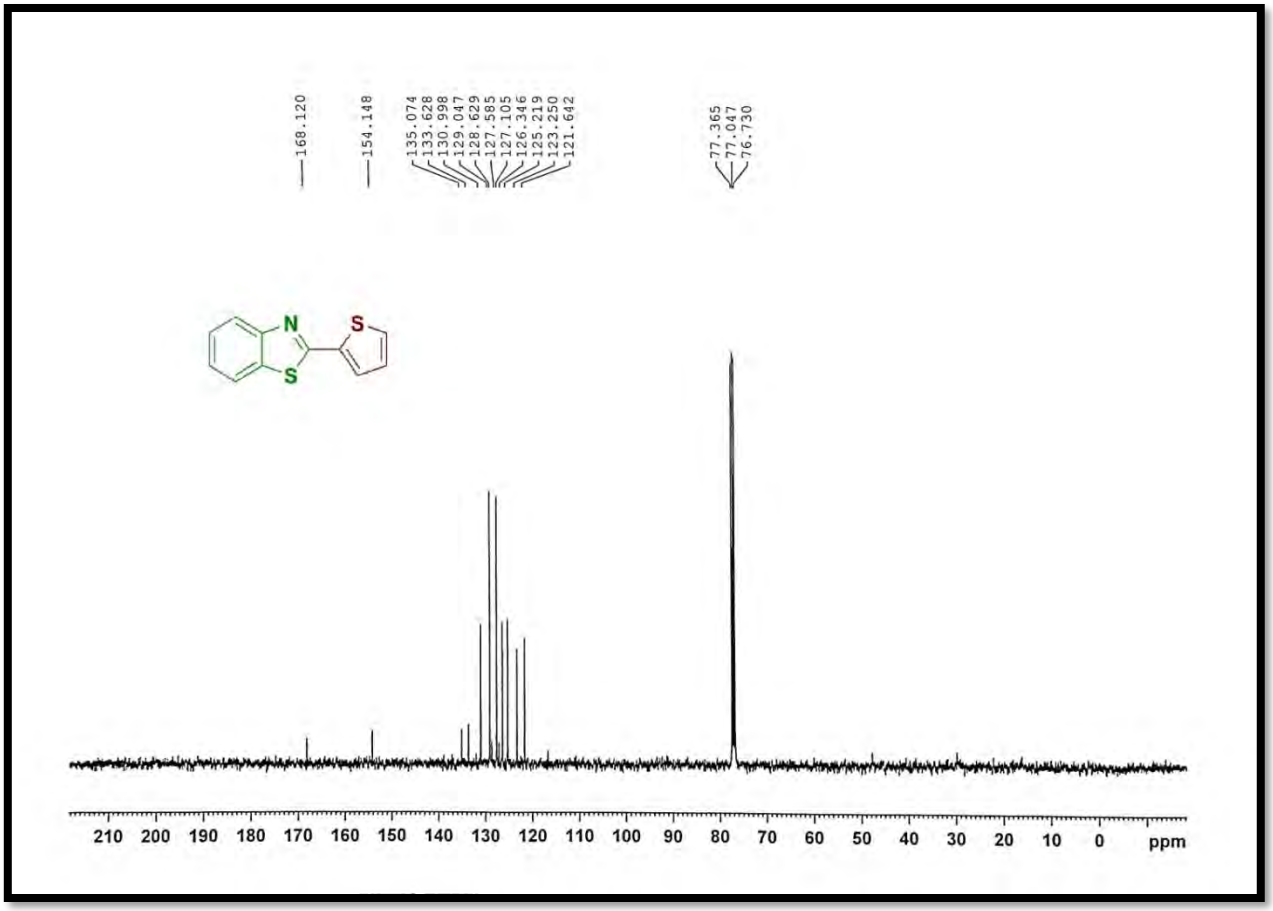


Figure I.A.13. ^{13}C Spectroscopical representation of 2-(Thiophen-2-yl)benzo[*d*]thiazole

4-(Benzo[*d*]thiazol-2-yl)-2-methoxyphenol (Figure I.A.14.).

M.P. : 168 – 169 ºC; yellowish white solid, yield : 94%; **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 2.170 (s, 1H), 4.037 (s, 3H), 5.960 (s, 1H), 7.006 (d, *J* = 8.4, 1H), 7.357 (s, 1H), 7.471 (s, 1H), 7.540 – 7.560 (m,1H), 7.724 (d, *J* = 2 Hz, 1H), 8.023 (d, *J* = 8 Hz, 1H) **(Figure I.A.15.).**

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 56.240, 109.285, 114.702, 121.512, 121.958, 122.759, 124.845, 126.223, 134.859, 146.933, 148.498, 154.104, 168.110 **(Figure I.A.16.).**

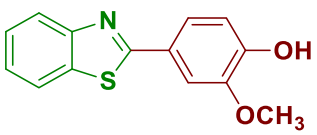


Figure I.A.14. Structure of 4-(Benzo[*d*]thiazol-2-yl)-2-methoxyphenol

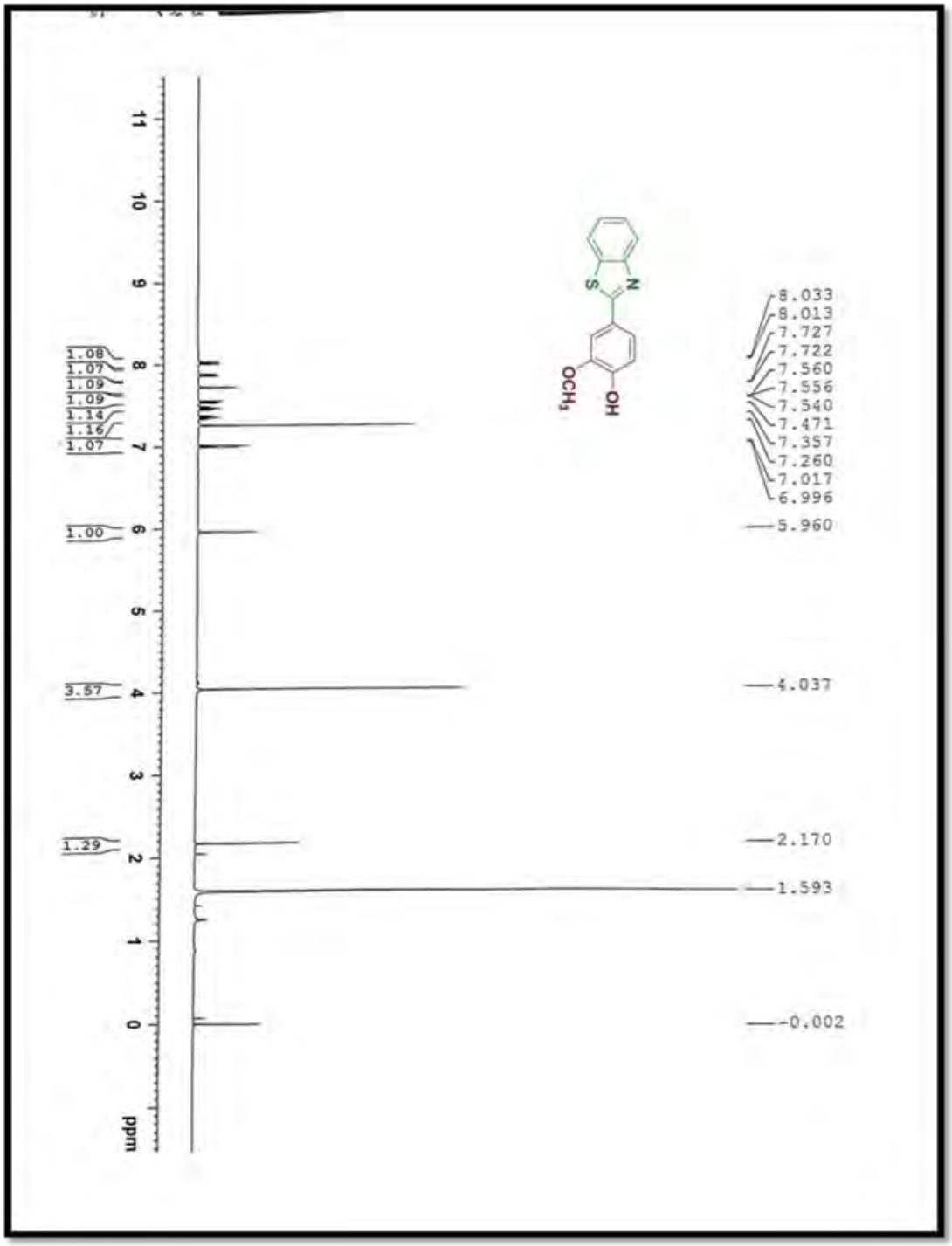


Figure I.A.15. ^{1}H Spectroscopical representation of 4-(Benzo[*d*]thiazol-2-yl)-2-methoxyphenol

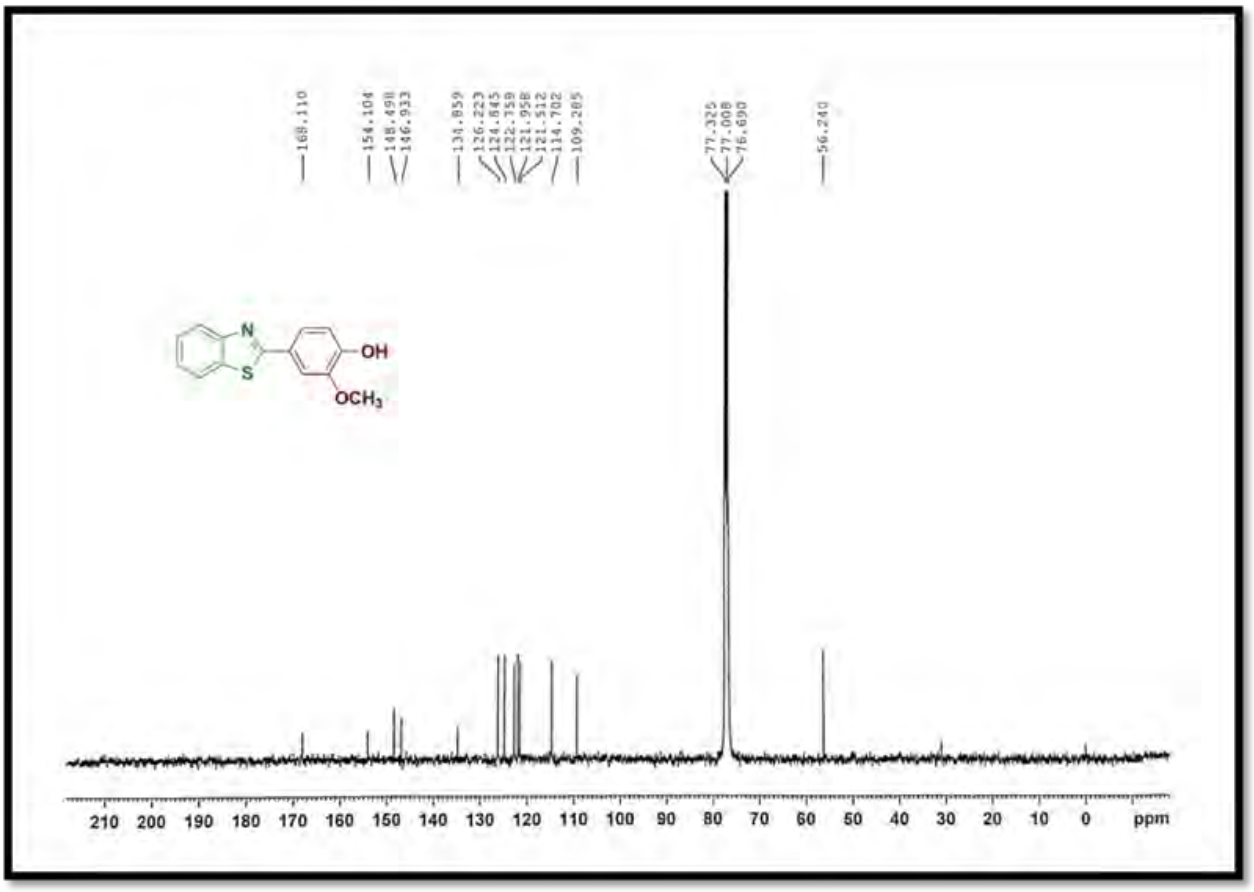


Figure I.A.16. ^{13}C Spectroscopical representation of 4-(Benzo[*d*]thiazol-2-yl)-2-methoxyphenol

4-(Benzo[*d*]thiazol-2-yl)-*N*, *N*-dimethylaniline (Figure I.A.17.).

M.P.: 160 – 162 ºC; yellowish powder, yield : 89%; **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 3.042 (s, 6H), 6.738 (dd, *J* = 2 Hz, *J* = 3.2 Hz, 2H), 7.282 -7.322 (m, 1H), 7.416 – 7.458 (m, 1H), 7.837 (d, *J* = 8 Hz, 1H), 7.951 – 8.001 (m, 3H) **(Figure I.A.18.).**

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 40.178, 111.693, 121.368, 122.282, 124.195, 125.988, 128.874, 134.560, 152.184, 154.433, 168.837 **(Figure I.A.19.).**

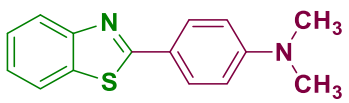


Figure I.A.17. Structure of 4-(Benzo[*d*]thiazol-2-yl)-*N*, *N*-dimethylaniline

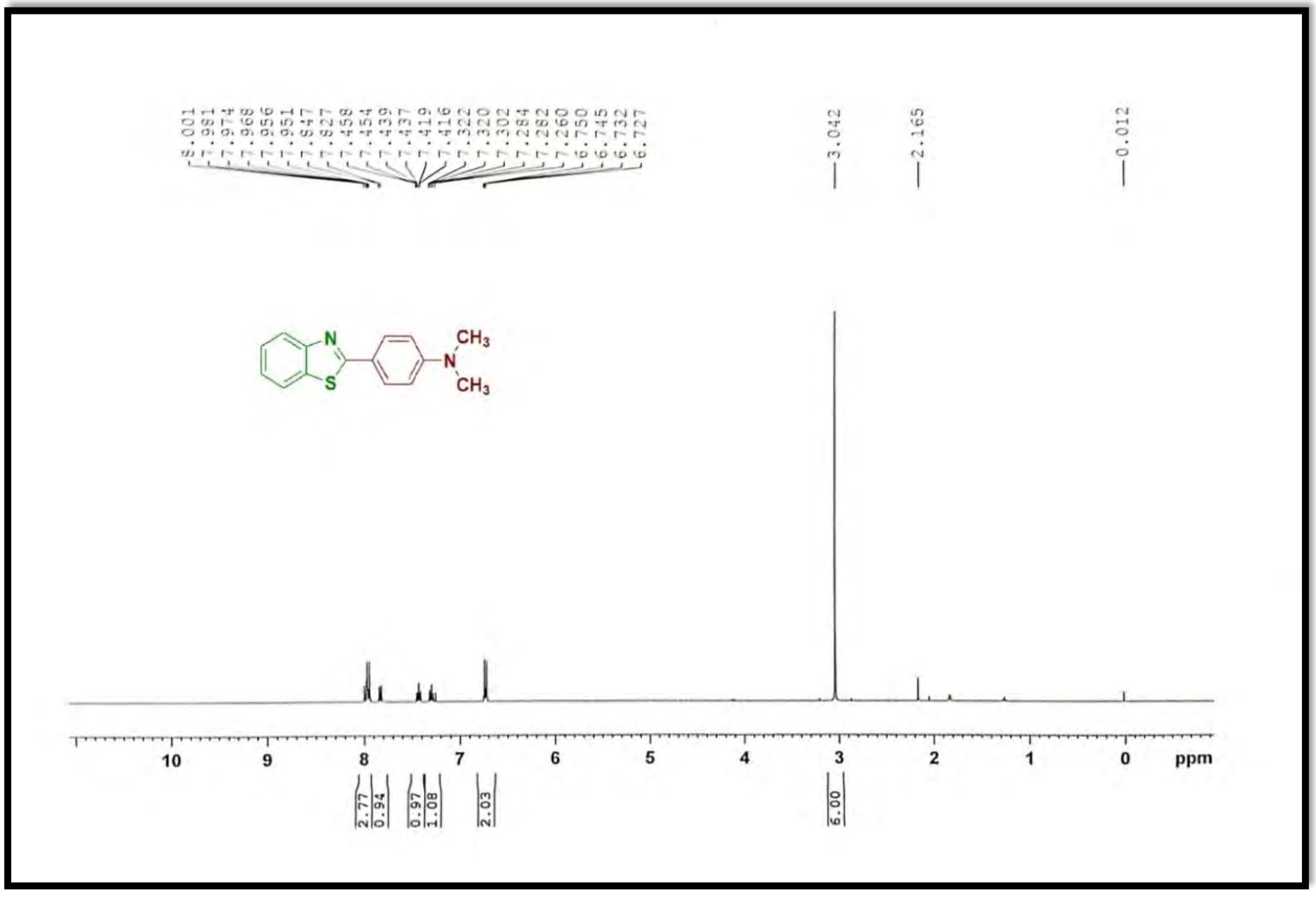


Figure I.A.18. ^{1}H Spectroscopical representation of 4-(Benzo[*d*]thiazol-2-yl)-*N*, *N*-dimethylaniline

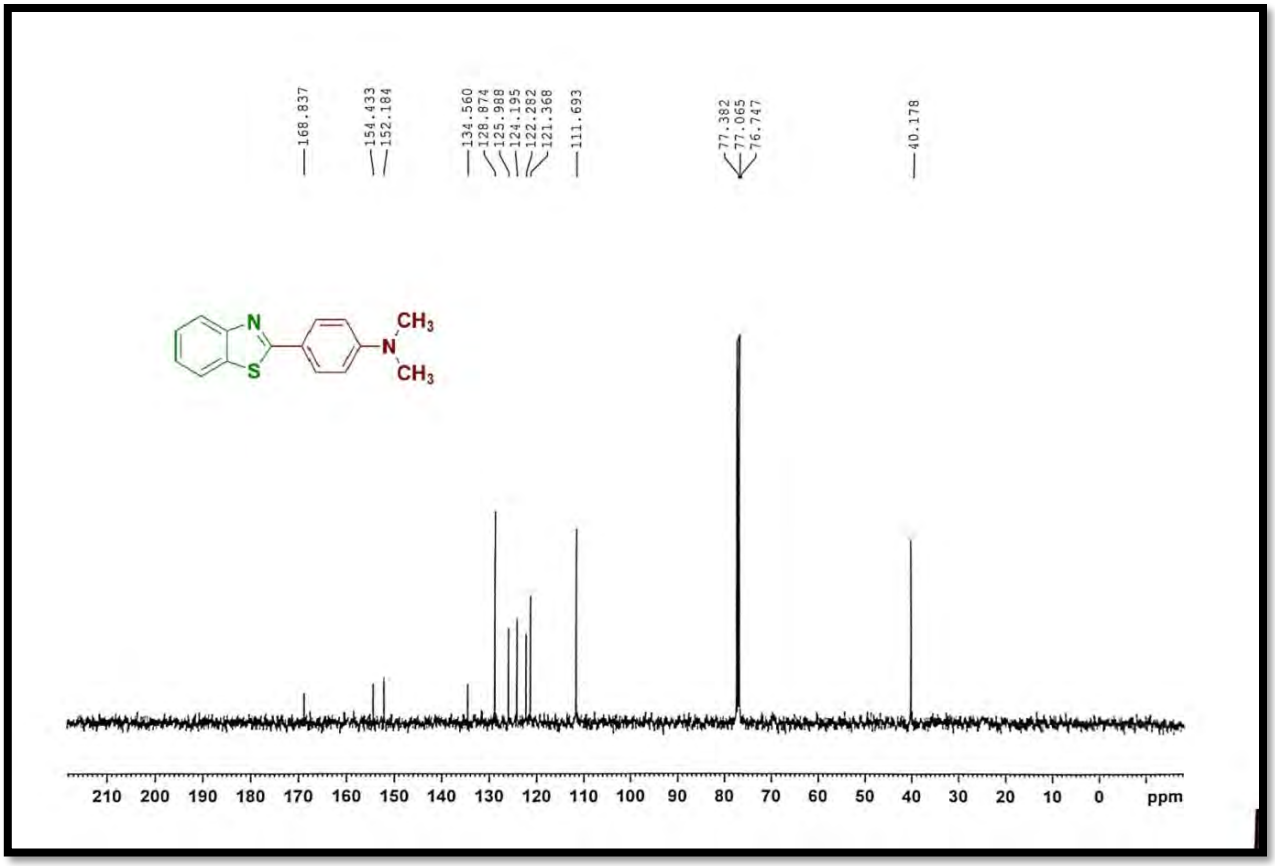


Figure I.A.19. ^{13}C Spectroscopical representation of 4-(Benzo[*d*]thiazol-2-yl)-*N*, *N*-dimethylaniline

2-(Furan-2-yl)benzo[*d*]thiazole (Figure I.A.20.).

M.P. : 102 -104 ºC; yellowish powder; yield : 85%; **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 6.243 (s, 1H), 6.564 (q, *J* = 1.6 Hz, 1H), 7.180 (d, *J* = 3.2 Hz, 1H), 7.332 – 7.489 (m, 1H), 7.575 (d, *J* = 1.16 Hz, 1H), 7.845 – 7.865 (m, 1H), 8.051 (d, *J* = 8.16 Hz, 1H) **(Figure I.A.21.).**

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 111.458, 112.558, 121.591, 123.128, 125.212, 126.497, 134.290, 144.717, 148.760, 153.760, 157.575 **(Figure I.A.22.).**

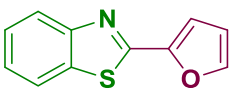


Figure I.A.20. Structure of 2-(Furan-2-yl)benzo[*d*]thiazole

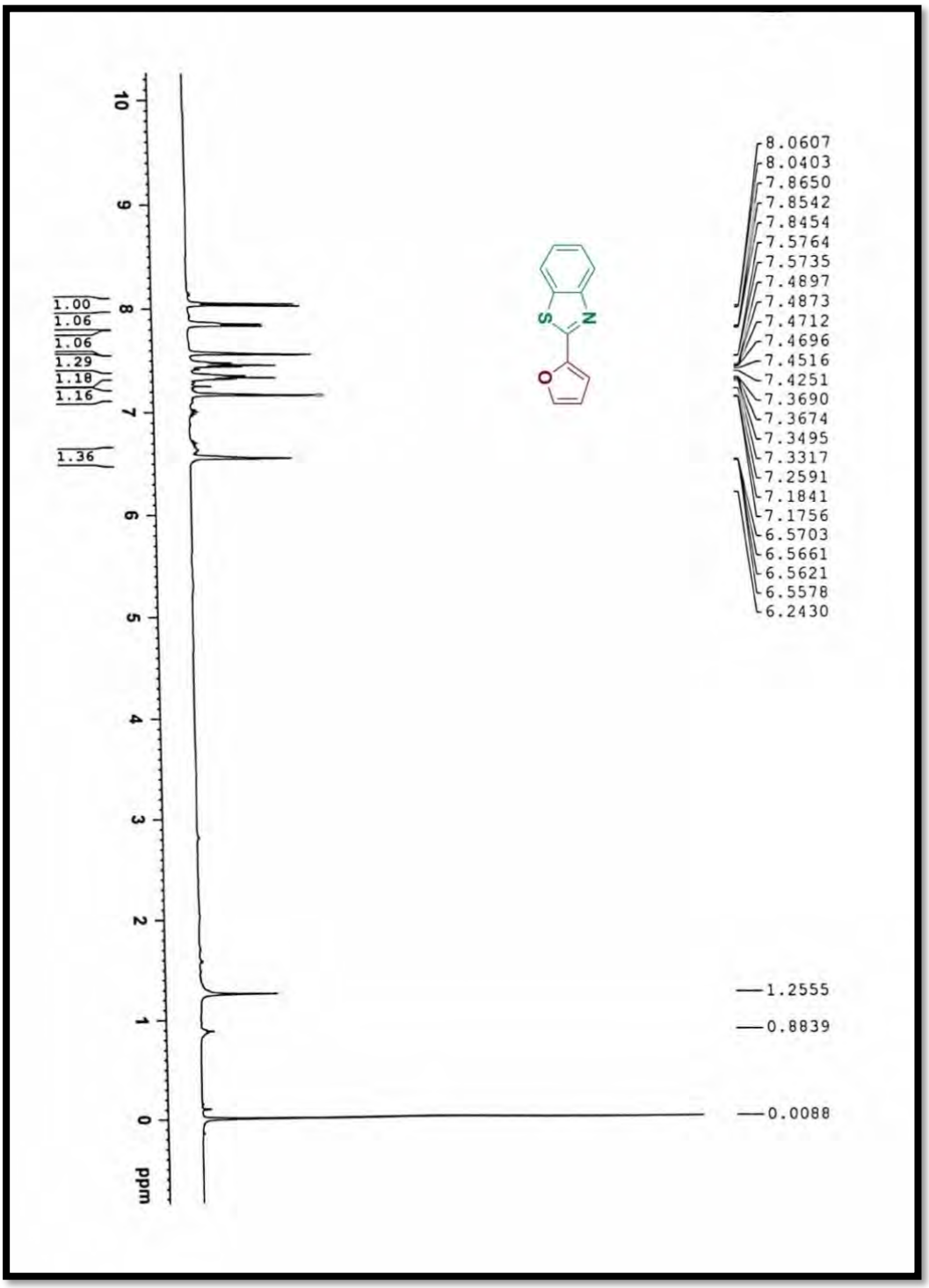


Figure I.A.21. ^{1}H Spectroscopical representation of 2-(Furan-2-yl)benzo[*d*]thiazole

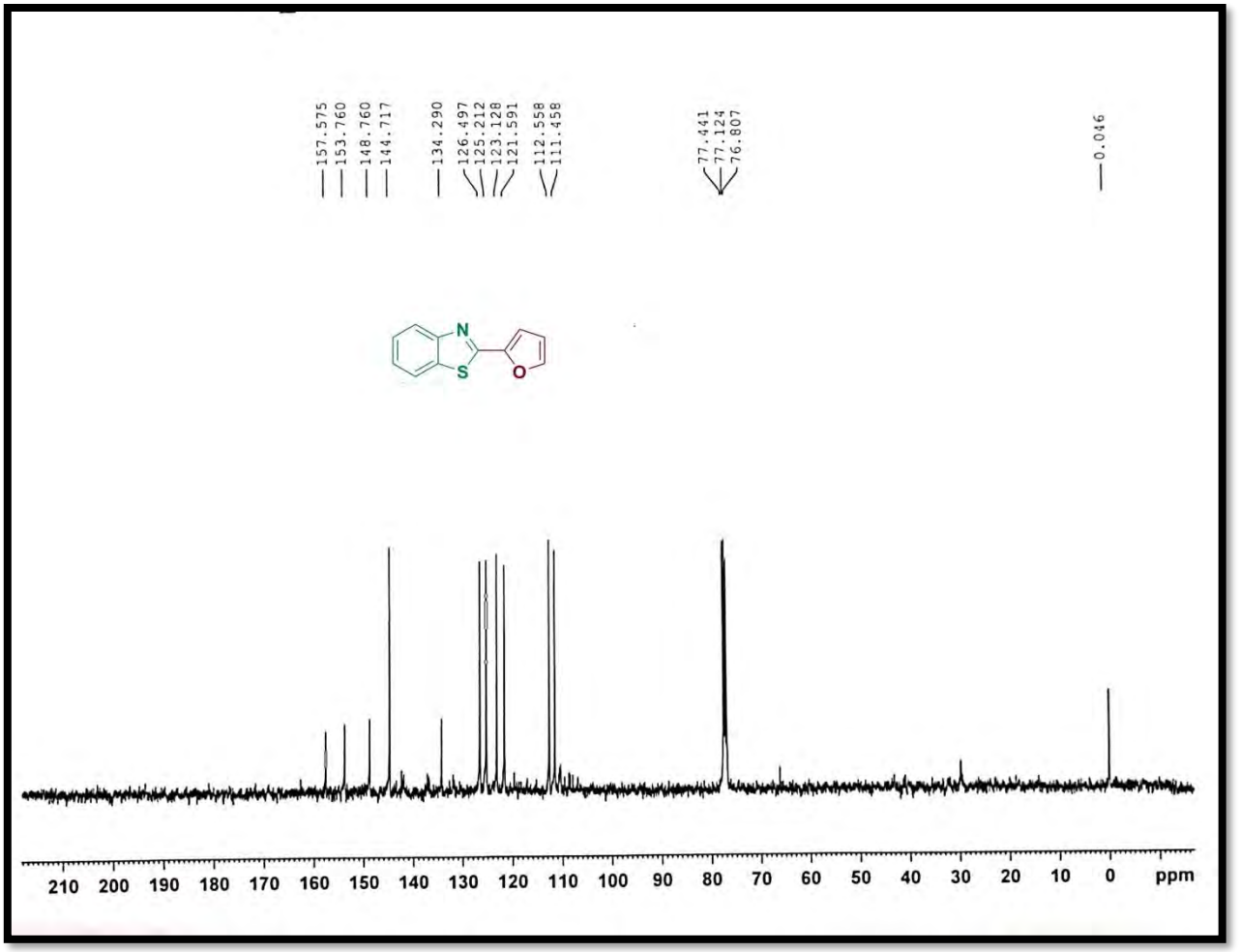


Figure I.A.22. ^{13}C Spectroscopical representation of 2-(Furan-2-yl)benzo[*d*]thiazole

2-(*p*-Tolyl)benzo[*d*]thiazole (Figure I.A.23.).

