O-ARYLATION OF ANGULAR DIAZAPHENOXAZINE AND RELATED CARBOCYCLIC ANALOGUE USING BUCHWALD CATALYST

BY

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TITLE PAGE

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BEING M.Sc PROJECT SUBMITTED TO THE
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CERTIFICATION

Ogbonna, Onyinyechi, a postgraduate student in the Department of Pure and Industrial Chemistry with the Reg. No. PG/MSc/13/65023 has satisfactorily completed the requirement for research work for the award of the Degree of Masters in Pure and Industrial Chemistry.

_____ _____

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Date: _____ Date: _____

_____

External Examiner

Date: _____

DEDICATION

This work is dedicated to the Almighty God in the person of Holy Spirit for His wisdom, knowledge, strength, understanding, guidance, protection and provision throughout the course of this research, may His name alone be glorified.

ACKNOWLEDGEMENT

I am grateful to the Most High God whose enabling grace made this dream come true. My thanks go to my beloved supervisor Dr. (Mrs.) M. A. Ezeokonkwo whose immeasurable assistance, positive criticism, moral, prayer and material support made it possible for this work to be completed. I lack words to express my gratitude to Dr. J. N. Asegbeloyin who assisted in no small measure that I analysed my samples. To the Head of Department Engr. E.A. Ochonogo, I say thank you for making himself available whenever his assistance is needed. I am also indebted to other staff (academic and non-academic) of the department of Pure and Industrial Chemistry whose contribution at one point or the other made this work possible.

Words cannot express my profound gratitude to my wonderful parents Mr. and Mrs. Nicodemus Ogbonna who laid the foundation and made me roll on the wheels of educational lime light. I will not fail to appreciate my sister Uchechi Ogbonna and my beloved friend Alikor Edward Achinike Daniel for their love and prayers and understanding throughout the hectic period. Without mincing words, I love you and it is my prayer that God will make me a blessing to all of you.

I appreciate the staff of Chemical Science Evangel University, Akaeze, Ebonyi State, especially Mrs. Precious Udeozor, Mr. Chukwu C. J Miss Onwere Chidiebube and Mr. Obasi David, for the understanding and love they showered on me during this hectic period.

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I am immensely grateful to my brethren in the Lord ï Assemblies of God church Hilltop Nsukka (Mega church) and Living Faith Chapel, 135 Ezeamgbo Ebonyi State, especially Pastor Chris Orumah and Pastor Joseph Okoroigwe who upheld me in prayers and encouraged me too.

To all I say thank you and God bless.

OGBONNA, ONYINYECHI N.

ABSTRACT

Synthesis of twelve O-arylated diazabenzo[a]phenoxazine-5-one and its carbocyclic analogue is reported in 46 - 99 % yields. The intermediates were prepared by anhydrous base catalyzed reaction of 2,3-dichloro-1,4-naphthoquinone with 4,5-diamino-6-hydroxyl-2-mercaptopyrimidine and 2-aminophenol. The O-arylation process occurred smoothly in non-polar solvent, toluene with the inexpensive base, K_2PO_4 at 110^oC. The intermediates were combined with a variety of electron-deficient, electrically neutral and electron-rich phenols in the presence of a catalyst combination of $Pd(OAc)_2$ and electron rich, bulky alkyldiarylphosphine ligand in which the alkyl groups are tert-butyl (t-Buxphos), to furnish the arylated compounds. Bulky yet basic nature of the phosphine ligand is thought to be responsible for these transformations. The highest yields were obtained when the intermediates coupled with electron rich phenols, with the carbocyclic analogue giving better yields. IR, ^1H NMR and ^{13}C NMR spectra data, confirmed the structures of all the synthesized compounds. The effect of the synthesized compounds on bacteria and fungi growth was studied. The studied compounds were found to be potent antibacterial and antifungal agents as they showed significant biological activity against *Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa* and *Candida albicans.* In addition, they may be useful as dyes in industries since they absorb in the UV- visible region.

ABBREVIATIONS

Brethphos: 2-(dicyclohexylphosphino)-3,6-dimethoxyl-2^1,4^1,6^1-triisopropyl-1^1,1^1-biphenyl

BINAP: 2,2ϕBis (diphenyl phosphino)-1,1ϕbinaphthyl.

DBA: Dibenzenyzylideneacetone

DME: Dimethoxyethane

DMF: N, N- Dimethylformamide

DMSO: Dimethylsulfoxide

DNA: Deoxyribonucleic acid

DPBA: 2, 2ϕ- Bis(phenylphosphino)biphenyl

DPEPHOS: Bis(2-diphenylphosphinophenyl) ether

DPPb: 1, 4-Bis (diphenylphosphino)butane

DPPF: 1, 1-Bis (diphenylphosphino) ferrocene

Davephos: 2-dicyclohexylphosphino-2^1-(N,N-dimethyamino)biphenyl

Johnphos: (2-biphenyl)di-tert-butylphosphine

Jackie phos: 2-(bis-[3,5-bis](trifluoromethylphosphino)-3,6-dimethoxy-2^1,4^1,6^1-triisopropyl-1,1^1-biphenyl

LHMDS: lithium hexamethyl disilazine or Lithium bis(trimethysily)amide MIC: Mimimum Inhibitory Concentration

Mephos: 2-dicyclohexyphosphino-2^1-methylbiphenyl

RT: Room temperature

Ruphos: 2-dicyclohexylphosphino-2^1, 6^1-diisopropoxylbiphenyl

Sphos: 2-dicyclohexylphosphino-2^1, 6^1-dimethoxybiphenyl

THF: Tetrahydrofuran

TPP: Triphenylphosphine

TPPTS: Phosphinidynetris (benzenesulfonic acid)trisodium salt or sodium triphenylphosphinetrisulfonate

t-Buxphos: 2-ditertiarybutylphosphino-1,2,3-triisopropylbiphenyl

tBuBrethphos: 2-(di-tertbutylphosphine)-2^1,4^1,6^1-triisopropyl-3,6-dimethy-$1,1^1$-biphenyl

tBumephos: 2-di-tert-butylphosphino-2^1-methylbiphenyl

tBuDavephos: 2-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine

XANTPHOS: 4, 5-Bis (diphenylphosphino)-9, 9-dimethylxanthene

Xphos: 2-(Dicyclohexylphosphino)-2, 4, 6-triisopropylbiphenyl

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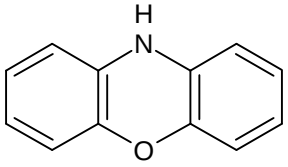
CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND OF STUDY:

Angular phenoxazines are defined as the polynuclear phenoxazines that have non-linear arrangement ring system[1]. Angular phenoxazines and its aza analogues constitute important classes of organic compounds because of their wide range of commercial uses. They are used as dyes[1] and drugs[2]. They exhibit strong biological activities ranging from antidepressant[3], antitumour[4], anticancer[5], antibacterial[6], and antituberculosis[7] and schizophrenia agents[8]. Among the several industrial applications of angular phenoxazine derivatives are their use as acid-base indicator[9], biological stains[10], laser dyes[11] and chromophoric compounds[12].

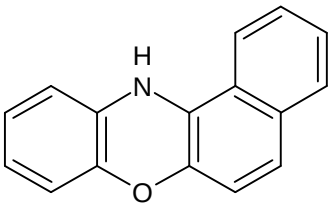
The report of the basic structure of the parent phenoxazine 1 prompted the synthesis of several hundreds of derivatives, not only to improve their usefulness but also to open up new area of applications.



1

These structural modifications have given rise to benzo[a]phenoxazine **2**, benzo[c]phenoxazines **3**, benzo[b]phenoxazine **4**, benzo[j]phenoxazine **5**,

benzo[i]phenoxazine **6** and benzo[h]phenoxazine **7**[10] among others. These are all carbocyclic phenoxazines.



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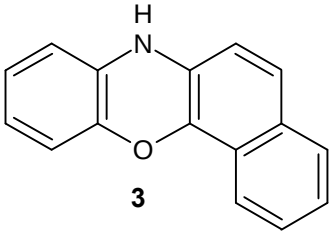

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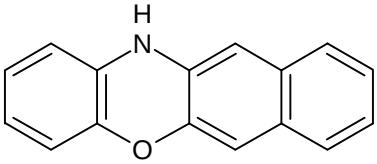

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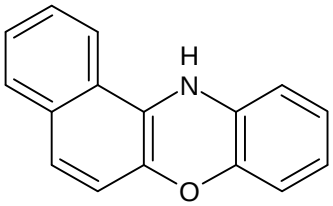

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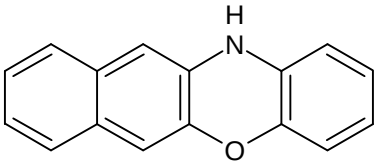

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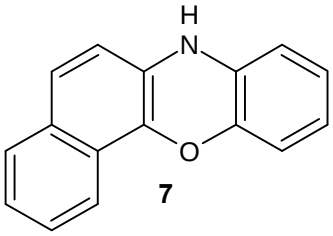

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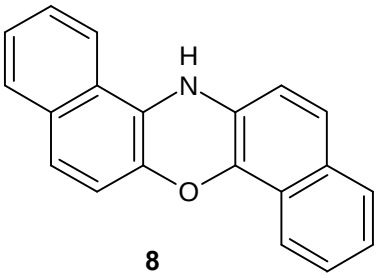
Structures **4** and **6** are linear phenoxazines while structures **2**, **3**, and **5** are angular phenoxazines.

Phenoxazine compounds that have two benzo groups attached to phenoxazine nucleus are called dibenzophenoxazines. These include compounds **8**, **9**, and **10**.



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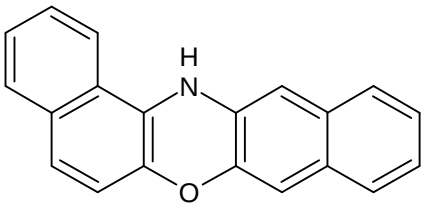

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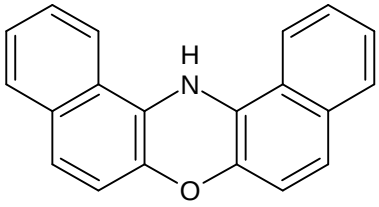

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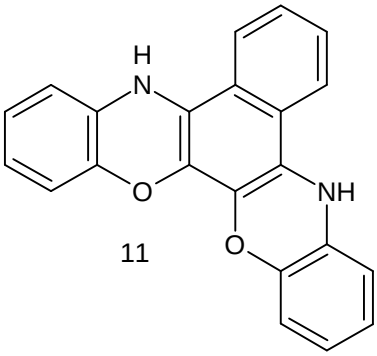
Some of the structures of angular phenoxazines are very complex. For example compounds **11**[14], **12**[15],**13**[16] and **14**[17].



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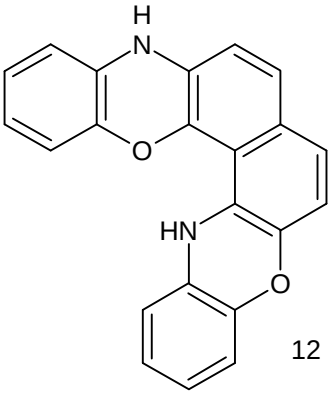

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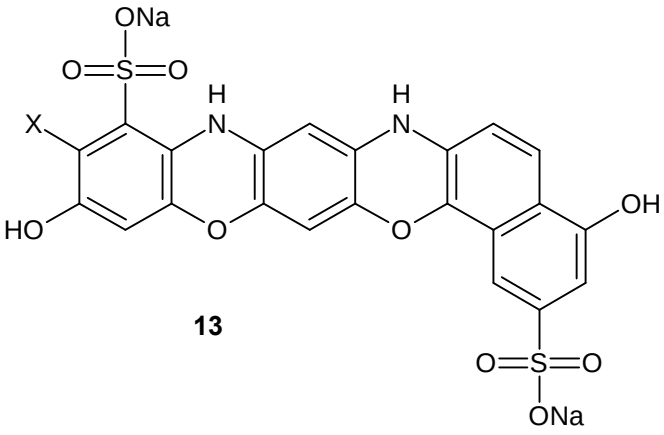

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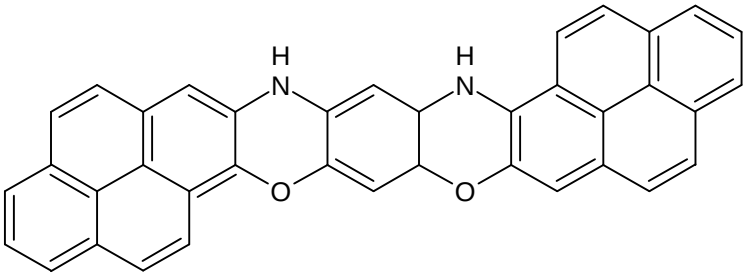

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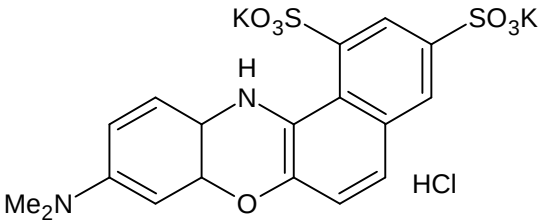
Phenoxazine derivatives produced by the fusion of the benzo group at óaô position or 1, 2 bonds have been reported; **15**[18],**16**[13] and **17**[19] which have been used as dyestuff[20] and good indicators[21]. They have been shown to exhibit anticancer[22, 23] and antibacterial activities[24].



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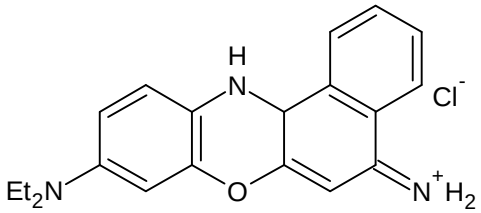

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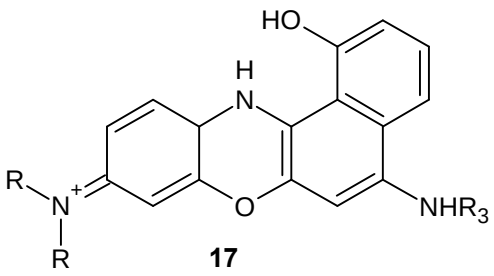

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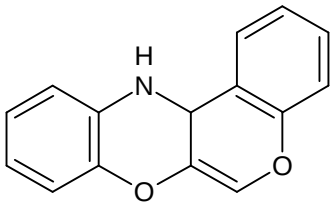
Replacement of one of the ring carbon atoms of angular phenoxazine analogues with heteroatom such as oxygen, gives phenoxazines called pyranophenoxazines[13]: **18**, **19**.



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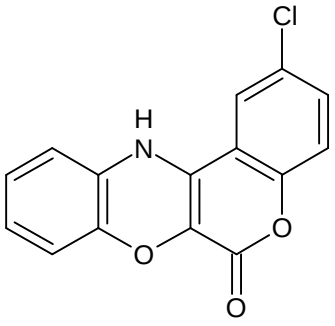

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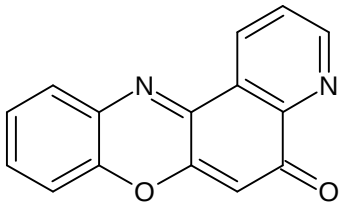
Variations in phenoxazines ring system because of replacement of one or more CH groups by annular nitrogen have given rise to monoaza **20**, diaza **21**, and triaza **22** analogues of phenoxazines. Compounds in each of these aza family have been synthesized and reported[25].



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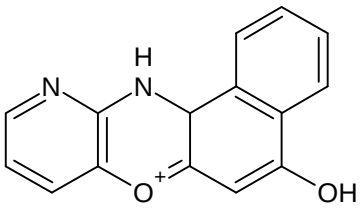

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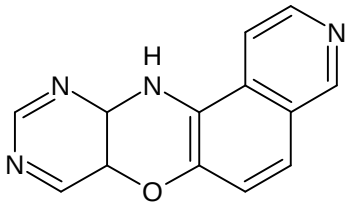

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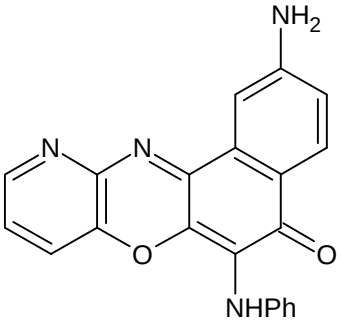
Some of these aza derivatives have substituents; **23** and **24**[26].



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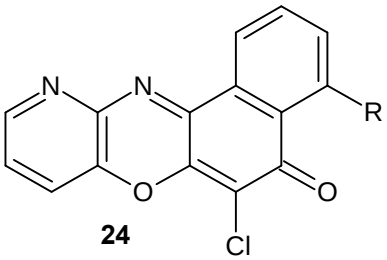

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R = NH_2, NO_2, NHOAc.

Several authors have reported cross coupling reactions used for the synthesis of these derivatives[27]. Such coupling reactions includes Sonogashira cross coupling reaction, Suzuki cross coupling reaction, Stille cross coupling reaction, Buchwald-Hartwig cross coupling reaction and Heck-Mozoroki cross coupling reaction. The discovery of these cross-coupling reactions constitutes one of the most striking breakthroughs in organic chemistry, and it has brought many benefits to organic chemists:

- It is extremely powerful and a general strategy for the formation of C ï C and C ï hetero aromatic bonds.

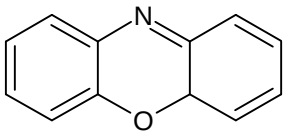
- It has changed the methodology for the retro synthesis enabling the Organic Chemists to shorten the synthetic procedure[27,28]
- The reaction has gained wide use in synthetic organic chemistry finding application in many total synthesis and industrial preparation of numerous pharmaceuticals [27, 29].

Several transition metal catalysts have been developed in response to the increasing demand of these coupled products in chemical pharmaceutical industries. The sole aim is to exert the highest turnover frequency[27,28]. Literature has shown that palladium catalyzed cross coupling reactions and the Hartwig-Buchwald coupling are the most frequently used routes for the formation of carbon hetero aromatics bond [28]. Buchwald group developed a series of catalyst based butyl electron rich phosphine ligands that have attracted much attention due to their ability to affect various C ï C, C ï N and C ï O bond formation[28]. Prominent amongst these are 2-(dicyclohexylphosphino)-2, 4, 6-triisopropylbiphenyl(Xphos), 2-ditertiarybutylphosphino-1,2,3-triisopropyl biphenyl(t-Buxphos), 2-dicyclohexylphosphino-2^1, 6^1-dimethoxybiphenyl (Sphos), 2-dicyclohexylphosphino-2^1, 6^1-diisopropoxylbiphenyl(Ruphos) and 2-(dicyclohexylphosphino)-3,6-dimethoxyl-2^1,4^1,6^1-triisopropyl-1^1,1^1-biphenyl (Brettphos). Dialkylbiarylphosphine ligands and the pre catalysts derived from them are commonly referred to as Buchwald ligands and pre catalysts

respectively. These reagents have developed into a highly valuable class of compounds for palladium-catalysed reactions, and can be used for a broad range of reactions. Palladium catalysed cross-coupling reactions have been tools for C-C and C-heteroatom bond formation in academic and industrial settings [30, 31]. However, palladium sources can have significant problems in generating active catalyst[32]. For example, stable Pd (0) sources such as Pd_n(dba) contains dibenzyldeneacetone (dba) ligands that can impede the catalytic cycle. These Pd species can also contain varying degrees of free dba and palladium nanoparticles [33]. As researchers explore cross-coupling reactions that are more complex, the method for generation of the catalytically active LnPd (0) species has often proven to be vital to the success of cross-coupling reactions [32]. Pd (II) sources such as $Pd(OAc)_2$ and $PdCl_2$ need to be reduced to Pd (0) in situ before entering a Pd (0) ï Pd (II) cross-coupling cycle. The palladium (II) sources are usually reduced using ligands. t-Buxphos has been found to be excellent supporting ligand for pd-catalyzed C - O bond forming reactions[33] due to the presence of monophosphine in the structure. Consequently, Buchwald catalyst, which is combination of palladium complex and Buchwald ligand (t-Buxphos), was used in this study.

1.2 Statement of problem

Although a wide range of linear and angular phenoxazine compounds have been synthesized, only a limited number of their derivatives have been prepared. Furthermore, their biological activities are understudied. Because of this, parent phenoxazine **1** has been continuously modified in this direction to open new area of application.



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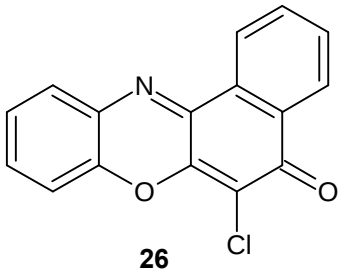
Benzo[a]phenoxazine **26** and diazabenzo[a]phenoxazine nucleus **25** have been known for years but their chemistry remains poorly developed [34]



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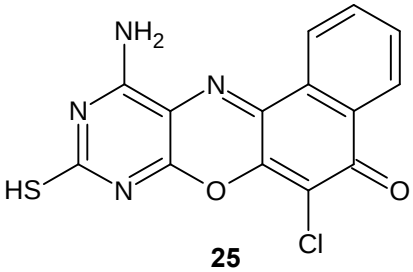


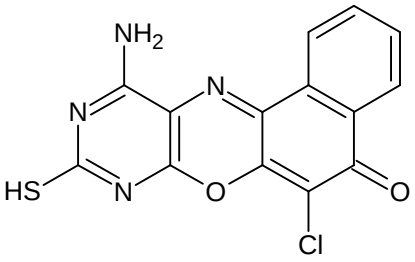
25

Still more grossly under studied is the O-arylated angular phenoxazines. Before now, no significant work has been done using Buchwald catalyst to O-arylate diazaphenoxazine and related carbocyclic analogue. Interest in this type of ring system made us to synthesize twelve new phenoxazines nucleus, which are O-arylated using Buchwald catalyst.

1.3 Objectives of the study

The objectives of this work therefore are to

- Synthesize angular diazaphenoxazine and related carbocyclic analogue compound of the type 2 and 3.



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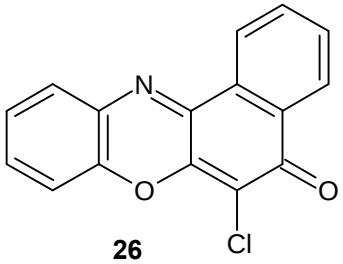

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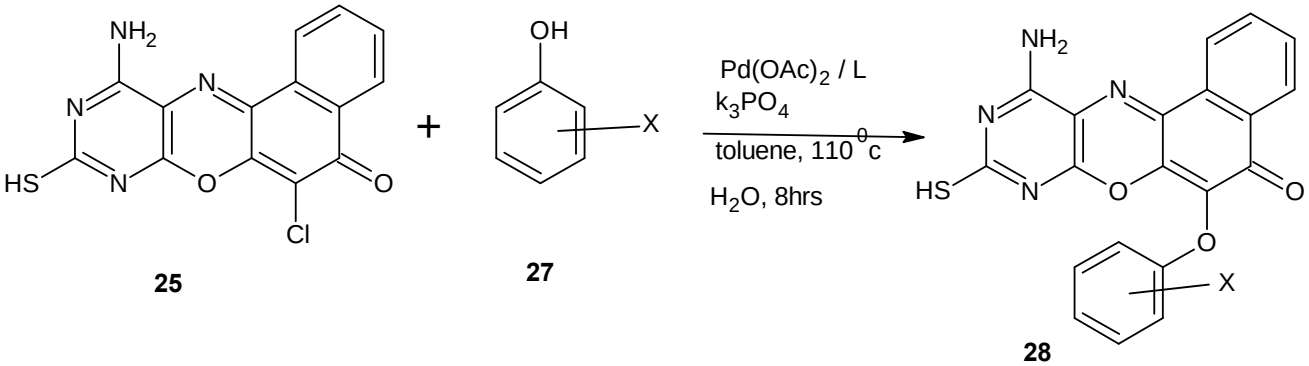
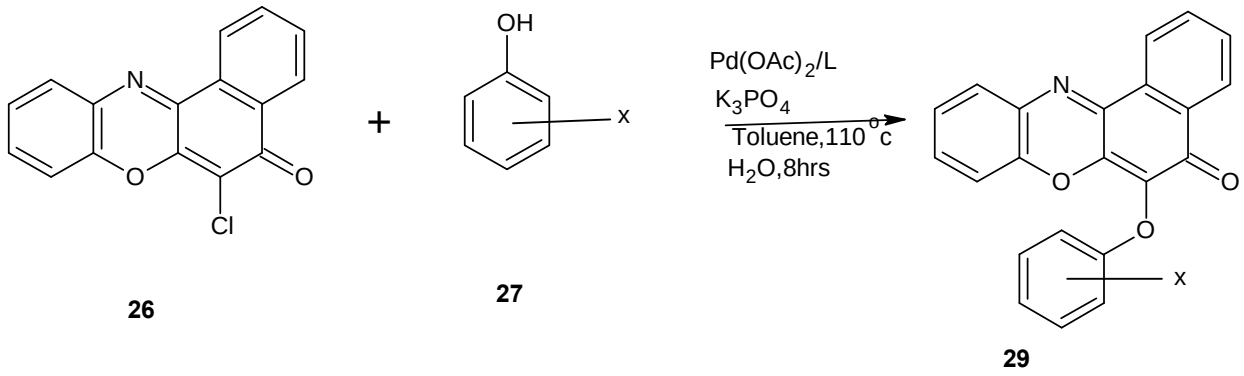
- O-Arylate the angular diazaphenoxazine and the related carbocyclic analogue using Buchwald catalyst as shown below:



25 **27** **28**



26 **27** **29**

X = H, Me, isopropyl, methoxy, chlorine, and benzene ring

L = t-Buxphos.

- Characterize the compounds synthesized using UV, IR and NMR spectrophotometer.
- Carry out antimicrobial screening on the new phenoxazine scaffold.

1.4 Justification for the study

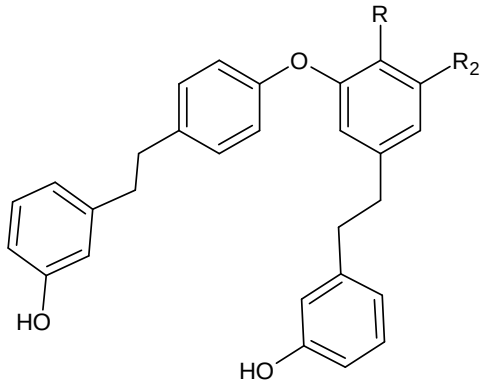
The study provides new and facile route of making novel polycyclic ring systems thereby extending methods available for obtaining phenoxazine derivatives. Thus, it generates new area for further research. The newly synthesized compounds could be useful as potent antimicrobial agents in medicine and may be used as dyes in the industries since they show absorption in UV-visible region.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Buchwald-Hartwig C–O Coupling Reactions

Aryl ethers are key structural motifs found in naturally occurring biologically and medically active compounds such as perrottetin **30**[3], riccardin B **31**[35], and K-13 **32** [35]. The diaryl ether structural motifs are very useful; not only in life science but also in agriculture to prevent various weed killing chemicals[29]. However, mild, aromatic C-O bond formation necessary in aryl ether synthesis is one of the difficult transformations in organic synthesis[36].



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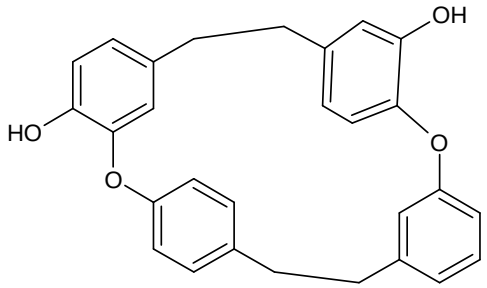

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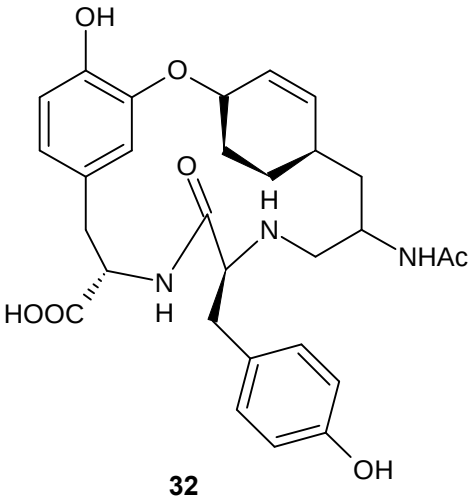

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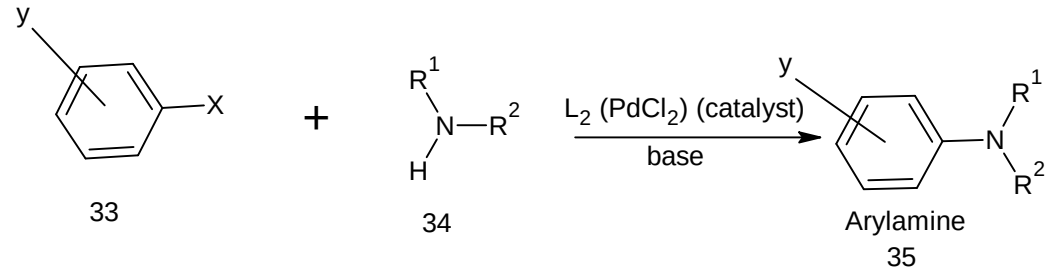
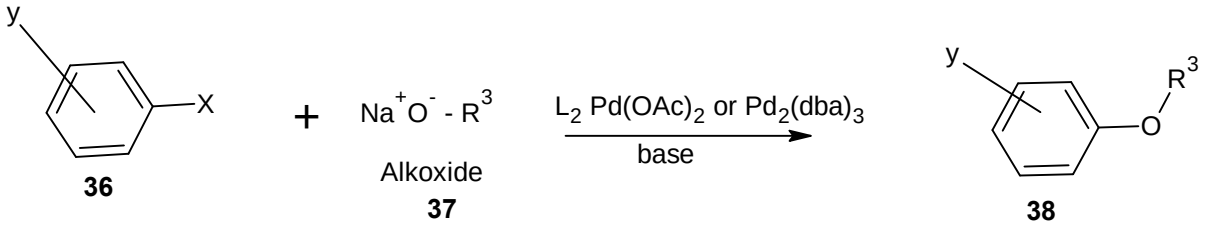
Copper catalyzed C ï O couplings exhibited a draw back in the previous years because of their low to moderate yields, long reaction times, difficulty with substrates containing ortho-substituent, lack of heterocyclic substrates and the necessity to employ aryl iodide or aryl boronic acid as well as coupling partners [33]. Diazotization and displacement of oxygen nucleophiles that is used in the preparation of aromatic ethers are generally limited to phenol synthesis and requires stiochiometric amounts of copper [37].

In an attempt to salvage this menace Buchwald[38] and. Hartwig[39] in 1995 concurrently discovered what seemed to be a relief to the problems. This gave rise to a named reaction known as Buchwald-Hartwig cross-coupling reaction. Traditional Buchwald-Hartwig cross-coupling reaction involves the direct Pd-catalyzed C-N and C-O bond formation between aryl halides or triflouromethanesulphonates and amine (1^o, 2^o aliphatic or aromatic amines,

imides, amides, Sufonamides, sulfoxines) or between aryl halides or triflates and alcohols (aliphatic alcohols and phenols) in the presence of stiochiometric amount of base[40]. The structural definition of this reaction has given rise to amination (Pd-catalyzed C-N bond formation between aryl halides and amine) and O ï arylation (C-O bond formation between aryl halides, triflates and alcohols: (aliphatic alcohols and phenols) reactions. The original scope of this protocol requires either an aryl bromide or iodide, while the Pd(0) catalyst is usually complexed with chelating phosphine type ligands such as BINAP, DPPF, XANTHPHOS and DPBP. The base is present in stiochiometric amounts and temperature for the reaction can be low, sometimes as low as 25 ^{o}C [41].





X = Cl,Br, OTf, y = o, m, p - alkyl, phenoxyl, amine, alkoxyl

R^{1-2} = 1^{o} or 2^{o} aromatic, R^{3} = 1^{o}, 2^{o}, or 3^{o} aliphatic or aromatic

L = $P(O - Tol)_3$, BINAP, dppf, dba, Base = NaOt - Bu,LHMDs, K_2CO_3, Cs_2CO_3

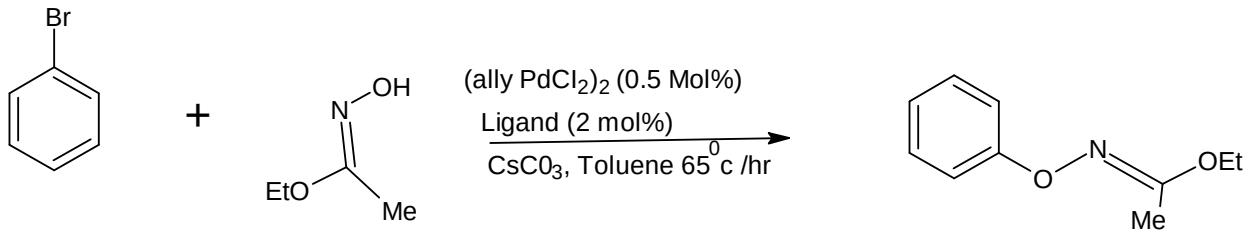
The Buchwald - Hartwig protocol opened a new chapter in the field of transition metal-catalyzed cross-coupling chemistry with a new approach of how to make derivatives of anilines and aryl ethers. Palladium catalyzed C ï N and C ï O coupling is not only another interesting field to note, but also a new reaction that truly fulfills the requirement of a modern synthetic method: versatility, reliability and applicability on small and especially larger scale. This technology has reached the multi-hundred production level in many companies, this shows that the technology has spread from the original inventors into many independent groups, both academic and industrial[42]. Examples are bound in the literature that show the strength of the methodology from view point of the medicinal chemist, who seeks for modular technologies that allow the quick production of a variety of different mg amounts of products from the set-up of structure activity relations. In addition, the perspective of total synthesis now present in the literature shows reliability of the chemistry with highly functional real-world problems. This technology also contributes to the field of the material science, showing the possibilities for making new functional polymers [43].

The field of C ï O coupling is by far not elaborated as palladium catalyzed C ï N coupling when compared with the former methods[43]. Slow reductive elimination and strongly competing ß-hydride elimination with primary and secondary alcohols may explain this[44]. Several researchers have

pointed out that the use of monophosphine as catalyst components is one of the major factors for successful C ï O coupling.

The use of palladium catalysis for the coupling of phenols and aryl halides is a desirable extension of other recently reported carbon-hetroatom bond-forming techniques. However, the scope of the reported process was limited to the reaction of electron-deficient aryl bromides and iodides, and the procedures usually required the use of the sodium salt of the phenol. Moreover, the yields in most cases were only moderate [45].

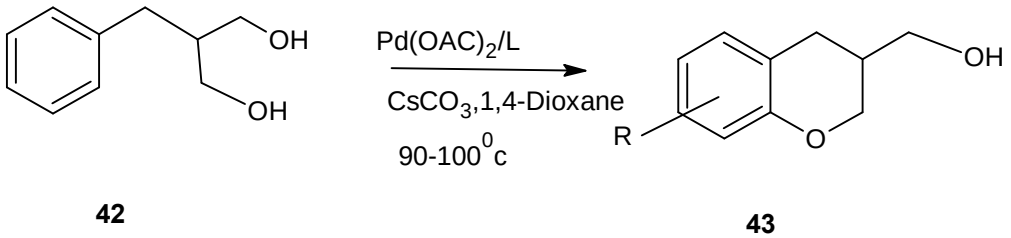
Owing to the various limitations observed in the traditional Buchwald-Hartwig cross-coupling reaction, researchers have continued to carry out modifications on the earlier reported procedure, in search of methods with milder reaction conditions, more aryl halide tolerance, as well as better yields. Maimme and Buchwald[33] in 2010 envisioned this in their work titled, ñPd-catalyzed O-arylation of ethylacetohydroximate: Synthesis of O-aryl hydroxylamines and substituted benzoforansò. This is shown in the equation below.



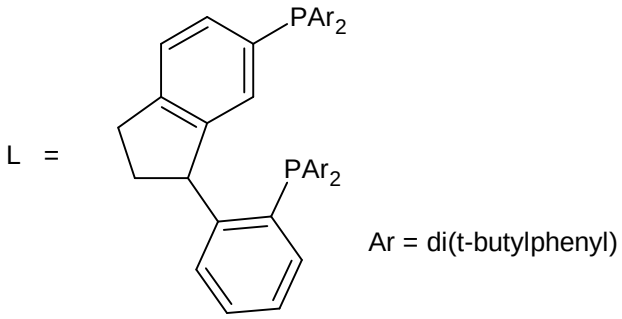
39 **40** **41**

They reported that key to success of the reaction was the use of bulky biarylphosphine ligands, t-Bubrettphos and t-Buxphos which promote C ï O reductive elimination under relatively mild condition. They found out that ligand Johnphos as well as ligand Brettphos and Xphos, which do not contain di-tert-butylphosphine moiety, were ineffective under these conditions. They observed that the high activity of t-Bubrettphos was crucial due to both the thermal sensitivity of the product N ï O linkage and the ability of Pd (0) to oxidatively add into this bond at elevated temperature[41]. They obtained complete conversion within 1hr at 65^{o}C in toluene using 1% Pd, 2% of t-Bubrettphos and Cs_2CO_3 as base. They found out that the use of t-buxphos gives superior results to that of t-buBrettphos, presumably due to its smaller size. They concluded that broad substrate scope and short reaction time makes this an attractive method to prepare highly substituted O-arylhydroxylamines and benzofuran from simple aryl halides.

In 2013 Wengiang etal [46], reported that enatioslective intramolecualr O-arylation was achieved through desymmetrization with Pd-catalyzed coupling reactions. They observed that the intramolecular asymmetric aryl C ï O coupling reactions of 2-(2-halo aryl) propane-1,3-diols led to the enantioselective formation of chiral (3,4-hydro-2H-chromen-3-yl) methanol in good yields and high enantiometic selectivity.



42 **43**



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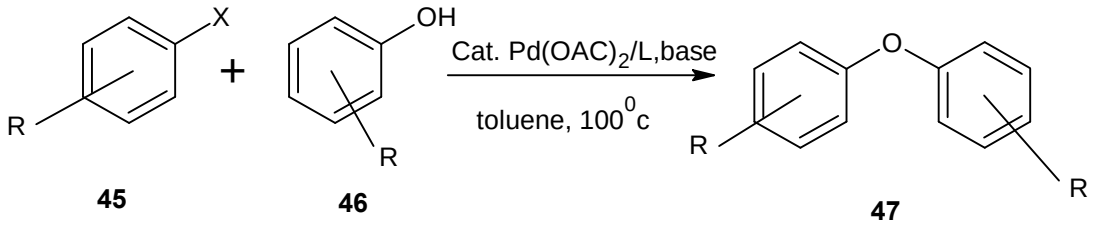
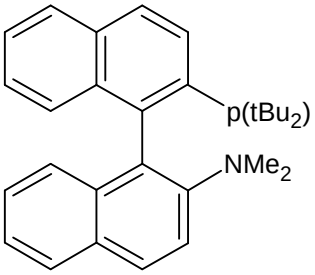
In another development, Buchwald and his coworkers[47] described a general method for the palladium-catalyzed formation of diarylethers. Electron rich, bulky aryldiaryl phosphine ligands, in which the two-alkyl groups are either tert-butyl or 1-adamantyl, were the key to the success of this transformation.