M. P.: 105 - 107 ºC, white solid, yield : 81%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 2.374 (3H, d, *J* = 38 Hz), 7.284 – 7.351 (2H, m), 7.369 – 7.389 (1H, m), 7.465 – 7.506 (1H, m), 7.884 (1H, d, *J* = Hz), 7.990 (2H, d, *J* = 8 Hz), 8.074 (1H, d, *J* = 8 Hz) **(Figure I.A.24.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.089, 121.594, 123.057, 125.027, 126.269, 127.105, 128.856, 129.308, 129.741, 130.962, 134.957, 141.450, 154.176, 168.281 **(Figure I.A.25.).**

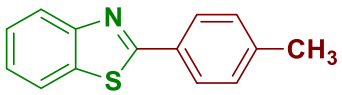


Figure I.A.23. Structure of 2-(*p*-Tolyl)benzo[*d*]thiazole

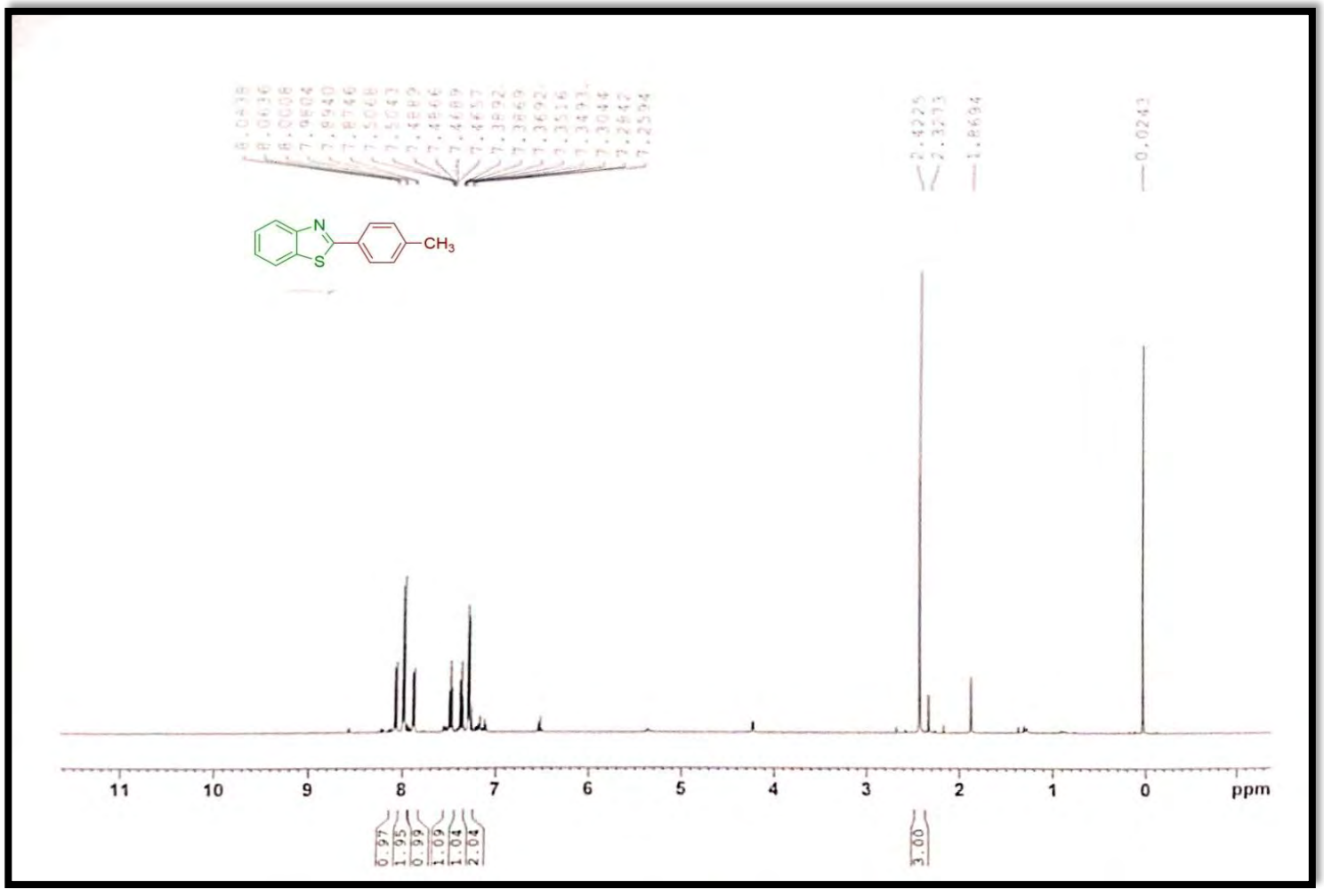


Figure I.A.24. ^{1}H Spectroscopical representation of 2-(*p*-Tolyl)benzo[*d*]thiazole

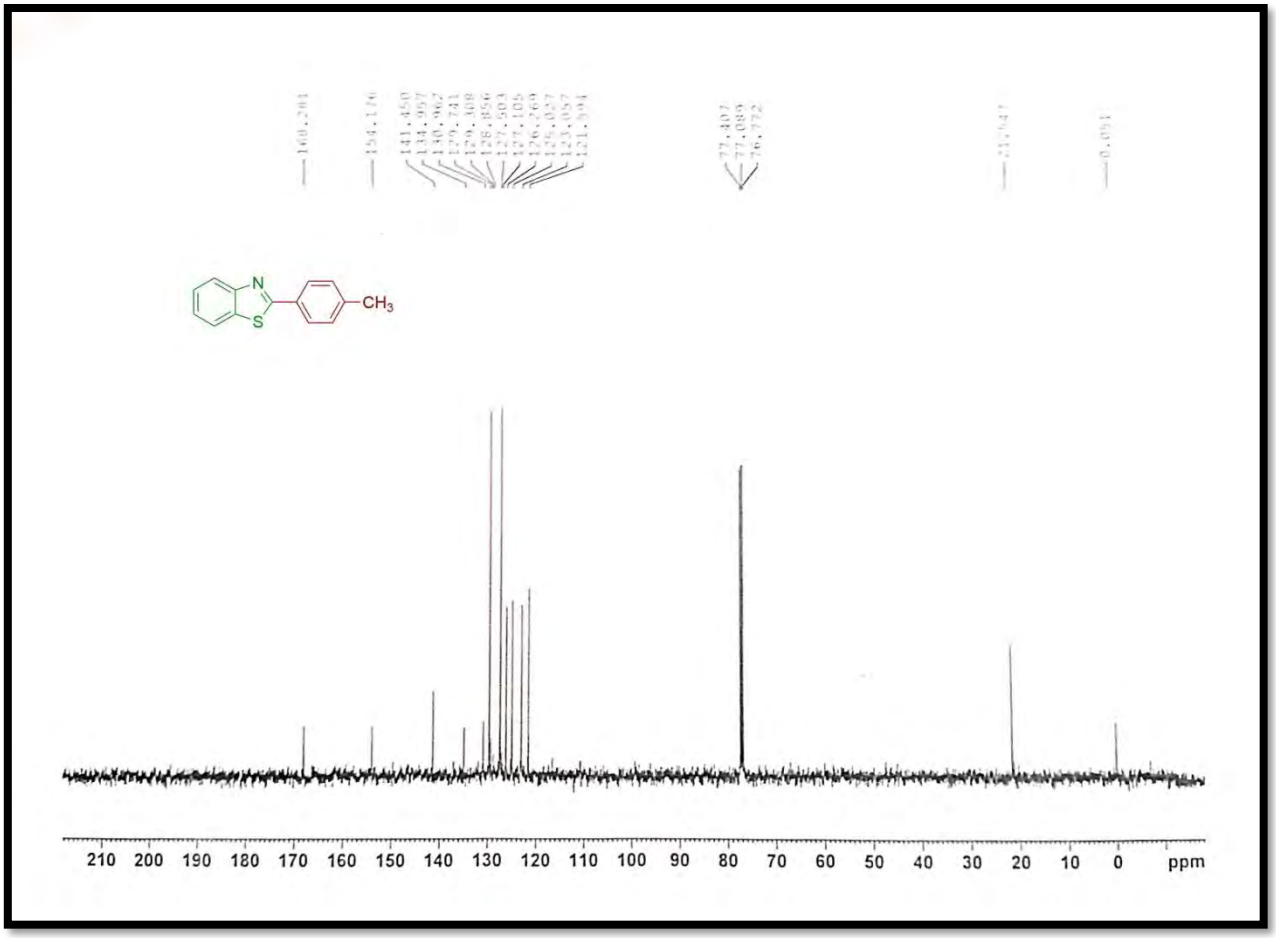


Figure I.A.25. ^{13}C Spectroscopical representation of 2-(*p*-Tolyl)benzo[*d*]thiazole

2-(3-Fluorophenyl)benzo[*d*]thiazole (Figure I.A.26.).

M. P.: 98 - 100 °C, white solid, yield : 83%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 7.189 (1H, dd, *J* = 0.4 Hz, *J* = 2 Hz), 7.392 – 7.532 (3H, m), 7.823 – 7.840 (2H, m), 7.842 – 7.923 (1H, m), 8.086 (1H, d, J = 8 Hz) **(Figure I.A.27.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.029, 114.330, 117.836, 121.693, 123.372, 125.561, 126.534, 130.635, 135.097, 135.651, 135.731, 153.983, 164.204 **(Figure I.A.28.).**

19F NMR (376 MHz, $CDCl_3$): δ (ppm): - 112.003 **(Figure I.A.29.).**

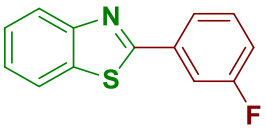


Figure I.A.26. Structure of 2-(3-Fluorophenyl)benzo[*d*]thiazole

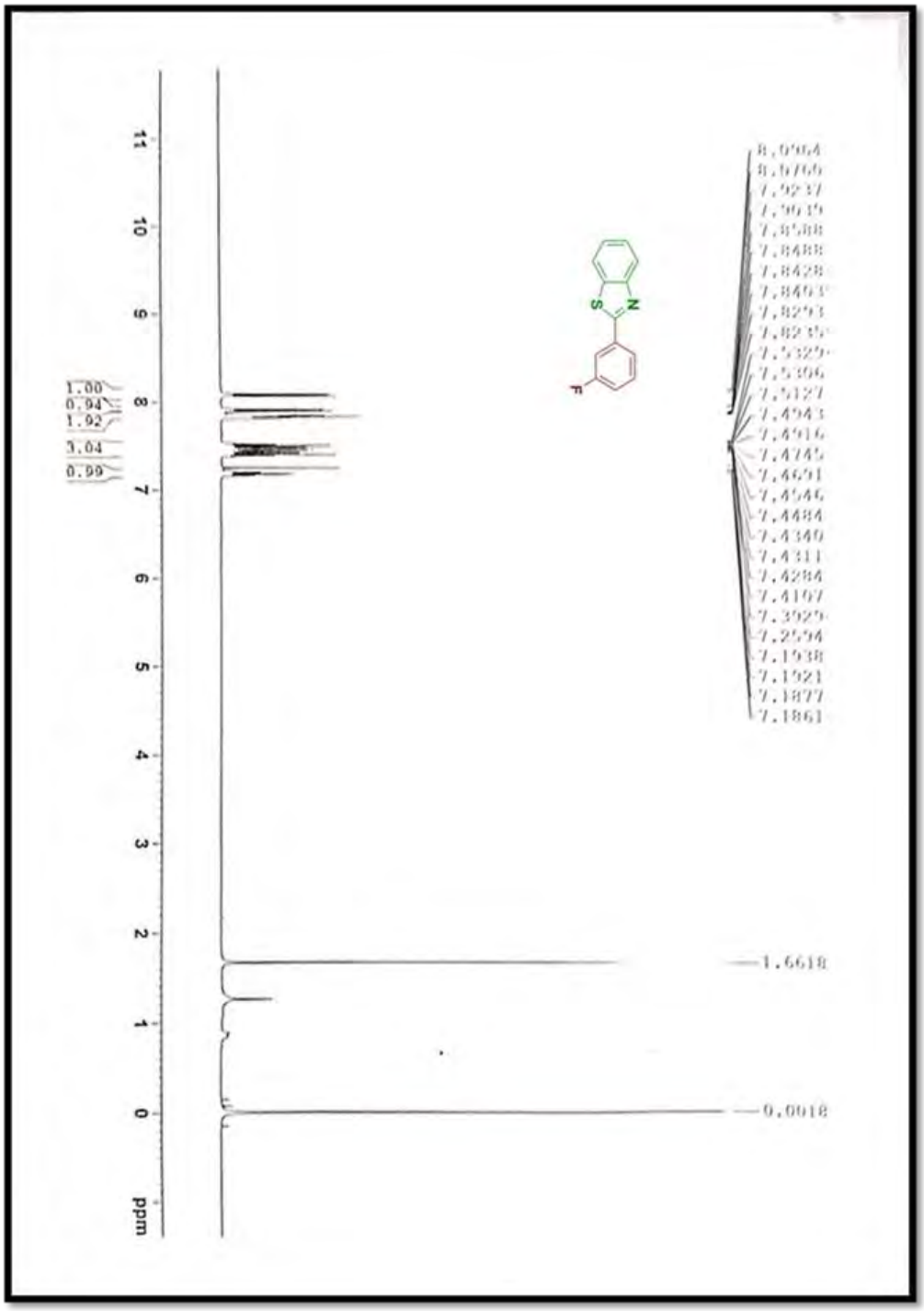


Figure I.A.27. ^{1}H Spectroscopical representation of 2-(3-Fluorophenyl)benzo[*d*]thiazole

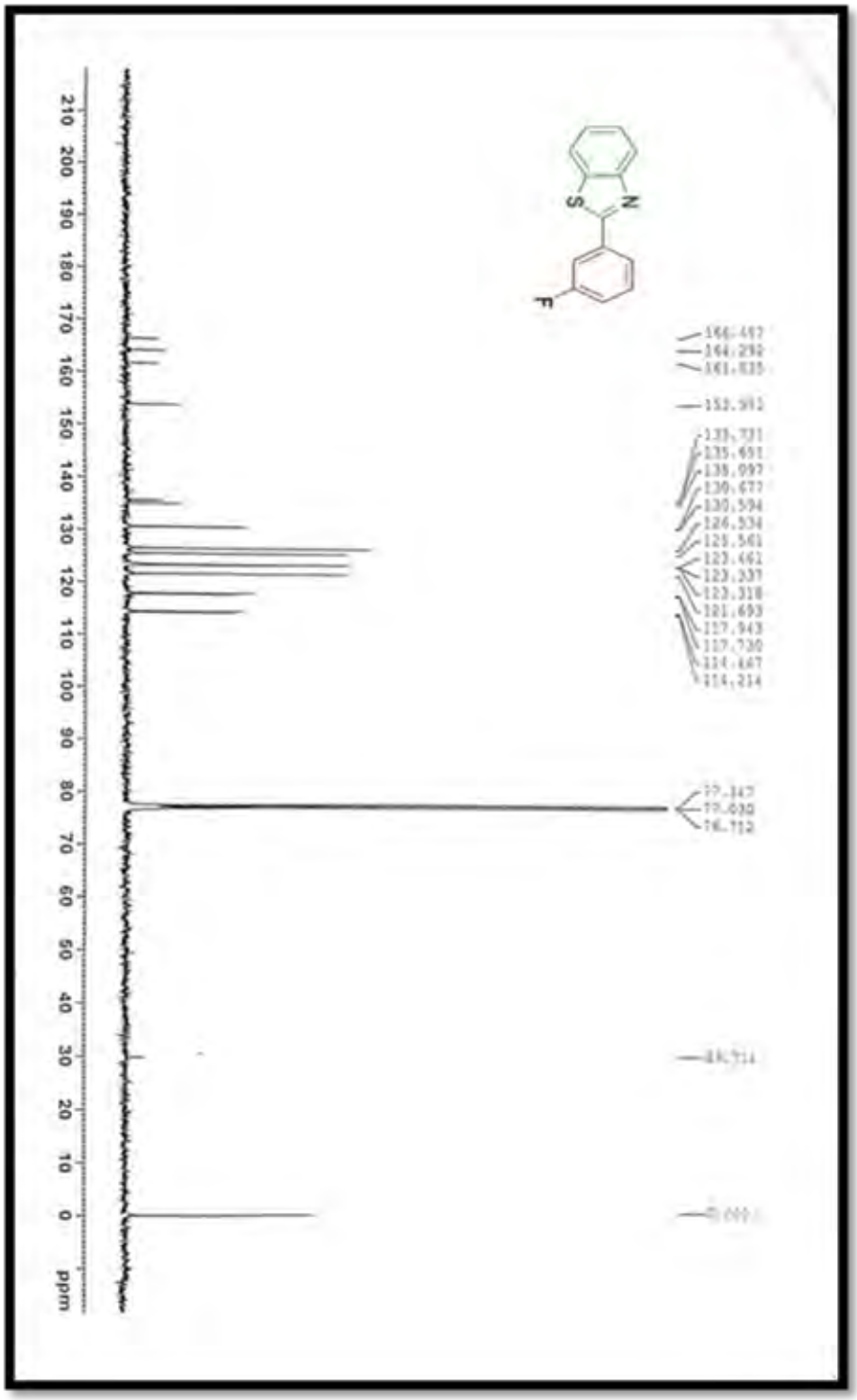


Figure I.A.28. ^{13}C Spectroscopical representation of 2-(3-Fluorophenyl)benzo[*d*]thiazole

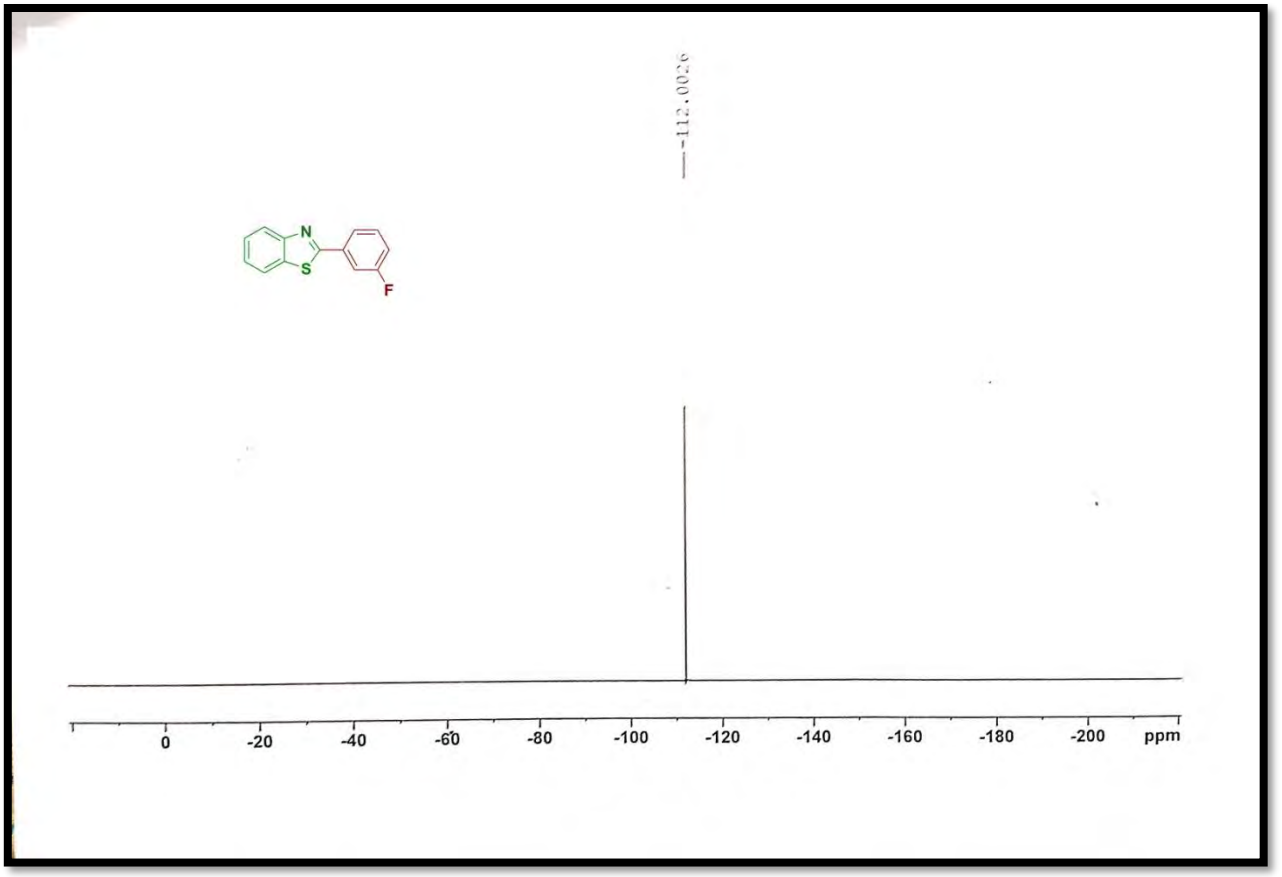


Figure I.A.29. ^{19}F Spectroscopical representation of 2-(3-Fluorophenyl)benzo[*d*]thiazole

2-(4-(Trifluoromethyl)phenyl)benzo[*d*]thiazole (Figure I.A.30.).

M. P.: 157–158 °C, white solid, yield : 94%, **^{1}H NMR (400 MHz,$CDCl_3$): δ (ppm):** 7.485 – 7.596 (2H, m), 7.923 (2H, d, *J* = 8 Hz), 8.148 (2H, dd, *J* = 8 Hz), 8.294 (2H, d, *J* = 8 Hz) **(Figure I.A.31.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 123.066, 123.766, 126.601, 126.846, 127.449, 128.438, 135.250, 136.899, 153.896, 166.042 **(Figure I.A.32.).**

19F NMR (376 MHz, $CDCl_3$): δ (ppm): - 59.178 **(Figure I.A.33.).**

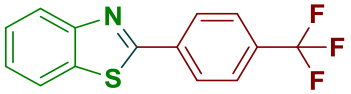


Figure I.A.30. Structure of 2-(4-(Trifluoromethyl)phenyl)benzo[*d*]thiazole

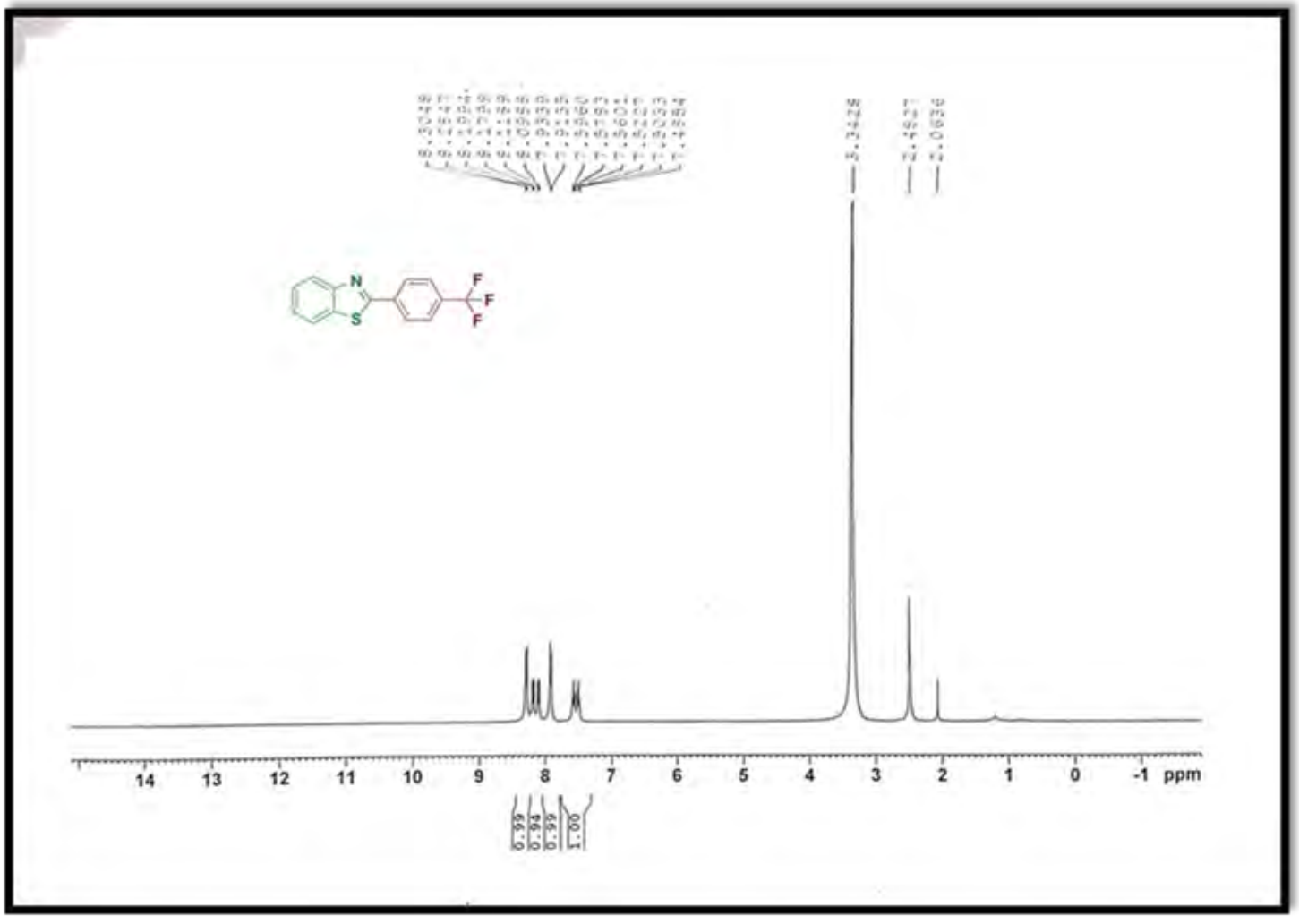


Figure I.A.31. ^{1}H Spectroscopical representation of 2-(4-(Trifluoromethyl)phenyl)benzo[*d*]thiazole

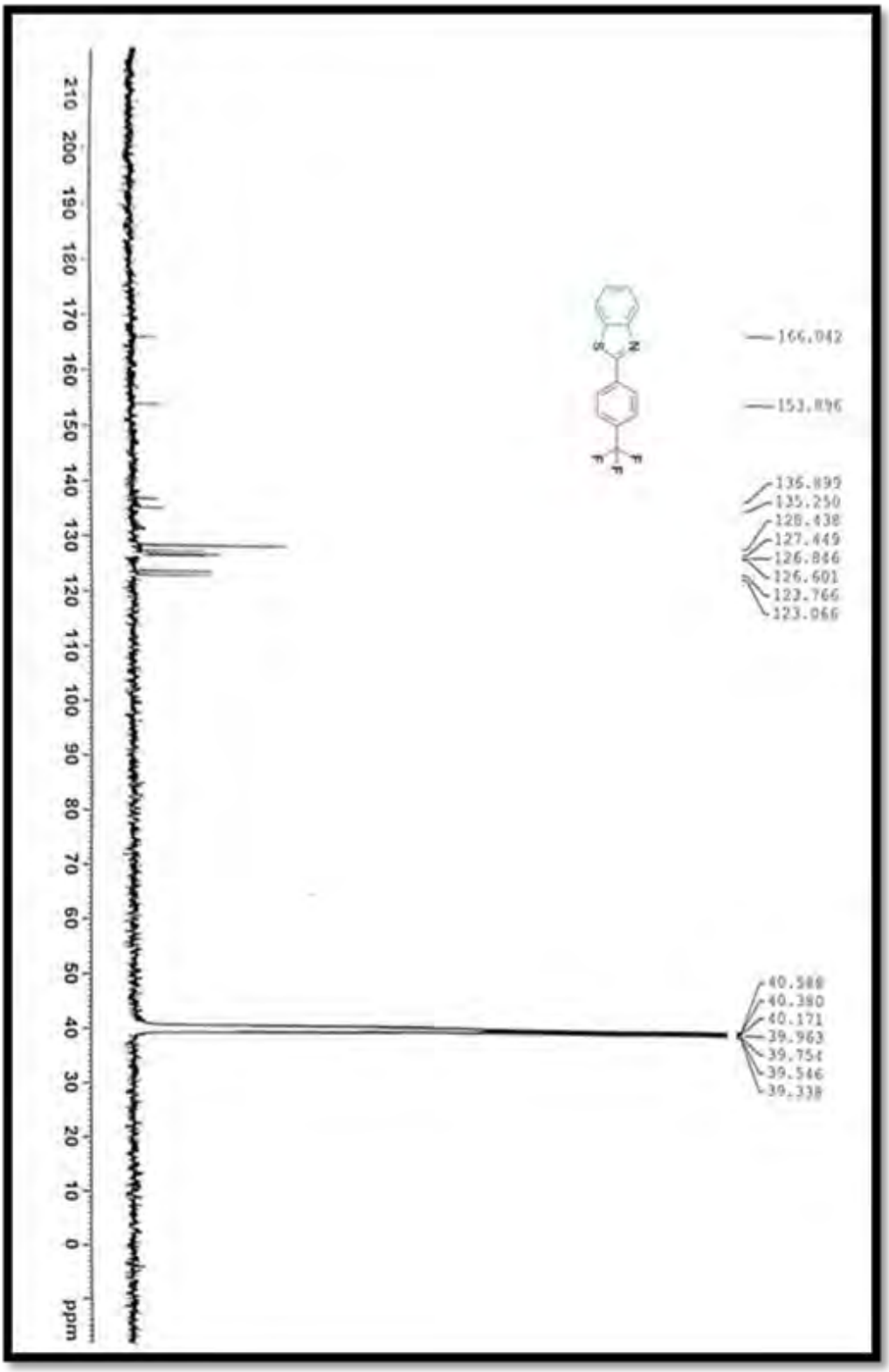


Figure I.A.32. ^{13}C Spectroscopical representation of 2-(4-(Trifluoromethyl)phenyl)benzo[*d*]thiazole

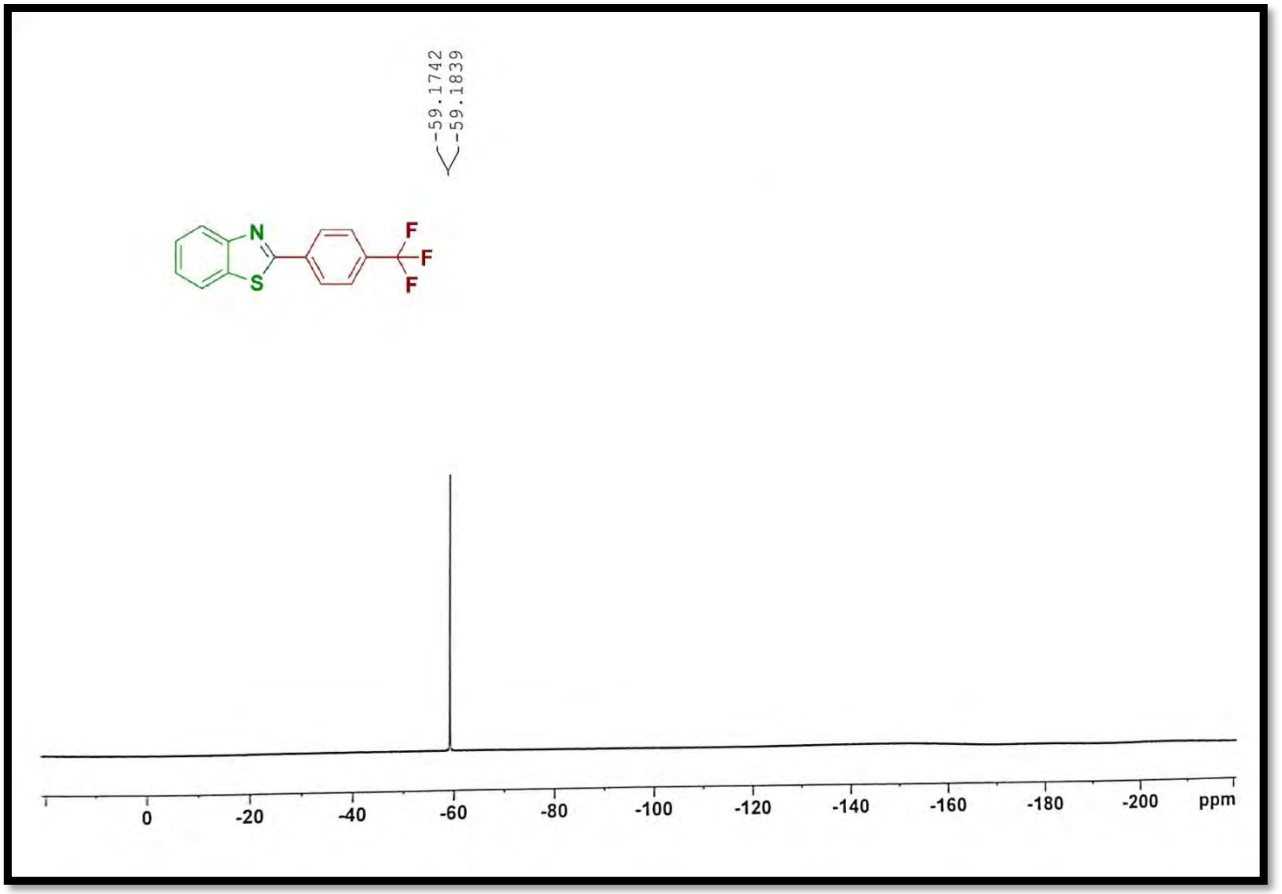


Figure I.A.33. ^{19}F Spectroscopical representation of 2-(4-(Trifluoromethyl)phenyl)benzo[*d*]thiazole

2-(2-Hydroxyphenyl)benzo[*d*]thiazole (Figure I.A.34.).

M. P.: 110 °C; yellow solid; yield : 90%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 6.926 – 6.966 (1H, m), 7.102 – 7.123 (1H, m), 7.358 – 7.510 (3H, m), 7.659 – 7.682 (1H, m), 7.861 – 7.997 (2H, m), 12.526 (1H, s) **(Figure I.A.35.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.091, 116.789, 117.874, 119.532, 121.511, 122.172, 125.542, 128.424, 132.590, 132.761, 151.827, 157.948, 169.377 **(Figure I.A.36.).**

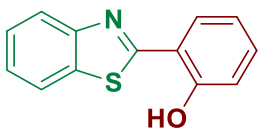


Figure I.A.34. Structure of 2-(2-Hydroxyphenyl)benzo[*d*]thiazole

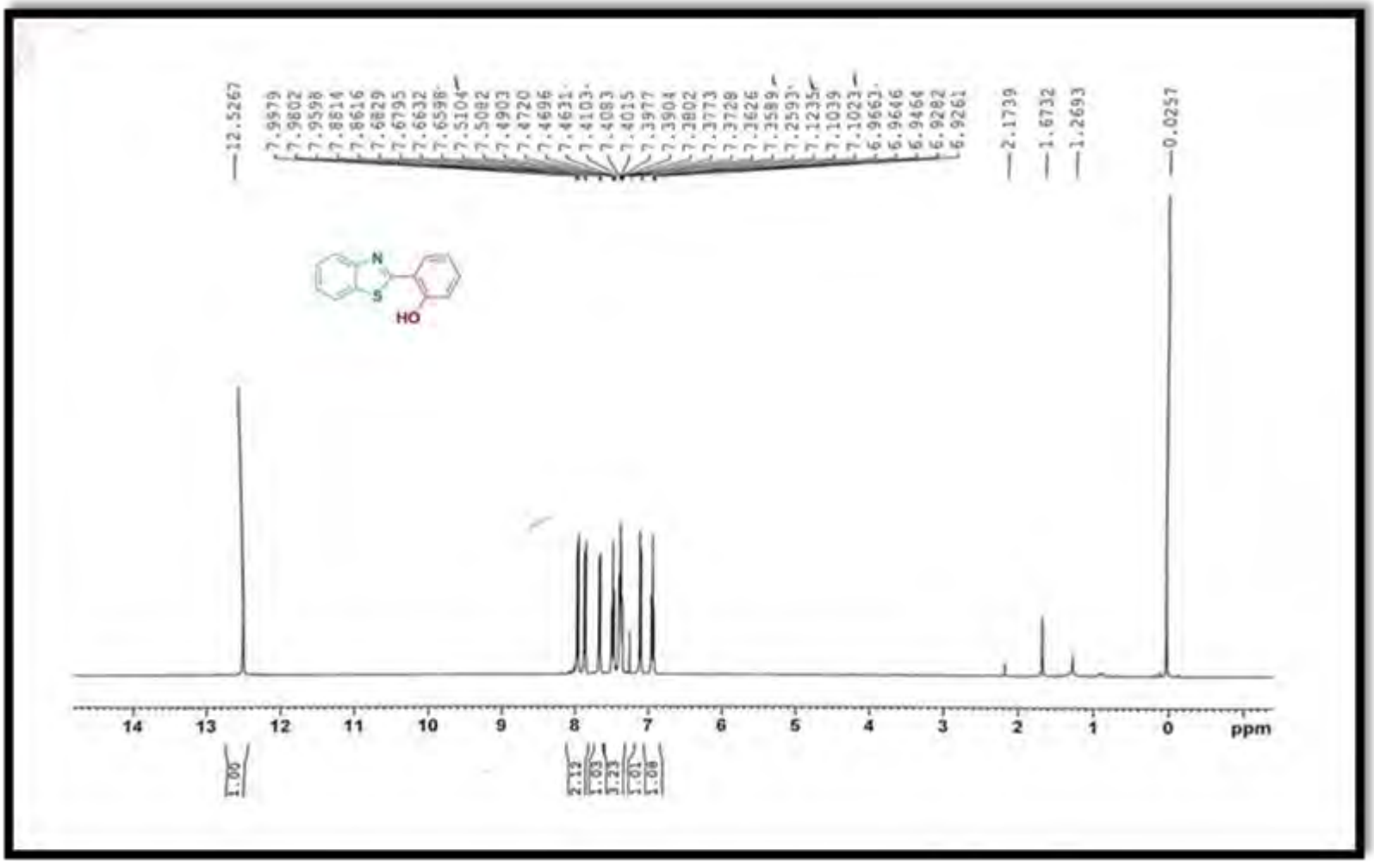


Figure I.A.35. ^{1}H Spectroscopical representation of 2-(2-Hydroxyphenyl)benzo[*d*]thiazole

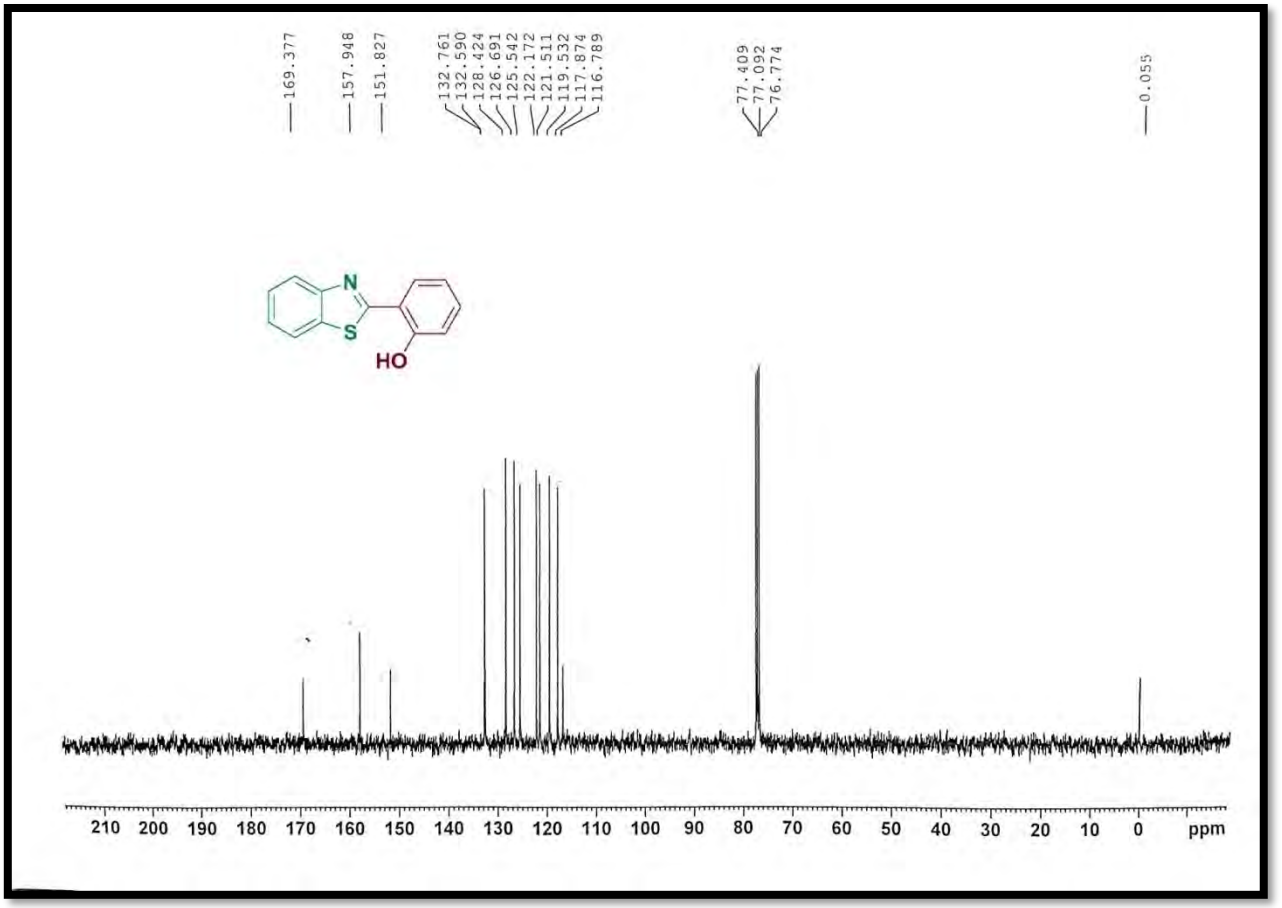


Figure I.A.36. ^{13}C Spectroscopical representation of 2-(2-Hydroxyphenyl)benzo[*d*]thiazole

2-(4-Biphenyl)benzo[*d*]thiazole (Figure I.A.37.).

M. P.: 248 °C, yellowish white solid, yield : 94%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 7.380 – 7.533 (5H, m), 7.696 (4H, dd, *J* = 8 Hz), 7.910 (1H, d, *J* = 8 Hz), 8.139 (3H, dd, *J* = 8 Hz, *J* = 17.6 Hz) **(Figure I.A.38.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.076, 121.660, 123.228, 125.223, 126.391, 127.137, 127.662, 128.019, 128.964, 132.512, 135.089, 140.068, 143.730, 154.236, 167.740 **(Figure I.A.39.).**

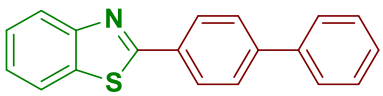


Figure I.A.37. Structure of 2-(4-Biphenyl)benzo[*d*]thiazole

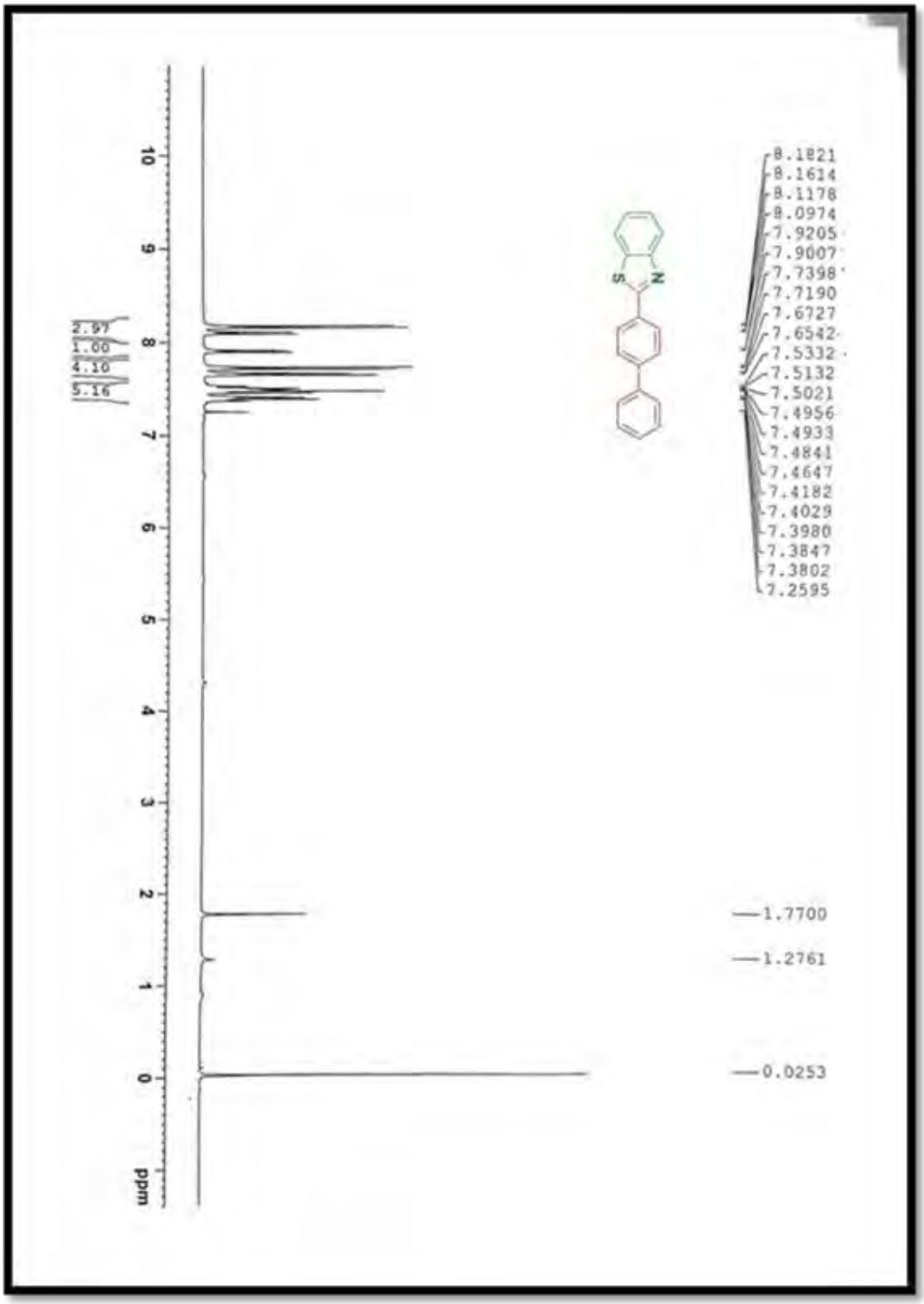


Figure I.A.38. ^{1}H Spectroscopical representation of 2-(4-Biphenyl)benzo[*d*]thiazole

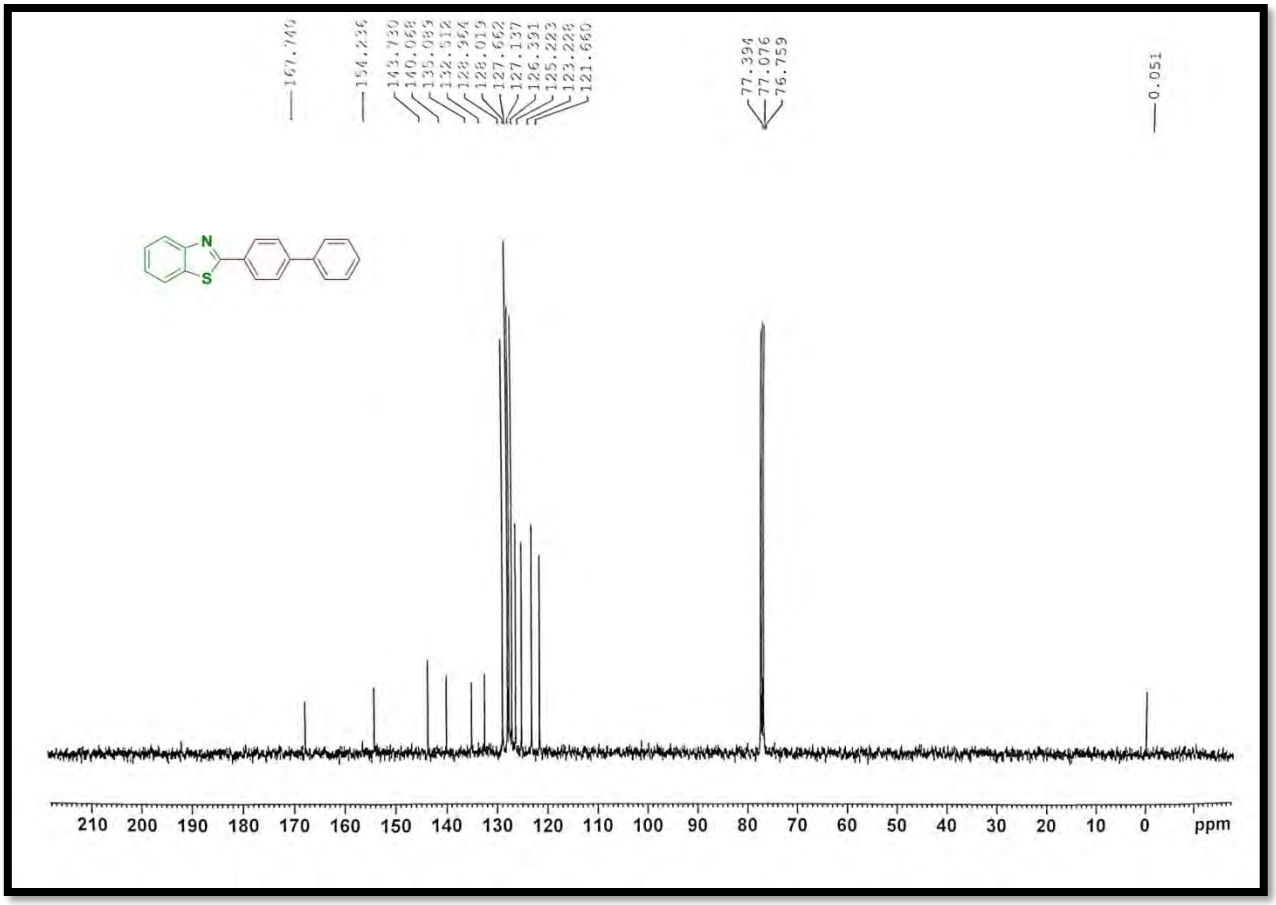


Figure I.A.39. ^{13}C Spectroscopical representation of 2-(4-Biphenyl)benzo[*d*]thiazole

2-(4-Chlorophenyl)benzo[*d*]thiazole (Figure I.A.40.).

M. P.: 105 °C, yellowish white solid, yield : 92%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 7.390 (1H, q, *J* = 0.8 Hz), 7.416 – 7.521 (3H, m), 7.897 (1H, d, *J* = 8 Hz), 8.076 – 8.004 (3H, m) **(Figure I.A.41.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.037, 121.667, 123.312, 125.433, 126.503, 128.351, 128.724, 129.289, 132.120, 135.063, 137.047, 154.072, 166.646 **(Figure I.A.42.).**

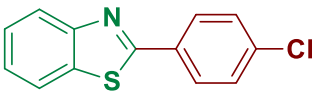


Figure I.A.40. Structure of 2-(4-Chlorophenyl)benzo[*d*]thiazole

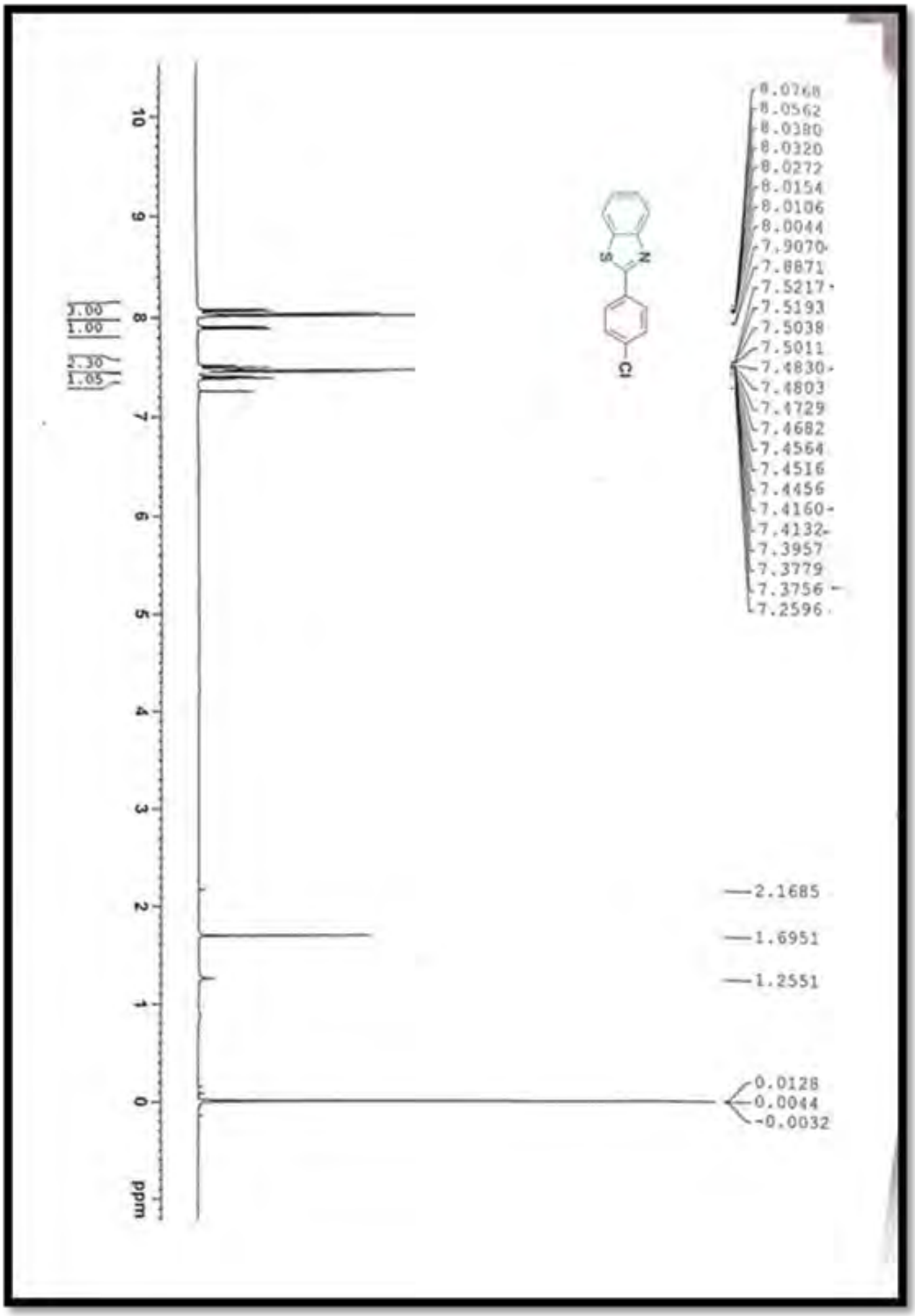


Figure I.A.41. ^{1}H Spectroscopical representation of 2-(4-Chlorophenyl)benzo[*d*]thiazole

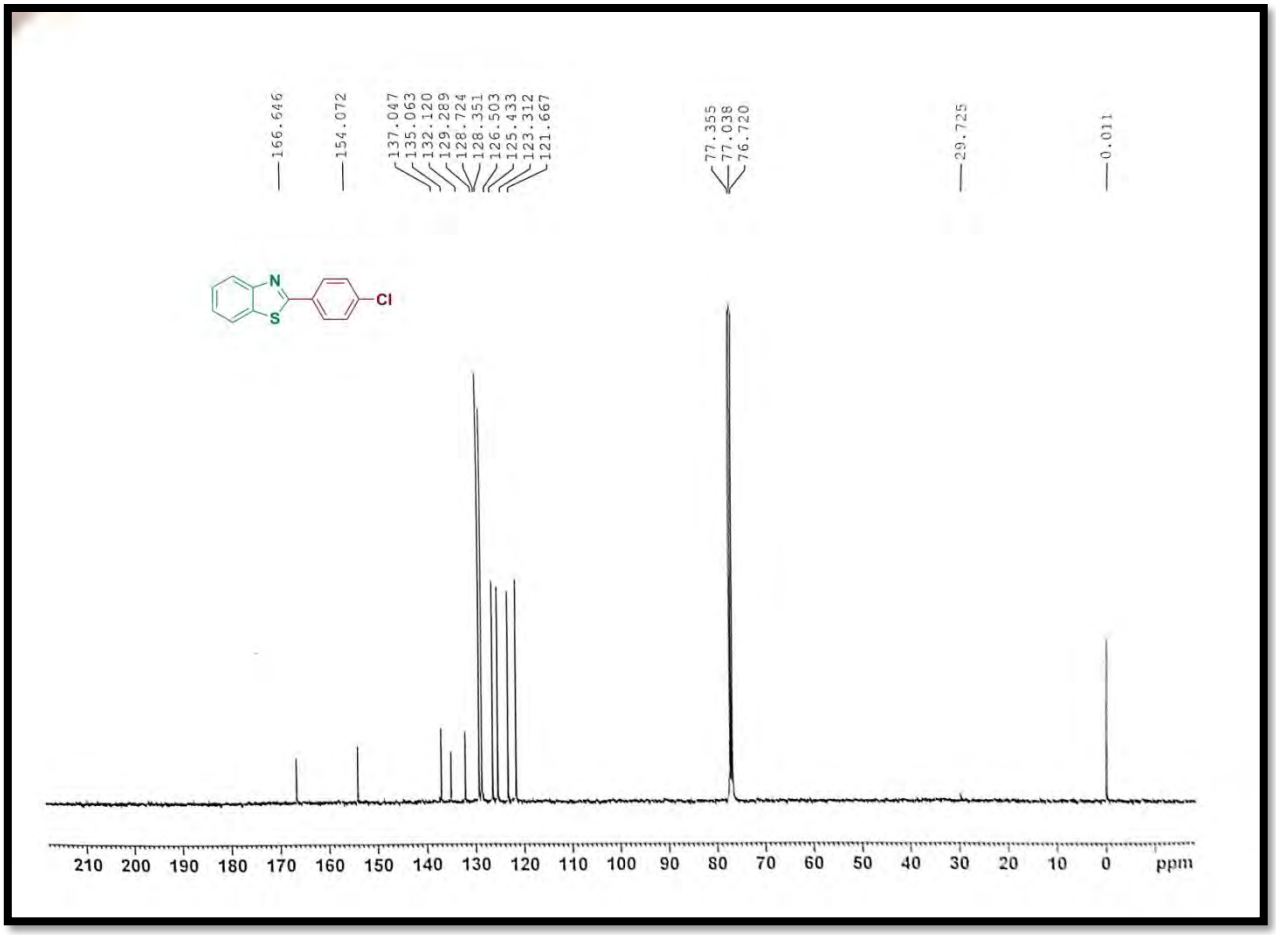


Figure I.A.42. ^{13}C Spectroscopical representation of 2-(4-Chlorophenyl)benzo[*d*]thiazole

2-(2-Naphthyl)benzo[*d*]thiazole (Figure I.A.43.).

M. P.: 245 - 248 °C, white solid, yield: 93%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 7.392 (1H, t, *J* = 8 Hz), 7.495 – 7.565 (3H, m), 7.852 – 7.965 (4H, m), 8.125 – 8.220 (2H, m), 8.559 (1H, s) **(Figure I.A.44.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.109, 121.673, 123.263, 124.454, 125.268, 126.416, 126.897, 127.478, 127.604, 127.896, 128.846, 130.993, 133.203, 134.628, 135.163, 154.260, 168.135 **(Figure I.A.45.).**

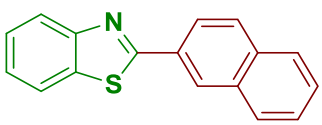


Figure I.A.43. Structure of 2-(2-Naphthyl)benzo[*d*]thiazole

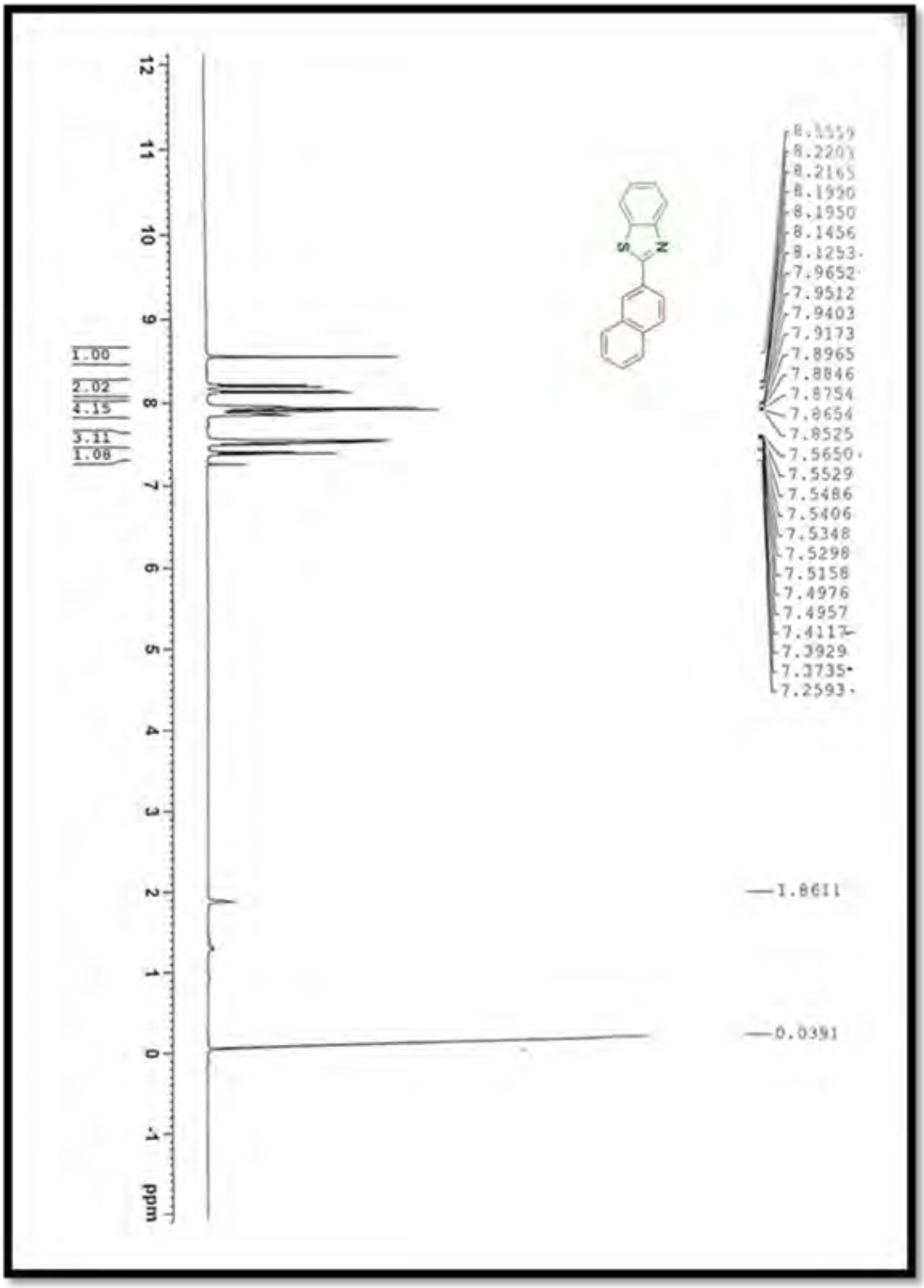


Figure I.A.44. ^{1}H Spectroscopical representation of 2-(2-Naphthyl)benzo[*d*]thiazole

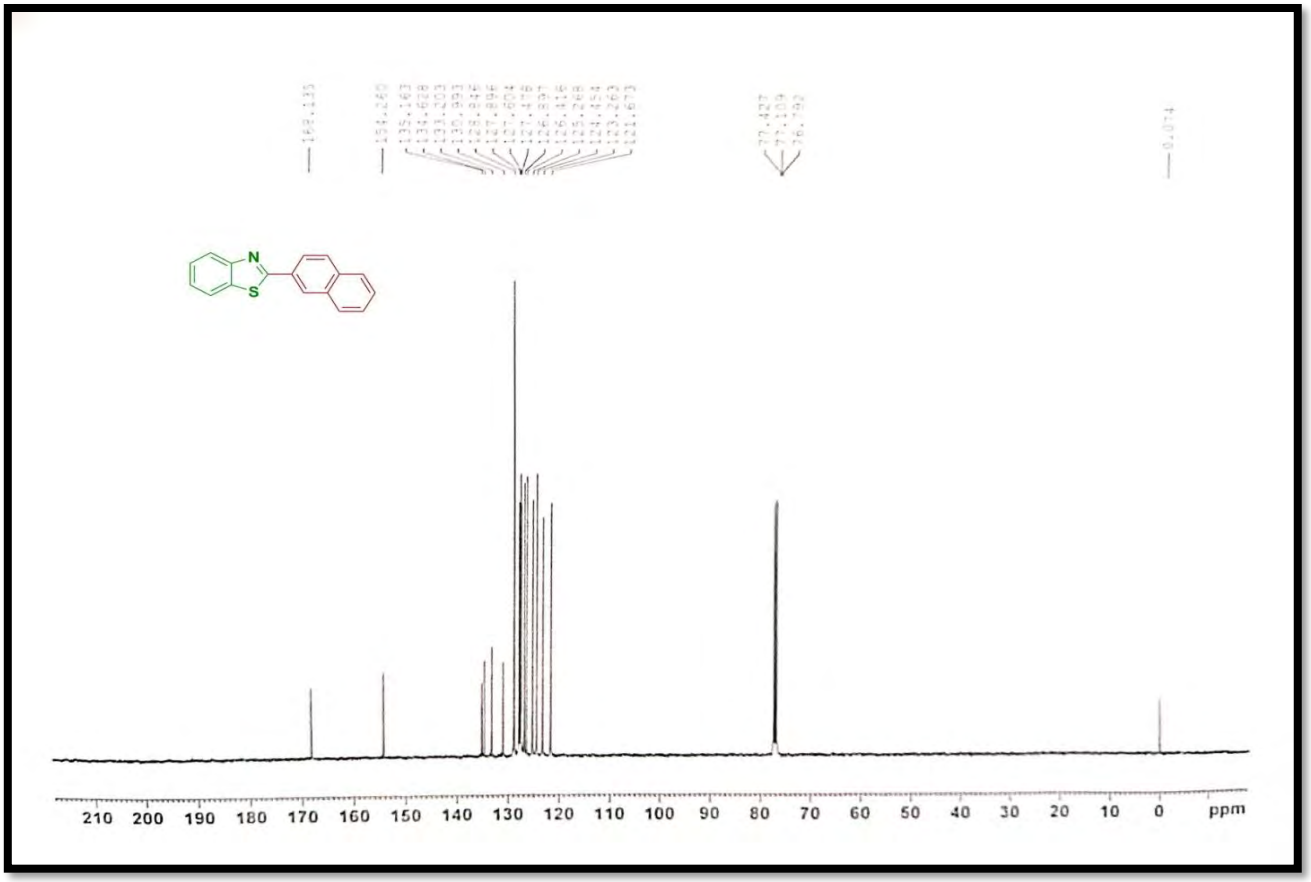


Figure I.A.45. ^{13}C Spectroscopical representation of 2-(2-Naphthyl)benzo[*d*]thiazole

2-(4-Fluorophenyl)benzo[*d*]thiazole (Figure I.A.46.).