45 **46** **47**

They reported that wide range of electron-deficient electronically neutral and electron-rich aryl bromides and chlorides and triflates can be combined with a variety of phenols with the use of sodium hydride or potassium phosphate as base in toluene at 100 ^{o}c. The bulky yet basic nature of the phosphine ligand is

said to be responsible for increasing the rate of reductive elimination of the diaryl ether from palladium[47]. However, little to no product was observed from the reactions of phenols with aryl halides that possess strongly electron withdrawing or electron donating ortho substituent. They discovered that electron-deficient phenols were poor substrates. Additionally, the reactions of phenols that did not possess an ortho substitutent at least as large as a methyl group were inefficient in most cases[48]. The use of many examples of ligands that are neither commercially nor readily available further discouraged the utility of their previous method whereby ligands **48-50** were used.



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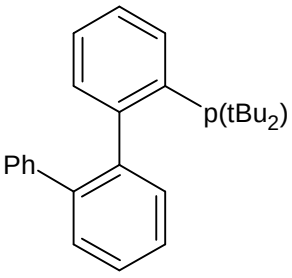

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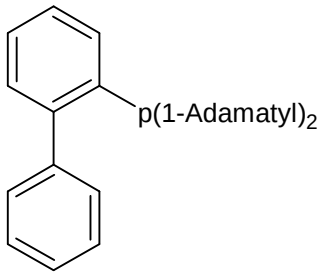

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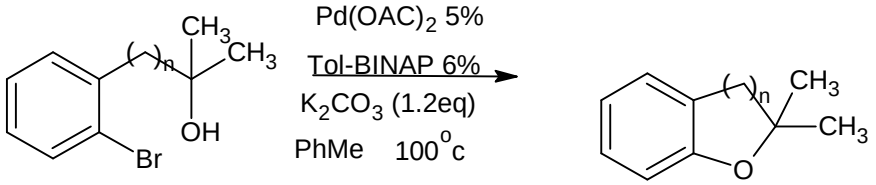
In their search for better procedure, Buchwalds and his coworkers[49] expanded the earlier method in other to overcome the above-mentioned difficulties as well as improve on the coupling of hetaroaryl halides with phenols, using two new ligands. They discovered the structural derivatives of the ligands above that generate catalyst system with both a greater degree of activity and stability. During the course of these investigations, the use of 2-di-tert-

butylphosphino -2,4,6-triisopropylbiphenol (di-tBuxphos), the more hindered counterpart and 2-dicyclohexylphosphino-2, 4, 6-triisopropylbiphenyl (xphos) were examined. They reported that the reactivity of the catalyst based on di-tbuxphos in C ï N and C ï O bond forming process was less than those based on xphos. Therefore, they believed that the increase in size based on di-tbuxphos would prove beneficial in C ï O bond forming reaction[49]. With this, they examined a number of electron-deficient aryl halides with phenols using di-tbuxphos as the supporting ligand and this gave an excellent yield.

Other examples of C-O coupling reactions with Buchwald catalyst (palladium-based catalyst) which were published by Stephen Buchwald and his co- workers are

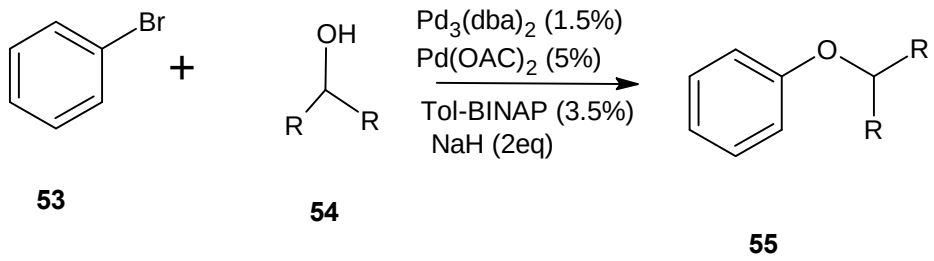
Intramolecular C ï O bond formation: [50]



51 **52**

Hint: The alcohol used must be tertiary alcohol

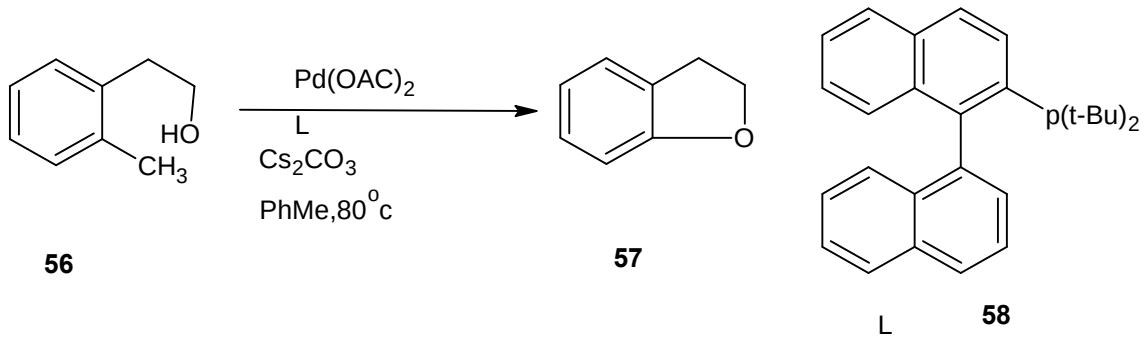
Intermolecular C ï O bond formation [51]



53 **54** **55**

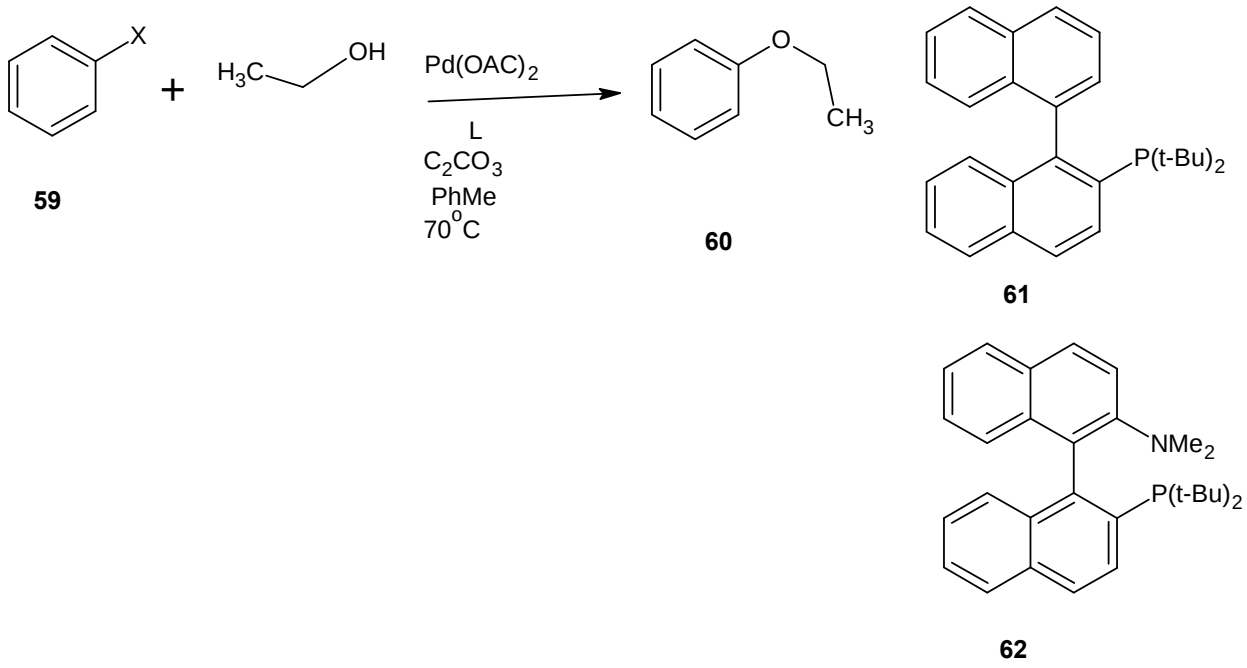
Improve intramolecualr C ï O formation: [52]

Biaryl ligands now allow primary alcohol to be used.



56 **57** **58**

Intermolecular Aryl ether synthesis: [53]

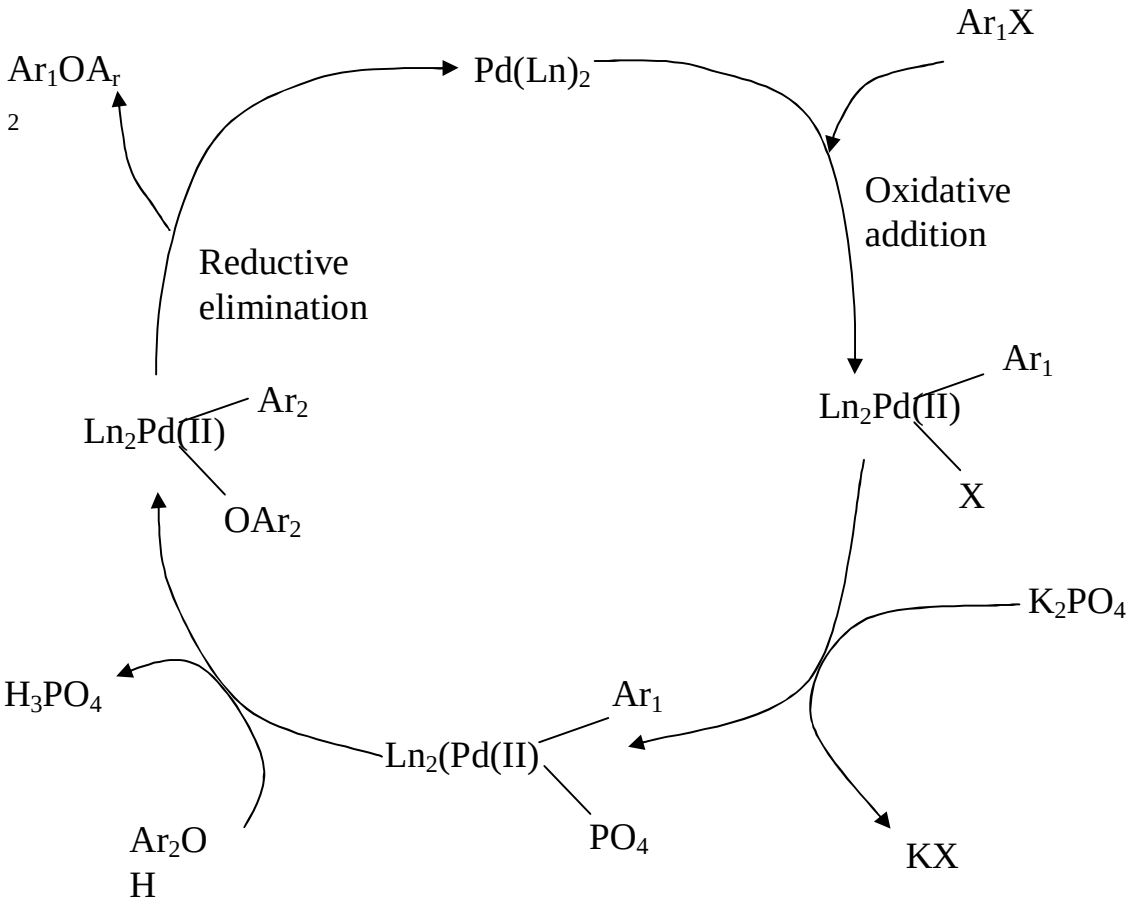


59 **60** **61** **62**

2.2 Mechanism of Buchwald-Hartwig C-O coupling reactions

Cross-coupling reaction has grown into an extremely powerful and general strategy for forming C- C and C-heteroatom bonds. Pd (0) is most commonly used, but Ni (0)-catalyst is known. All the reaction starts with the oxidative addition of the low valent metal into an organic electrophile (eg. Organohalide), followed by transmetallation step with another organometallic reagent (The nucleophile), and a reductive elimination to regenerate the catalyst. The name of the reaction refers to the organometallic (or nucleophilic) partner. One of the examples is Pd-catalyzed O-arylation of ethylacetohydroximate: synthesis of O-arylhydroxylamines and substituted benzofuran[54]

Catalytic cycles



Ar_1X = Aryl halids. Ln =Ligand
X = Cl, Br. ArOH = Phenol, 4-methoxyiphenols etc

A palladium precursor is typically stabilized in solution by an adequate ligand that also raises the electron density of the metal to facilitate oxidative addition and provides sufficient bulkiness to accelerate reductive elimination[43]. A base is required to deprotonate the substituent prior to or after coordination to the palladium centre. The solvent plays a more prominent role owing to the often-heterogeneous nature of the reaction due to solubility of the base or

substrates. These parameters mentioned above are important in designing a screen of reaction set up[43]. They are not always independent of each other.

The temperature is usually set inside a window typical for activity of the respective ligand or the reactivity of the coupling partners. It was shown by B. Jons and S. Utrich [43] that stirring efficiency, order of addition of compounds, particle sizes of solids, ratio of ligand to palladium or catalyst loading have to be taken into account for the efficiency of the reaction.

That is why it is noted that monophosphine ligands are used for C- O coupling[43]. He also noted that the success of this C-O high catalytic activity coupling is because of the steric shielding of the catalyst.

2.3 Factors influencing the performance of a given C-O coupling reactions

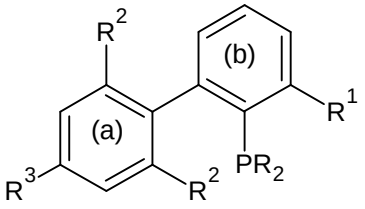
Four factors (parameters) that greatly influence the performance of , C-O coupling reactions are [55]

Ligand

Catalyst system containing no ligand has been reported over the last years for some organometallic transformation [56, 57]. C-O and C-N coupling reactions are usually carried out with an added ligand. The ratios of ligand to palladium depends mostly on the ligand employed and have a distinct influence on the catalytic performance [43] The quest for suitable ligands showing higher reactivity

and selectivity has been a field of enomorous activity over the last years [58-63]. The development of adequate systems has passed through various stages. These ligands greatly enhanced the scope of aminations and arylations to aryl chloride [63]. The ligands constitute the most versatile choice with respect to performance and reliability of the reactions. A researcher is always faced with problem of which system of ligand to choose for his specific task because of the different appilications of this ligand.

Up to date ligand costs are one of the determining factors in Buchwald Hartwing coupling reaction process on the large scale. Air stability and handling often do not constitute major problem in a typically inertized product in vessel environment[43].The structural features of dialkylbiarylphosphine ligand that influences C-O coupling reactions positively are: [64-80]



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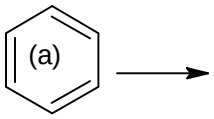


Prevents oxidation at P by O_2, accelerates reductive elimination

63

R^2: Increase catalyst stability by preventing cyclometallation, encourages formation of LnPd(0)

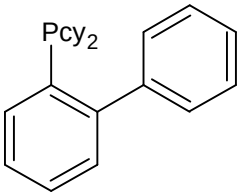
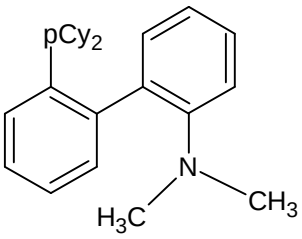
R^3: when not equal to H, usually only for ease of synthesis

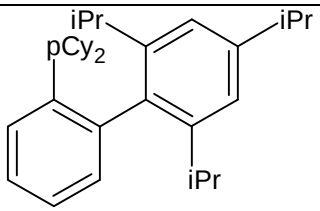
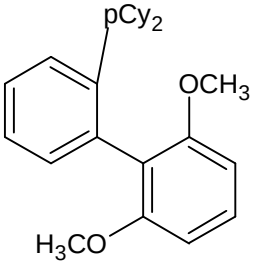
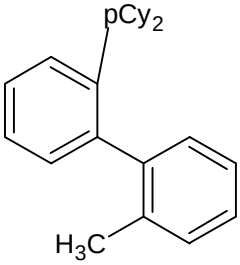
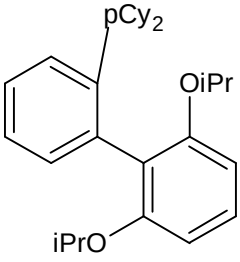
R^1: substitution promotes reductive elimination

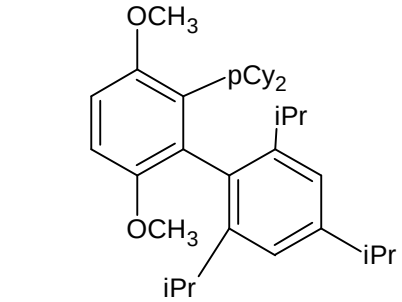
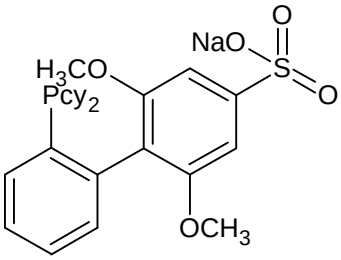
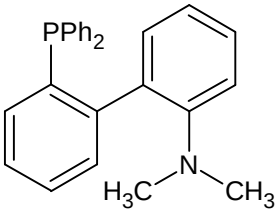
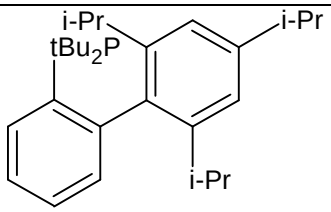
R_2: Electron-rich groups accelerate rate of oxidative addition.

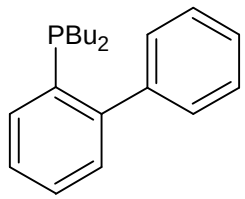
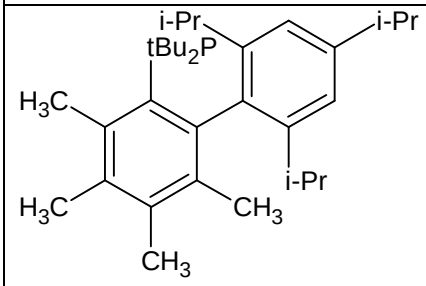
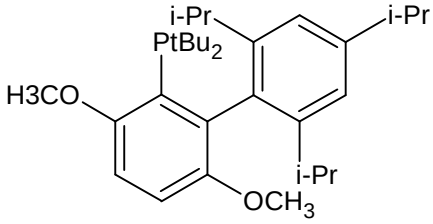
The table below describes where these dialkylbiarylphosphine ligand can be influenced and applied.

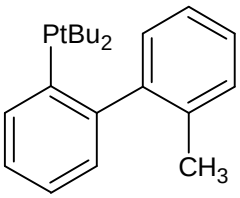
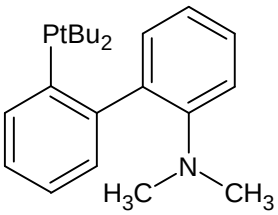
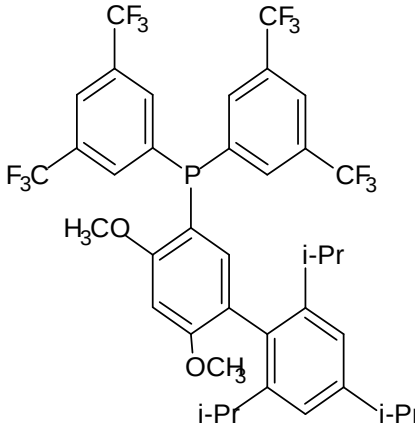
Table 1: Buchwald ligands and their applications for palladium catalyst [64-80].