M. P.: 102–103 °C, white solid, yield: 95%, **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 7.150 – 7.207 (2H, m), 7.364 – 7.405 (1H, m), 7.474 – 7.515 (1H, m), 7.891 (1H, d, *J* = 8 Hz), 8.052 – 8.106 (3H, m) **(Figure I.A.47.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 77.036, 116.051, 116.270, 121.621, 123.211, 125.258, 129.491, 129.576, 129.971, 135.068, 154.118, 163.215, 166.230 **(Figure I.A.48.).**

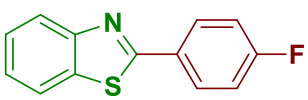


Figure I.A.46. Structure of 2-(4-Fluorophenyl)benzo[*d*]thiazole

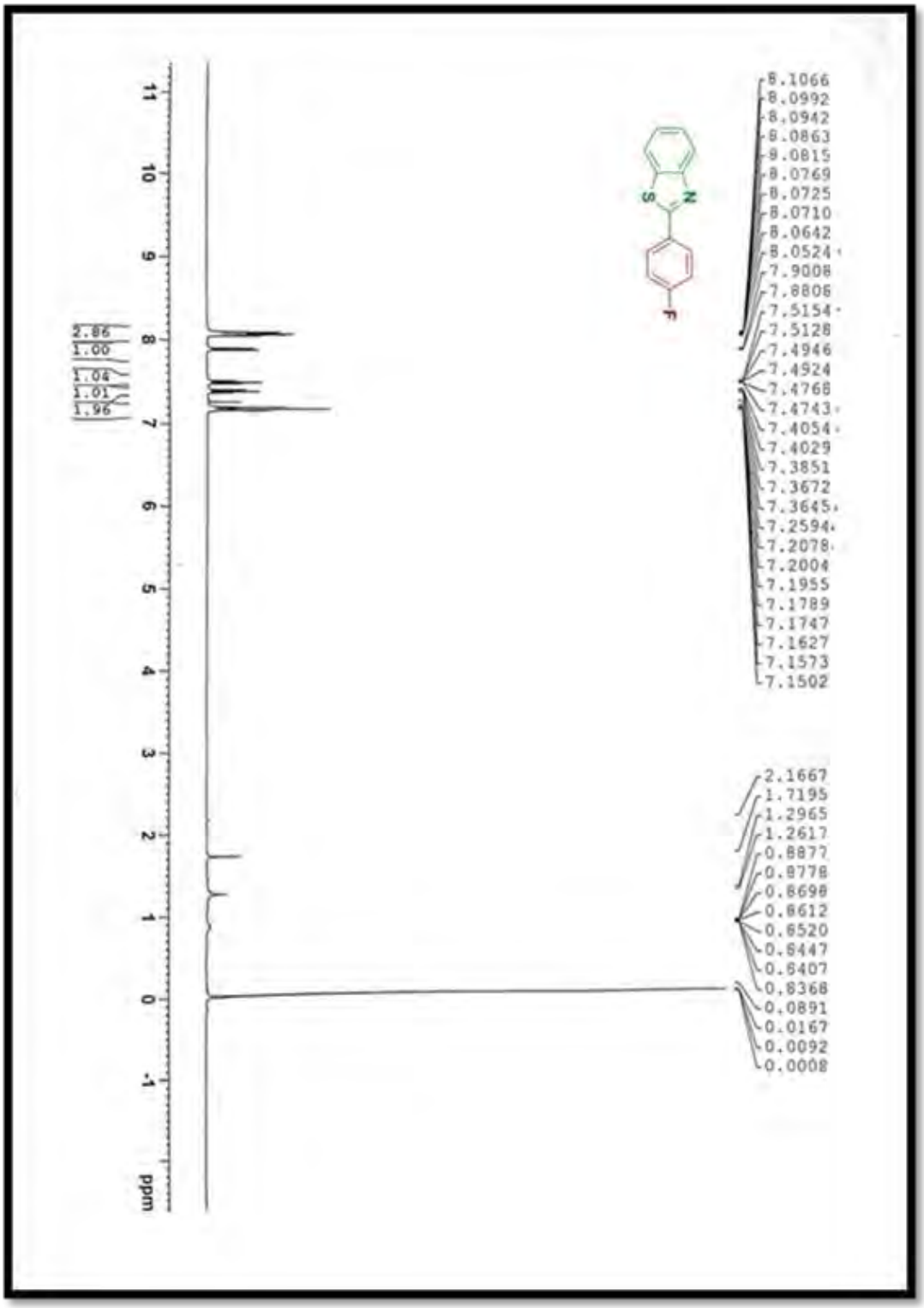


Figure I.A.47. ^{1}H Spectroscopical representation of 2-(4-Fluorophenyl)benzo[*d*]thiazole

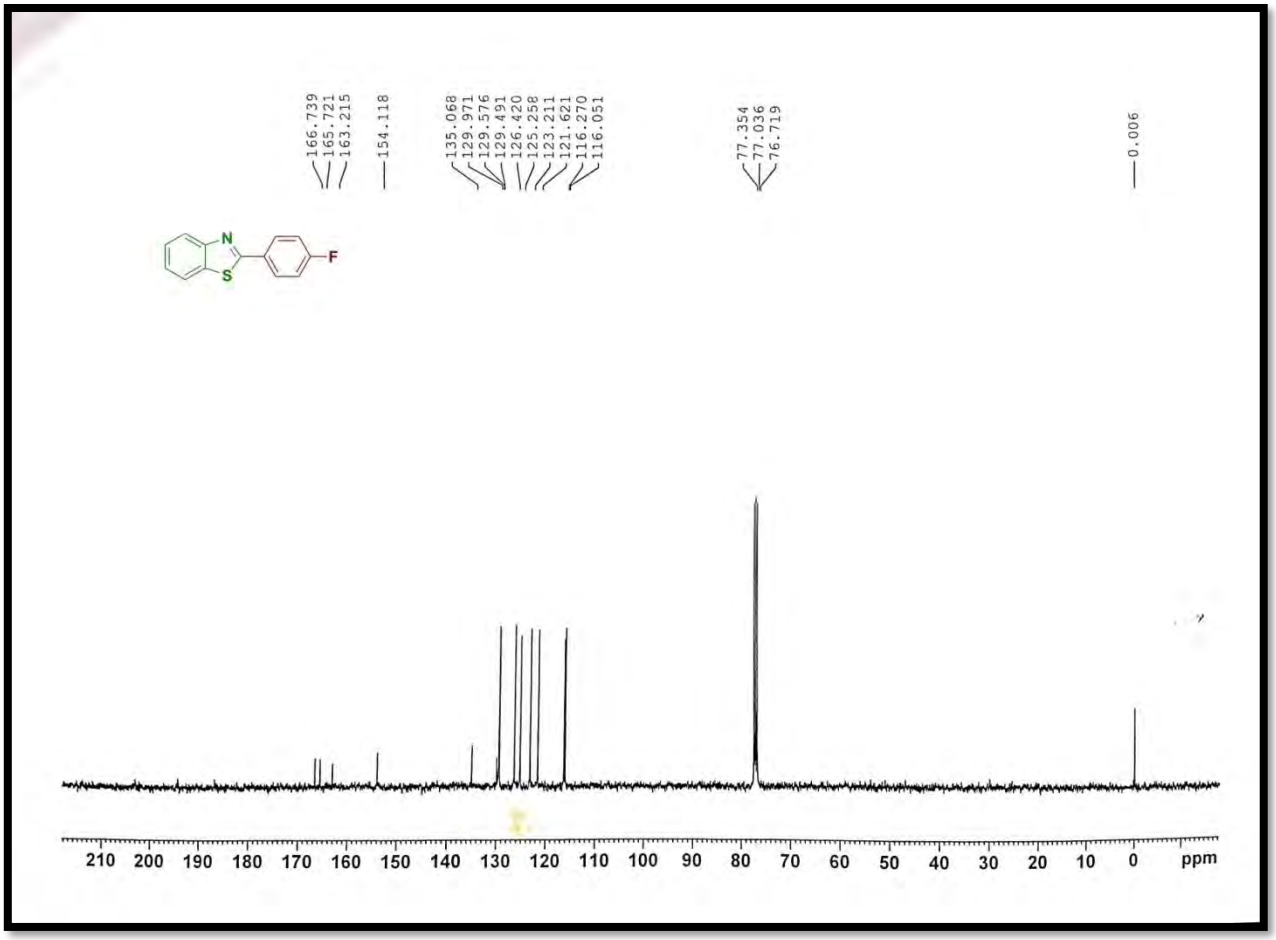


Figure I.A.48. ^{13}C Spectroscopical representation of 2-(4-Fluorophenyl)benzo[*d*]thiazole

2-(4-Methoxyphenyl)benzo[*d*]thiazole (Figure I.A.49.).

M.P.: 125–126 °C °C, white solid, yield : 85%, **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm):** 3.888 (3H, s), 6.988 – 7.024 (2H, m), 7.334 – 7.374 (1H, m), 7.449 – 7.490 (1H, m), 7.879 (1H, d, J = 8 Hz), 8.021 – 8.057 (3H, m) **(Figure I.A.50.).**

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 55.470, 77.003, 114.386, 121.505, 122.834, 124.794, 126.203, 126.466, 129.126, 134.876, 154.242, 161.948, 167.875 **(Figure I.A.51.).**

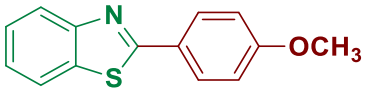


Figure I.A.49. Structure of 2-(4-Methoxyphenyl)benzo[*d*]thiazole

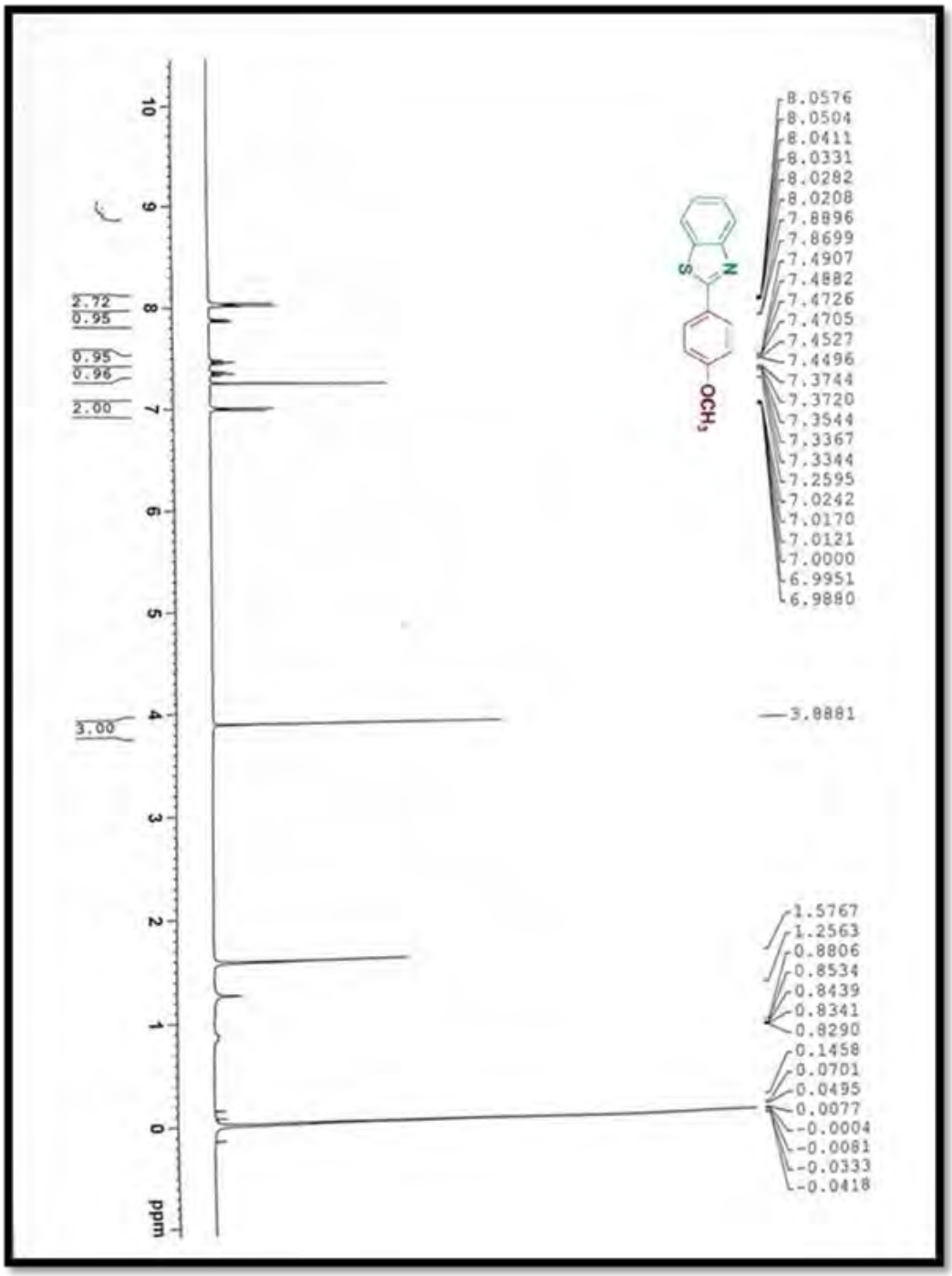


Figure I.A.50. ^{1}H Spectroscopical representation of 2-(4-Methoxyphenyl)benzo[*d*]thiazole

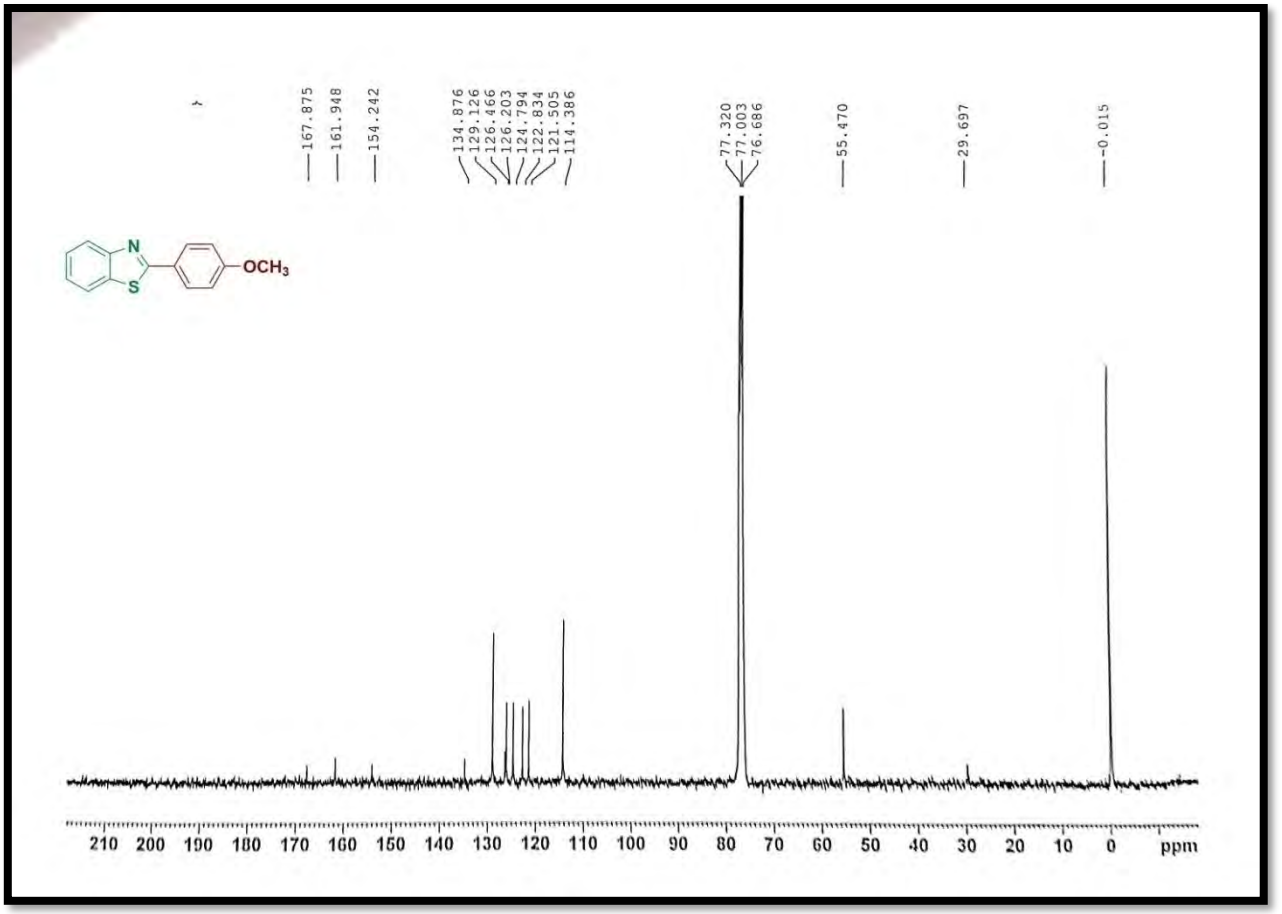


Figure I.A.51. ^{13}C Spectroscopical representation of 2-(4-Methoxyphenyl)benzo[*d*]thiazole

Ethyl 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (Figure I.A.52.)

M.P. : 174 - 176 ºC; pale yellow crystal; yield : 90%; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm):** 1.157, (t, *J* = 7.2 Hz, 3H), 2.469 (quintet, *J* = 1.7 Hz, 3H), 4.018 (t, *J* = 7.2 Hz, 2H), 6.431 (s, 1H), 7.174 (s, 5H), 7.256 (quintet, *J* = 1.28 Hz, 3H), 7.391 (t, *J* = 5.6 Hz, 1H) **(Figure I.A.53.).**

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ (ppm): 14.005, 23.128, 57.018, 60.045, 102.594, 112.391, 122.268, 126.784, 129.006, 137.559, 141.960, 154.267, 162.887, 165.504

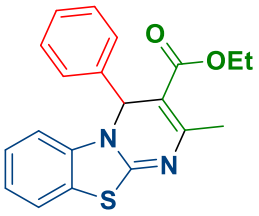


Figure I.A.52. Structure of Ethyl 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

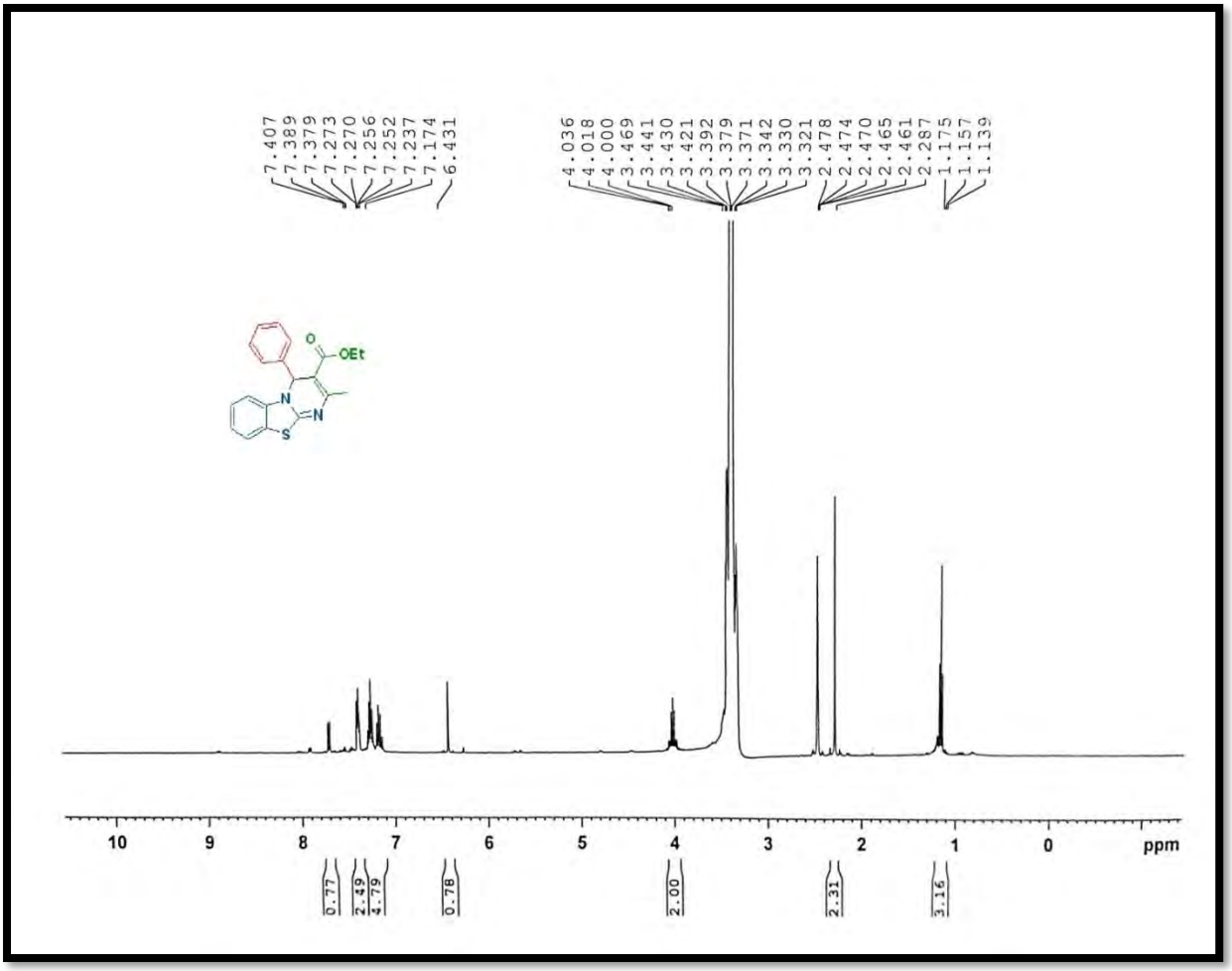


Figure I.A.53. ^{1}H Spectroscopical representation of Ethyl 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

Ethyl 2-methyl-4-(3-nitrophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (Figure I.A.54.).

M.P. : 261 – 262 °C; off - white solid; yield : 92%; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm):** 1.085 (t, *J* = 7 Hz, 3H), 2.419 (s, 3H), 4.026 (q, *J* = 6.8 Hz, 2H), 6.662 (s, 1H), 7.175 (t, *J* = 7.6 Hz, 1H), 7.282 (t, *J* = 7.6 Hz, 1H), 7.511 (d, *J* = 8 Hz, 1H), 7.576 (t, *J* = 8 Hz, 1H), 7.737 (d, *J* = 7.6 Hz, 1H), 7.827 (d, *J* = 7.6 Hz, 1H), 8.058 (d, *J* = 8 Hz, 1H), 8.315 (s, 1H) **(Figure I.A.55.). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ (ppm):** 14.448, 23.774, 56.338, 60.227, 102.428, 112.873, 122.225, 123.246, 123.478, 123.809, 124.861, 127.510, 130.956, 133.875, 137.646, 143.997, 148.160, 155.598, 163.556, 165.707 **(Figure I.A.56.).**

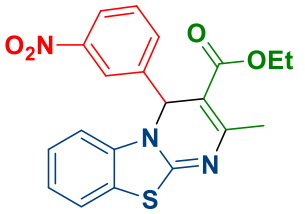


Figure I.A.54. Structure of Ethyl 2-methyl-4-(3-nitrophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

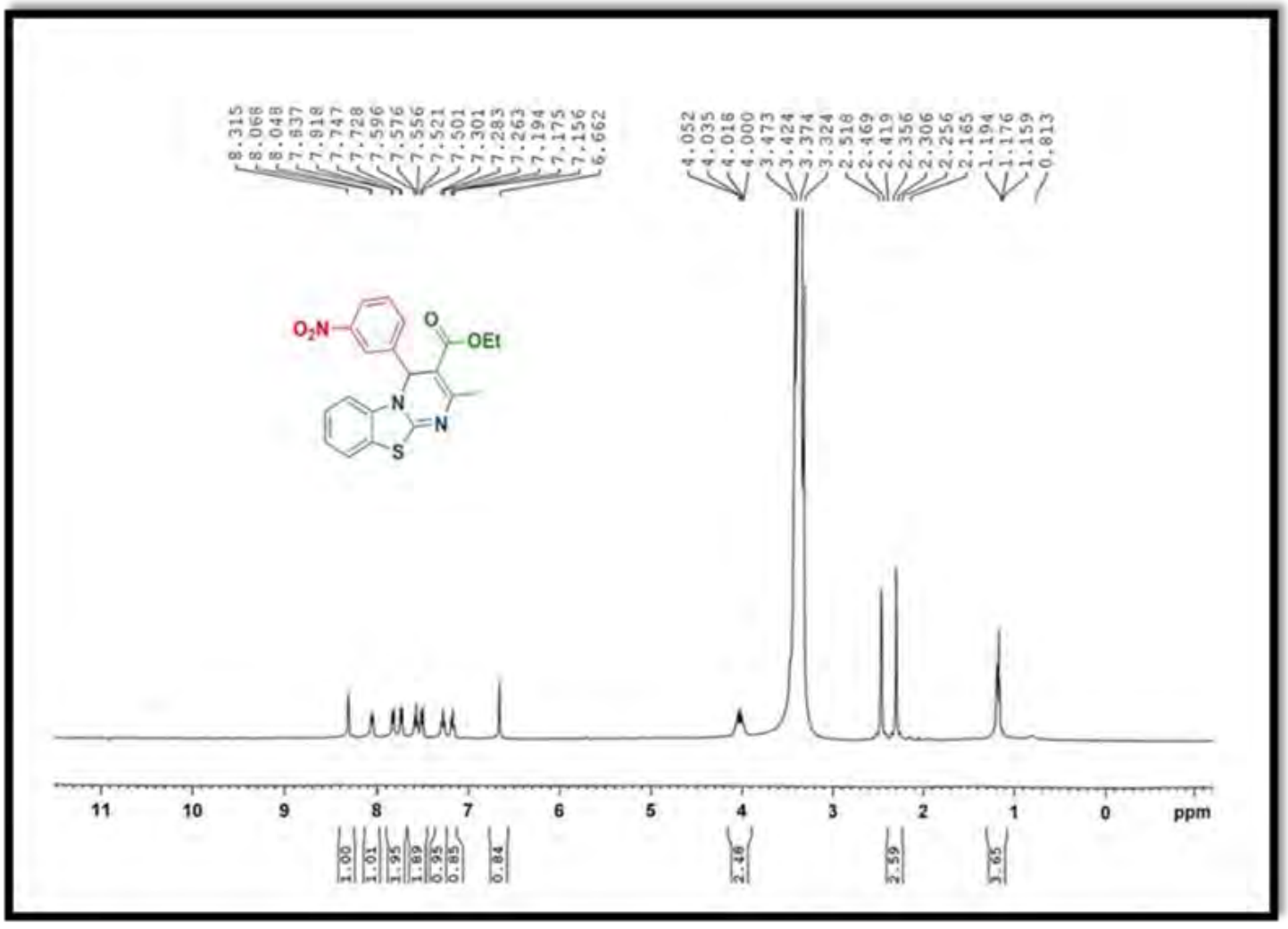


Figure I.A.55. ^{1}H Spectroscopical representation of Ethyl 2-methyl-4-(3-nitrophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

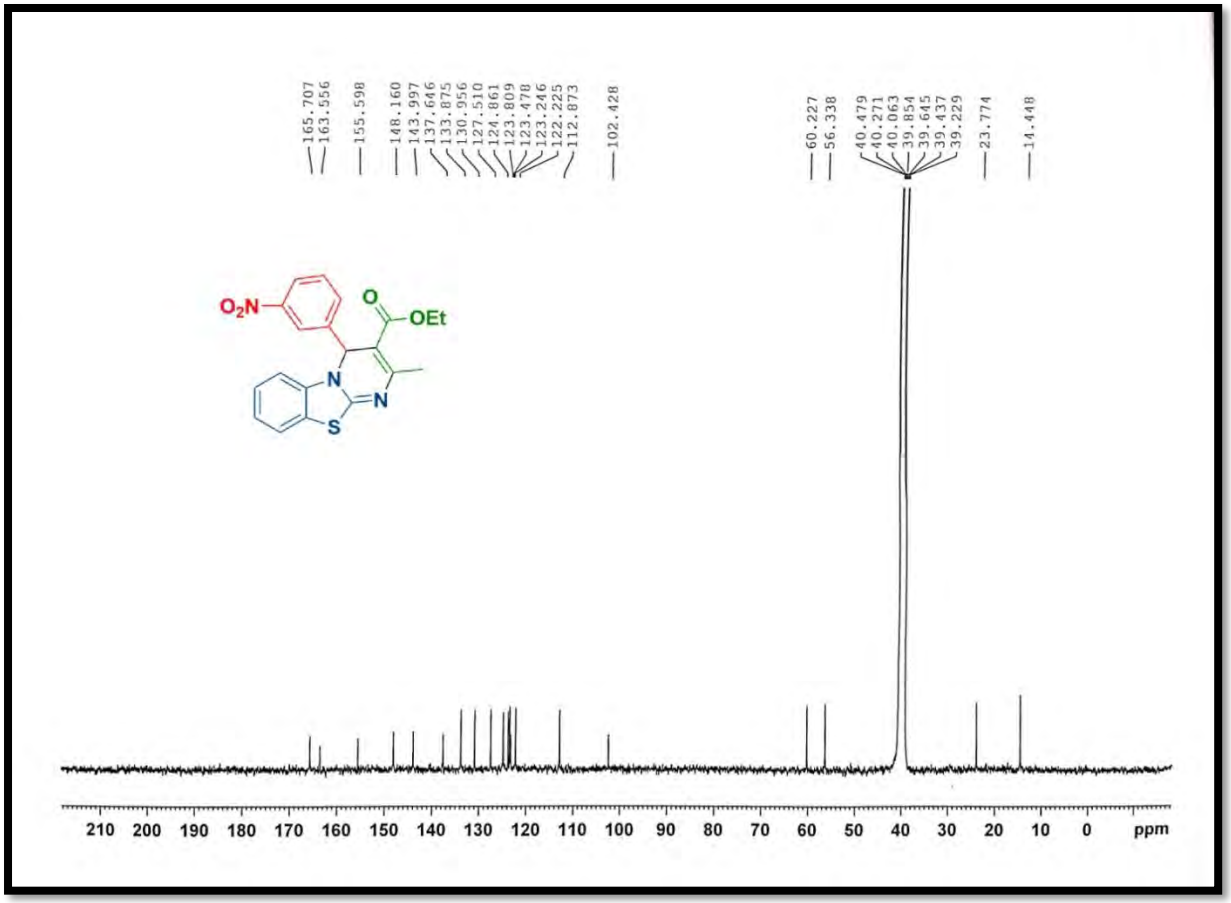


Figure I.A.56. ^{13}C Spectroscopical representation of Ethyl 2-methyl-4-(3-nitrophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

Ethyl 2-methyl-4-(4-(trifluoromethyl)phenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (Figure I.A.57.).

M.P. : 169 – 172 ºC; yellow powder, yield : 92%; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm):** 1.154 (t, *J* = 7 Hz, 3H), 2.301 (s, 3H), 3.986 - 4.066 (m, 2H), 6.547 (s, 1H), 7.145 (t, *J* = 7.4 Hz, 1H), 7.259 (t, *J* = 7.6 Hz, 1H), 7.404 (d, *J* = 8.4 Hz, 1H), 7.635 - 7.718 (m, 5H) **(Figure I.A.58.).**

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ (ppm): 14.497, 23.784, 56.614, 60.126, 102.575, 112.687, 123.156 (d, *J* = 25.8Hz, 1C), 123.401, 124.692, 125.729, 126.076, 127.366, 128.396, 129.040, 129.355, 137.750, 146.258, 155.258, 163.395, 163.808, (**Figure I.A.59.).**

^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ (ppm): -61.211 (s) **(Figure I.A.60.).**

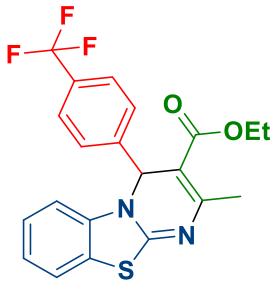


Figure I.A.57. Structure of Ethyl 2-methyl-4-(4-(trifluoromethyl)phenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

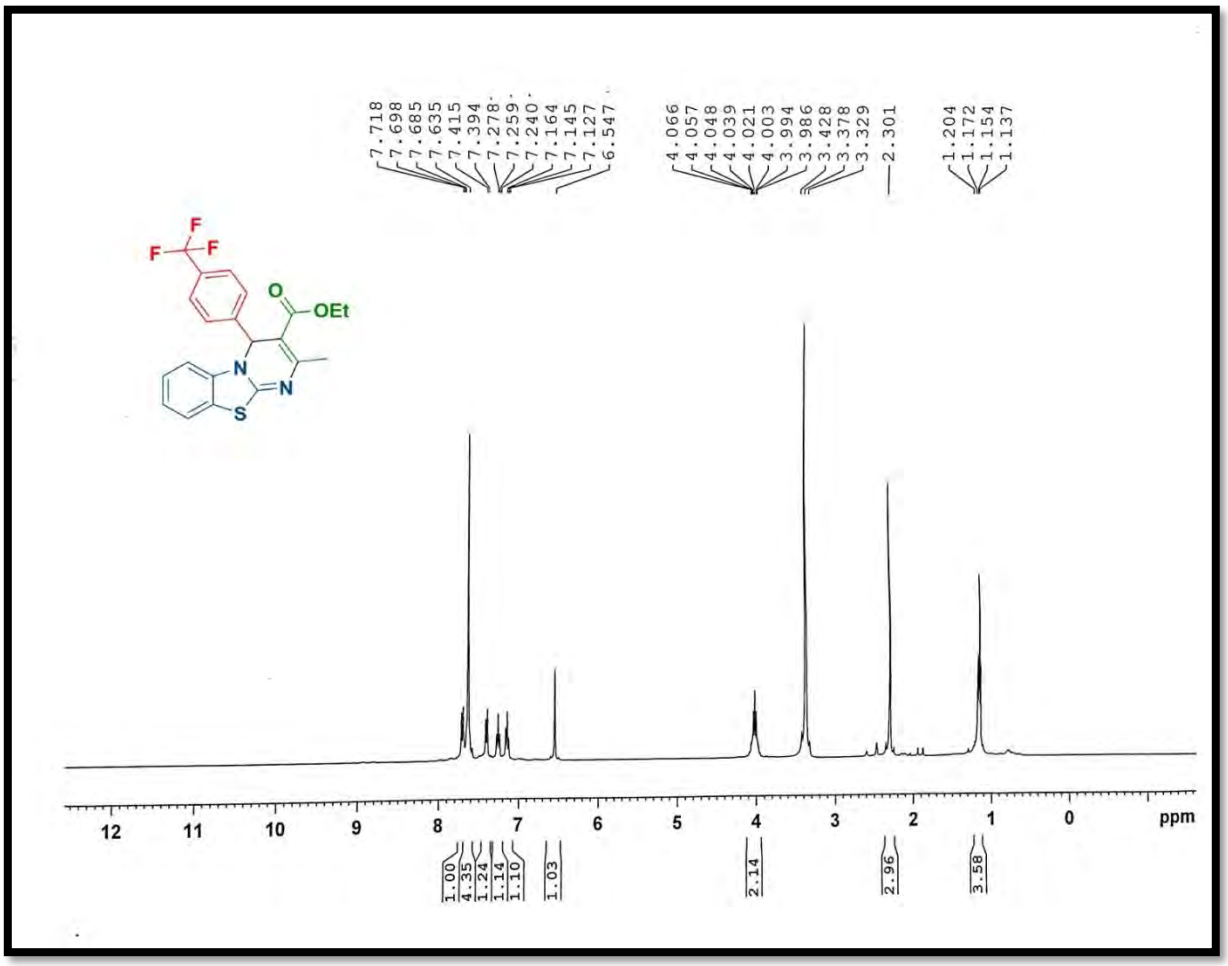


Figure I.A.58. ^{1}H Spectroscopical representation of Ethyl 2-methyl-4-(4-(trifluoromethyl)phenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

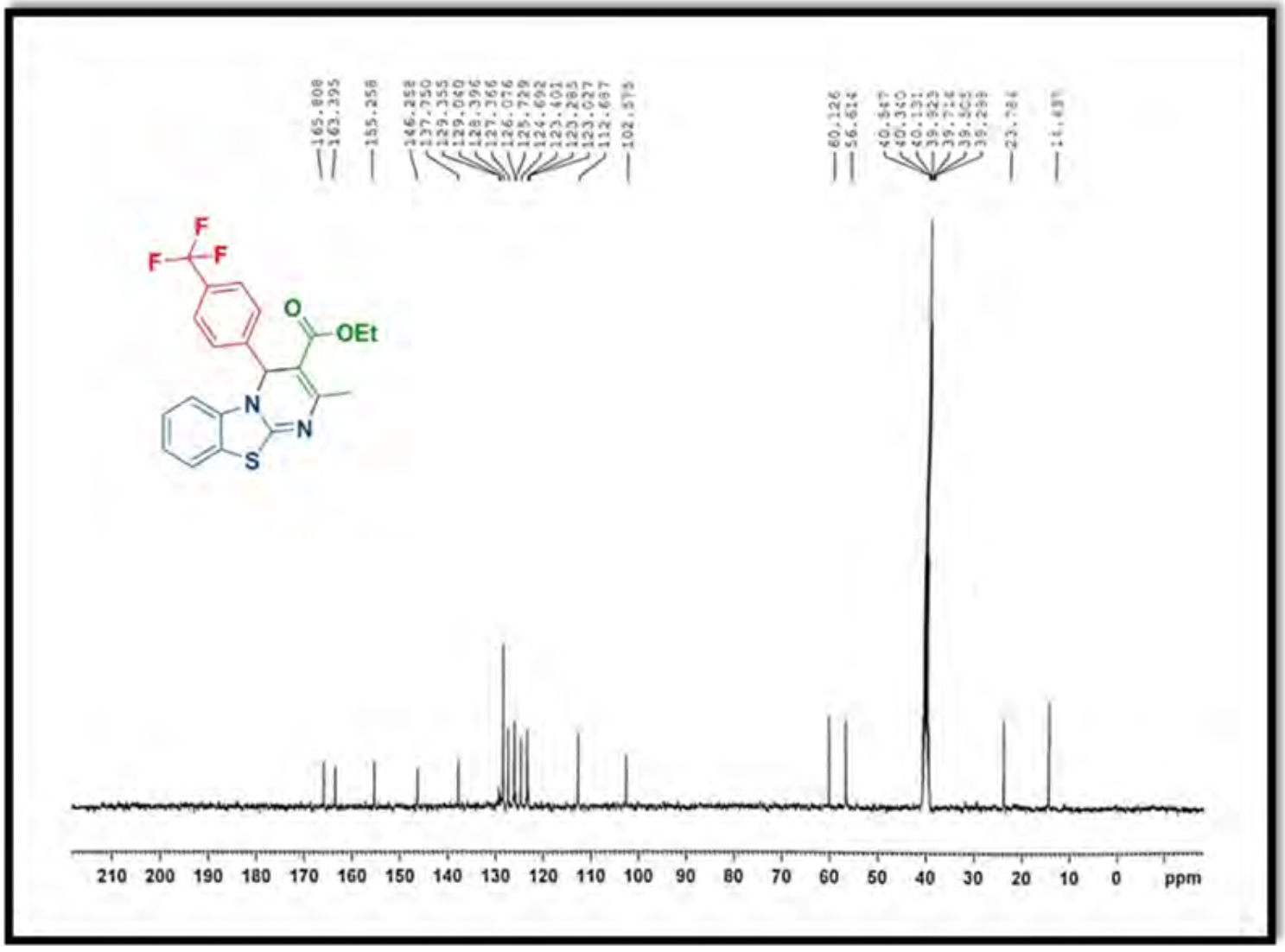


Figure I.A.59. ^{13}C Spectroscopical representation of Ethyl 2-methyl-4-(4-(trifluoromethyl)phenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

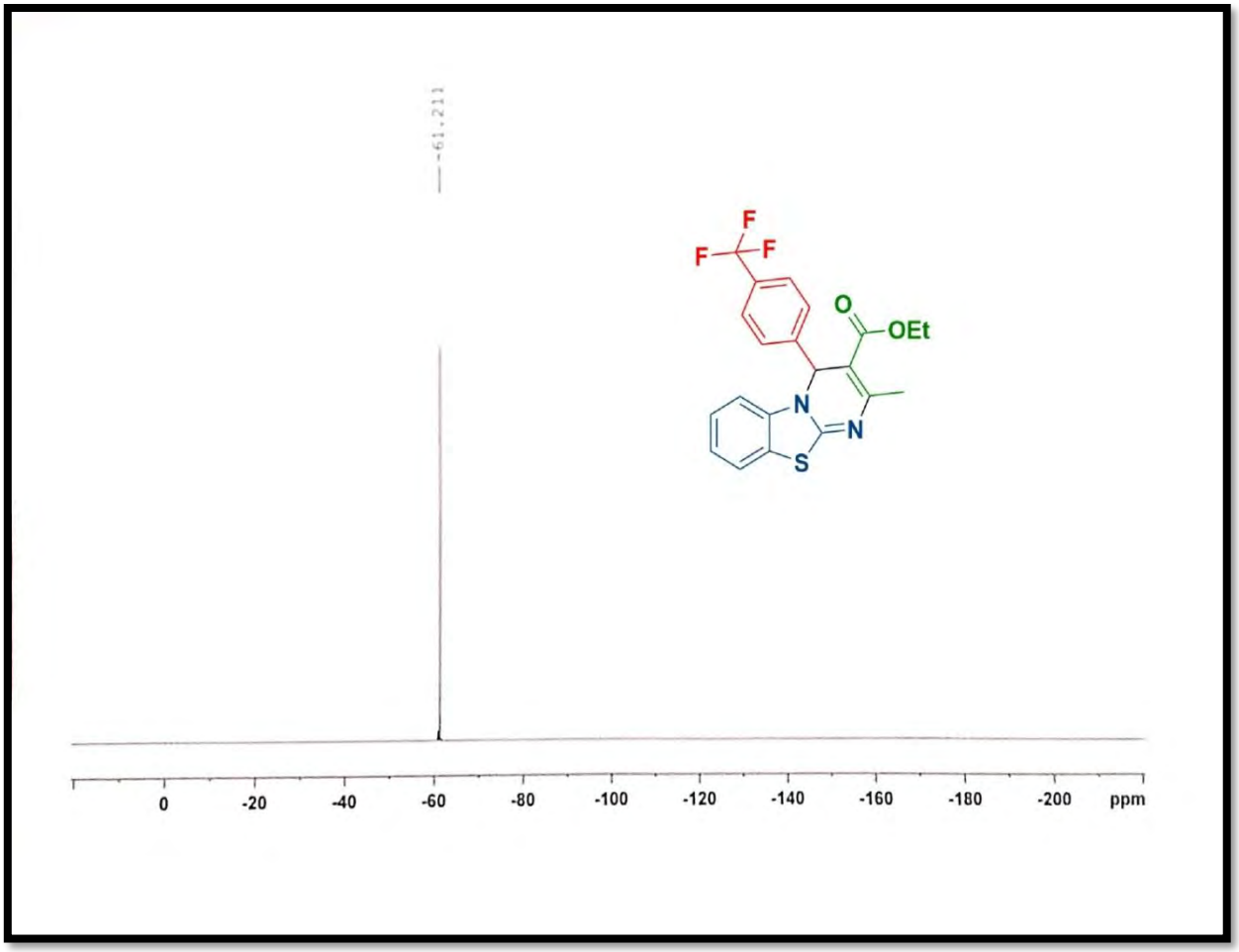


Figure I.A.60. ^{19}F Spectroscopical representation of Ethyl 2-methyl-4-(4-(trifluoromethyl)phenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

Ethyl 4-(2-bromophenyl)-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (Figure I.A.61.).

M.P. : 168 – 170 ºC; yellowish powder; yield : 85%; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm):** 1.095 (t, *J* = 7 Hz, 3H), 2.274 (t, *J* = 2.19 Hz, 3H), 4.022 (d, *J* = 6.8 Hz, 2H), 6.630 (s, 1H), 7.139 (d, *J* = 8.4 Hz, 2H), 7.276 - 7.322 (m, 2H), 7.386 (s, 1H), 7.522 (m, 2H), 7.683 (s, 1H) **(Figure I.A.62.).**

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ (ppm): 14.725, 23.679, 57.225, 59.908, 102.625, 106.887, 112.227, 119.253, 121.799, 122.947, 123.398, 124.685, 127.202, 127.476, 129.315, 130.888, 131.286, 133.511, 138.175, 140.956, 154.738, 163.107, 165.824 **(Figure I.A.63.).**

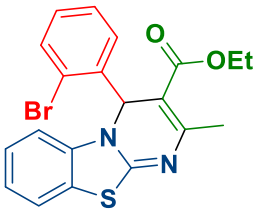


Figure I.A.61. Structure of Ethyl 4-(2-bromophenyl)-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

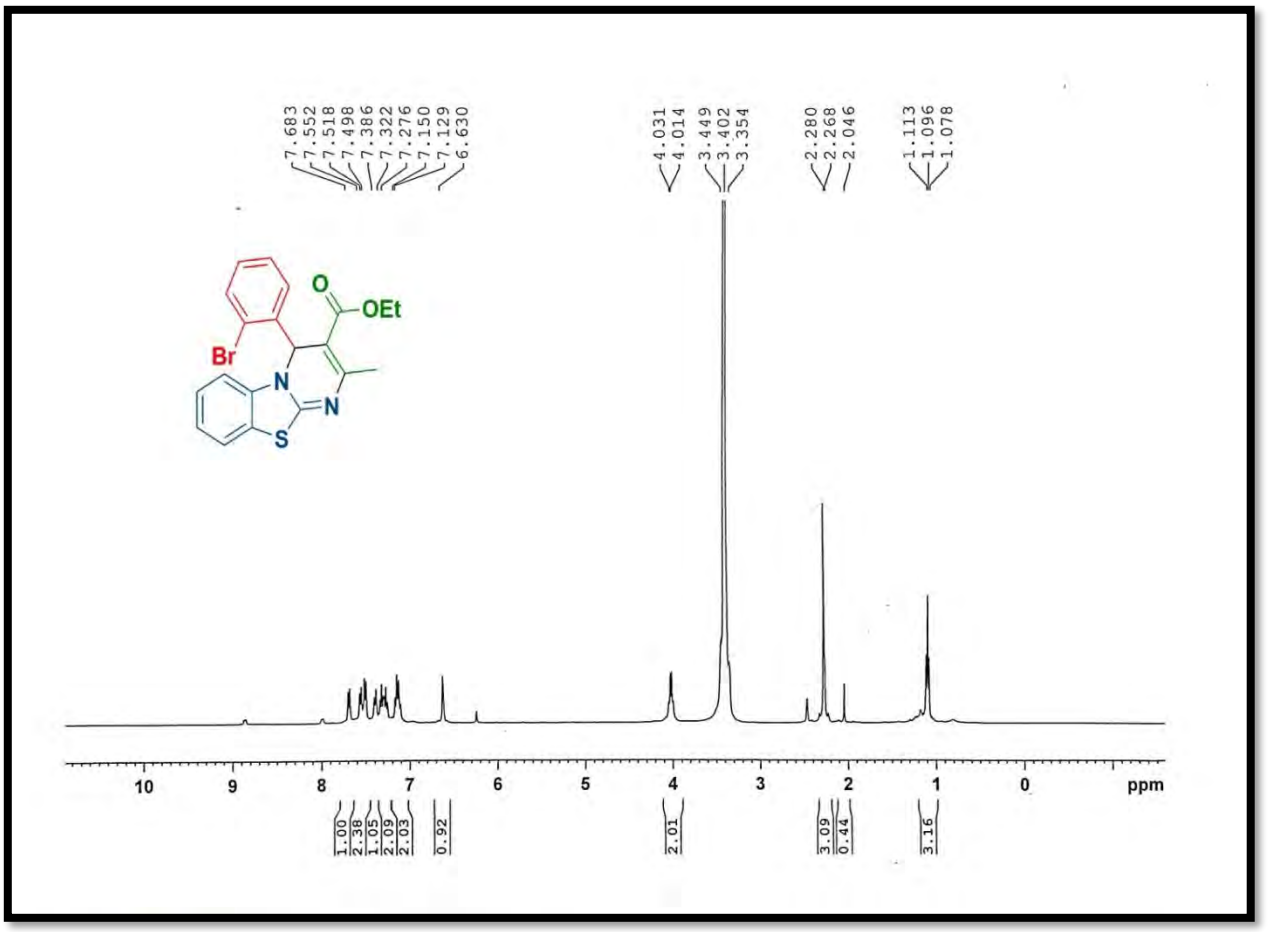


Figure I.A.62. ^{1}H Spectroscopical representation of Ethyl 4-(2-bromophenyl)-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

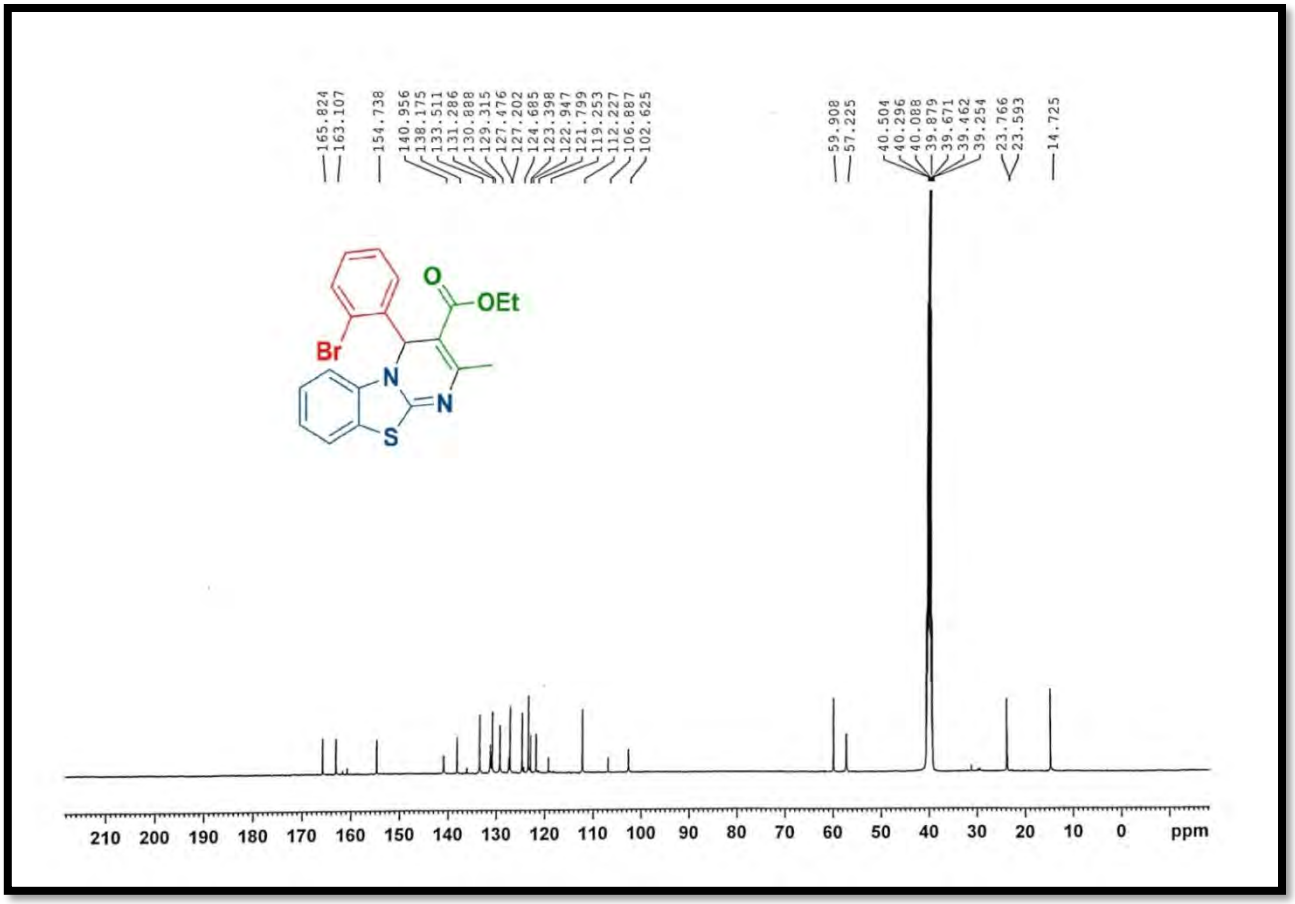


Figure I.A.63. ^{13}C Spectroscopical representation of Ethyl 4-(2-bromophenyl)-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

Ethyl 2-methyl-4-(pyridine-3-yl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (Figure I.A.64.).

M.P. : 175 – 176 ºC; yellowish solid; yield : 90%; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm):** 1.131 – 1.196 (m, 3H), 2.461 - 2.478 (m, 3H), 4.026 (q, *J* = 7.2 Hz, 2H), 6.513 (s, 1H), 7.175 (s, 1H), 7.301 (d, *J* = 8 Hz, 2H), 7.486 (d, *J* = 8 Hz, 1H), 7.727 (d, *J* = 7.6 Hz, 2H), 8.382 (d, *J* = 3.2 Hz, 1H), 8.678 (d, *J* = 1.6 Hz, 1H)

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ (ppm): 14.374, 23.355, 54.878, 60.442, 102.289, 112.628, 123.229, 123.420, 124.904, 125.056, 127.628, 135.512, 137.364, 137.524, 148.137, 149.807, 155.343, 165.927 **(Figure I.A.65.).**

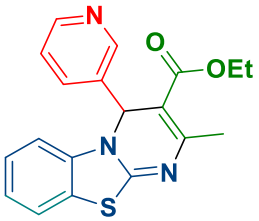


Figure I.A.64. Structure of Ethyl 2-methyl-4-(pyridine-3-yl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

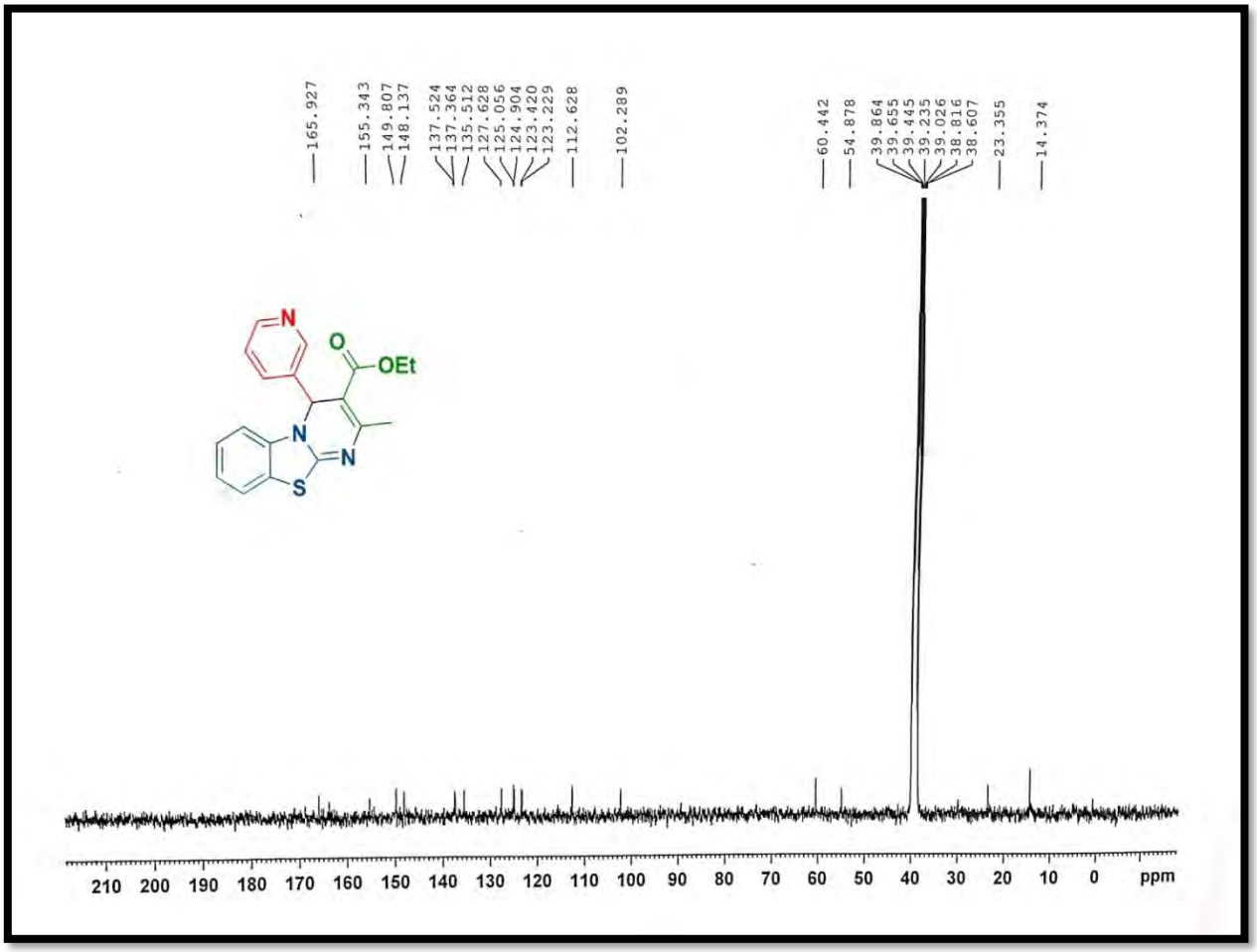


Figure I.A.65. ^{13}C Spectroscopical representation of Ethyl 2-methyl-4-(pyridine-3-yl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

Ethyl 2-methyl-4-(4-fluorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (Figure I.A.66.).