Structures of ligands	**Common name**	**Application for Pd catalyst**
	CyclohexylJohnphos	• Suzuki coupling • Negishi coupling • Hiyama coupling • Methylation of aryl halides • Ŭ-arylation of ketones • Buchwald hartwig amination • C-B bond formation • Oxidation of alcohol to ketones and aldehydes
	Davephos	• Suzuki coupling • Kumada-Carriu coupling • Ŭ-arylation of ketones • Buchwald Hartwig amination • Rh-catalyzed hydroamination

	Xphos	• Suzuki coupling • Sonogoshira coupling • Hiyama coupling • Stille coupling • Carbonyl enolate coupling • Buchwald-Hartwig amination
	Sphos	• Suzuki coupling • Kumada coupling • Negishi coupling • Buchwald-Hartwig amination
	Mephos	• Suzuki coupling • Negishi coupling • Ŭ-arylation of ketone • Buchwald Hartwig amination
	Ruphos	• Suzuki coupling • Negishi coupling • Ŭ-arylation reaction of oxindoles • Buchwald Hartwig amination

	Brettphos	• Buchwald Hartwig amination • Trifluoromethylation of aryl chlorides
	Sphos	• Suzuki coupling • Rh. Catalyzed 1,2 addition of arylboronic acids to aldehydes and ketones
	PhDavephos	• Ŭ-arylation of amino acid esters • heteroarene benzylation • Buchwald-Hartwig amination
	t- Buxphos	• Ŭ-arylation of tetranic acid • Decarboxylative coupling of aromatic acids and aryl iodides • Carboxylation of aryl bromides with CO_2 • Buchwald Hartwig amination

		• Buchwald Hartwig C-O coupling
	Johnphos	• Suzuki coupling • Heck coupling • Buchwald Hartwig amination • Buchwald Hartwig C-O coupling • C-Si bond formation
	Tetramethyl di-tbuxphos	• Conversion of arylhalide • Buchwald Hartwig amination • Buchwald Hartwig C-O coupling
	tBuBrettphos	• Buchwald Hartwig amination • C-F bond formation • O-arylation of ethyl acetohydroximate • Conversion of aryl and Vinyltriflates to bromides and chlorides, triflates and nonaflates to nitroaromatic

	tBuMephos	• Ŭ-arylation of ketones • Buchwald Hartwig C-O coupling • Formate reduction of N-heterocyclic allylic acetates
	tBuDavephos	• Ŭ-Arylation of esters • Buchwald-Hartwig C-O coupling • Coupling of ammonia with aryl halides • C-Si bond formation
	Jackiephos	• N-arylation of secondary amides

BASE

Base is a second component of the reactive system, which greatly influences the performance of C ï O, cross coupling reactions. This is because it deprotonates the amine or phenols before or after coordination to palladium[43]. Because stoichiometric quantities of this component are needed, two types of bases can be distinguished as follows:

a. Bases which are sparingly soluble in the typically used aproatic solvent (e.g. toluene)
b. Bases that gives nearly homogenous reaction mixtures[54].

The majority of side reactions to be found in Buchwald-Hartwig C- O couplings are caused by the added base. The relative base strength determines the functional group tolerance. Direct comparison of the base strengths are difficult owing to heterogeneous mixtures in which solubility plays a significant role, as well as the broad variety of the solvent employed. The most common bases for C ï N and C ï O coupling are t-BuONa, t-BuOK, LHMDs, Cs_2CO_3, K_2CO_3, K_3PO_4, NaOMe, NaOH, KOH and t-AmONa[40]. Particle size of the base also plays a crucial role in the Buchwald- Hartwig cross coupling reactions. In a homogenous reaction set up, it is advantageous to use finely powdered base, due to the large surface area[43].

Apart from the base sensitivity to the substrate, the combination of base and ligand as well as base/temperature is also important parameters[43], for example strong base such as t-BuONa, have been used very frequently, and these are very suitable for low temperature process and or low catalyst loadings; CS_2CO_3 is most effective when chelating bisphosphine ligands are used. Many transformations using this base have been reported recently [48, 81, 82-95].

K_3PO_4 tends to show good results with biphenyl-base substances[,96,-98, 99]. Recently Hartwig and Buchwald[47] even reported the use of the most inexpensive bases (KOH, NaOH) in aqueous solution, which are active in combination with biphenyl based system as well as Hartwig palladium-dimer-complex. The base also serves as the deprotonating agent for the imidazonium salt precursor, which often requires the use of strong bases[100, 101].

The mild base like K_3PO_4 now represents cheap alternatives to the substrates rather than expensive CS_2CO_3 [83]

Catalyst

The combination of palladium complex and Buchwald ligand is known as Buchwald catalyst. An important point concerning the reliability of the Buchwald-Hartwig coupling reaction involving catalyst is the purity of the components of that catalyst system. Organic or inorganic impurities in the ligand

or palladium precursor can have a large impact on the performance of the reaction [102]. It is advisable to use material from different suppliers to test for difference in reactivity [43].

The table below shows the features of some catalysts and pre catalysts, which influence C-O coupling reactions.

Table 2: Features of some catalysts and precatalysts that influence C-O coupling reactions

Pre catalyst Air stable	**$Pd(OAc)_2$** Air stable	**$Pd_2(dba)_3$** Air stable
• Pd(II) complex	• Pd(II) complex	• Pd (0) complex
• Efficient formation of active moonlighted catalysts under basic conditions without reducing agent	Addition of exogenous reluctant (NR_3 or $PhB(OH)_2$) or phosphine ligand) for reduction of Pd(II)	Without reducing agent
Low catalyst loading	High catalyst loading	dba can bind Pd center

		and reduce catalyst activity. High catalyst loading
Short reaction time	Long reaction time	Short reaction time

Solvent/temperature

Buchwaldï Hartwig cross coupling reactions are usually run within an organic solvent system. The roles of the solvent are to dissolve the coupling partners as well as serve as part of the base. It also creates room for a respective temperature window for the reaction, and stabilizes the intermediate in the catalytic cycle[43].

Majority of the reactions reported are run in toluene [58-62]. Frequently, ethers, DMF, THF or dioxanes are used. For solubility reasons, the polar solvent DMF, and DMSO can also be used for C- O coupling[43]. The solvents usually have to be dry and deoxygenated, but this is strongly dependent on the air sensitivity of the catalyst system used[43]. If slightly air sensitive phosphine reagents are used, reaction can be run entirely in air without significant changes in yield[103]. Besides, the addition of water can be beneficial in C-N, C -O coupling reactions as can be seen from the use of aqueous bases in tsome

coupling reactions [104, 105, and 106]. This is only use for substrates that are not hydrolyzed under basic conditions[43]..

Sometimes it is beneficial to premix the catalyst and the ligand in a suitable solvent such as THF to allow time for the formation of the catalytically active complex before adding this to the actual reaction mixtures.

C ï O and C ï N cross coupling reactions can be run even under rather concentrated and condition up to 30% w/w, which is important to the space-time yield on a production scale[43]. Most times concentration is limited by the undissolved component such as base, starting material or product forming suspensions with stirring becoming a limiting factor [107].

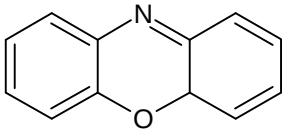
Regarding the temperature, the vast majority of reaction is run inside a range of 70 ï 110^{o}C [90, 108 and 109].

2.4 Angular phenoxazines

2.4.1 Benzophenoxazine ring system

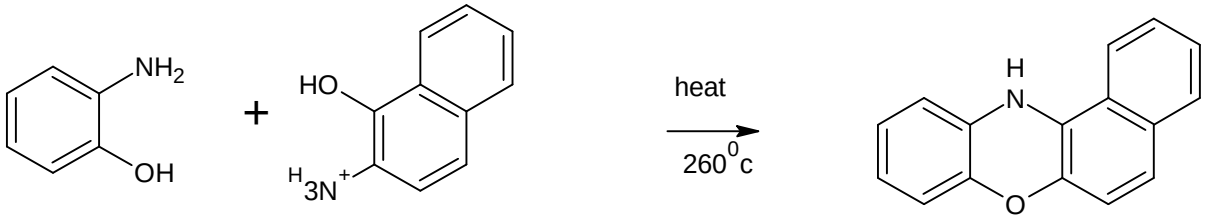
Meidola[54] reported the chemistry of the angular phenoxazine in 1879. His interest was particularly in the dying properties of this compound. In 1887, Bernthsen synthesized the parent phenoxazine (1)[110]. The parent phenoxazine (1) has been continuously structurally modified to enhance their biological

activities and minimize their undesirable effects, in other to open new area of application.



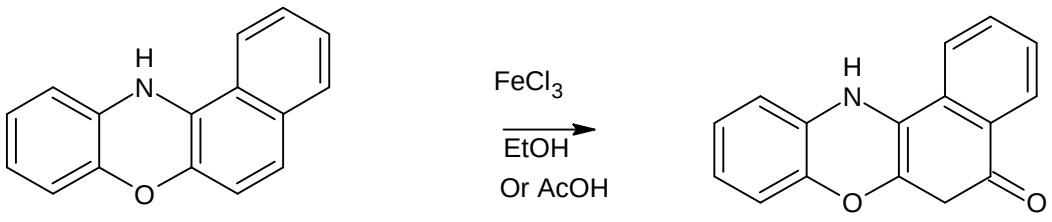
1

Goldsten and Coworkers[111] synthesized the simplest class of angular phenoxazines-benzo[a]phenoxazines **2**. This was discovered in their search for new phenoxazine compounds. They synthesized the parent benzo[a]phenoxazine **2** by heating a mixture of 2-aminophenol **64** and 1-amino naphthol **65** in hydrochloric acid at high temperature[112]



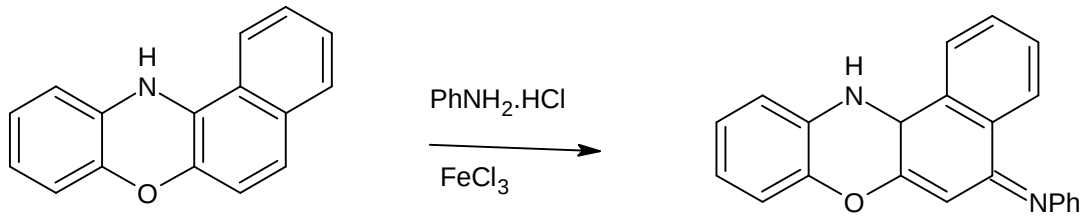
64 **65** **2**

This benzo[a]phenoxazine **2** undergoes oxidation in ethanolic ferric chloride to give benzo[a]phenoxazin-5-one **66**.



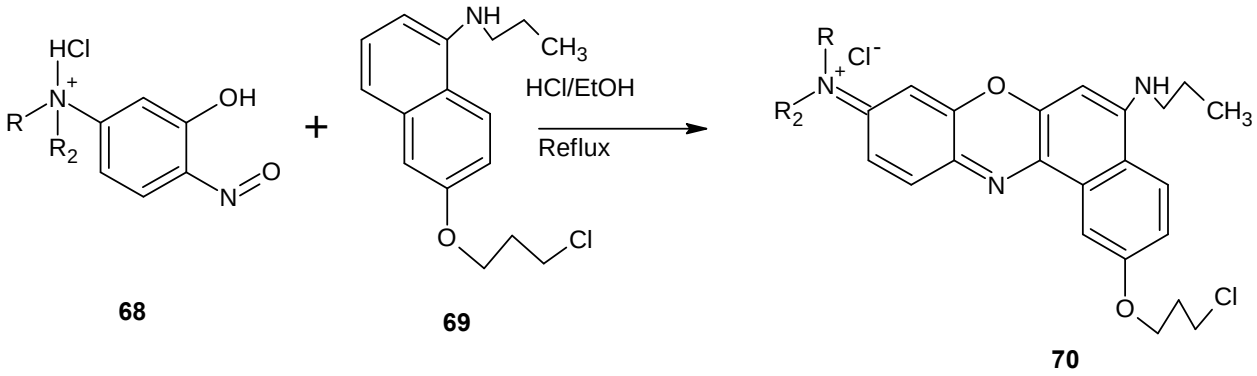
2 **66**

When benzo[a]phenoxazine **2** was reacted with aniline hydrochloride in the presence of excess ferric chloride as an oxidizing agent, a more intensely coloured benzo[a]phenoxazin-5-phenylamine **67** was obtained.



2 **67**

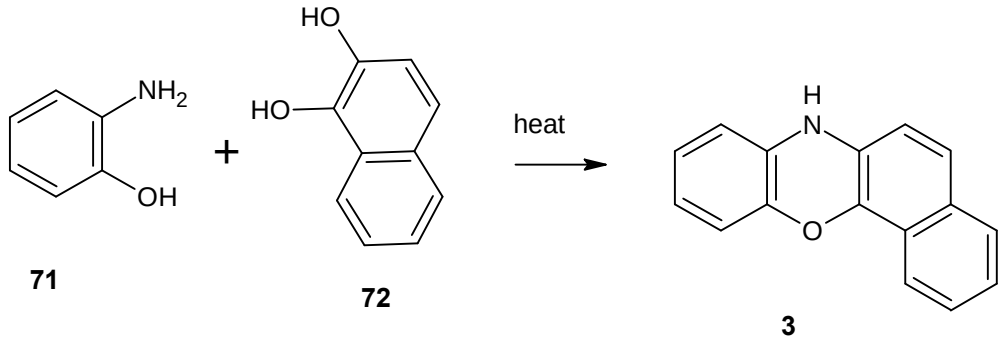
Benzo[a]phenoxazine chloride possessing one, two or three chlorinated terminals as their substituents in 2 and 9- position of the polycyclic moiety **70** was synthesized by Daniela and his coworkers[113]. This was achieved by condensation of the 2-nitrosophenol **68** precursors with 6-(a-chloropropoxy)-N-propylnaphthalene-1-amine **69** in acid media



68 **69** **70**

The presence of chloride atoms increased the possibility of being potential biologically active compounds. The cationic dye **70** is used as non-covalent probes of bimolecular non-natural nucleoside analogue[113].

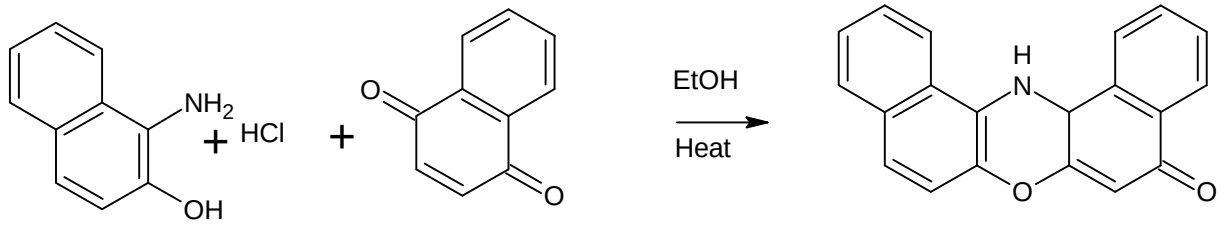
Pyrolysis of o-aminophenol **71** and naphthalene-1,2-diol **72** lead to the formation of compound **3**[111, 114]**.**



71 **72** **3**

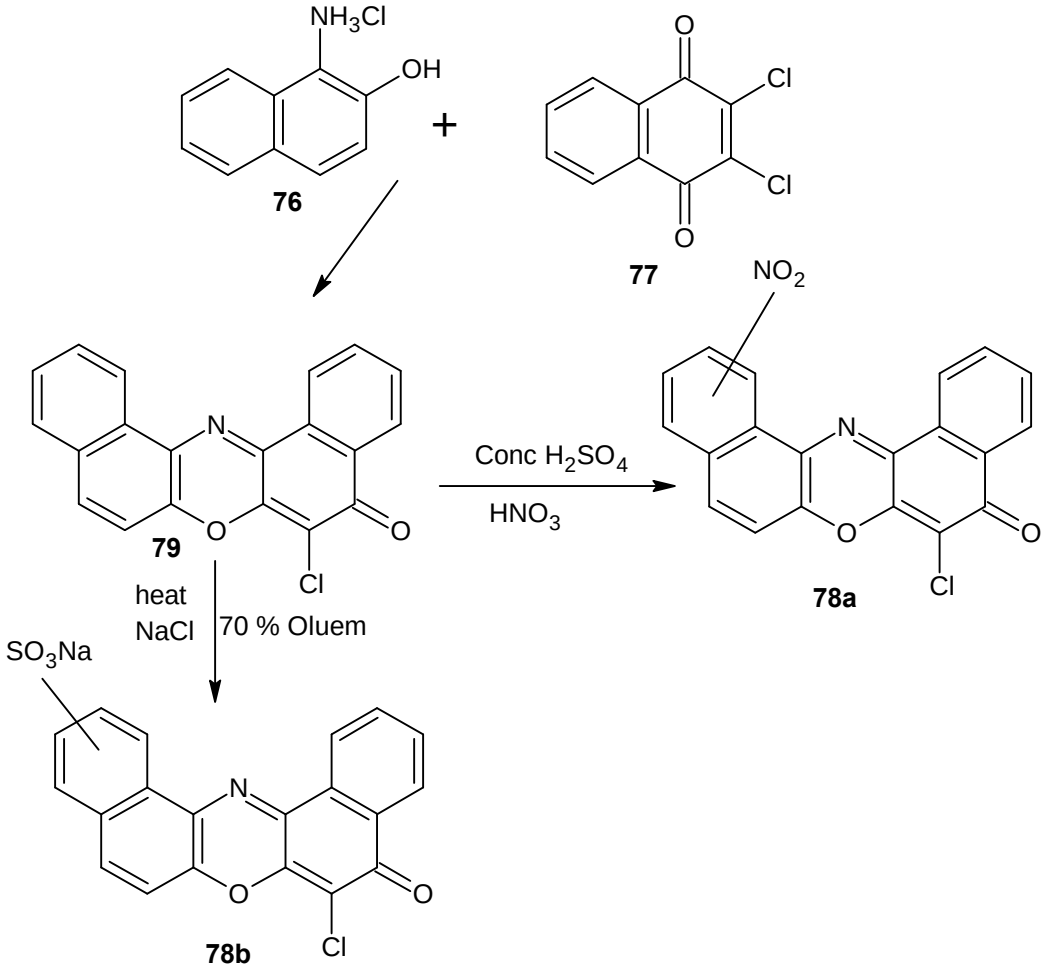
2.4.2 Dibenzophenoxazine ring system

In continuation for the production of new phenoxazine and commercial useful compound in the phenoxazine class, Goldsetins in his work in 1928[111] synthesized dibenzo[a]phenoxazine **75** by refluxing a mixture of 1-amino-2-naphtholhydrochloride **73** with naphthoquinone **74** in ethanol.

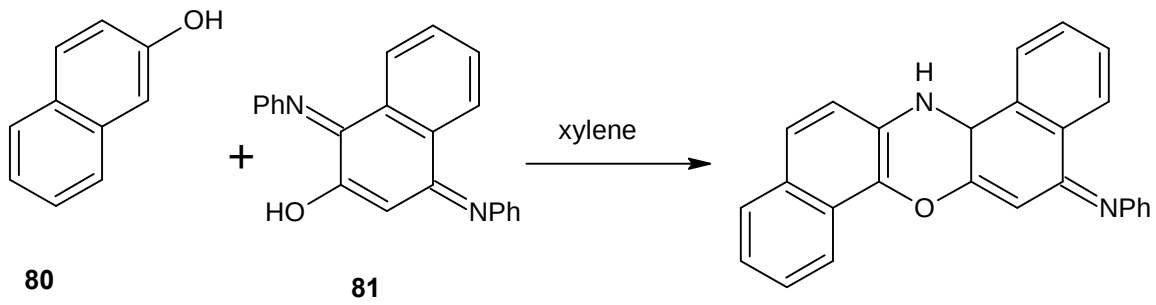


73 **74** **75**

Okafor and Ekere [115] synthesized nitro-6-chlorodibenzo[a,j]-1,4-phenoxazin-5-one **78a** and 6-chlorodibenzo[a,j]phenoxazin-5-one sulphonic acid **78b** as shown below.

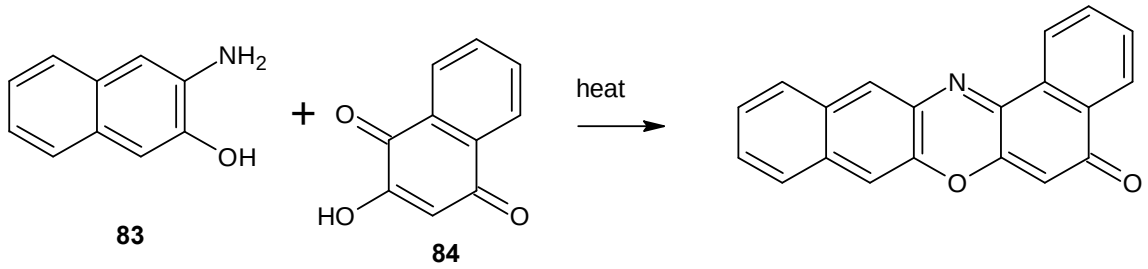


Lantz[116] obtianed dibenzo[a,h]phenoxazin-5-phenylimine **82** by heating a mixture of 2-naphthol **80** and 2-hydroxy-1,4-naphthoquinonephenylimine **81** in xylene.