M.P. : 165 – 167 ºC; yellowish solid; yield : 90%; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm):** 1.136 – 1.197 (m, 3H), 2.316 – 2.483 (m, 3H), 4.042 (d, *J* = 7.2 Hz, 2H), 6.517 (s, 1H), 7.185 (s, 1H), 7.304 – 7.323 (m, 2H), 7.468 (s, 1H), 7.725 (d, *J* = 7.6 Hz, 2H), 8.383 (s, 1H), 8.677 (s, 1H) **(Figure I.A.67.).**

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ (ppm): 14.494, 23.663, 54.908, 60.170, 102.393, 112.713, 123.281, 123.444, 124.695, 124.800, 127.464, 135.166, 137.428, 137.633, 148.539, 149.955, 155.426, 163.442, 165.767. **(Figure I.A.68.).**

^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ (ppm): -108.796 (s) **(Figure I.A.69.).**

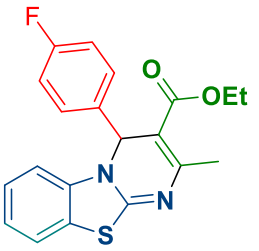


Figure I.A.66. Structure of Ethyl 2-methyl-4-(4-fluorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

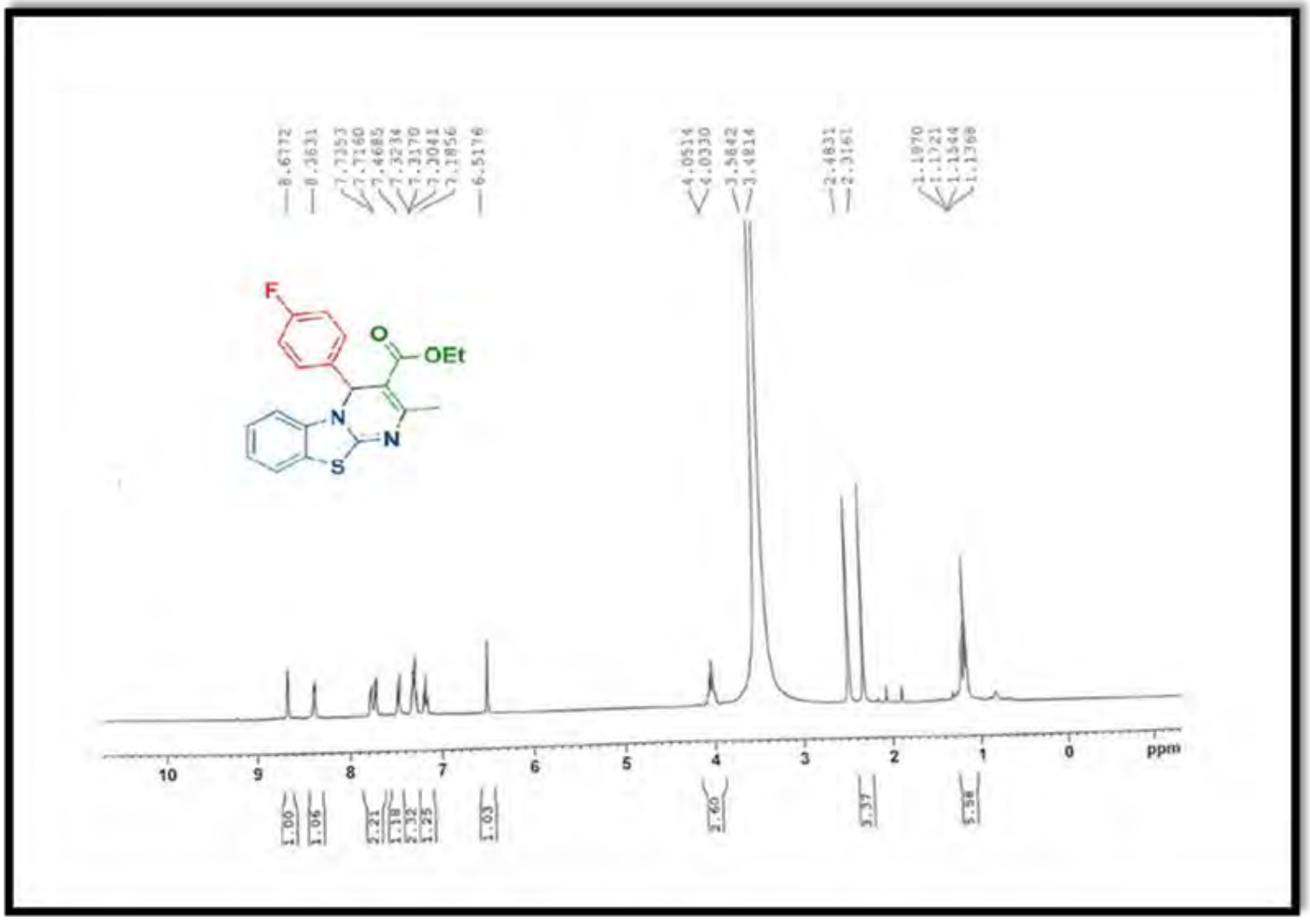


Figure I.A.67. ^{1}H Spectroscopical representation of Ethyl 2-methyl-4-(4-fluorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

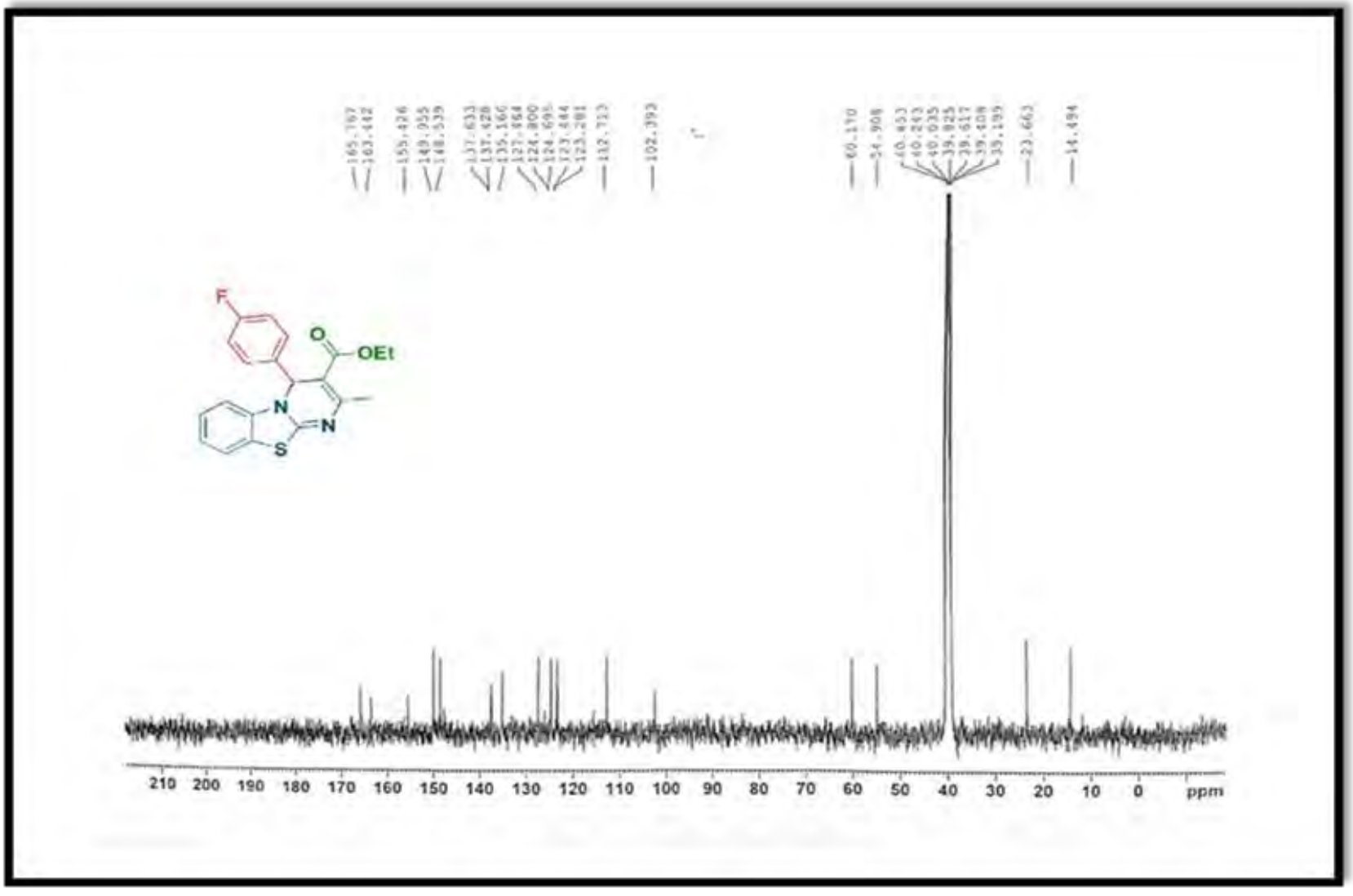


Figure I.A.68. ^{13}C Spectroscopical representation of Ethyl 2-methyl-4-(4-fluorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

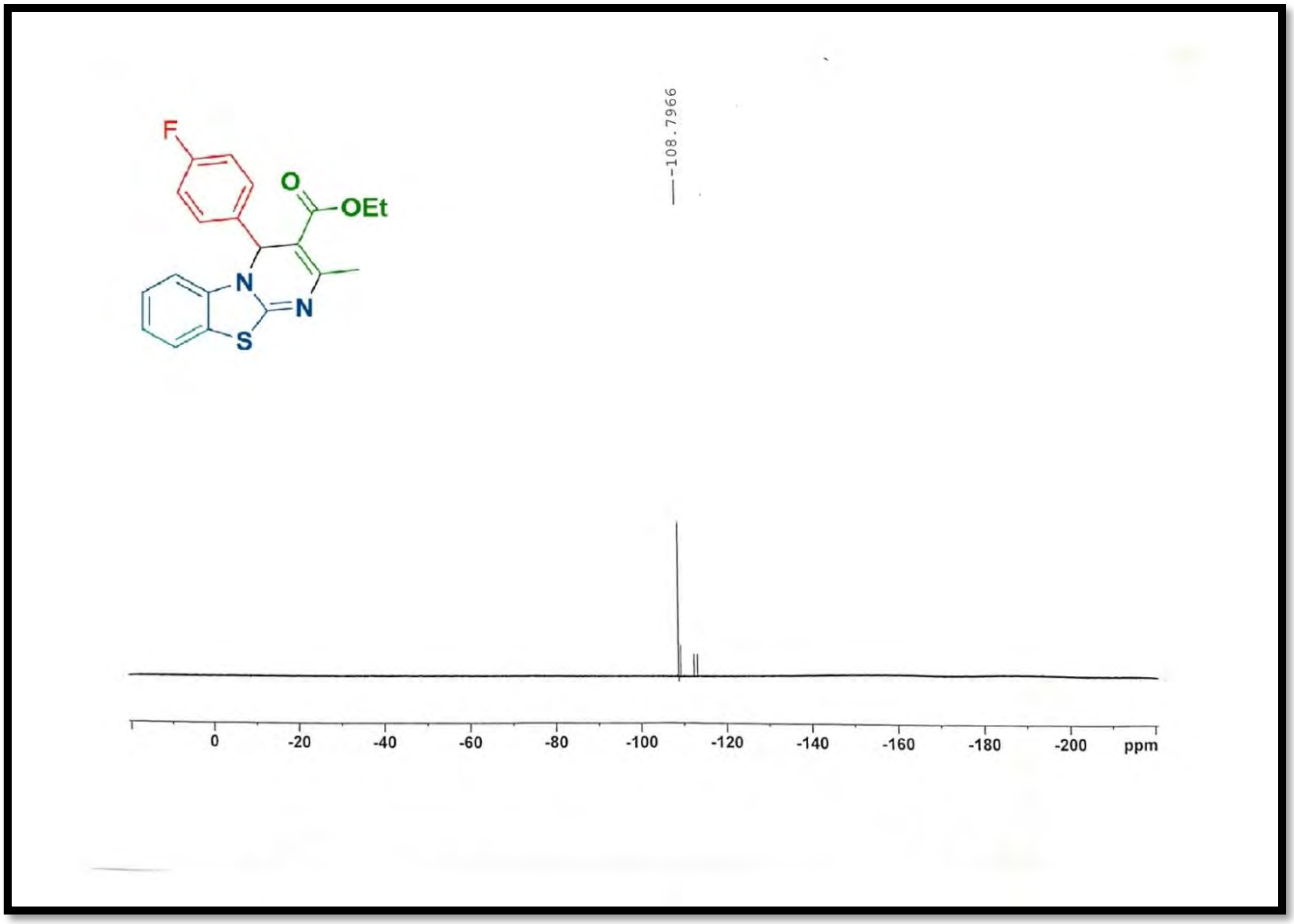


Figure I.A.69. ^{19}F Spectroscopical representation of Ethyl 2-methyl-4-(4-fluorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate

I.A.8. References:

References are displayed in **BIBLIOGRAPHY** under **Chapter I, Section A,** that is, "**Humic Acid: A Rarely Explored, Robust, Green Catalyst for Solvent-Free Synthesis of 4*H*-Benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate and Benzo[*d*]thiazole"** (pp. 199-206**).**

Section B

Beta – Cyclodextrin (β-Cyclodextrin) mediated Solvent-Free Synthesis of 3,3'-(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) and 4,4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

I.B.1. Introduction:

One of the main concerns in organic conversions is with catalysts and solvents. The main drawbacks of solvents are their ignitable properties and their dangerous character, which includes excessive volatility and inadequate recuperation. The primary drawback of the metal catalyst is that, at the conclusion of the chemical reaction, it causes metal infection, which is harmful to the ecosystem. Any environmentally friendly solvent and biocatalyst could be used to address these drawbacks. By employing β - cyclodextrin in the form of a supramolecular catalyst, we have created a metal-free protocol[1]. Water[2] is an extremely beneficial reaction system in terms of both environmental friendliness and nature of small atomic consumption. The development of homogeneous catalysis and supramolecular chemistry has made the supramolecular catalyst a valuable device in the synthesis of organic heterocyclic compounds[3]. A significant enzyme model amongst the variety of supramolecular organisms is cyclodextrin (CD)[4–7]. Since cyclodextrins are hydrophobic cavities found in cyclic oligosaccharides, they are capable of binding with targets in selective ways, allowing them to facilitate chemical procedures along with a large selectivity [8–12]. Using non-covalent bonding, CDs can reversibly attach to a host-guest complex formed by the supporting materials throughout the reaction. This complex is what changes the spatial arrangement of products throughout organic reactions. Because the guest molecules are incorporated to the CD hole, the features are associated with the formation of morphological limitations in the guest molecules. It employs the hydrophobic chamber, just like β - cyclodextrin, to encapsulate physiologically beneficial substances from aqueous solutions, thereby improving biological availability and the stability of medicinal compounds. Because of these qualities, CDs are now a valuable resource for pharmaceutical firms. Additionally, CDs are inexpensive, widely accessible, non-virulent, and consequently recyclable [13, 14].

β - Cyclodextrin, a key category of cyclodextrins, is an assortment of cyclic oligosaccharides comprised of a macrocyclic ring of seven glucose subunits attached through a-1,4 glycosidic bonds and is a crucial enzyme simulation [16]. Like other cyclodextrins, β - cyclodextrin also utilizes its inner hydrophobic chamber to trap molecules that function biologically, from water solution and to selectively fasten the organic substrates. In modern times, there is growing curiosity in the employing of homogeneous catalysts and supra molecular chemistry as significant players in the synthesis of organic heterocyclic materials [15] and pharmaceutically significant elements. By non-covalent supra molecular bonding and the reversible generation of host-guest

complexes, as observed in enzymes, β - cyclodextrin catalyzes organic reactions with great selectivity[17]. This slowly boosts the stability and biological accessibility of therapeutic molecules. Numerous chemical molecules, including aldehydes, ketones, anhydride, oximes, amines, and nitriles, are activated by β - cyclodextrin, which also speeds up reactions[18]. These characteristics of β - CD make this a valuable tool for synthetic chemistry and pharmacological manufacturers. In addition, β - CD is a benign and non hazardous supramolecule that is readily attainable, able to be recycled, affordable, and dissolves in water smoothly because of its hydrophilic exterior part [19]. Here, **Figure I.B.1.** is representing the Structure of β – Cyclodextrin.

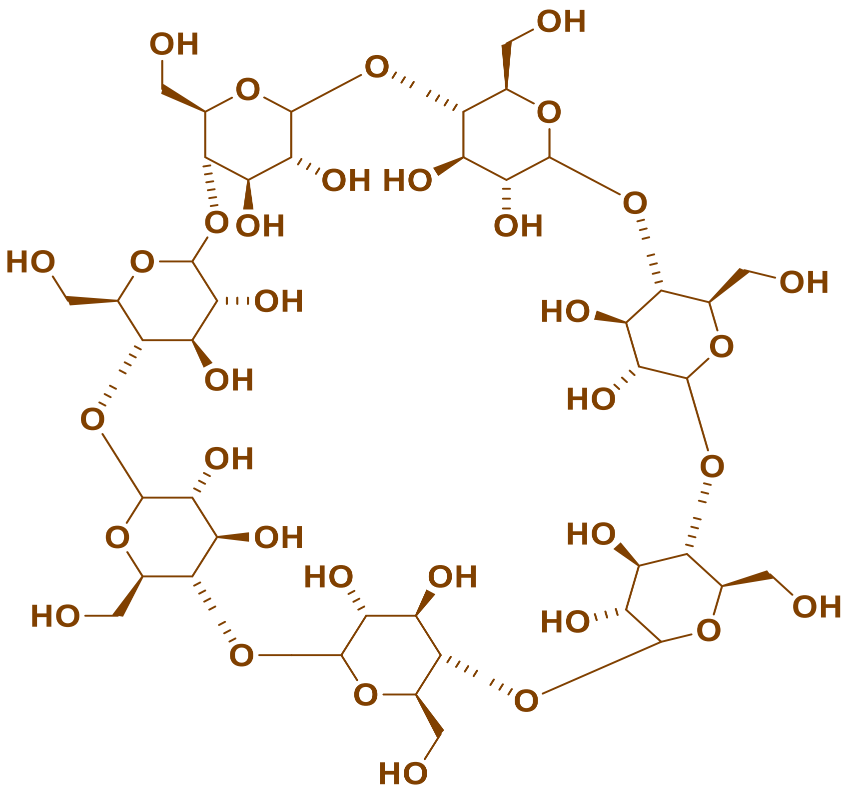


Figure I.B.1.: Structure of β – Cyclodextrin

Because of their several distinct bio capabilities, pyrazolone derivatives, one class of N-accommodating heterocycles, are a vital component of many fields in the sciences, including materials science and pharmaceuticals. Nowadays, pyrazolone derivatives are included in many commercially available medications for myocardial ischemia [69] and brain ischemia [70]. Among these, bis(pyrazolyl)methanes are widely employed as drugs that stimulate gastric secretion[71],

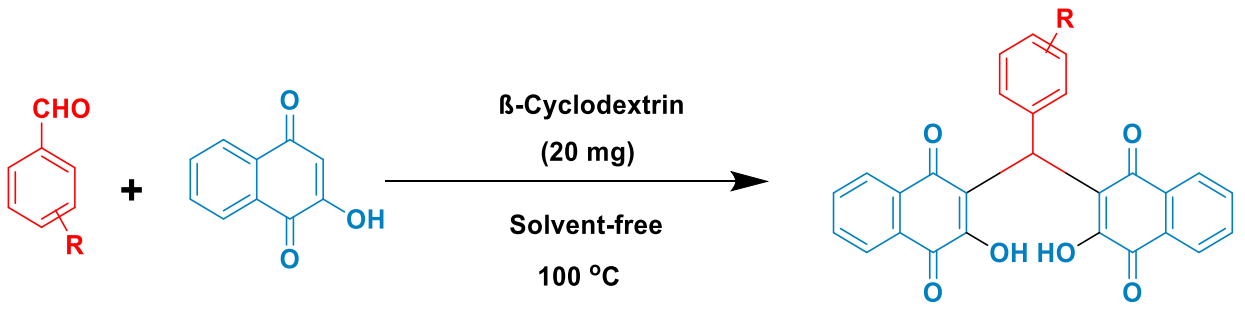
have been shown to have permissive biological activity, and are antibacterial [72], antipyretic [73], anti-inflammatory [74], antidepressant [75], and antifilarial [22–27]. Additionally, such substances are found in a large number of insecticides [28], fungicides [29], dyes, and the chelating and extraction agents for different metal ions [30], in addition to pesticides [31]. Pyrazoles that have been appropriately functionalized can be identified as sodium channel inhibitors and HIV-1 reverse transcriptase antagonists [32, 33]. The most popular technique for creating 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) is combining the Knoevenagel-Michael reaction in one pot with a variety of catalysts, including sodium dodecyl sulfate [34], electrocatalytic approach [35], SDBS [36], silica-SO_3H [37], PEG-SO_3H [38], phosphomo lybdic acid [39], biological surfactant [40], 3-aminopropylatedsilica gel [41], Caffein-H_3PO_4 [42], 1,3-disulfonic acid imidazolium tetrachloroaluminate [43], and metal complexes [44]. Many protocols have been developed recently based on this component [45]. Nonetheless, a number of limitations plague the majority of techniques, including the utilization of poisonous solvents and harsh catalysts, poor yields, extended reaction durations, unfavorable reaction circumstances, and laborious work-up protocols. For this reason, creating an efficient and ecologically friendly technique for the production of bis(pyrazolyl)methanes is essential.

In the domain of heterocyclic chemistry, 3,3'-(aryl/alkyl-methylene)bis(2-hydroxynaph thalene-1,4-dione), additional physiologically significant compound known as bis-Lawson derivatives, has become extremely significant. It is readily made using the Lawson substance (2-hydroxy-1,4-naphthoquinone), a renowned endogenous red-orange dye that is produced through the leaves of the henna plants (Lawsonia inermis Linn.) and is one of the medicinal plant's most essential ingredients [46]. Because of its biological adaptability, various portions of which have been employed conventionally for over 5000 years in the form of cosmetics (body paint, tattoo color, and hair dye) all throughout the world [47]. Because of its all-natural origin, it is a suitable herbal cure for multiple diseases and useful in the creation of partially long - lasting hair dyes [48]. It has a miscellaneous application in the pharmaceutical industries including diuretic, CNS depressing, anti-inflammatory, antipyretic, hepatoprotective, antimicrobial, wound healing, hypoglycaemic, analgesic, tuberculostatic and antiparasitic actions of the plant [49-63]. This substance has also been shown to have several important pharmacological and biological properties, including anti-oxidant [64], cytotoxic [65], anticoagulant [66], anti-acute pancreatitis [67], antibacterial [68], trypsin inhibitor [69], antifungal [70], inhibitory agent of the accumulation of advanced glycated

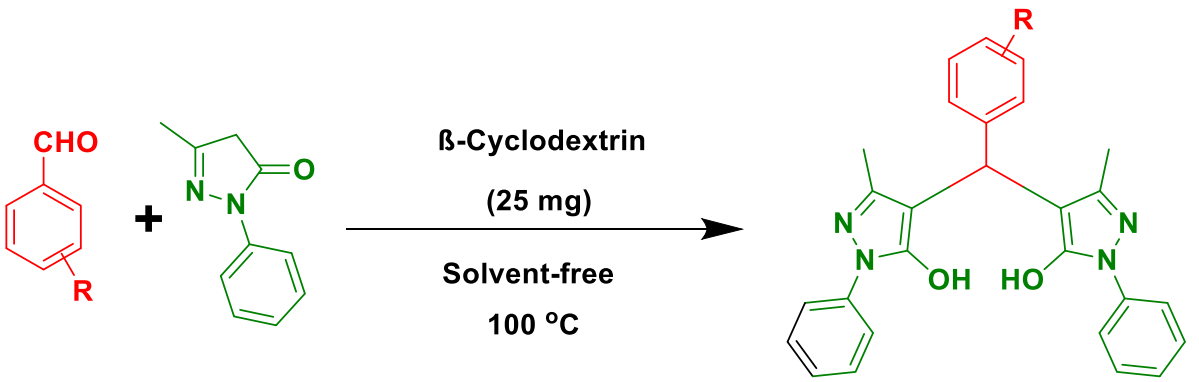
end products (AGEs) [71], and many more. Because it has the ability to provide ligands for metal complexations, it is also helpful in coordination chemistry [72]. The simple reaction of 2-hydroxy-1,4-naphthoquinone with aromatic aldehyde may be used to create bis-Lawson. β-alanine and acetic acid [73], TFA [74], O-carboxymethyl chitosan [75], Sulfamic acid [76], H_2SO_4 or ionic liquid [77], LiCl [78], and lipase [79] are a few previously published methodologies. Still, compared to the others, such domain has not been fully investigated. Therefore, there is a significant chance that this strategy can be investigated subsequently for advancements.

β - Cyclodextrin is a cheap, safe, non-toxic, readily available, and ecologically relevant catalyst. In light of such considerations, we have chosen β-cyclodextrin in the form of a catalyst in the development of a environmentally sustainable approach for the One – Pot, Solvent - free synthesis of 3,3'–(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) from number of aldehydes and 2-hydroxy-1,4-naphthoquinone (Lawson Reagent) and for the One – Pot, Solvent - free synthesis of 4,4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) from a number of aldehydes and 3-methyl-1-phenyl-1H-pyrazol-5-ol **(Scheme I.B.1., I.B.2)**.

Scheme I.B.1. represented here, the reaction of a number of aldehydes and 2-hydroxy-1,4-naphthoquinone (Lawson Reagent) via simple Nucleophilic Addition Reaction along with the formation of functionalized 3,3'–(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione); on the other hand, **Scheme I.B.2.** represented below, the reaction of a number of aldehydes and 3-methyl-1-phenyl-1H-pyrazol-5-ol via simple nucleophilic addition (Knoevenagel Michael addition) Reaction; along with the formation of functionalized 4,4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol); in presence of β - Cyclodextrin catalyst, under absolute solvent – free condition.



Scheme I.B.1. : β - Cyclodextrin mediated synthesis of functionalized 3, 3'–(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione)



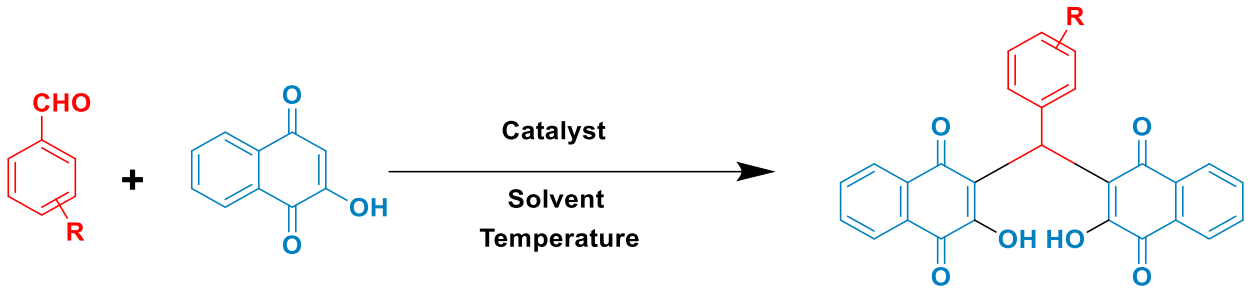
Scheme I.B.2. : β - Cyclodextrin mediated synthesis of functionalized 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

I.B.2. Result and Discussion:

The most crucial factors are Solvent, Temperature and Catalyst for propelling chemical reactions. For this reason, during the intended synthetic process, it is essential to preserve the appropriate levels of these three cores of such systems. 1 mmol of benzaldehyde and 1 mmol of 2-hydroxy-1, 4-naphthoquinone were considered here in the form of reactants to undertake target reaction **(Scheme I.B.1.).** We started our optimization performance (Optimization technique of **Scheme I.B.1.,** has been depicted in **Table I.B.1.**, here, in broader way) initially, with the solvents, by using of 40 mg amount catalyst and then, it was scrutinized that, doing reflux with methanol DMF and water, the yield of the product was comprehensively small (Table I.B.1., entry 1, 2, 3). Next, by applying PEG – 200, at 100 °C for continuous 5 hours, the yield of the product was 30% only (Table I.B.1., entry 4). After that, employing of DMSO and water along with constant 5 hours application of reflux procedure, the yield was 33% and 54% respectively (Table I.B.1., entry 5, 6). When we carried out the similar reaction, under neat condition, at 100 °C, with similar quantity of catalyst, then the yield of the product was enriched up to 97% (Table I.B.1., entry **7**). Then we commenced the optimization of catalyst by reducing the amount as, 35 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg and 5 mg, by maintaining the same 100 °C temperature and time as 5 hours; as a result, we saw the yield trend, like, 97%, 95%, 95%, 93%, 88%, 82% and 75% respectively (Table I.B.1., entry 8, 9, 10, 11, 12, 13, 14). Thus, we observed that, 20 mg of catalyst was sufficient to undergo this approach and the yield of the product was 93% (Table I.B.1., entry 11). On the other hand, the reaction could never be possible to run in devoid of catalyst (Table I.B.1., entry 15).

After that, by lowering the temperature up to room temperature, the yield of the product was reduced gradually (Table I.B.1., entry 16, 17, 18). Subsequently, we reserved record of the requisite time, for proceeding of the reaction and we found that, 1 h is adequate for reaching towards the highest quantity of product, under the indistinguishable reaction circumstances (Table I.B.1., entry 21).

Table I.B.1.: Optimization of reaction condition **(Scheme I.B.1.)**[a]



Entry	Solvent	Catalyst loading (mg)	Temperature (°C)	Time (h)	Yield (%)[b]
1.	Methanol	40	reflux	5	-
2.	DMF	40	reflux	5	trace
3.	Ethanol	40	reflux	5	trace
4.	PEG - 200	40	100	5	30
5.	DMSO	40	reflux	5	33
6.	Water	40	reflux	5	54
7.	Neat	40	100	5	97
8.	Neat	35	100	5	97
9.	Neat	30	100	5	95
10.	Neat	25	100	5	95
11.	Neat	20	100	5	93
12.	Neat	15	100	5	88
13.	Neat	10	100	5	82
14.	Neat	5	100	5	75
15.	Neat	Nil	100	5	-
16.	Neat	20	70	5	87

17.	Neat	20	50	5	81
18.	Neat	20	r. t.	5	trace
19.	Neat	20	100	3	93
20.	Neat	20	100	2	93
21.	**Neat**	**20**	**100**	**1**	**93**

The **bold** part signifies the optimized conditions;

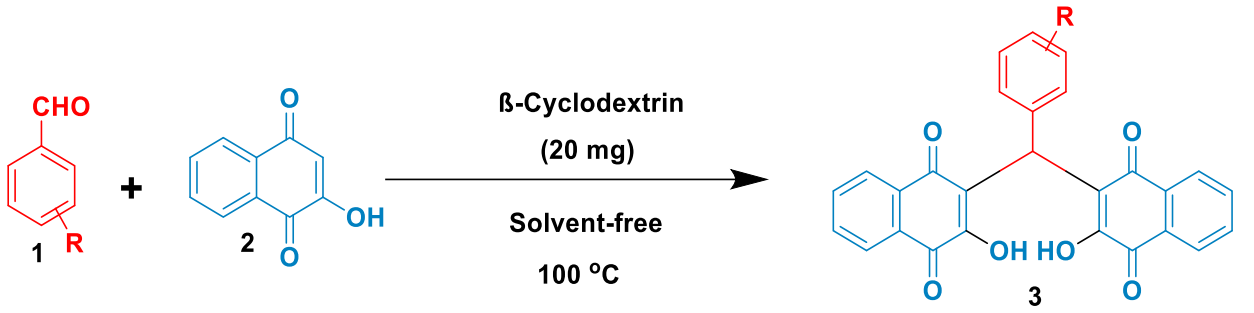
[a]Reaction of benzaldehyde (1 mmol) and 2-hydroxy-1,4-naphthoquinone (1 mmol) ;

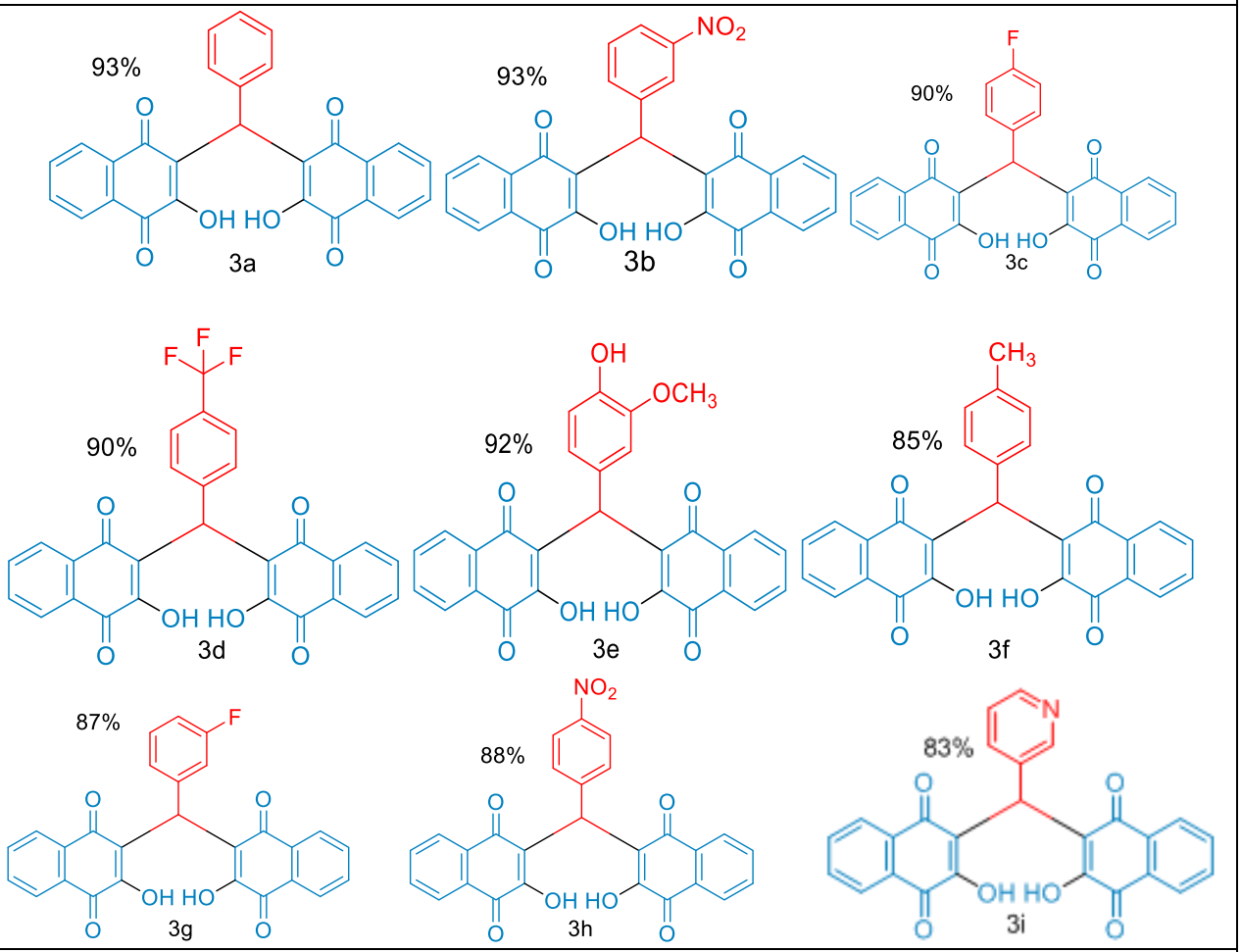
[b]Isolated yield was extracted through column chromatography.