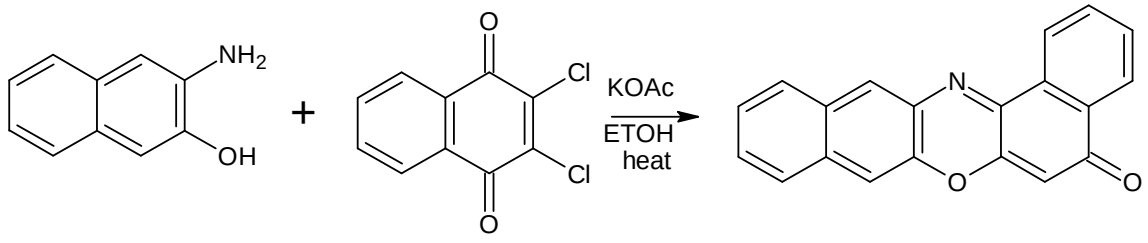
80 **81** **82**

Goldestein and his co-worker[117] obtained 5h-dibenzo[a,i]phenoxazine-5-one **85** by heating a mixture of 2-amino-3-naphthol **83** and two hydroxyl-1,4-naphthoquinone **84**.



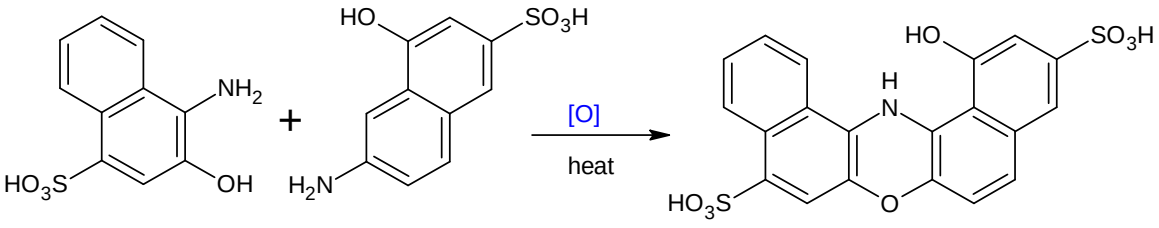
83 **84** **85**

Agarwal and Schafer[118] synthesized compound **86** by refluxing a stiochiometric mixture of 2-amino-3-naphthol **83** and 2,3-dichloro-1,4-naphthoquinone **77** in the presence of anhydrous potassium acetate in ethanol, methanol and triethylamine in 18 % yield. These derivative of benzo[a,i] phenoxazine are intensly coloured and are applicable as dye stuffs.



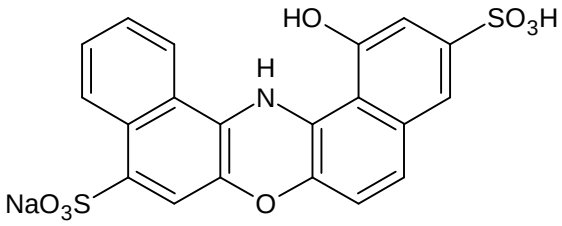
83 **77** **86**

Disulphonic acid derivative of dibenzo[a,j]phenoxazine was prepared by condensing 1-amino-2-naphthol-4-sulphonic acid **87** with 2-amino-8-naphthol-6-sulphonic acid **88** in the presence of an oxidizing agent,1-hydroxydibenzo[a]phenoxazin -3,9-disulphonic acid **89** was obtained[111].



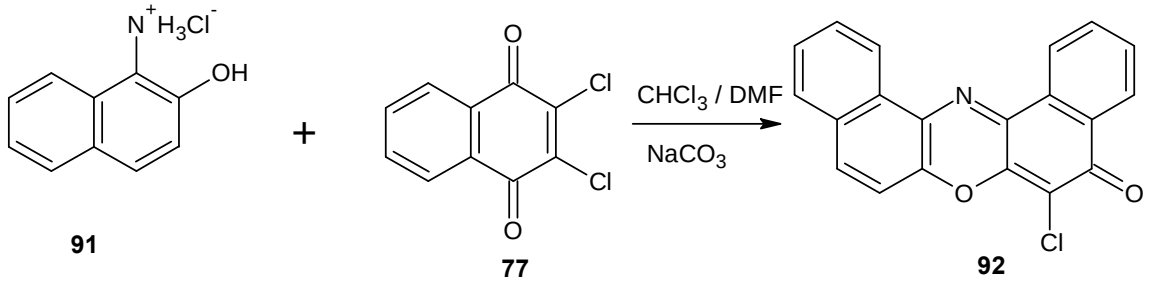
87 **88** **89**

When compound **89** is converted into disodium salt; a brown dye **90,** it became suitable for dyeing silk and wools.



90

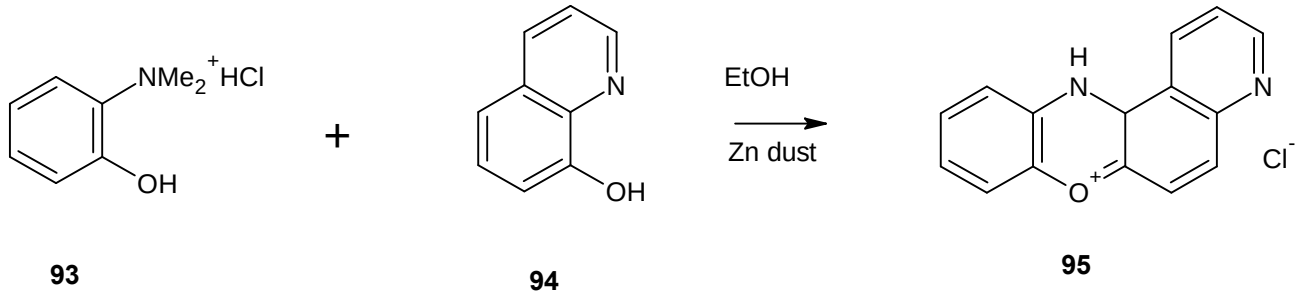
Successful synthesis of 6-chlorodibenzo[a,j]phenoxazin-5-one **92** was obtained by condensing 1-amino-2-naphthol hydrochloride **91** with 2,3-dichloro-1,4-naphtoquinone **77** in chloroform/ DMF as solvent in the presence of anhydrous sodium carbonate[119, 120].



Compound **118** is of commercial significance as a dye for textile, cellulose, paper, sheopolish and plastics

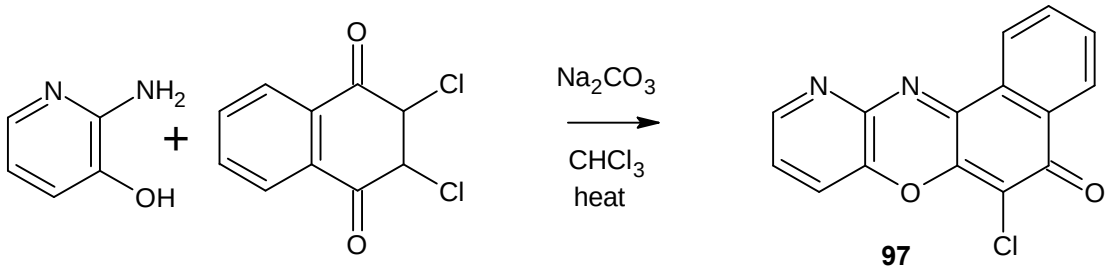
2.4.3Aza analogues of benzo[a]phenoxazines

Research into aza analogues of phenoxazine derivatives has grown over the years. Some angular aza analogues such as pyrido (3, 2, a) phenoxazine **95** occur naturally. Noeting[55] synthesized this in 1922. He obtain this by reacting 8-hydroxyquinoline **94** with o-hydro-N, N-dimethylaniline hydrochloride **93** in ethanol in the presence of zinc dust



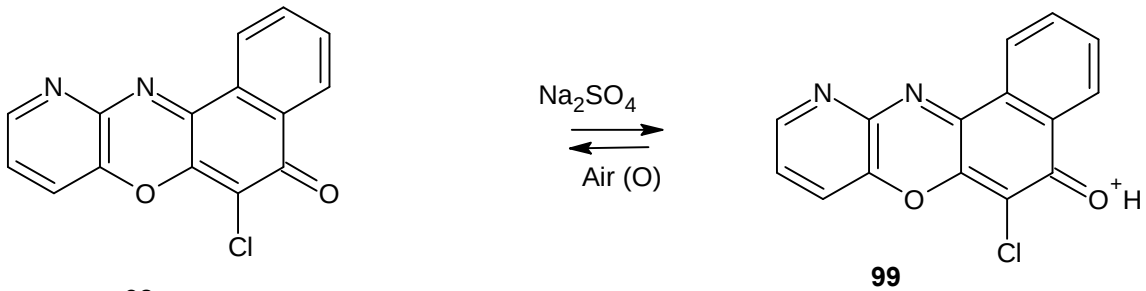
6-Chlorobenzo[a]-11-azaphenoxazine-5-one **97** which can be used as vat dye was synthesized by Okafor[42]. He obtained this by reacting 2-amino-3-

pyridinol **96** with 2, 3-dichloro-1, 4-naphthoquinone **77** in chloroform in the presence of anhydrous sodium carbonate



96 **77** **97**

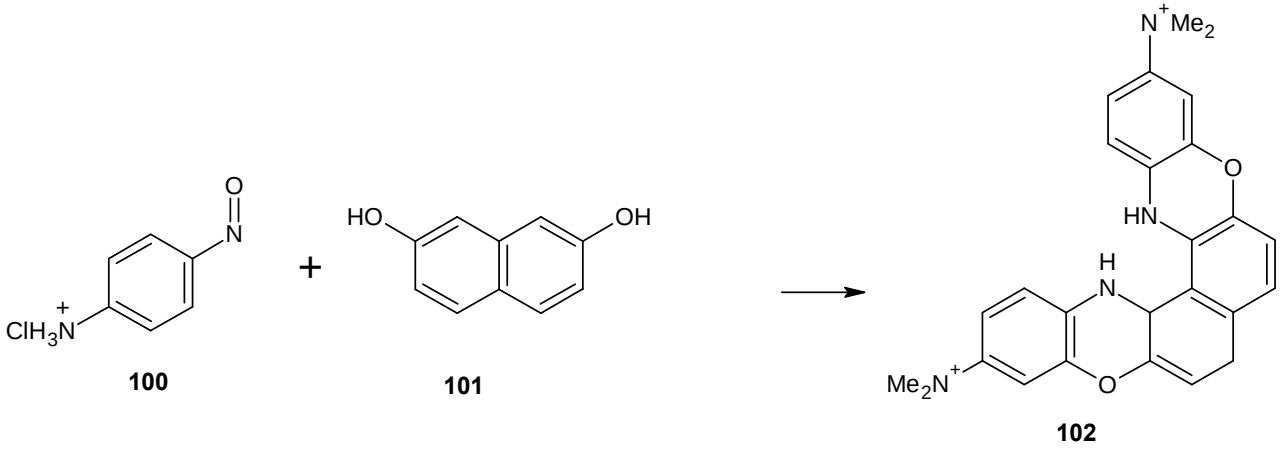
When reflux compound **98** with sodium dithionite, the orange colour of the compound was discharged due to the formation of angular azaphenoxazinol of the type **99**. However due to instability of compound **99** it quickly reverted to compound **98** on exposure to air.



98 **99**

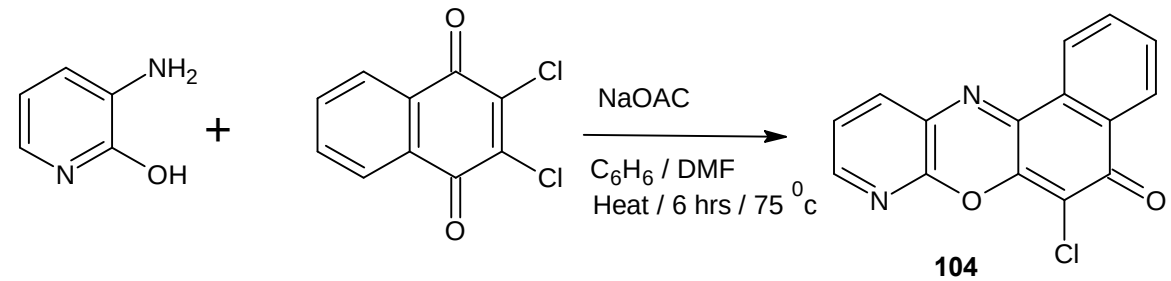
Dut[121] carried out the synthesis of a dark crystalline powder, phenoxazinol (1, 2-a) phenoxazin-3, 1,2-bis (dimethylimine) complex **102** analogue which when dissolved in organic solvent produces a dark green colouration. This was done by condensation reaction between the alcoholic

mixture of p-nitrosodimethyl-aniline hydrochloride **100** and 2,2[1]-dihydroxynaphthalene **101** for 24 hrs.



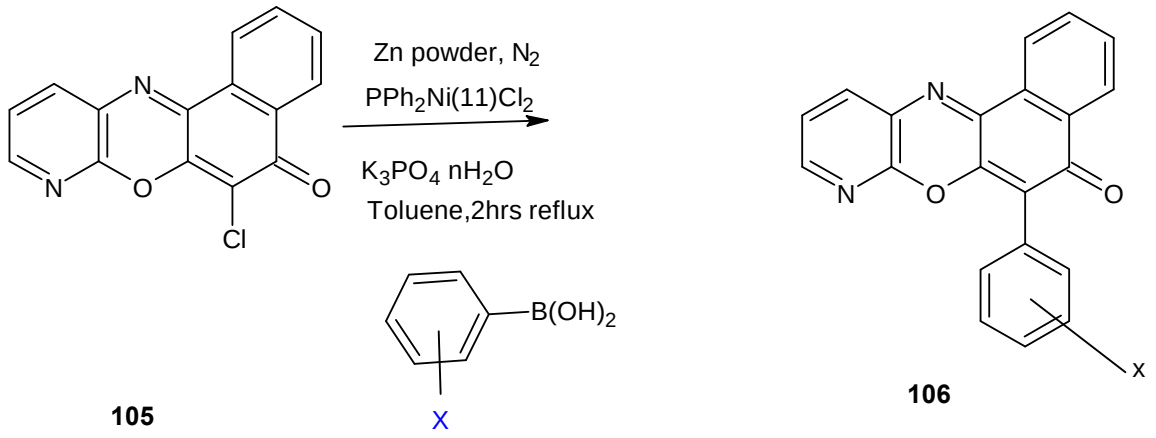
100 **101** **102**

The synthesis of new angular monoazabenzo[a]phenoxazine and its substituted aryl derivatives via nickel-catalyzed system was reported by Anoh V.A etal[122].This they achieved by condensing 3-amino-2-Pyridonol **103** and 2,3-dichloro-1,4-naphthoquinone **77** in anhydrous basic medium to produce a new heterocyclic-6-chloro-8-azabenzo[a]phenoxazine-5-one **104** as an intense brown product in 64.77% yield as shown below.



103 **77** **104** 66.77 %

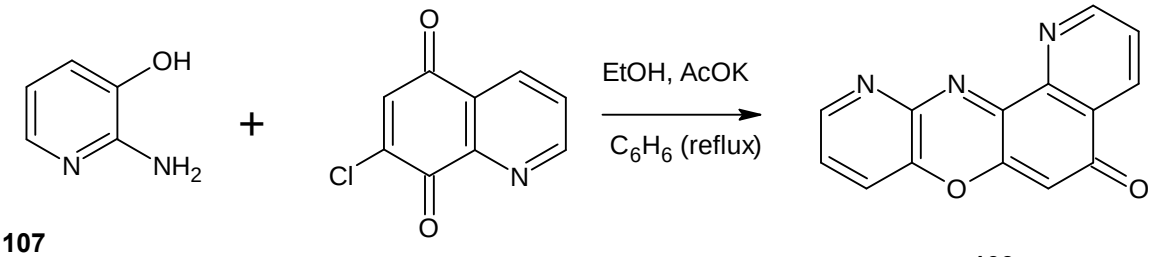
Upon applying Suzuki-Miyaura cross coupling reaction, it resulted to their synthesis of some aryl derivatives as shown below.



105 **106**

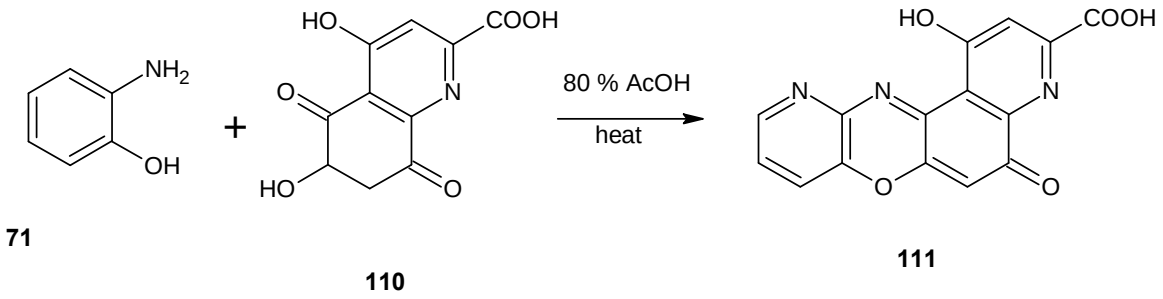
X= Br,Cl,N_2O

Okoro and Ugwuoke[123] reported the synthesis of a diaza-analogue of non-linear phenoxazine compounds **109**.They accomplished this by reacting 2-amino-3-hydroxylpyridine **108** and 7-chloro-5,8-quinolinequinone **107** in anhydrous potassium acetate in benzene which on refluxing for 3 hrs produced compound **109** in 93 % yield.



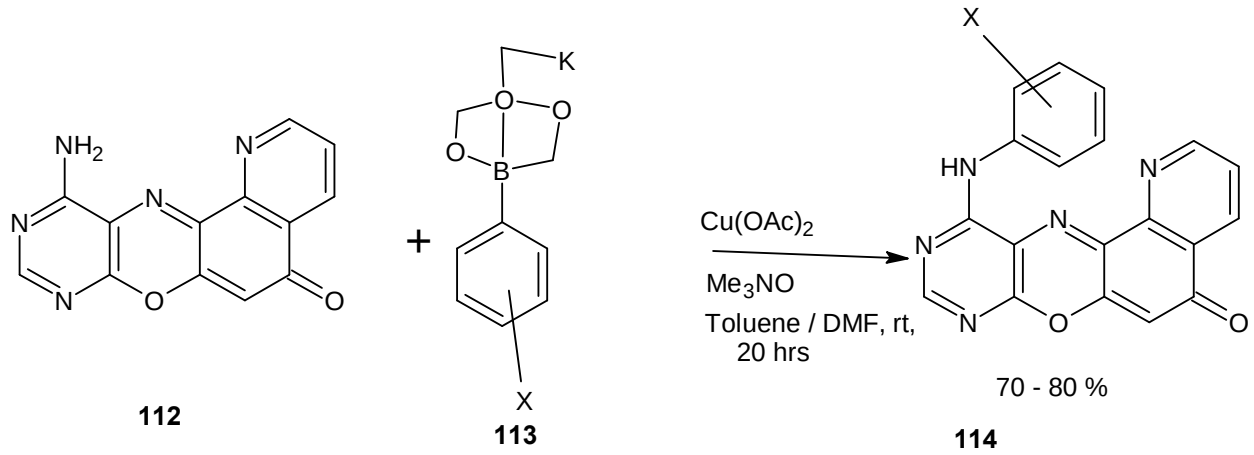
107 **108** **109**

Catalin **111** a pyrido[3,2,a]phenoxazine was synthesized by the acid catalysed condensation of 2-aminophenol **71** with 4,6-dihydroxyquinoline-5,8-dione-2-carboxylic acid **110**[109].