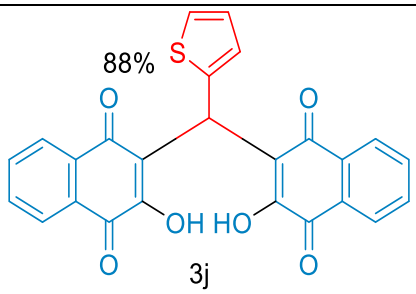
To perform in detailed study of our schemes, functionalized aldehydes were treated with 2-hydroxy-1,4-naphthoquinone **(Scheme I.B.1.),** under optimized condition and a variety of a number of 3, 3'–(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives were constructed. The resulted compounds have been listed below in Table I.B.2.

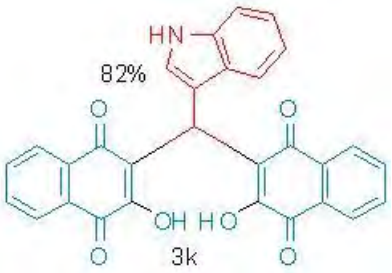
It was observed in this table that, when electron withdrawing groups, especially nitro, trifluoromethyl, fluoro, biphenyl and 2-naphthaldehyde were present in aldehyde, the product yield was highly satisfactory (Table I.B.2., entry 3b, 3c, 3d, 3l, 3n respectively). However, when electron withdrawing nitro group was at four positions, the yield was medium and well (Table I.B.2., entry 3h). But it was observed that, when aldehyde contained hydroxy and methoxy groups at ortho position with each other, or in case of vaniline, the yield of the product is so much good although these were not typical electron withdrawing groups except the presence of some negative inductive effect (Table I.B.2., entry 3e). In case of the presence of heterocyclic moiety, like thiophene, 3-pyridine and 3-indole, the product yield was medium to good (Table I.B.2., entry 3j, 3i, 3k respectively). However, aldehyde with positive inductive effect at para position produced the product with medium yield (Table I.B.2., entry 3f). On the other hand, aliphatic group at para position gave very poor yield of the product (Table I.B.2., entry 3m).

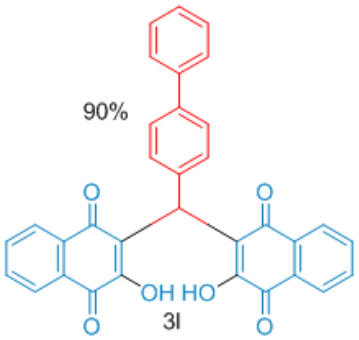
[a]**Table I.B.2.:** Synthesis of functionalized 3, 3'–(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione)derivatives **(Scheme I.B.1.)**

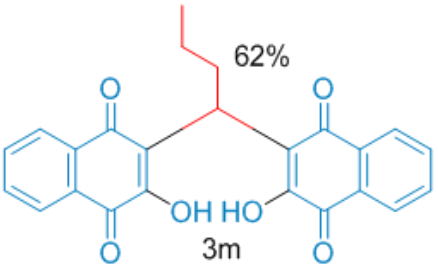


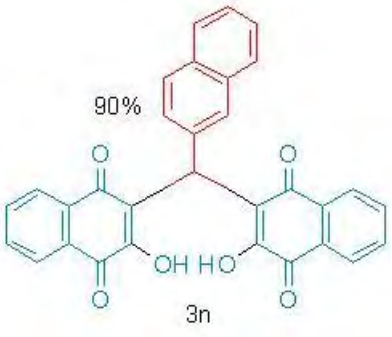








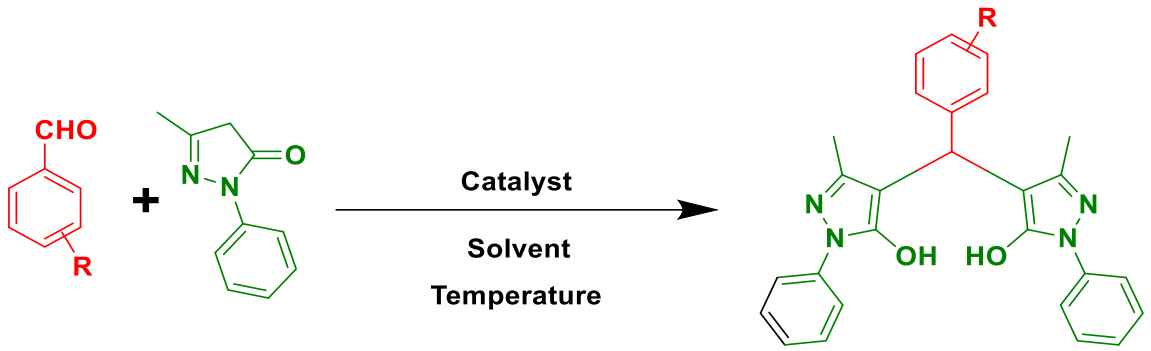




[a]Reaction of benzaldehyde (1 mmol) and 2-hydroxy-1,4-naphthoquinone (1 mmol) and β - Cyclodextrin (20 mg), under solvent-free condition for 1 h.

In Scheme I.B.2., we took 1 mmol of 3-methyl-1-phenyl-1H-pyrazol-5-ol and 1 mmol of benzaldehyde as reactants to undergo model reaction (Scheme I.B.2.). In the screening method of this reaction, (Optimization procedure of Scheme I.B.2., has been represented in Table I.B.3., below, in details), at first we choose solvent, in presence of 40 mg of catalyst, refluxing with methanol, ethanol, water and DMF, the yield of the product was considerably small (Table I.B.3., entry 1, 2, 3, 4). By maintaining of 100 ^{o}C temperature consistently for 4 h, the yield of the product was 95% under neat condition (Table I.B.3., entry 5). Then we commenced the optimization of catalyst, by dropping the quantity of catalyst (Table I.B.3., entry 6, 7, 8, 9, 10, 11). Thus, it was observed that, 25 mg of catalyst was enough to carry out this procedure and the yield of the product was 90% (Table I.B.3., entry 8). On the other hand, the reaction could never be feasible in devoid of catalyst (Table I.B.3., entry 12). After that, by reducing the temperature up to room temperature, the yield of the product was reduced frequently (Table I.B.3., entry 13, 14, 15). Next, we kept an eye on the mandatory time for happening of the reaction and we exposed that, 1h is adequate for gaining the maximum amount of product, under exactly the same reaction condition (Table I.B.3., entry 17).

Table I.B.3.: Optimization of reaction condition **(Scheme I.B.2.)**[a]



Entry	Solvent	Catalyst loading (mg)	Temperature (°C)	Time (h)	Yield (%)[b]
1.	Methanol	40	reflux	5	trace
2.	Ethanol	40	reflux	5	20
3.	Water	40	reflux	5	50
4.	DMF	40	reflux	5	40
5.	Neat	40	100	5	95
6.	Neat	35	100	5	93
7.	Neat	30	100	5	92
8.	Neat	25	100	5	90
9.	Neat	15	100	5	88
10.	Neat	5	100	5	47
11.	Neat	Nil	100	5	40
12.	Neat	25	100	5	-
13.	Neat	25	70	5	75
14.	Neat	25	50	5	60
15.	Neat	25	r. t.	5	trace
16.	Neat	25	100	3	90
17.	**Neat**	**25**	**100**	**1**	**90**

The **bold** part signifies the optimized conditions;

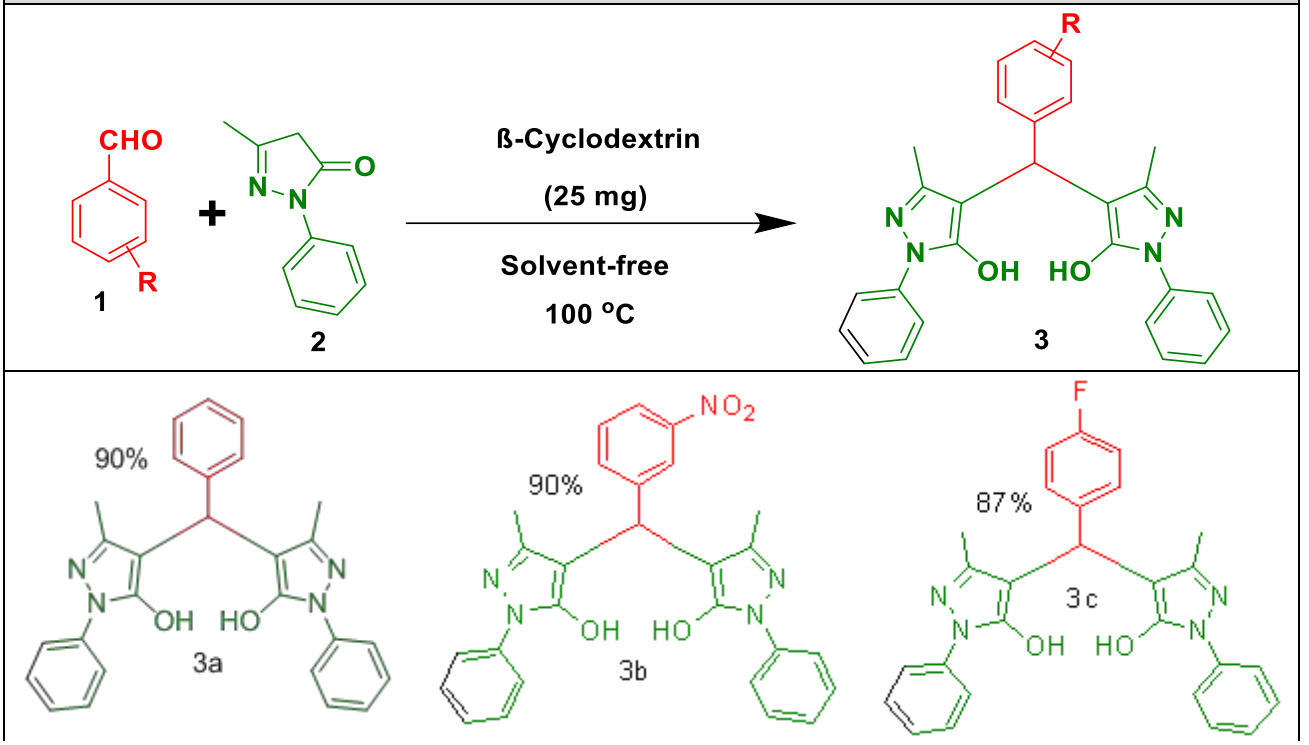
[a]Reaction of benzaldehyde (1 mmol) and 3-methyl-1-phenyl-1H-pyrazol-5-ol (1 mmol) ;

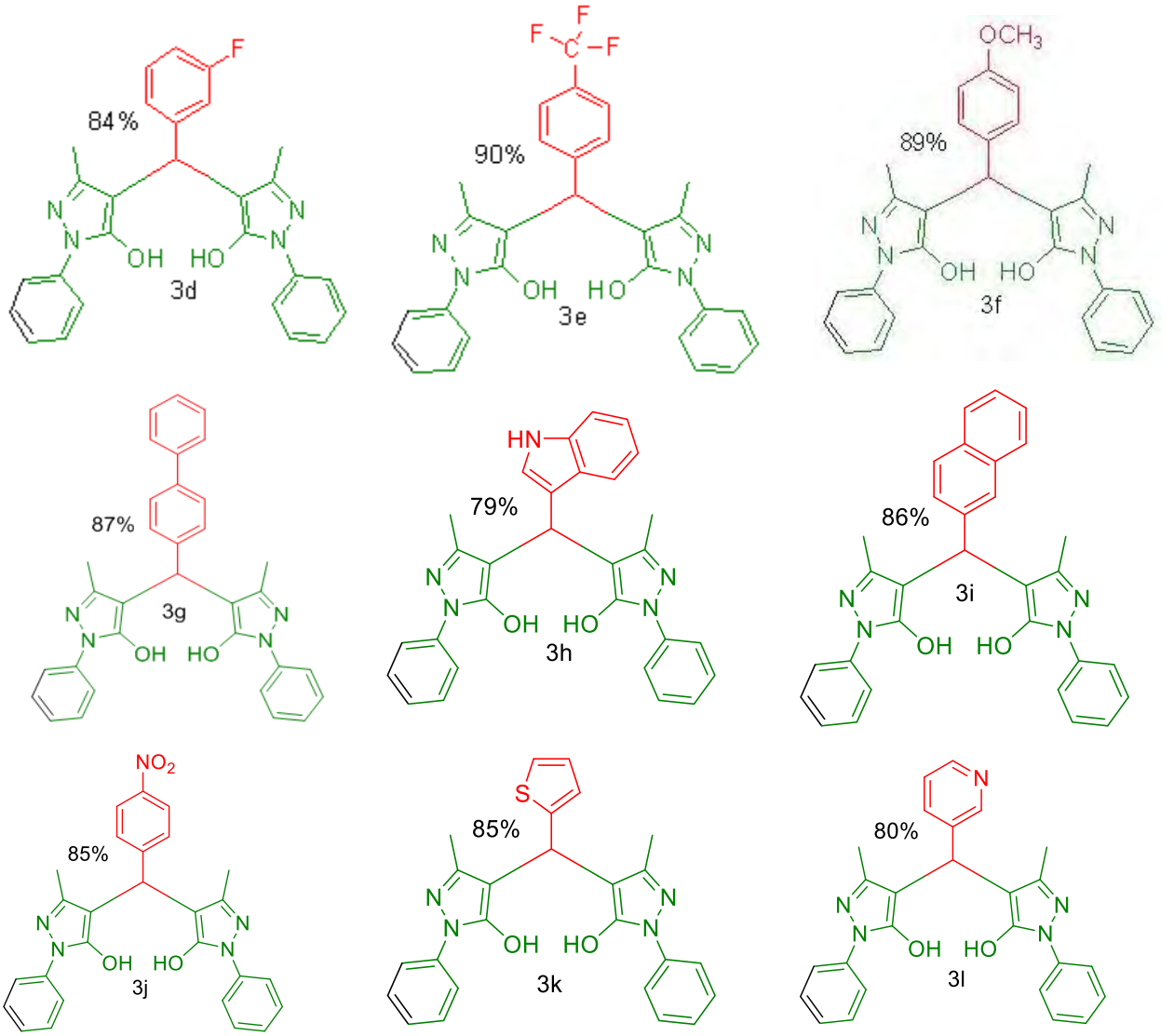
[b]Isolated yield was extracted through column chromatography.

To go through the detailed study of scheme 2, functionalized aldehydes were treated with 3-methyl-1-phenyl-1H-pyrazol-5-ol **(Scheme I.B.2.)** under optimized condition and a variety of a number of 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives were prepared. The resulted compounds have been listed below in Table I.B.4.

From this table, it was observed that, when electron withdrawing groups i.e. nitro at meta position and trifluoromethyl at para position, were present in aldehyde, the product yield was excellent (Table I.B.4., entry 3b, 3e respectively). But it was also observed that, when an aldehyde contained electron withdrawing group i.e. fluoro at para and meta positions, the yield was medium (Table I.B.4., entry 3c, 3d respectively). When an aldehyde contained electron withdrawing groups like, nitro at para position, biphenyl and 2-naphthaldehyde, the product yield were medium (Table I.B.4., entry 3j, 3g, 3i respectively). Heterocyclic moieties like 3- indole, thiophene and 3-pyridine, the product yield were medium to low (Table I.B.4., entry 3h, 3k, 3l respectively). Aldehyde, containing negative inductive effect methoxy group, at para position, produced a satisfactory yield of the product (Table I.B.4., entry 3f).

[a]**Table I.B.4.:** Synthesis of functionalized 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives **(Scheme I.B.2.)**





[a]Reaction of aldehydes (1mmol), 3-methyl-1-phenyl-1H-pyrazol-5-ol (1 mmol) and β - Cyclodextrin (25 mg) under solvent-free condition for 1 h.

I.B.3. Reusability Experiment:

Renewability of β - Cyclodextrin was established through a replica reaction, with benzaldehyde (5 mmol) and 2-hydroxy-1, 4-naphthoquinone (5 mmol) in occurrence of 75 mg β - Cyclodextrin, underneath optimized reaction circumstance. After finishing of the first run, ethyl acetate (4 ml) was added to the reaction mixture. Catalyst was taken back effortlessly, from the reaction mixture, by straightforward work – up, followed by filtration procedure, after the first run. Then the recovered catalyst was sponged down with ethyl acetate (3×4 ml) and next it was dried before being passed down for the next run. The filtrate of reaction mixture was shifted to another

container and this method was done for two times repetitively. The catalyst was then cleaned with ethyl acetate again and after that, it was dried for affording the white coloured β - Cyclodextrin, which was used in the next run, with its dryness. Recuperation of β - Cyclodextrin was slightly lower than the amount used in the first run. However, the recuperated catalyst was used continuously for 3 runs with almost similar affinity and there was no notable degradation in the conversion. This Recyclability test of β - Cyclodextrin catalyst has been depicted in **Figure I.B.2.**, below, by the way of bar diagram. It signifies that, β - Cyclodextrin can expose its catalytic efficacy up to four succeeding runs without any substantial lessening in it and in reducing of the yield of the product.

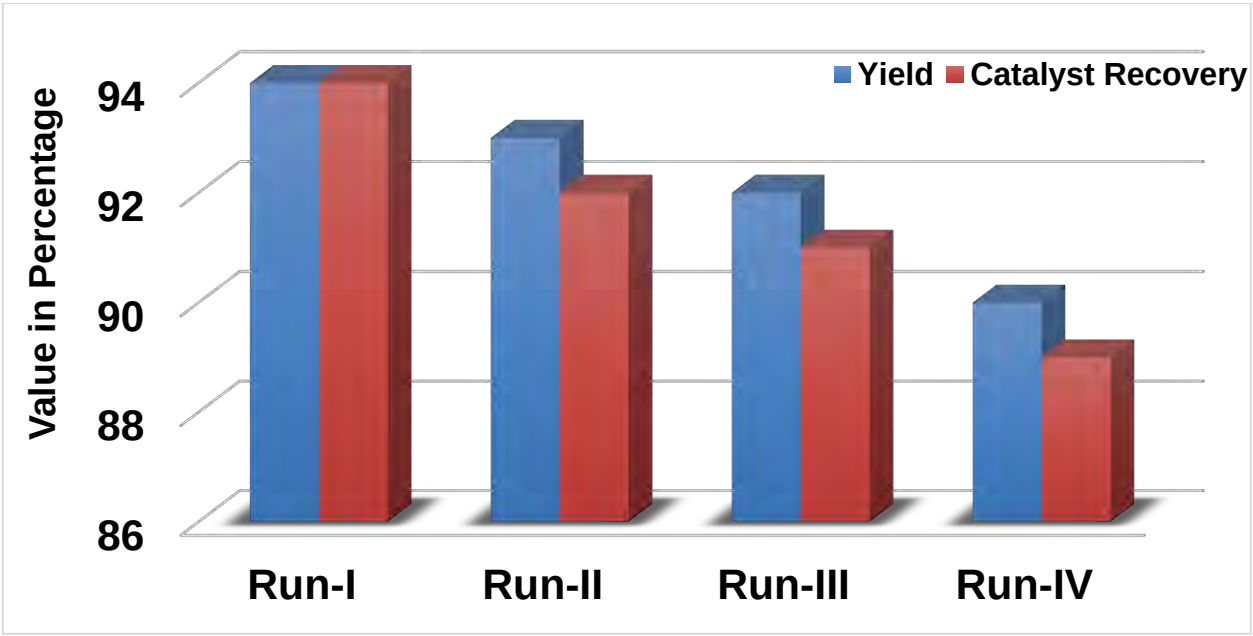


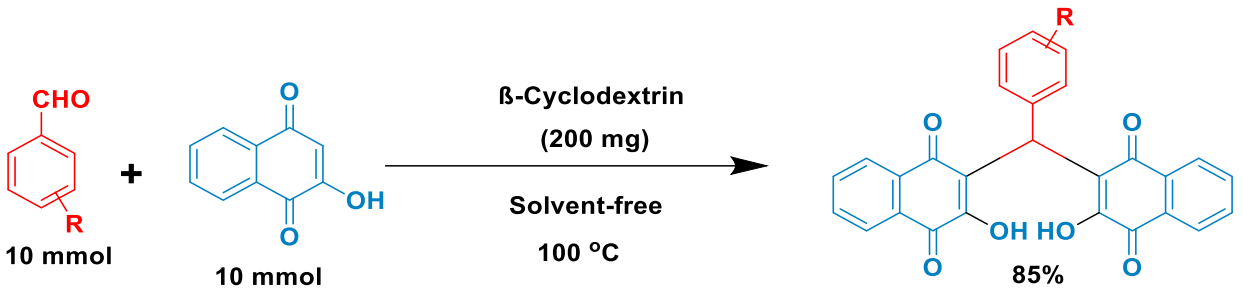
Figure I.B.2.: Reusability of β – Cyclodextrin

I.B.4. Gram - Scale Reaction:

The application of this methodology was examined in large scale, through carrying out the reactions in **gram-scale** (10 mmol scale) procedure. These also produced good yield, like the yield obtained in small scale reaction techniques. This Gram – Scale Reaction technique has been represented below, schematically, through **Figure I.B.3.**

Scale-up experiments:

Scheme I.B.1.:



Scheme I.B.2.:

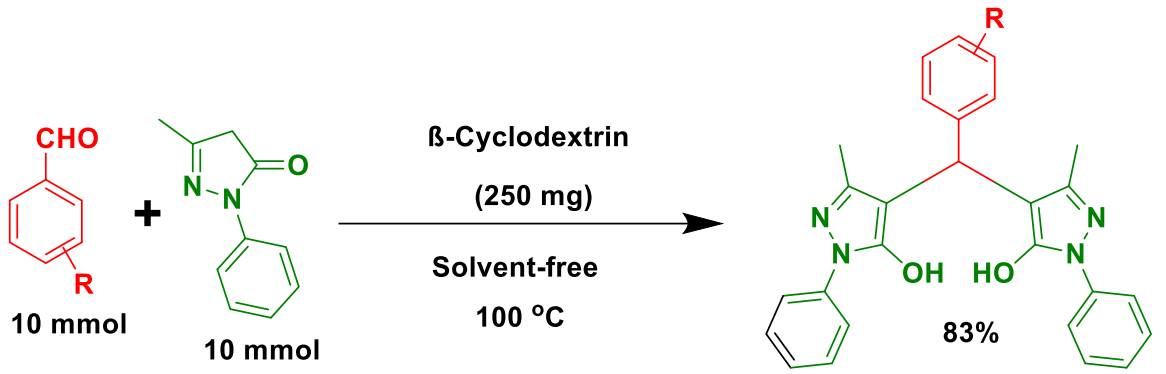
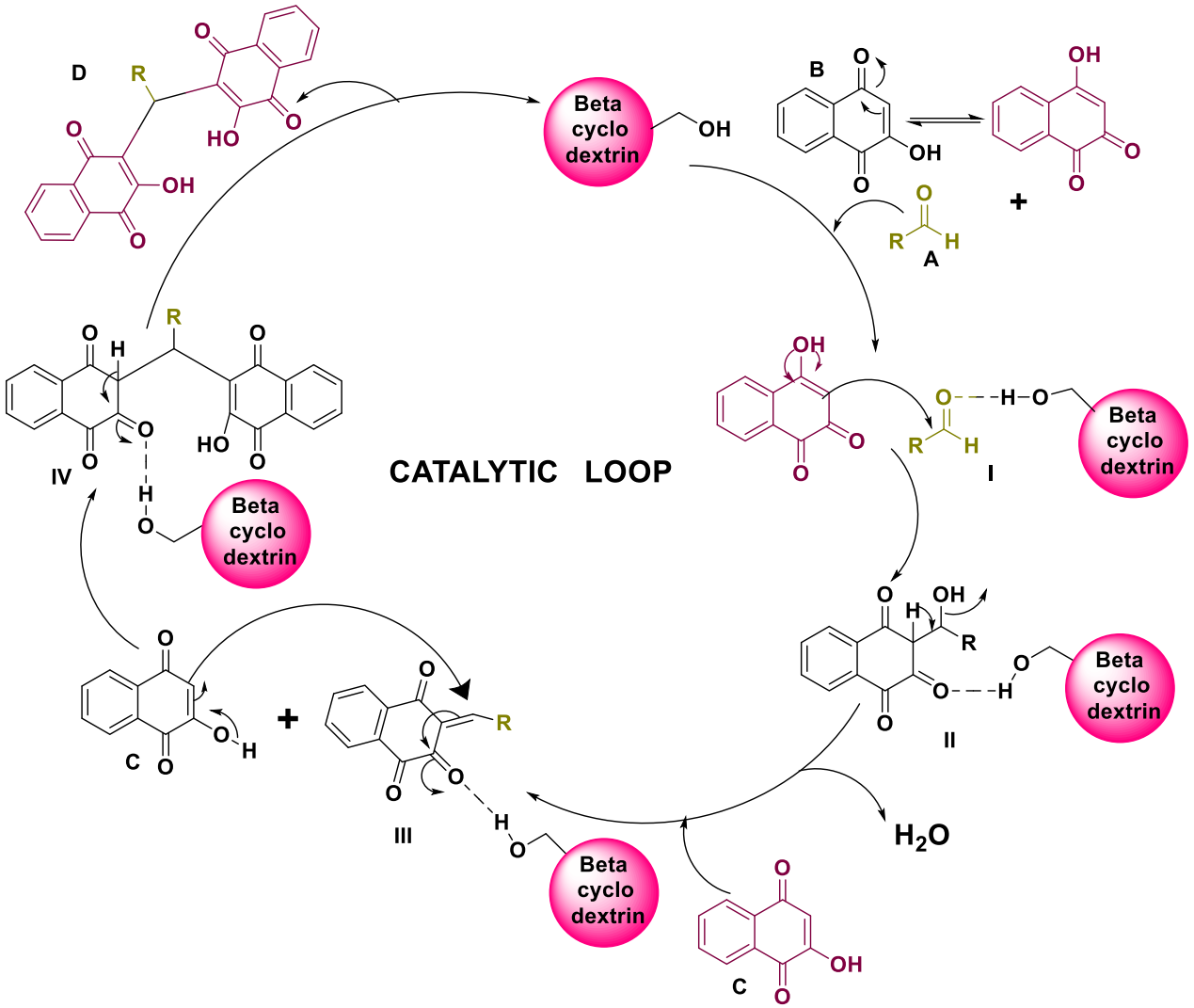


Figure I.B.3.: Gram – Scale Reaction

I.B.5. Plausible Mechanism for the Synthesis of 3, 3'-(phenylmethylene)bis(2-hydroxynaphthalene 1,4-dione) and 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol):

From the literature investigation we have prepared the plausible mechanism for the synthesis of 3, 3'–(phenylmethylene)bis(2-hydroxynaphthalene 1,4-dione), which is depicted in scheme I.B.3. At first, the catalyst stimulates the aldehyde (A), by the way of its acidic hydrogen (-OH) to augment the electrophilicity of the carbonyl portion so that it may facilitate the nucleophilic attack by enolized form of the first mole of 2-hydroxy-1,4-naphthoquinone (Lawson Reagent) (B), through straightforward nucleophilic addition manner and the intermediate (II) is constructed. β – Cyclodextrin activates further, one of the carbonyl carbons of intermediate (II). Then after water elimination we get the intermediate (III), into which, the nucleophilic centre of another mole of 2-

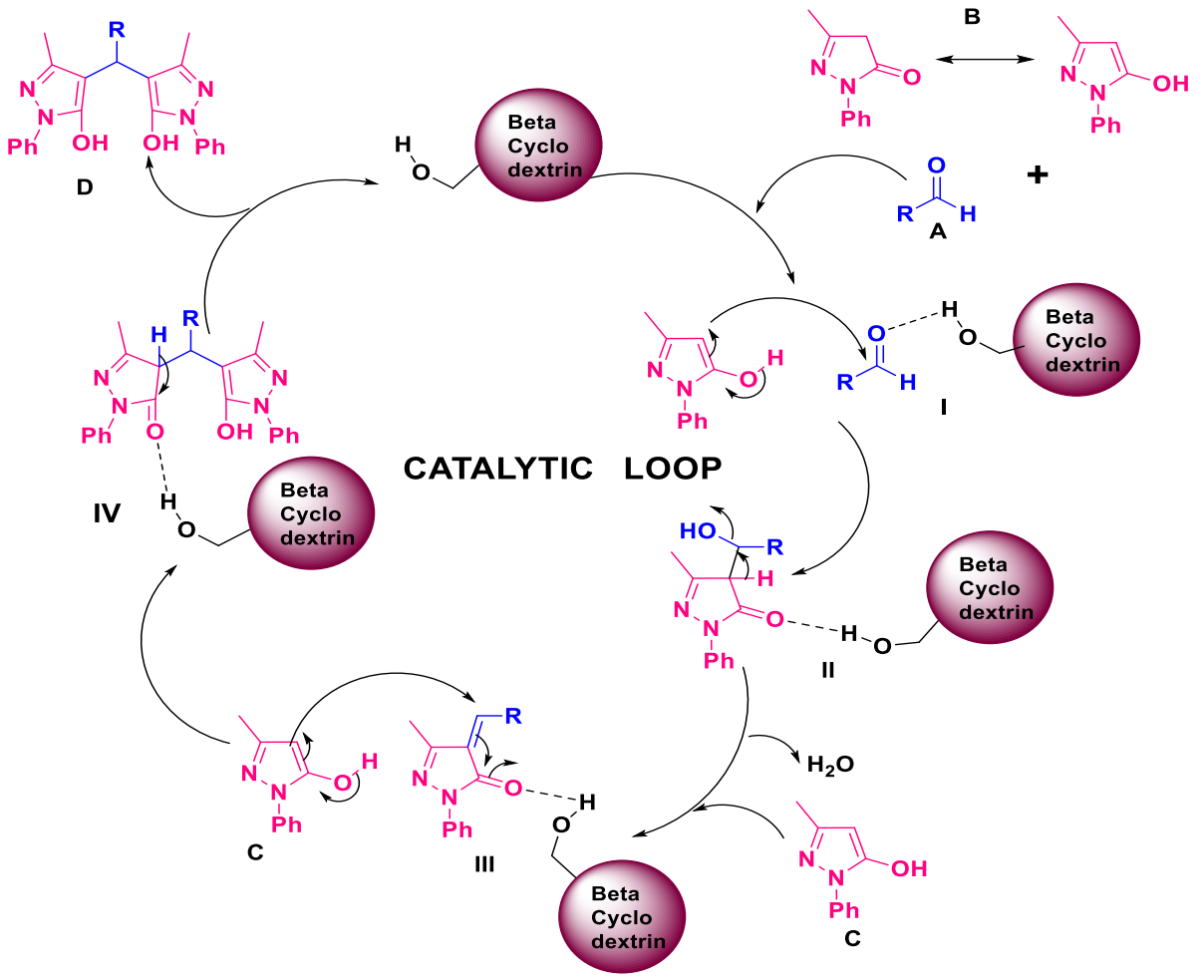
hydroxy-1, 4-naphthoquinone (C) attacks by following Michael addition pathway i.e. at the 4 position of activated intermediate (III). Thus we get the intermediate (IV) in which carbonyl carbon is activated again by β – Cyclodextrin catalyst. After that, through aromatization, we get the ultimate product (D). With this approach, the β – Cyclodextrin catalyst is restored at the last step of such mechanism. This reaction mechanism and pathway have been diagrammatically represented through the following **Scheme I.B.3.**



Scheme I.B.3.: Plausible mechanistic pathway for synthesis of 3, 3'–(phenylmethylene)bis(2-hydroxynaphthalene 1,4-dione)

From the literature survey we have prepared the plausible mechanism for the synthesis of 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol), which is designed in **Scheme I.B.4**. At first, the catalyst activates the aldehyde (A), through its acidic hydrogen (-OH) to enhance the

electrophilicity of the carbonyl group so that it can help the nucleophilic attack by enolised form of the first mole of 3-methyl-1-phenyl-1H-pyrazol-5-ol (B), by simple nucleophilic addition pathway and the intermediate (II) is formed. β – Cyclodextrin activates further, one of the carbonyl carbons of intermediate (II). Then after water elimination we get the intermediate (III), into which, the nucleophilic centre of another mole of 3-methyl-1-phenyl-1H-pyrazol-5-ol (C) attacks through Michael addition pathway i.e. at the 4 position of activated intermediate (III). Thus we get the intermediate (IV) in which carbonyl carbon is activated again by β – Cyclodextrin catalyst. After that, through aromatization, we get the ultimate product (D). With this approach, the β – Cyclodextrin catalyst is restored at end. This reaction mechanism and pathway have been diagrammatically represented through the following **Scheme I.B.4.**



Scheme I.B.4.: Plausible mechanistic pathway for synthesis of 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

I.B.6. Conclusion:

Using supramolecular β-cyclodextrin as an organocatalyst, we triggered the carbonyl oxygen of the corresponding aldehydes to strengthen the electrophilicity of the carbonyl carbon, subsequently performing nucleophilic addition into that location. In summary, we can demonstrate an environmentally sound and achievable strategy for generating numerous examples of functionalized 3, 3'–(phenylmethylene)bis(2-hydroxynaphthalene 1,4-dione) and 4, 4'–(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives with no involvement of any solvent. The general process encompasses the Cascade reaction, comprising the well-known Michael Addition and Knoevenagel route. Since no metal was utilized in this process, the entire synthetic approach remained more environmentally friendly. Once more, the protocol's solvent-free requirement greatly enhances its ecological viability. The β-cyclodextrin catalyst can be retrieved using a simple filtration process, and its restoration aspect can continue without any typical deviations in its level of effectiveness until the fourth run. Therefore, the fundamental innovation and inventiveness of this technology is the adoption of supramolecular β-cyclodextrin catalyst, which is inexpensive, readily available, and secure for the environment in place of any detrimental, deadly, perilous, extensive, hazardous, and overpriced metal catalyst. The currently underway study's technique ought to be viewed as an integral component of the scientists' and researchers' ongoing efforts, contributing to a notable advancement in the chemical realm of medicines, natural product synthesis, and the drug industry in subsequent years.