71 **110** **111**

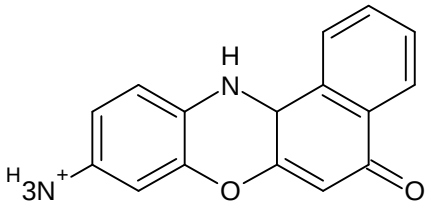
Jacob et al[124] synthesized 11-(N-substituted) angular triazaphenoxazine **114** via copper catalyzed N-arylation. Their key intermediate 7-chloro-5,8-quinolinequinone was obtained in five ï steps reaction starting from 8-hydroxyquinoline.Thereafter it was coupled with 4,5-diamino-6-hydroxypyrimidine in the presence of sodium acetate under anhydrous condition. The final product was obtained by reaction of 11-amino-1,8-triazabenzo[a]phenoxazin-5-one **112** with substituted potassium lithium phenyltriolborate **113**,under the catalytic influence of copper (11) acetate in the presence of trimethylamine N-oxide as shown below



112 **113** **114**

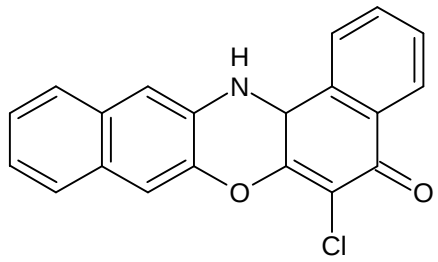
2.5 Applications of angular phenoxazines

Nile red **115** has been used as florescent probe as a spectrophotometric reagent for the determination of the amount of nitrile. It is also a good biological stain for bulk stains of nerve tissues.[108]



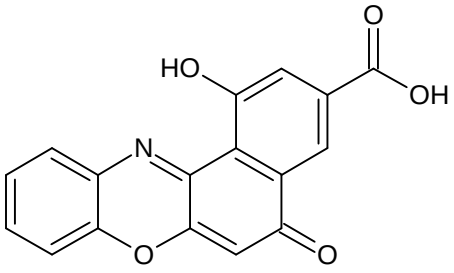
115

An intensely coloured compound, 6-chloro-5H-dibenzo[a]phenothiazin-5-one **116** is applicable as dyestuff.



116

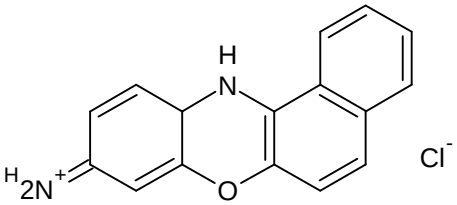
Another phenoxazine derivative catalin **117** prepared by acid-catalyzed condensation of o-amino-phenol with 4, 6-dihydroxyquinoline-5, 8 dione -2-carboxylic acid is in current use as an anti cataract drugs[109].



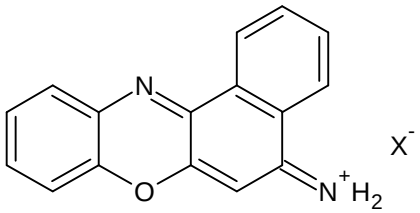
117

This compound **117** is related to omination, rhodamatin and Xanthanmatin.

Medola blue **118**, Nile blue **119** and Nile red **115** belong to the class of aminobenzo[a]phenoxazines dyes. Nile blue **119** was found to be a good photosensitizer for diazo-system, which facilitate the production of good metal image [108]. It is also a good stain for fats and for the differentiation of melanins and lipofuscins.



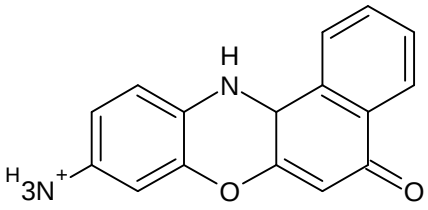
118



119

x=hemisulphate

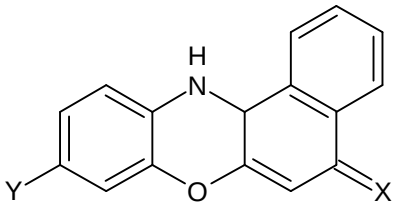
Generally, Meldola Blue (II) **118** and Nile blue **119** have the same desirable attributes as fluorescent probes just like Nile red **95**[99]. In addition, Nile blue A **119** and some closely related dyes were discovered to be useful indicators for titrimetric and equilibrium studies[43].



95

Nile blue **119**, is useful material for extraction and photometric determination of tin [125], antimony[126], germenrium[127], rhenium[128] and gold[129], it is also used to improve the bright colour of copper plated material. This series of compounds was latter shown to be useful as industrial dyes and biological stains. Some of these compounds were also active against certain organisms such as mycobacterium.

Stuzka *et al*[130] in their study of the relationship between absorption maxima and luminescence of angular phenoxazine dyes found that position para to the heterocyclic nitrogen (C- S and C ï O centre) are the active position for the absorption and fluorescence properties **120.**

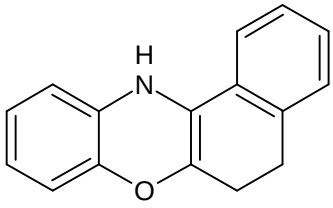


120

It was indicated that auxochromic substituent in the othor positions have only slight influence on the colour and the fluorescence disappears. It was also observed that there was decreased fluorescence when the substituents in the C-5

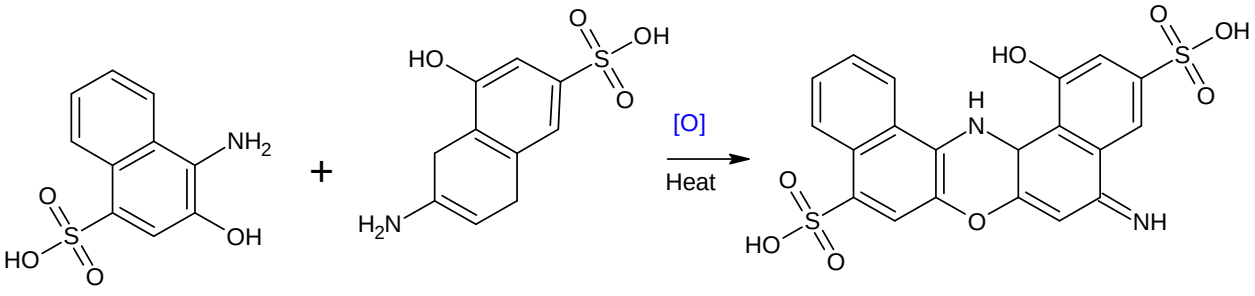
and C-9 centre were too large, like in aryl amino groups. They found out that these substituents when positioned at C-5 takes part in the shift of the electrons in the direction of the conjugated system of double bond of the phenoxazine skeleton, especially if it involves electron donor that is too bulky.

The benzo[a]phenoxazine **2** are also used as retardant in the manufacturing of polymethacrylates by the reaction of acetate cyanolydrin or methacrylonitrile and forming tetraoxosulphate (VI) acid.



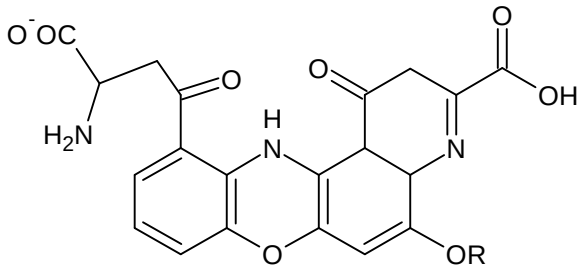
2

Levechenko[131] prepared phenoxazine -3, 9-disulphuric acid **123**. He obtained this by condensing 1-amino-2-naphthol-4-sulphonic acid **121** with 2-amino-2-naphthol-6-sulphonic acid **122** in the presence of oxidizing agent.



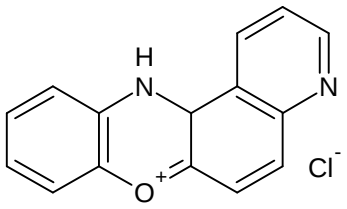
121 **122** **123**

Some angular azaphenoxazine like the pyrido (3, 2- a) phenoxazine occurs free in nature. The naturally occurring angular phenoxiazine pigments are numerous and have been classified as ommochrones fungi metabolites, questiono mycins and actinomycins[55, 107 and121]. The ommochrones such as xanthammatins**124** are acid pigments which are responsible for the coloration in wings, eyes and cuticle of insecticides.



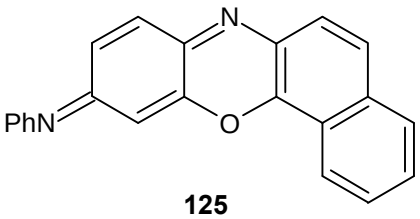
124

Pyrido(3,2-a)phenoxazine **121** has been confirmed to be a good blue mordant for cotton mordanted with tannin and fixed by iron, aluminium or chromium mordant.



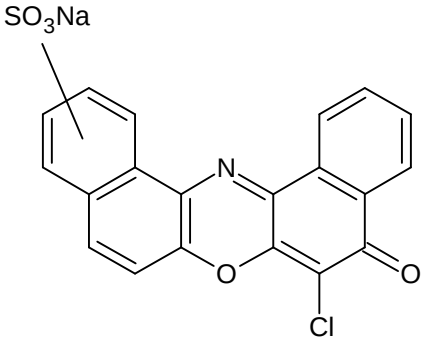
95

Benzo[c]phenoxazine **125** have been employed as retardant in the manufacture of polymethacrylates.

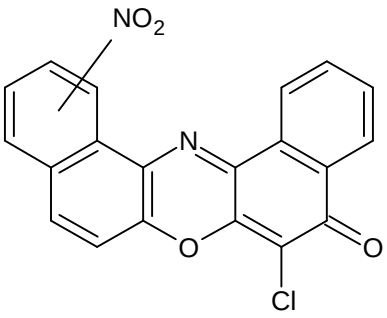


125

Nitro-6-chlorodibenzo[a,j]-1,4-phenoxazin-5-one **78a** and 6-chlorodibenzo[a,j]-1,4-phenoxazine-5-one sulphonic acid **78b** are reported[121] to be used as dyes for textile materials cellulose and soap.

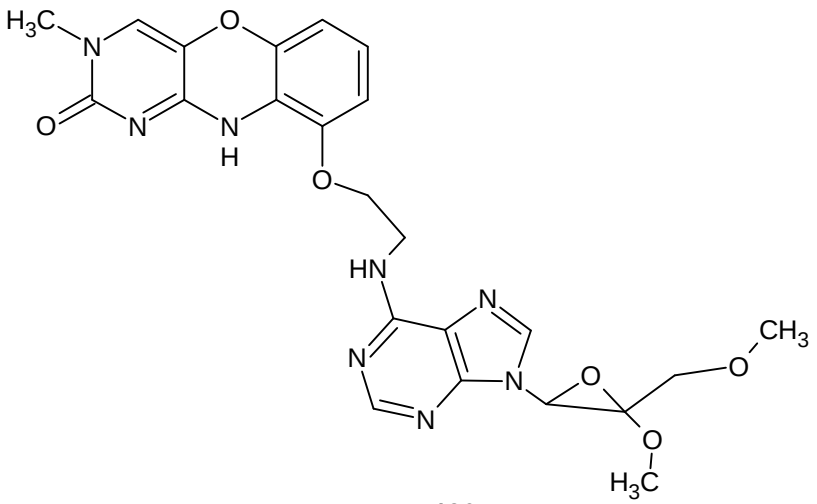


78a



78b

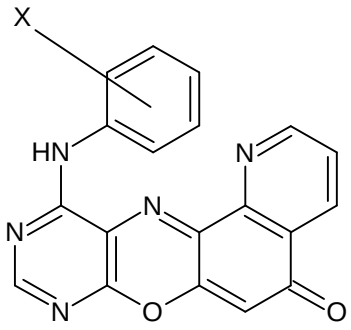
Adenosine-1, 3-diazaphenoxazine **126** was synthesized by Yosuke *et al*[103] in 2011 and used for selective recognition of 8-oxo-dG in DNA.



126

They showed by this study that compound **126** has highly selective stability effect on the duplex containing the Adonosine-1, 3-diazaphenoxazine base pairs. Furthermore, the fluorescent property of compound **126** was shown to be useful for the selective direction of 8-oxo dG in the duplex in DNA. According to the authors, this is the first successful demonstration of a non-natural nucleoside with a high selectivity for 8-oxo-dG in DNA.

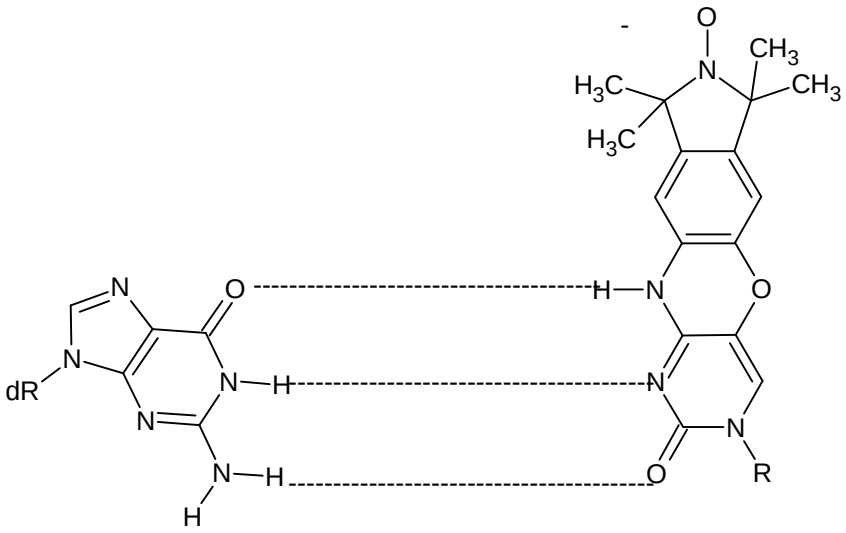
Derivatives of angular triazaphenoxazinone; aminotriazabenzo[a] phenoxazines (47) are applicable as laser dyes since these tetracyclic heterocycles absorb light in the visible region (400 ï 700 nm) [132a].



X = Br, N_2O, H, Cl

114

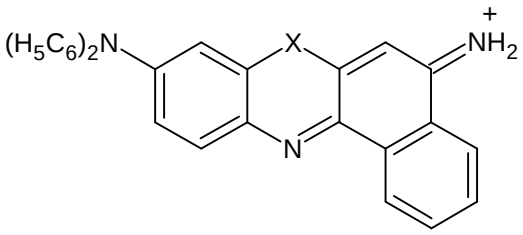
The structure analysis of D N A containing the planar phenoxazine **127**[132b] shows that it forms a planar structural non ï perturbed base. This indicates that it can be used with confidence in EPR ï or fluorescence based structural and dynamic studies.



127

In a research to develop effective new photosensitizer for tumor ï selective photodynamic therapy[133], it was revealed that phenoxazine dyes including several analogues are known to localize selectivity in animal tumors.

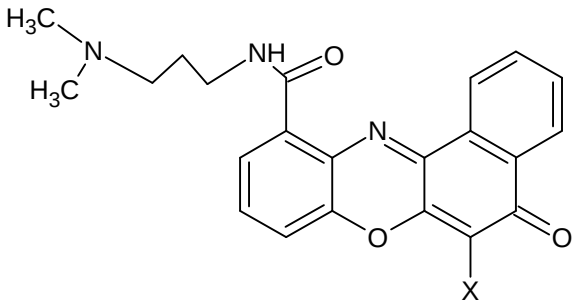
Nile blue derivatives containing halogens and / or sulphur substituents **128** [134] are effective in mediating photo killing of tumor cells.



X = O , S

128

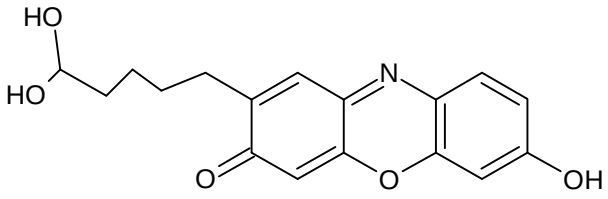
The cell ï based reporter assays are utilized in identification of new ï G Quadruplex binding molecules that modulates transcription; it was identified that benzo[a]phenoxazine derivatives **129** [135] is the potential anti tumor agents.



X = H , Cl

130

The power of Rosetta **131** for the major redesign of enzyme specificity was illustrated by Daniel *et al*[136]. He reported that compound **131** introduces a tool for minimally invasive, highly specific imaging of cellular proteins by both conventional and super resolution microscopies.



131

CHAPTER THREE

3.0 EXPERIMENTAL SECTION

3.1 GENERAL REAGENT INFORMATION

$Pd(OAc)_2$, ligand (t-Buxphos), 2-aminophenol, 4,5-diamino-6-hydroxyl-2-mercaptopyrimidine, 4-methoxyphenol, phenol, 4-chlorophenol, 4-isopropylphenol and benzene were purchased from Sigma Aldrich chemical company, Germany. 2,3-Dichloronaphthoquinone was purchased from Fluka Chemical Company and was used without further purification. $K_3PO_4.3H_2O$, sodium carbonate, diethylacetate and ethanol were purchased commercially without further purifications.

3.2 GENERAL ANALYTICAL INFORMATION

Melting points were determined using Fisher-Johns melting points apparatus and they remain uncorrected. Compounds were characterized by UV/visible, IR, ^1H NMR and ^{13}C NMR spectroscopy. Uv-visible spectra were recorded on a JENWAY 6645 UV/VIS spectrophotometer using matched 1 cm quartz cells, at Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka. The solvent was water. The absorption maxima are given in nanometers; the figures in parenthesis are Ɛvalues. IR spectra were obtained on an alpha Bruker spectrophotometer (University of Lagos, Akoka). Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were determined at University of New Castle,

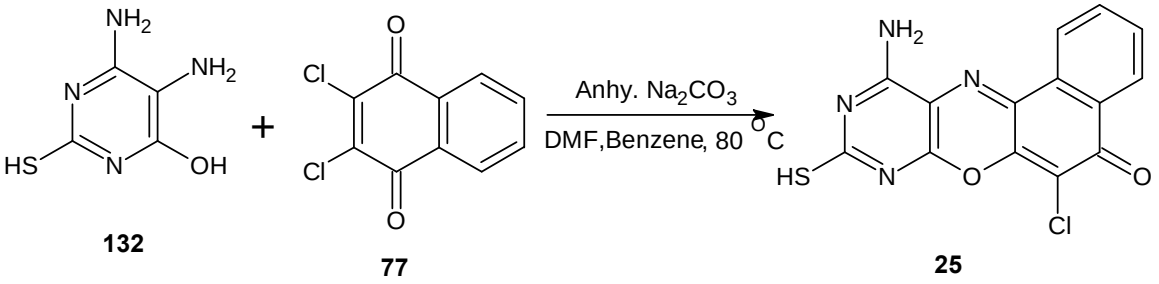
London, United Kingdom. Chemical shifts were recorded on the ŭ-scale (neat). Interpretation of spectral data was done with reference to literature [137]. Antimicrobial screening was done at the Faculty of Pharmacy, Department of Pharmacology, University of Nigeria, Nsukka.

3.2.1 Synthesis of 11-amino-6-chloro-9-mercapto-8,10 - diazabenzo[a]phenoxazin-5-one 3

This compound was prepared following the procedure of Okafor *et al*[12]

A measuring cylinder was used to measure benzene (100 ml) and transferred into a three-necked flask. 4, 5-Diamino-6-hydroxyl-2-mercapto pyrimidine 4.66 g, 37 mmol was then dissolved in the benzene (100 ml) followed by the addition of anhydrous sodium carbonate 3.92 g, 37 mmol. The mixture was warmed to boiling temperature. Then 2,3-dichloro-1,4-naphthoquinone (7.03 g, 37 mmol) was added and the mixture refluxed on a water bath with magnetic stirrer for 6 hours at a temperature of 80 ^{o}C. The reaction mixture was allowed to cool and then poured into a beaker containing crushed ice. The precipitate formed was air dried on the filter paper and the crude product recrystallized from ethanol-water (2:1) mixture to give a brown solid. The purity of the recystallized product was ascertained by thin layer chromatography. M.p :205 ^{o}C (204 -205 ^{o}C)

IR (cm^{-1}) :3320 (N-H), 1620 (C=O), 1585 (C=C, C-H), 1518 (C=C aromatic), 1372 (C=N), 7812 (C-Cl),



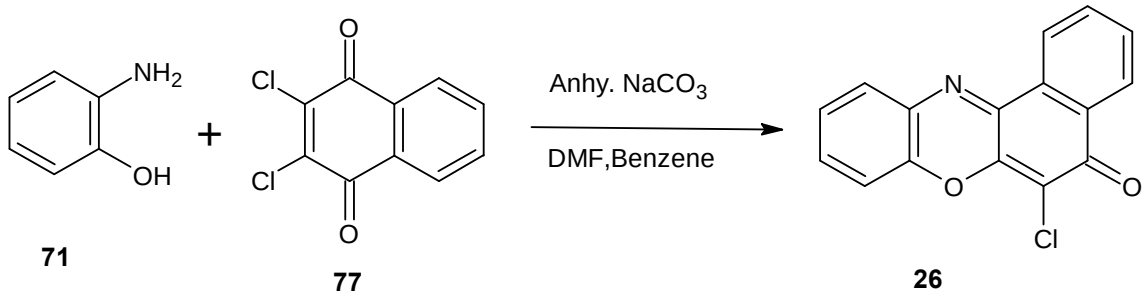
132 **77** **25**

3.2.2 SYNTHESIS OF 6-CHLOROBENZO[a]PHENOXAZIN-5-ONE 26

Compound 2 was prepared as described by Okafor *et al* [12]

A measuring cylinder was used to measure benzene (100 ml) and transferred into a three-necked flask. 2-aminophenol (4.033 g, 37 mmol) was dissolved in the benzene (100 ml) followed by addition of anhydrous sodium carbonate (3.92 g) and the mixture was warmed to boiling temperature in the three-necked flask. Then 2, 3-dichloro-1, 4-napthoquinone (7.08 g, 37 mmol) was added and the mixture refluxed on a water bath with magnetic stirring for 6 hours at a temperature of 80 ^{o}C. The reaction mixture was allowed to cool and then poured into a beaker containing crushed ice. The precipitate formed was air dried on the filter paper and the crude product recrystallizd from ethanol water (2:1) mixture to obtain yellow solid (mp 199 ï 201 ^{o}C) [11]. The purity of the product was ascertained using thin layer chromatography.**m.p** :200 ^{o}C (199-201^{o}C)

IR (Cm^{-1}) : 3373 (C=N), 1599 (C=O), 1561 (C=C, C-N), 1461 (C=C aromatic), 989 (C-H aromatic), 741 ï 704 (C-Cl).



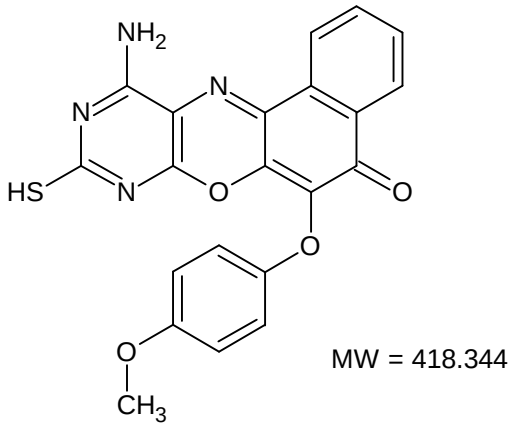
71 77 26

3.3 GENERAL PROCEDURE FOR Pd-CATALYZED COUPLING OF ANGULAR DIAZABENZO[a]PHENOXAZINE AND RELATED CARBOCYCLIC ANALOGUE WITH PHENOLS

The reactions were carried out according to the literature procedure [47]. An oven dried three-necked flask was fitted with a rubber septum and cooled to room temperature under a nitrogen purge. The septum was removed and the tube was charged with palladium acetate (4.5 mg, 0.02 mmol, 2.0 mol %), ligand (0.03 mol%, 3.0 mol%), potassium phosphate (424 mg, 2.0 mmol), phenol (1.2 mmol), and phenoxazine compound (1.0 mmol). The tube was capped with the septum and purged with nitrogen and then toluene (3 ml) was added through the spectrum. The tube was sealed with a teflon screw , and the reaction mixture was stirred at 100 ï 110 ^{o}C for 5-10 h (reaction times was not optimized).The

reaction mixture was allowed to cool to room temperature and then diluted with diethyl acetate (40 ml) and filtered. The purity of the products was ascertained using thin layer chromatography.**m.p** >360 ^{0}C

3.4 Synthesis of 9-mercapto-11-amino-6-(4-methylphenoxyl)-8,10-diazabenzo[a]phenoxazine-5-one 28a



28a

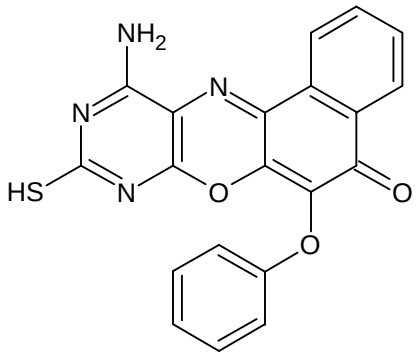
General procedure was used to convert 11-amino-9-mercapto-8,10-diazabenzo[a]phenoxazin-5-one and methoxy phenol in 8 h to 800 mg (95.6 %) of the title compound which was obtained as a dark brown solid, mp >360^{o}C.

UV (H_2O): λ_{Max} 224.2 (5958), 389.6 (1563) nm

IR (cm^{-1}): 33203 (N-H), 1580 (C-H, N-H) 1635.50 (C=O), 1376 (C=N), 1210 (R-OAr), 1634. (C=O), 1376 (C=N), 1210 (R-OAr),1058 (C-O-C), 616 (C-S).

^{1}H-NMR (ŭ):1.53 (s,1H), 3.65 (s,3H), 5.47 (s, 2H), 7.76 (d,2H), 7.89 (d, 2H), 8.98, 8.18, 7.65, 7.52(s,1H).

3.5 Synthesis of 11-amino-9-mercapto-6-(phenoxyl)-8,10-diazabenzo [a]phenoxazine-5-one 28b



28b

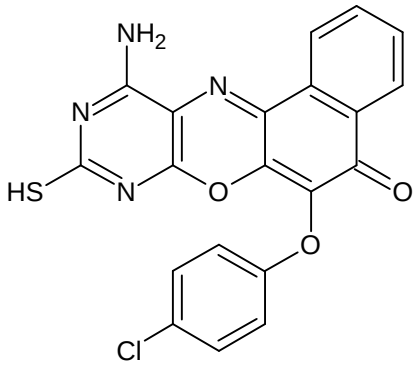
General procedure was used to convert 11-amino-9-mercapto -8,10-diazabenzo[a]phenoxazine-5-one and phenol in 10 h to 740 mg (95.5 %) of the title compound which was obtained as a dark brown solid, mp >360^{o}C.

UV (H_2O): λ_{max} 251 (1458), 481 (256) nm.

IR (cm^{-1}): 3183 (N-H), 1581 (C-H, N-H), 973 (C-H), 1632 (C=O), 1432 (C=C), 1060 (C-O-C), 1377 (C-N) 976 (C-H), 616 (C-S).

^{1}**HNMR** (ŭ):1.64 (s, 1H), 5.99 (s, 2H), 8.52, 8.16, 7.94, 6.92 (s, 1H), 7.78 (d, 1H), 7.65 (t, 3H).

3.6 Synthesis of 11-amino-9-mecaptho-6-(4-chlorophenoxy) 8,10-diazabenzo[a]phenoxazin-5-one 28c



28c

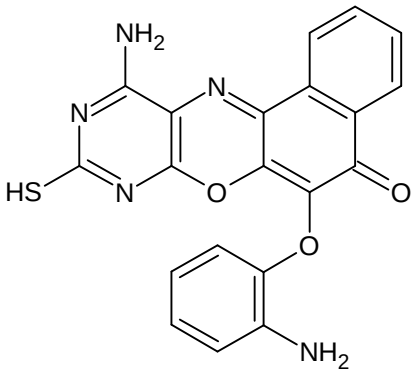
General procedure was used to prepare 11-amino-9-mercapto-8,10-diazabenzo[a]phenoxazin-5-one and 4-chlorophenol in 8 h to 630 mg (74.45 %) of the title compound, which was obtained as a dark brown solid mp >360^{o}C.

UV (H$_2$O): ə$_{max}$ 200 , 258 (342), 383 (158), 484 (71) nm.

IR (cm^{-1}): 3190 (N-H), 1635 (C=O), 1579 (C=C, C=N), 1266 (C-N), 1059 (C-O-C), 780 (C-Cl), 616 (C-S).

^{1}H NMR(ŭ) : 1.66 (s.1H,), 5.47 (s,2H), 7.86, 7.85, 7.77, 7.66 (s.1H), 6.77-7.20 (m,2H).

3.7 Synthesis of 11-amino-9-mercapto-6-(2-aminophenoxyl)-8,10-diazabenzo[a]phenoxazin-5-one 28d



Mw = 403.375

28d

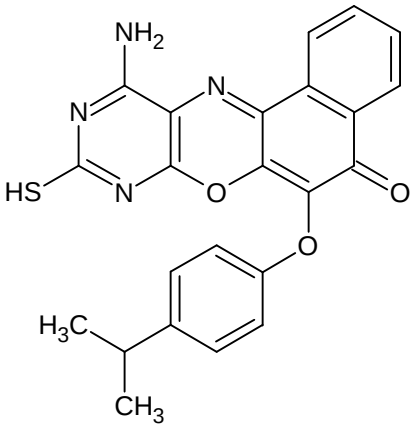
General procedure was used to prepare 11-amino-9-mercapto-6-chloro-8,10-benzo[a]phenoxazin-5-one and aminophenol in 10 h to 735.8 mg (91 %) of the title product which was obtained as a dark brown solid, mp>360 ^{o}C.

UV (**H_2O**): λ_{max} 200, 388 (632) nm.

IR (cm^{-1}): 3204 (N-H), 1630 (C=O), 1582 (C=N,C=C), 1306 (C-N), 1059 (C-O-C), 616 (C-S).

^{1}H NMR (ŭ): 1.67 (s, 1H), 5.99, 5.46, (s, 2H, NH), 7.71 (d,1H), 7.40 (t,1H).

3.8 Synthesis of 11-amino-9-mercapto-6-(4-isopropylphenoxy) benzo[a]phenoxazin-5-one 28e



28e

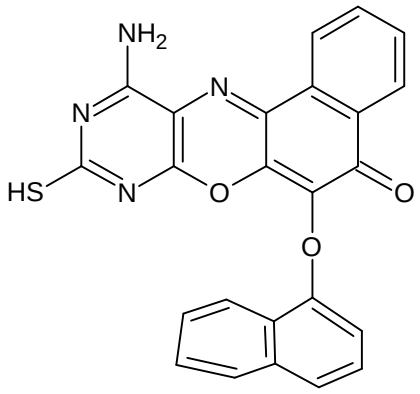
General procedure was used to prepare 11-amino-9-mercapto-6-chlorobenzo[a]phenoxazin-5-one and 4-isopropylpehnol in 7 h to 826 mg (96 %) of the title product as dark brown solid, melting point >360 ^{o}C.

UV (H_2O): λ_{max} 200, 263 (1426), 379 (509) nm.

IR (cm^{-1}): 3174 (C-H), 1635 (C-O), 1564 (C=N, C=C), 1378 (C-N), 1058 (C-O-C), 616 (C-S).

^{1}H NMR (ŭ): 2.78 (s,1H), 5.54 (s,1H) 3.64 (q, 3H) 7.78 (d, 1H) 9.96, 8.12, 7.64 and 7.52 (s,1H).

3.9 Synthesis of 11-amino-9-mercapto-6-(naphthoxyl)benzo[a] phenoxazin-5-one 28f



28f

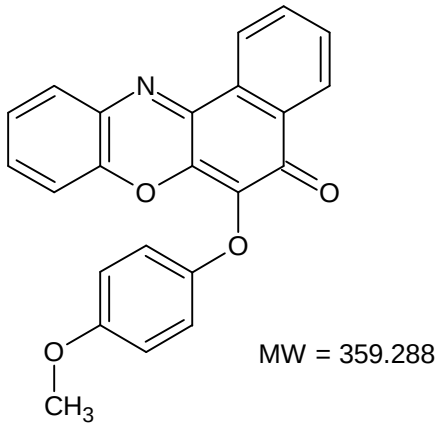
General procedure was used to prepare 11-amino-9-mercapto-6-chlorobenzo[a]phenoxazine-5-one and 1-naphthol in 10 h to 835.56 mg (99 %) of the title compound as a dark brown solid melting point >360 ^{o}C.

UV (H$_2$O): ə$_{max}$ 200, 217 (7041), 385 (1292) nm.

IR (cm^{-1}): 3190 (N-H), 1640 (C=O), 1581 (C=N,C=C), 1513 (C-C), 1441 (C=C), 1366 (C-N), 1226 (R-O-Ar), 1060 (C-O-C), 971 (C-H), , 617 (C-S).

^{1}H NMR (ŭ): 2.30 (s,1H), 5.47 (s,1H), 8.47 , 8.16 , 8.00 and 7.86 (s,1H), 7.50 ï 7.65 (q,1H), 6.67 ï 7.12 (m,4H), 7.74 (d,1H), 7.74 (d,1H).

3.10 Synthesis of 6-(4-methoxyl phenoxyl) benzo[a]phenoxazine-5-one 29a



29a

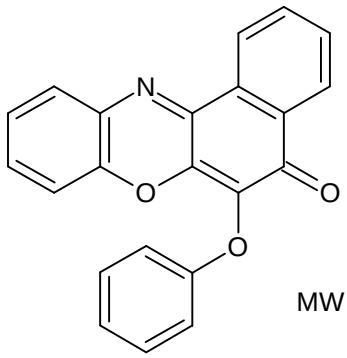
General procedure was used to convert 6-chlorobenzo[a]phenoxazin-5-one and methoxyphenol in 8 h to 710 mg (96 %) of the title compound, which was obtained as a black solid, mp<360^{o}C.

UV (H_2O): λ_{max} 200, 269 (67), 389(396), 456 (348) nm.

IR (cm^{-1}): 3163 (N-H), 1626 (C=O), 1582 (C=N,C=C) 1482 (R-O-CH_3), 1207 (R-O-Ar), 1060 (C-O-C), 977 (C-H).

^{1}H NMR (ŭ): 2.56 (s, 3H), 7.40 ï 7.44 (m, 4H), 7.06 ï 7.29 (m, 4H) 7.50, 6.99, 6.792 and 6.49 (s, 1H).

3.11 Synthesis of 6-phenoxylbenzo[a]phenoxazin-5-one 29b



MW = 338.289

29b

General procedure was used to prepare 6-chlorobenzo[a]phenoxazin-5-one and phenol in 10 h to 750 mg (94 %) of the title compound which was obtained as a black solid compound, melting point >360^{o}C.

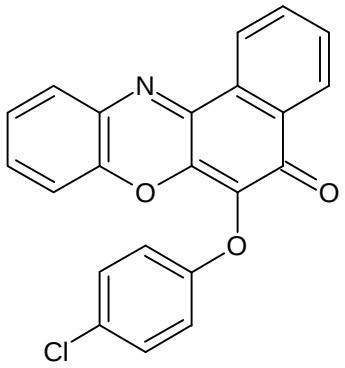
UV (H_2O): ɔ$_{max}$ 200, 270 (507), 390 (413), 470 (250).

IR (cm^{-1}): 1631 (C=O), 1563 (C=C, C=N), 1449 (C=C), 1264 (R-O-Ar), 1058 (C-O-C), 979 (C-H).

^{1}H NMR (ŭ): 6.52 ï 6.56 (m,4H), 7.97 (d, 2H), 7.23 (t, 1H), 8.55, 8.53,7.53 and 7.51 (s, 1H).

^{13}C NMR: 179.81 (C=O), 147.61 (C-O), 169.67 (C=N), 113.00 (Ar-C).

3.12 Synthesis of 6-(4-chlorophenoxyl)-benzo[a]phenoxazine-5-one 29C



29c

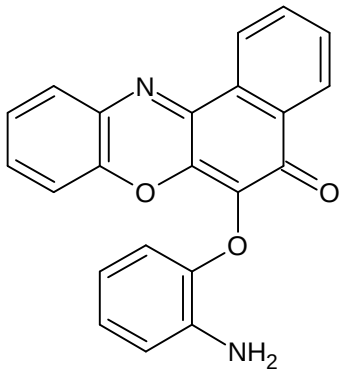
General procedure was used to prepare 5-chlorobenzo[a]phenoxazin-5-one and 4-chlorophenol in 8 h to 770 mg (46 %) of the title compound, which was obtained as a black solid mp. >360 ^{o}C.

UV (**H_2O**): λ_{max} 200, 265 (596), 387.2 (425) nm.

IR (cm^{-1}):, 1631 (C=O), 1563 (C=C, (C=N), 1410 (C=C) , 1263 (R-O-Ar), 1059 (C-O-C), 976 (C-H).

^{1}H NMR (ŭ): 6.92 (s, 2H), 7.45 ï 7.50 (m, 4H), 6.77 (d, 1H), 6.767 (t,1H) 7.17 (d, 1H), 7.24 (t, 1H).

3.13 Synthesis of (2-aminophenoxyl)benzo[a]phenoxazin-5-one 29d



29d

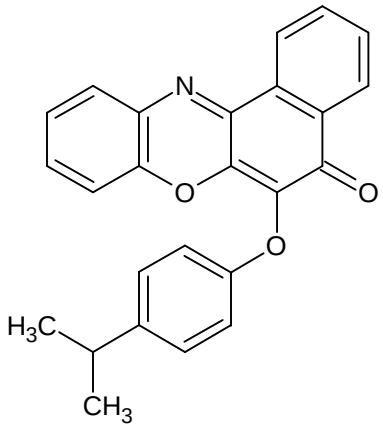
General procedure was used to prepare 6-chlorobenzo[a]phenoxazin-5-one and 2-aminophenol in 10 h to 682 mg (94 %) of the title product as black solid, mp >360 ^{o}C.

UV (H$_2$O): λ_{max} 200, 234 (264), 384 (146), 493 (93)

IR (cm^{-1}): 3197 (N-H, C=O) 1632 (C=O), 1561(C=C, C=N), 1459 (C=C), 1378 (C-N), 1268 (R-O-Ar), 1065 (C-O-C), 983 (C-H).

NMR (ŭ): 6.92 (s, 2H), 7.45 ï 7.40 (m, 4H), 6.77 (d, 1H), 6.77 (t, 1H) 7.17 (d, 1H), 7.24 (t, 1H).

3.14 Synthesis of 6-(4-isopropylphenoxyl)benzo[a]phenoxazin-5-one 29e



29e

General procedure was used to prepare 6-chlorobenzo[a]phenoxazin-5-one and 4-isopropylphenol in 7 h to 765 mg (98.4 %) of the title product as a black solid, mp >360 ^{o}C.

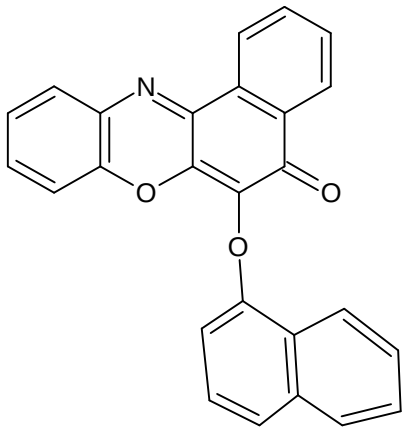
UV (H_2O): λ_{max} 200, 260 (1757), 384 (850), 485(769) nm.