I.B.7. Experimental Section:

I. Common Information:

All the compounds were acquired from commercial suppliers and used without doing further decontamination process. All the products were purified by column chromatography on silica gels (60−120 Mesh, SRL, India). For TLC, Merck plates coated with silica gel 60, F254 were utilized. ^{1}H NMR,^{19} F and ^{13}C NMR were recorded using 400 MHz, 376 MHz and 100 MHz, respectively, on Bruker AV 400 NMR spectrometer using TMS as internal standard. Splitting manners of protons were explained as s (singlet), d (doublet), t (triplet) and m (multiplet).

II. General course of action for the production of 3, 3'-(phenylmethylene)bis(2-hydroxynaphthalene 1,4-dione):

A mixture of 2-hydroxy-1,4-naphthoquinone (1 mmol), benzaldehyde (1 mmol) and β – Cyclodextrin (20 mg) was blended at 100 ºC for 1 h in open air in a reaction vessel (50 mL) using a magnetic stirring bar. The reaction progress was kept track of using TLC with a mixture of ethyl acetate and petroleum ether as the eluent medium. After finishing of the reaction, the mixture was exterminated to room temperature and ethyl acetate (5 mL) was employed to the reaction mixture and the catalyst was kept separated by straightforward filtration and was extracted with ethyl acetate twice (2×20 ml). Amalgamated extracts were cleaned with distilled water, dried over anhydrous Na_2SO_4 and concentrated. The primeval product was decontaminated by passing through a column packed with silica gel (eluent: ethyl acetate–petroleum ether). The products obtained were known compounds and were recognized by their color, melting point and NMR spectroscopy.

III. General procedure for the synthesis of 4, 4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol):

A mixture of 3-methyl-1-phenyl-1H-pyrazol-5-ol (1 mmol) benzaldehyde (1 mmol) and β – Cyclodextrin (25 mg) was blended at 100 ºC for 1 h in open air in a reaction vessel (50 mL) using a magnetic stirring bar. The reaction progress was kept an eye on using TLC with a mixture of ethyl acetate and petroleum ether as the eluent medium. After finishing of the reaction, the mixture was exterminated to room temperature and ethyl acetate (5 mL) was employed to the reaction mixture and the catalyst was kept separated by straightforward filtration and was extracted with ethyl acetate twice (2×20 ml). Amalgamated extracts were cleaned with distilled water, dried over anhydrous Na_2SO_4 and concentrated. The primeval product was decontaminated by passing through a column packed with silica gel (eluent: ethyl acetate–petroleum ether). The products obtained were known compounds and were recognized by their color, melting point and NMR spectroscopy.

IV. Spectral Data of some compounds:

3,3'-((3-Nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

(Chapter **I**, Section **B**, Table **I.B.2**, entry **3b) (Figure I.B.4.).**

M.P.: 215-217 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 6.796 (s, 1H), 7.498 - 7.723 (m, 1H), 7.768 - 7.809 (m, 6H), 7.907 - 8.009 (m, 6H) **(Figure I.B.5.).**

^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 33.573, 120.737, 121.728, 121.949, 125.754, 126.298, 129.819, 131.402, 132.570, 133.610, 134.423, 134.531, 144.632, 148.325, 165.003, 182.819, 183.933. **(Figure I.B.6.).**

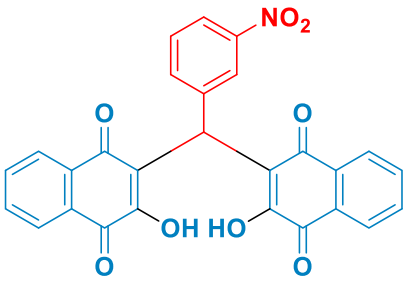


Figure I.B.4.: Structure of 3,3'-((3-Nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

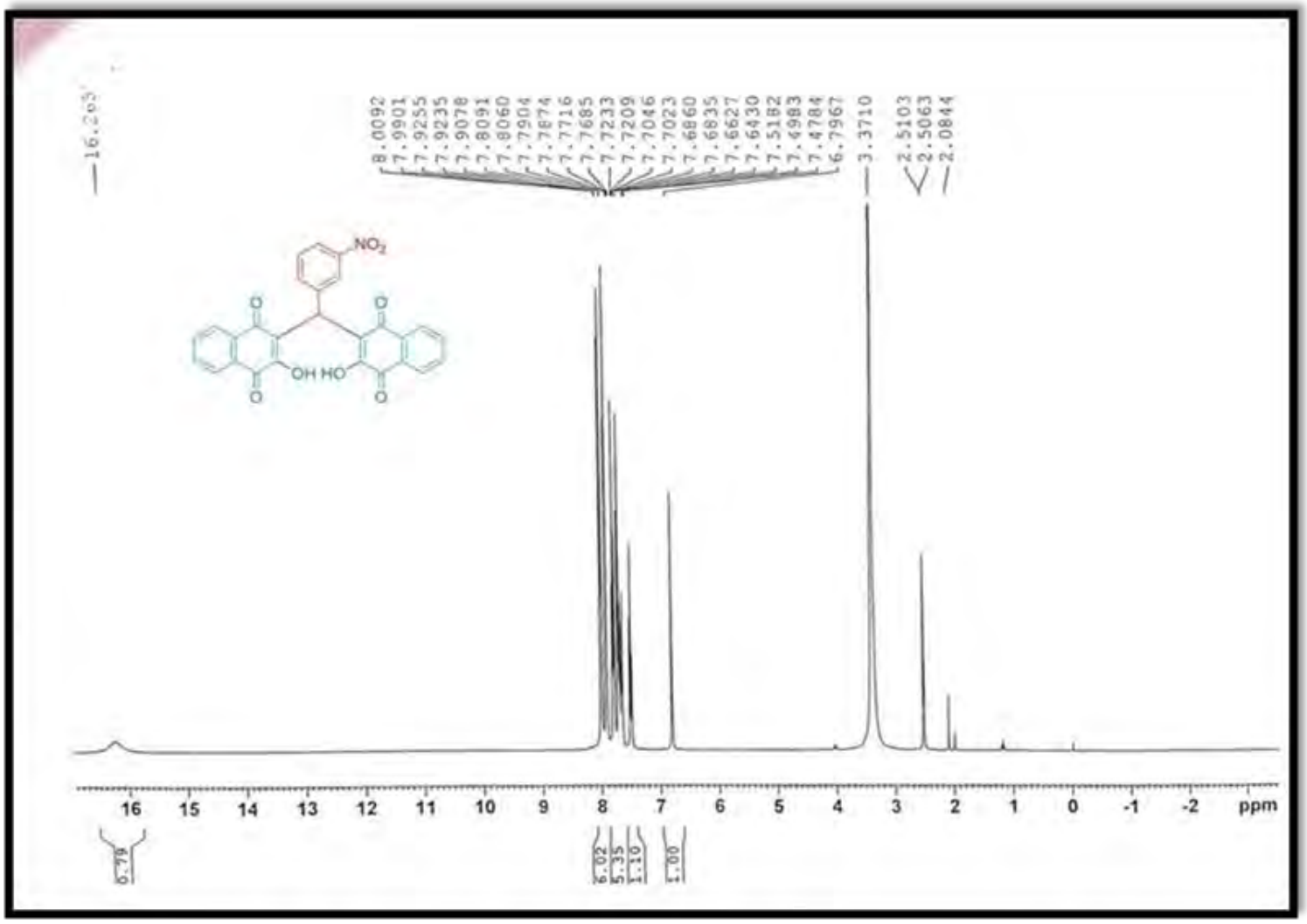


Figure I.B.5.: ^{1}H NMR spectroscopic representation of 3, 3'-((3-Nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

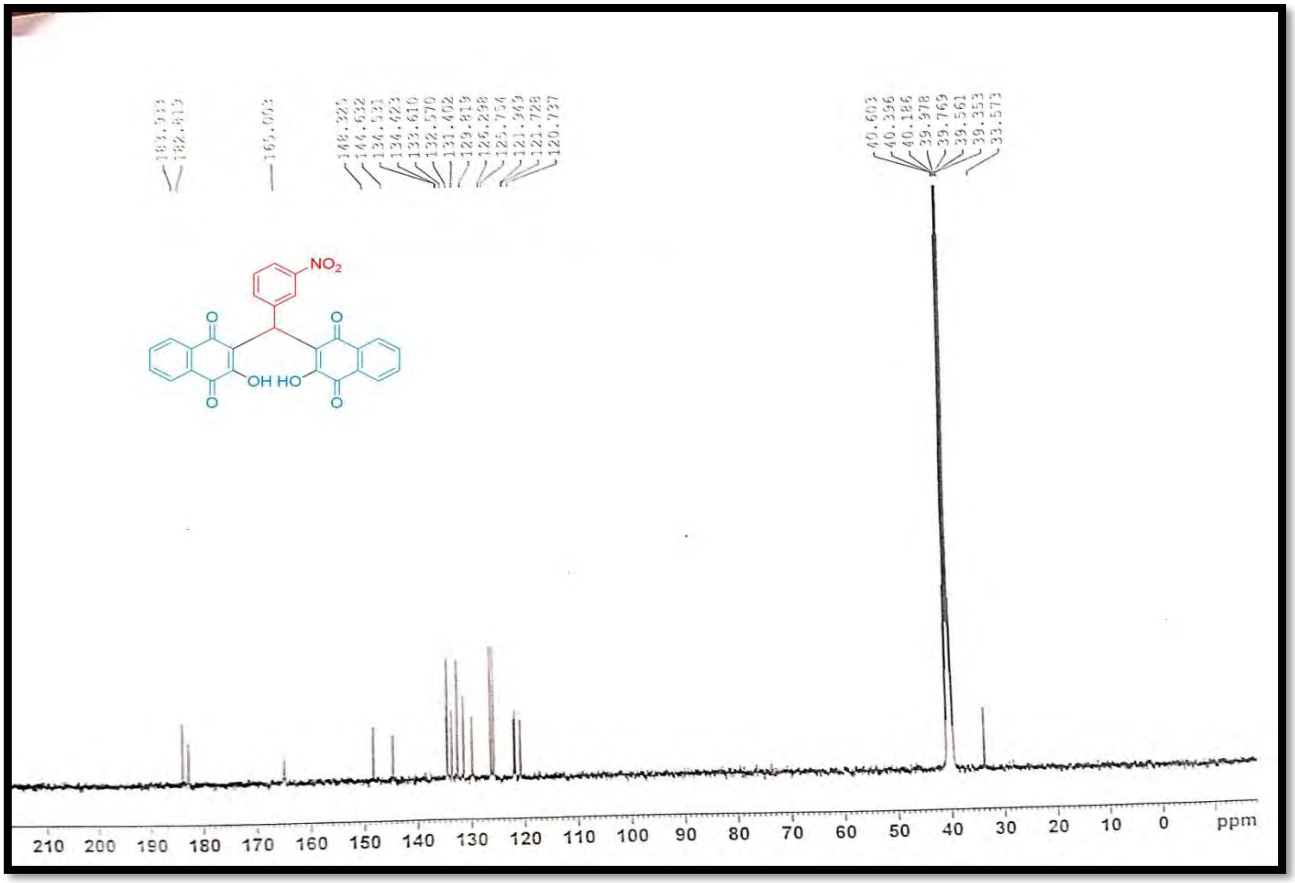


Figure I.B.6.: ^{13}C NMR spectroscopic representation of 3,3'-((3-Nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

3,3'-((4-trifluoromethyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

(Chapter **I**, Section **B**, Table **I.B.2**, entry **3d) (Figure I.B.7.).**

^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 6.754 (s, 1H), 7.356 (d, 2H, *J* = 8 Hz), 7.523 (d, 2H, *J* = 8 Hz), 7.692 – 7.778 (m, 5H), 7.903 (d, 2H, *J* = 7.2 Hz), 7.985 (d, 2H, *J* = 7.6 Hz) **(Figure I.B.8.).**

^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 33.682, 122.263, 123.723, 125.118, 125.689, 126.023, 126.255, 126.434, 128.023, 131.398, 132.509, 133.643, 134.375, 147.161, 165.042, 182.858, 184.018. **(Figure I.B.9.).**

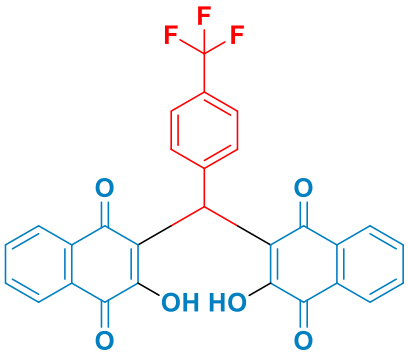


Figure I.B.7.: Structure of 3, 3'-((4-trifluoromethyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

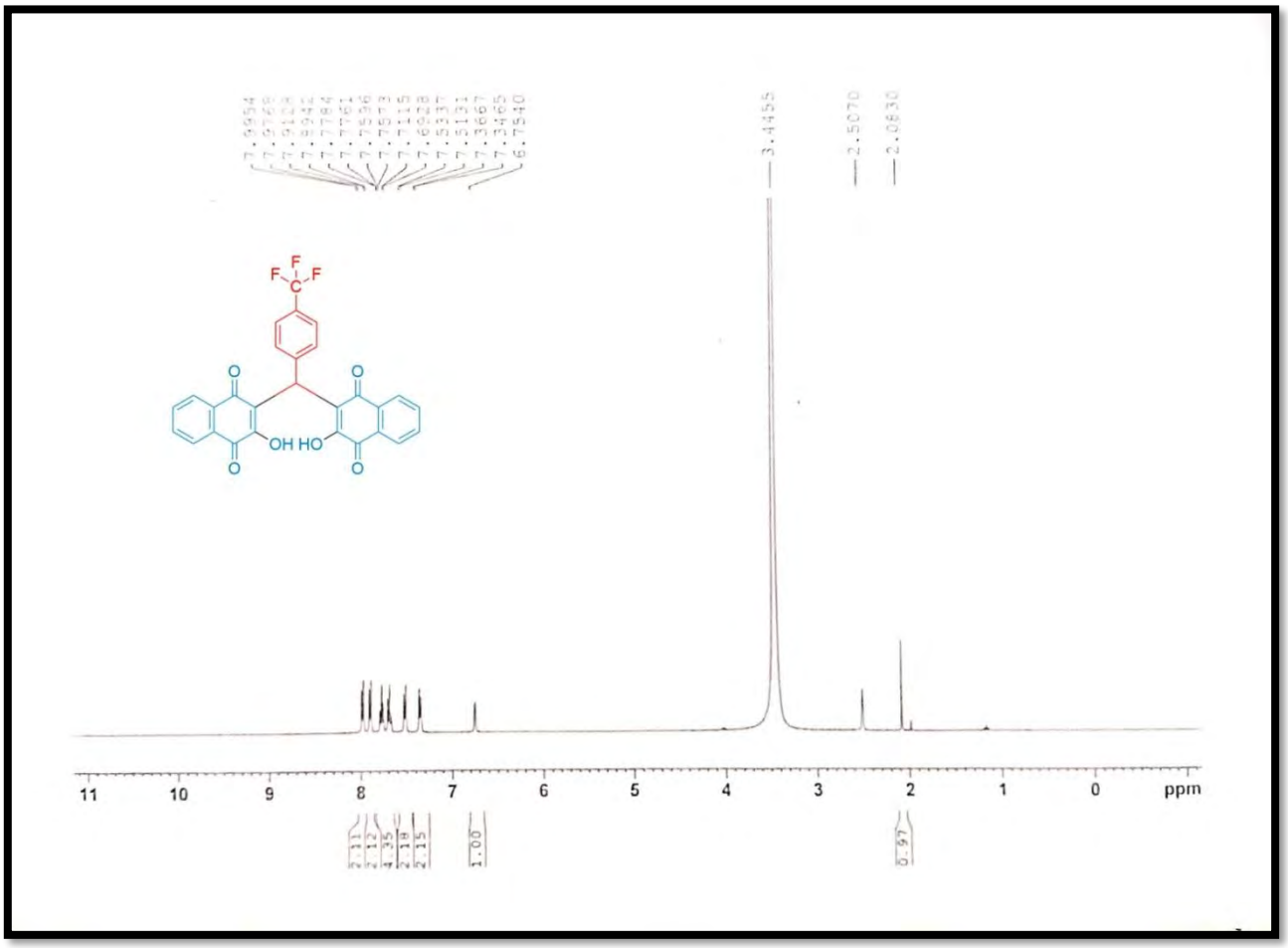


Figure I.B.8.: ^{1}H NMR spectroscopic representation of 3, 3'-((4-trifluoromethyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

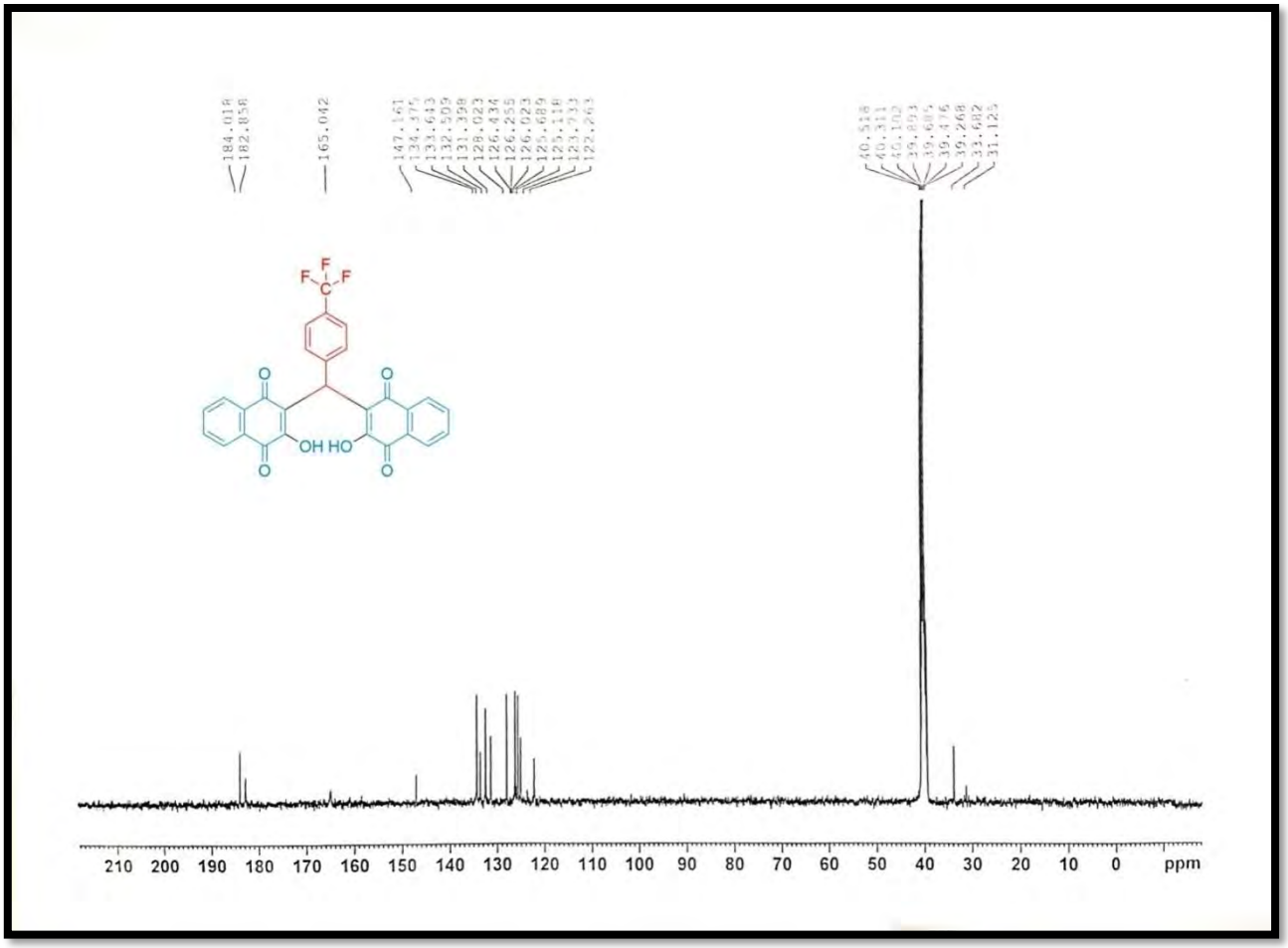


Figure I.B.9.: ^{13}C NMR spectroscopic representation of 3, 3'-((4-trifluoromethyl)methylene)bis(4-hydroxy-2H-chromen-2-one)

4,4′-[(4-Methoxylphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

(Chapter **I**, Section **B**, Table **I.B.4**, entry **3f) (Figure I.B.10.).**

^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 2.34 (s, 6H), 3.70 (s, 3H), 4.90 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.44 (t, J = 8.0 Hz, 4H), 7.71 (d, J = 8.0 Hz, 4H); **(Figure I.B.11.).**

^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 12.2, 32.9, 55.5, 114.0, 121.0, 126.1, 128.7, 129.4, 134.5, 146.7, 158.0. **(Figure I.B.12.).**

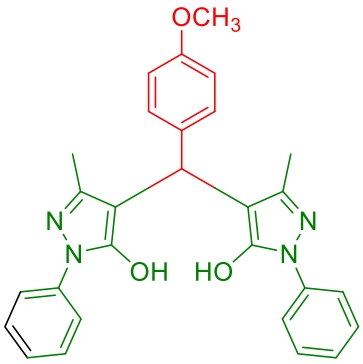


Figure I.B.10.: Structure of 4,4′-[(4-Methoxylphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

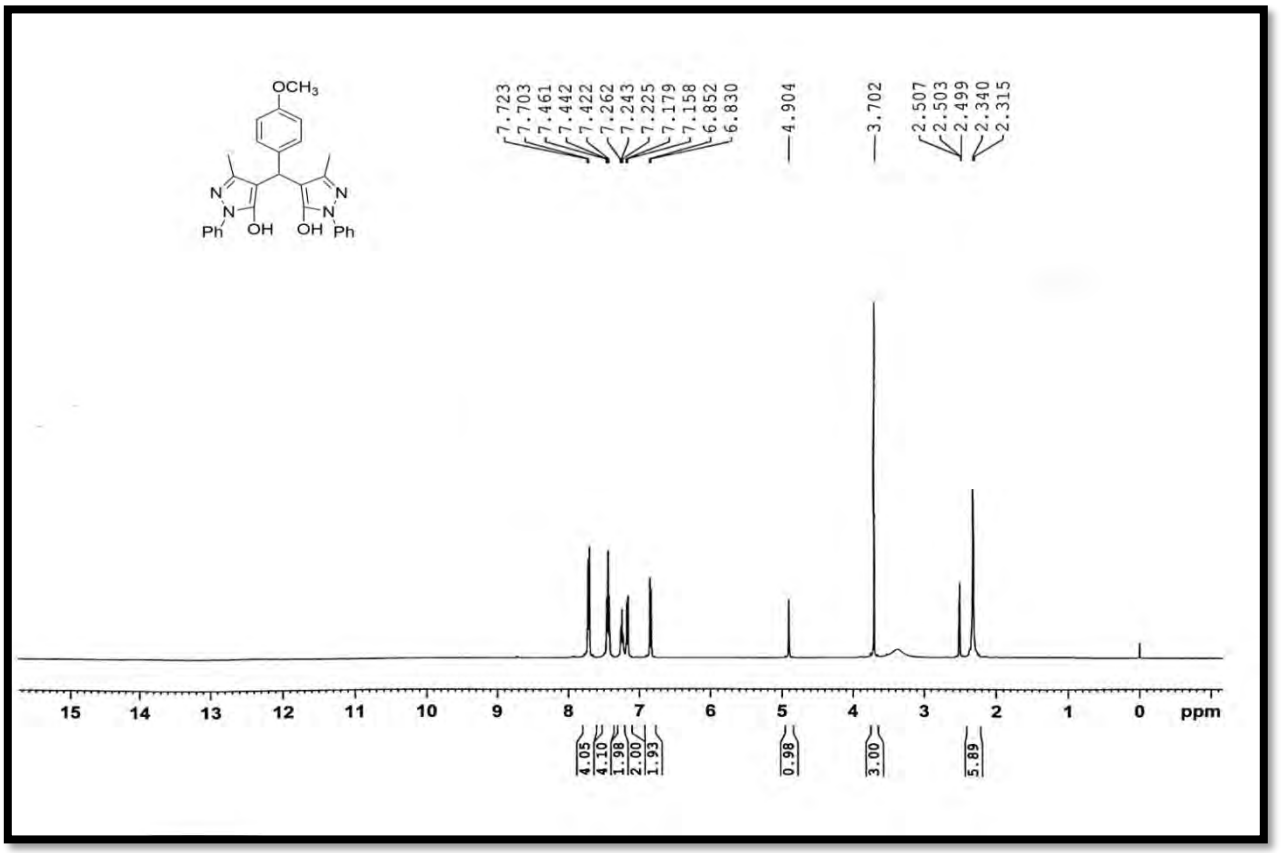


Figure I.B.11.: ^{1}H NMR spectroscopic representation of 4,4′-[(4-Methoxylphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

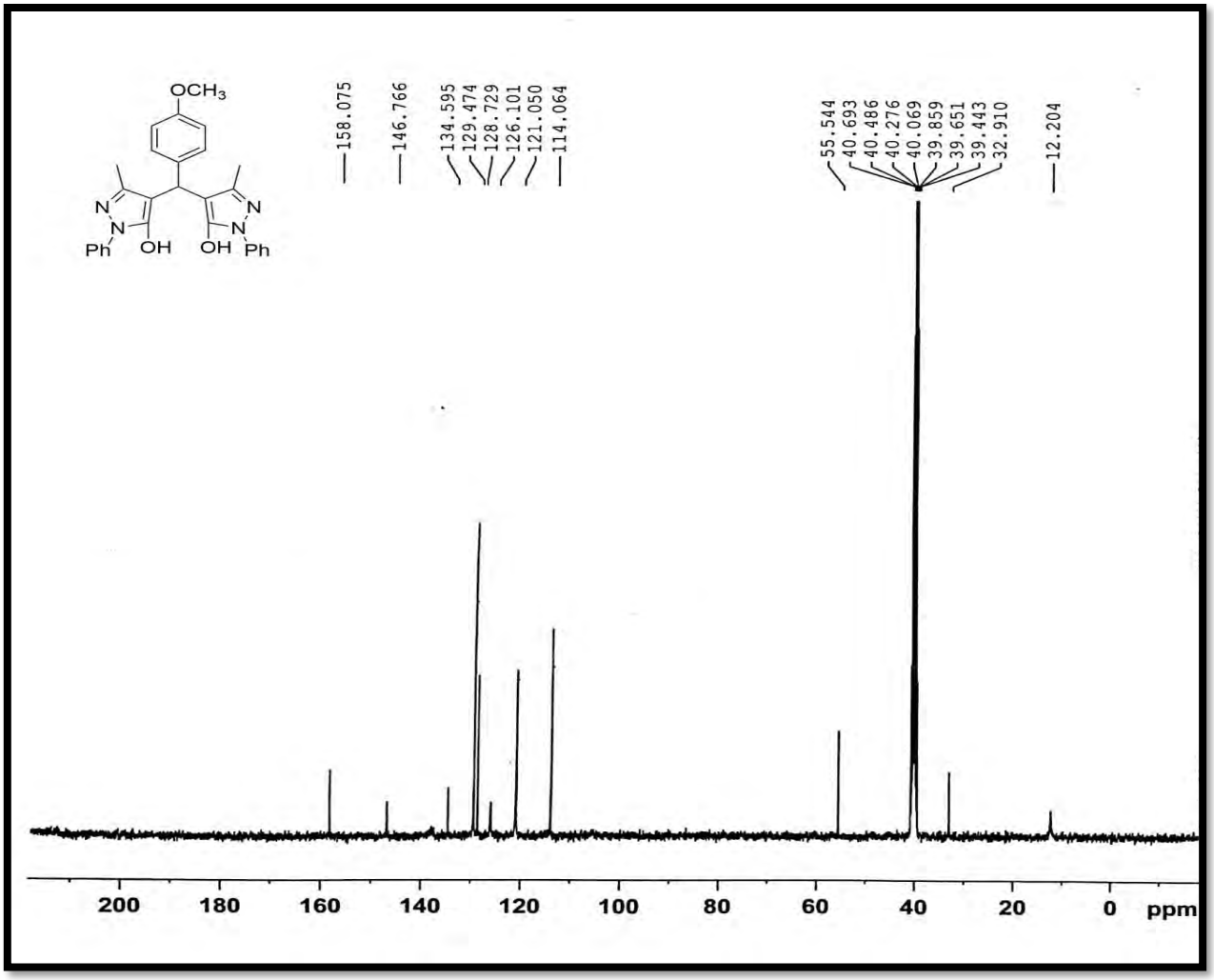


Figure I.B.12.: ^{13}C NMR spectroscopic representation of 4,4′-[(4-Methoxylphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

I.B.8. References:

References are displayed in **BIBLIOGRAPHY** under **Chapter I, Section B,** that is, "**Beta – Cyclodextrin (β-Cyclodextrin) mediated Solvent–Free Synthesis of 3,3'–(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) and 4,4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)"** (pp. 207-216**).**