IR (cm^{-1}): 3194 (C=O), 1641 (C=O), 1563(C=C, C=N), 1483 (C-C), 1410(C-H), 1266 (R-O-Ar), 1059 (C-O-C), 979 (C-H), 846.

^{1}H NMR (ŭ): 3.54 (s, 3H), 7.89 (d, 1H), 7.78 (d, 1H), 6.65 ï 6.68 (m, 4H), 7.47 (d, 1H), 6.49 (t, 1H).

^{13}C NMR : 174.61 (C=O), 115.50 (C-O), 125.77-127.34 (Ar-C), 174.61 (C=N), 21.51-25.714 (CH_3), 39.52 ï 40.38 (isopropyl)

3.15 Synthesis of 6-(1-naphthoxyl)benzo[a]phenoxazine-5-one 29f



29f

General procedure was used to prepare 6-chlorobenzo[a]phenoxazin-5-one and 1-naphthol in 10 h to 520 mg (68.42 %) of the title compound as black solid, melting point >360 ^{o}C.

UV (H$_2$O): ∂$_{max}$ 200, 1263 (1018), 385 (270.30) nm.

IR (cm^{-1}): 1626 (C=O), 1585 (C=C, C=N), 1059 (C-O-C), 973 (C-H).

^{1}H **NMR** (ŭ): 6.37 (d, 1H), 7.67 (m, 4H), 7.24 (d, 4H), 7.53 (d,1H), 7.66 (m,4H), 8.27, 7.39, 7.34 and 7.18 (s, 1H).

3.16 ANTIMICROBIAL SCREENING OF THE NOVEL COMPOUNDS

Antimicrobial screening of the synthesized compounds was done using agar diffusion method.

Materials: 1) Muller Hinton prepared and kept molten at 45 ^{o}C in 20 mL using malcartary bottle

2) Sterile empty petri ï dishess

3) Cork ï borer of 6 mm diameter

4) 24 h culture of test ï organism

Procedure: Seeded agar plates were prepared by pouring the molten agar over the organism suspension previously introduce into the plate mixed by swirling to ensure uniform dish distribution of the cells within the medium. The seeded agar plates were allowed to set. This was followed by creating cup/ well using the cork ï borer.

Preparation of anti ï microbial agents/ sample: The sample were carefully weighed and transferred into their respective containers, dissolved using their suitable solvents to obtain the require concentration of 10 microgram/ml. Each sample was transferred into its corresponding cup in four (4) drops; each drop is 0.015 ml volume. The plates were allowed to stand for pre ï diffusion. This was followed by incubation. Proper bacteria were incubated at 37 ^{o}C for 24 h and 25 ^{o}C for 48 h for fungi. After the incubation period, the plates were observed for the result. The inhibition zone Diameter (IZD) was measured in millimeter.

3.17 DETERMINATION OF MINIMUM INHIBITORY CONCENTRATION (MIC) OF THE NEW COMPOUNDS

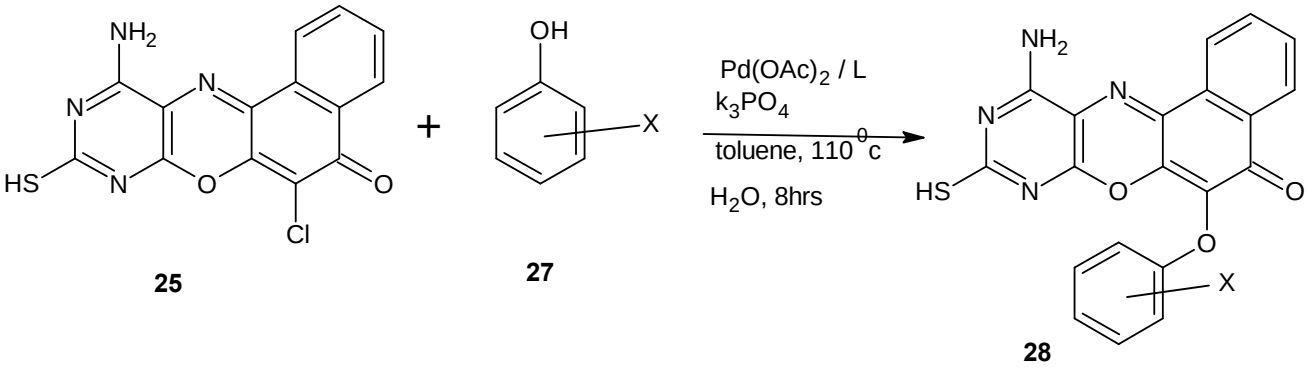
Minimum inhibition concentration is defined as the least concentration of the samples that shows appreciable IZD on sensitivity that can inhibit the growth of the microorganism under test. For this exercise, different dilution of stocks were prepared through two ï fold serial dilution techniques from 20 mg/ml, five dilution were made to the following concentrations 20.10, 5.25, 1.25, 0.625 mg/ml. Four drops of 0.151 ml was introduced in their corresponding cups previously cut in the agar; 30 minutes pre diffusion was allowed before incubation proper. The results were taken after 24 and 48 h for bacteria and fungi respectively. The IZD after measured were employed in the determination of the minimum inhibitory concentration by plotting graph of IZD against logarithm of serial concentrations. Then antilog of the intercept was determined and this gave the MIC.

CHAPTER FOUR

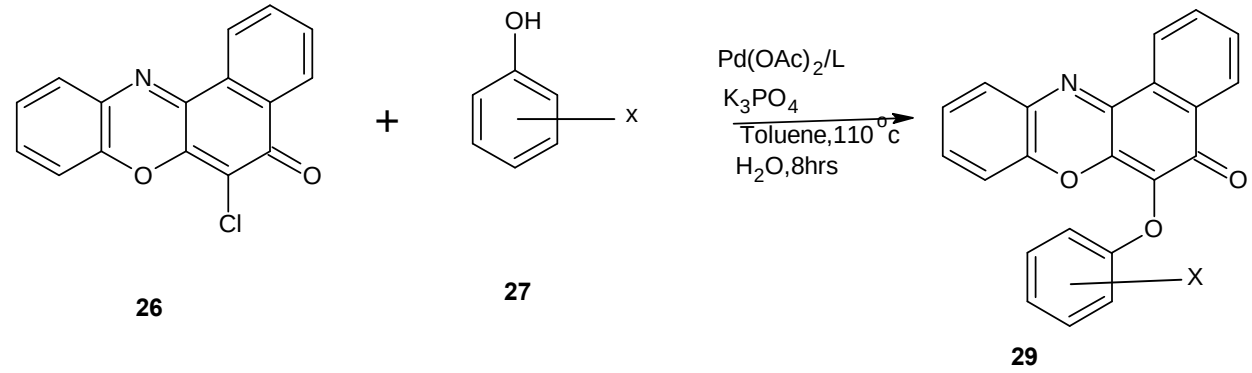
4.0 RESULTS AND DISCUSSION

4.1 General consideration of yield of the described products

The equation below summarized the general reaction of the yield presented in Table 3.



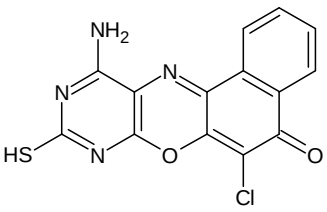
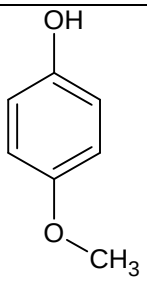
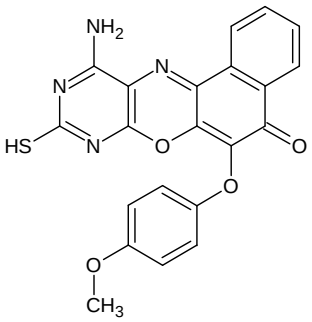
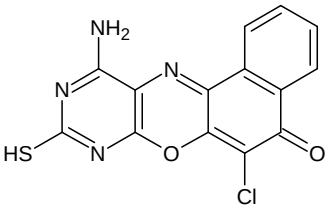
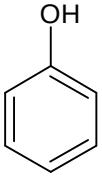
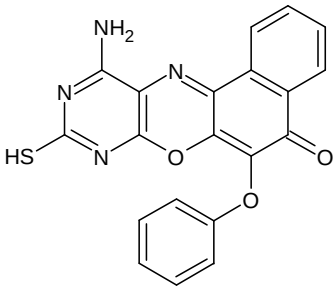
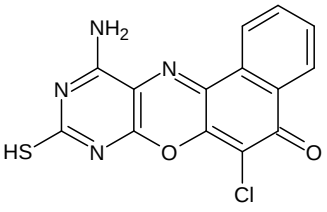
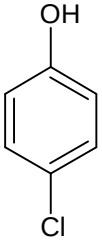
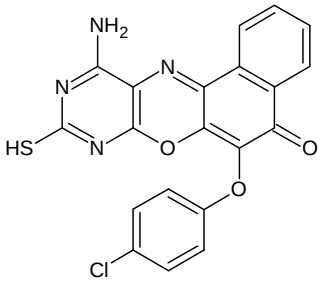
25 **27** **28**

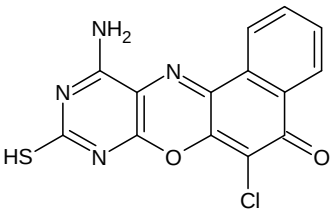
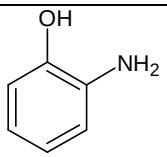
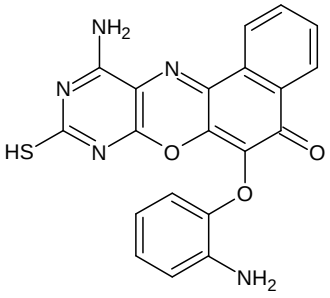
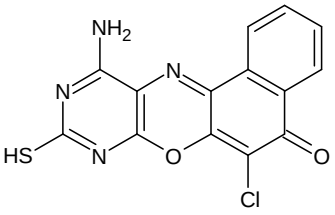
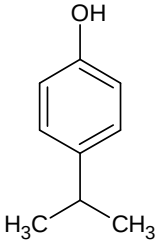
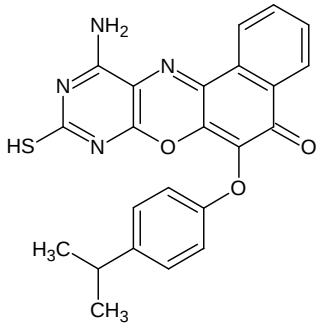
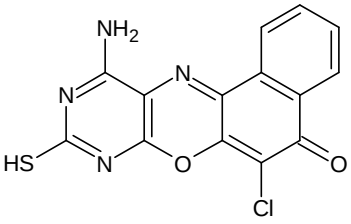
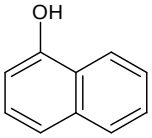
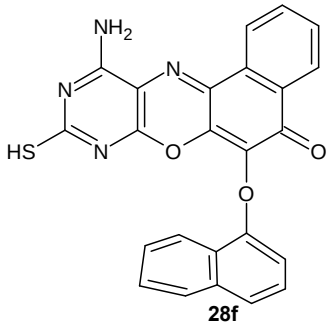
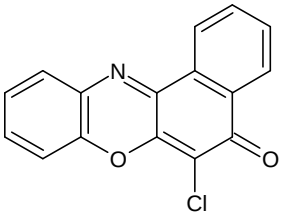
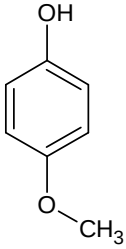
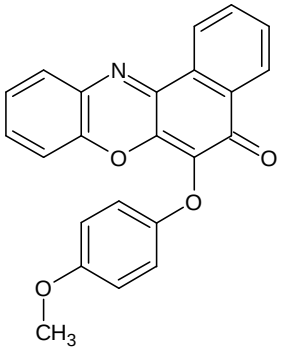


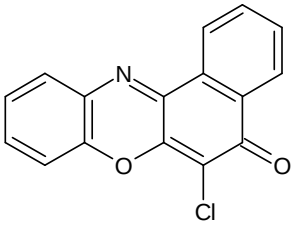
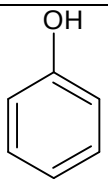
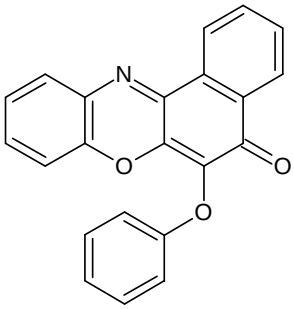
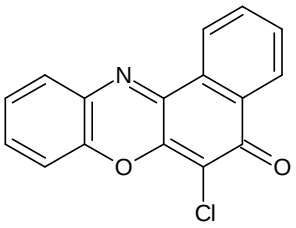
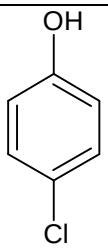
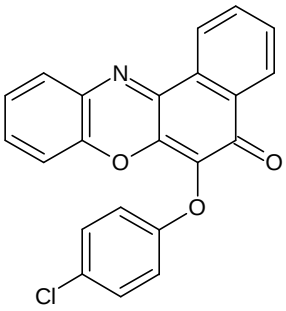
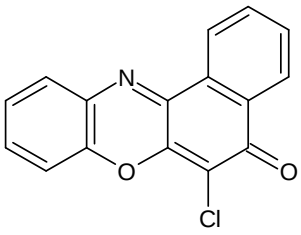
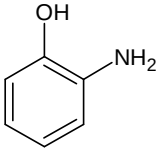
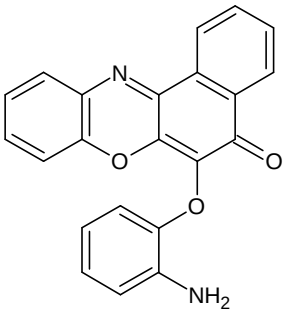
26 **27** **29**

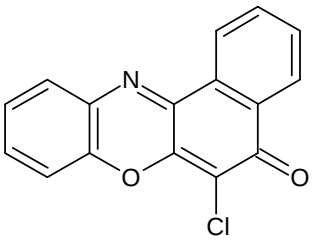
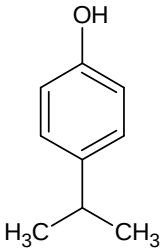
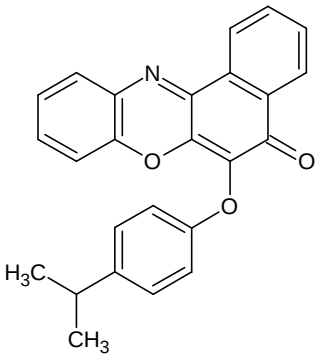
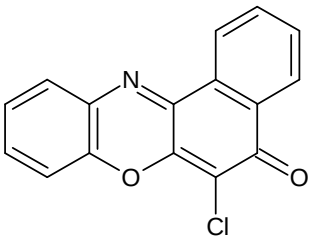
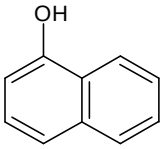
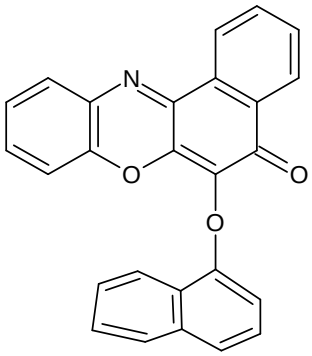
x = H, 4-OCH_3, Cl, 2-NH_2, 4-Isopropyl, Aryl. L = t-Buxphos.

Table 3: General consideration of the yield of the described products.

Entry	Phenoxazine compounds	Phenols	Products	Reaction time	% yields
1			 **28a**	8 h	96%
2			 **28b**	10 h	96%
3			 **28c**	8 h	74%

4			 **28d**	10 h	91 %
5			 **28e**	7 h	96 %
6			 **28f**	10 h	99 %
7			 **29a**	8 h	97 %

8			 **29b**	10 h	95 %
9			 **29c**	8 h	46 %
10			 **29d**	10 h	94 %

11			 29e	7 h	98 %
12			 **29f**	10h	68 %

Reaction conditions: (1.0 equiv), phenol (1.2 equiv), K_3PO_4 (2.0 equiv) ligand (3.0 mol %) toluene (0.3mL), 100 ï 110 ^oC, 6-24 hrs, reactions time were not optimized, palladium acetate (4.5 mg)

Ligand used: t-Buxphos

Texture of the products: deliquescent

Solubility of the products: water, DMF and DMSO

I report for the first time to the best of my knowledge successful C-O coupling reaction of 11-amino-9-mercapto-8,10-daizabenzo[a]phenoxazin-5-one and 6-chlorobenzo[a]pheno- xazin-5-one with a variety of electron-rich, electronically neutral, and electron-deficient phenols, which fulfill the requirement for fine chemical synthesis and generally worked in comparatively moderately low catalytic loading (2.0mmol%).

The results demonstrate that using t-Buxphos, an electron-rich phosphine ligand can achieve oxidative addition of benzo[a]phenoxazine and diazabenzo[a]phenoxazine nuclei to palladium centers. Our finding suggested that when this ligand was used, the rate limiting step in the catalytic cycle of a cross-coupling process may be shifted from oxidative addition of the diazabenzo[a]phenoxazine and benzo[a]phenoxazine analogue respectively to a Pd[0] complex to either Pd-O bond formation or the reductive elimination leading to the C-O bond formation.

When I examined the reactions of compound **25** and **26** with variety of electron rich and electron deficient phenols, phenol (C_6H_5OH) gave a high yield; 96% and 95% (entry 2 and 8) with compound **25** showing a lower yield

When phenol compound, which is substituted in the para-position with electron donating groups, coupled with compound **25** and **26**, it gave excellent yields (entries 1,5,7, and 11). The fact that these electron rich phenols are

particularly good reaction partners showed that the presence of compound **25** and **26** allows the delocalization of the negative charge which may build up in the transition state of the reductive elimination of the aryl ether from an intermediate $L_2Pd(OAr)\ Ar^1$ (L_2 = t-Buxphos)[138, 139]. The results are also in line with Hartwigôs previous finding in the palladium-catalyzed formation of diarylethers and other carbon-heteroatom bond forming processes.[116, 117]

When phenols with electron donating groups attached in position 2 is coupled with compound **25** and **26**, we have lower yields (91 and 95%) than the one attached in the Para position (entries 4 and 10 respectively).

The highest yield was obtained when 1-naphthol was coupled with compound **25** (entry 6). This may be attributed to the presence of the additional benzene ring in naphthol compound, which constituted increase in conjugation resulting in increased electron delocalization.Reaction of compound **26** with 1-naphthol, gave a lower yield 68%. This may be because of different in electro negativity of compound **25** and **26.**

The reaction of compound **25** and **26** with electron deficient phenol which has chlorine at the para position gave a better yield with compound **25** (78%, entry 3) than with compound **26** (46 %, entry 9). This is in agreement with the earlier observation[138, 139] that when an electron rich compound (in this case 11-amino-9-mercapto-8,10-diazabenzo[a]phenoxazin-5-one) is coupled with

electron deficient phenolic compound it gives higher yield and when lesser electron rich (6-chlorobenzo[a]phenoxazin-5-one) is coupled with electron deficient phenol compound (4-chlorophenol), it gives lower yield. 11-Amino-9-mercapto-8,10-diazabenzo[a]phenoxazin-5-one **3** is more electron rich compound than 6-chlorobenzo[a]phenoxazin-5-one, hence the difference in yields.

To identify structural features important for the catalyst efficacy in these Pd-catalyzed C-O bond-forming reactions, we undertook a structure-activity relationship study that employs various electron rich, electronically neutral, and electron deficient phenols (Fig 1, Fig 2 and Fig 3)

Fig 1: Illustration of the effect of palladium based t-Buxphos as catalyst on reaction of various electron difficient and electron rich phenol compounds with 11-amino-9-mecapto-8,10-diazabenzo[a]phenoxazine-5-on and 6-chlorobenzo[a]-phenoxazine-5-one re

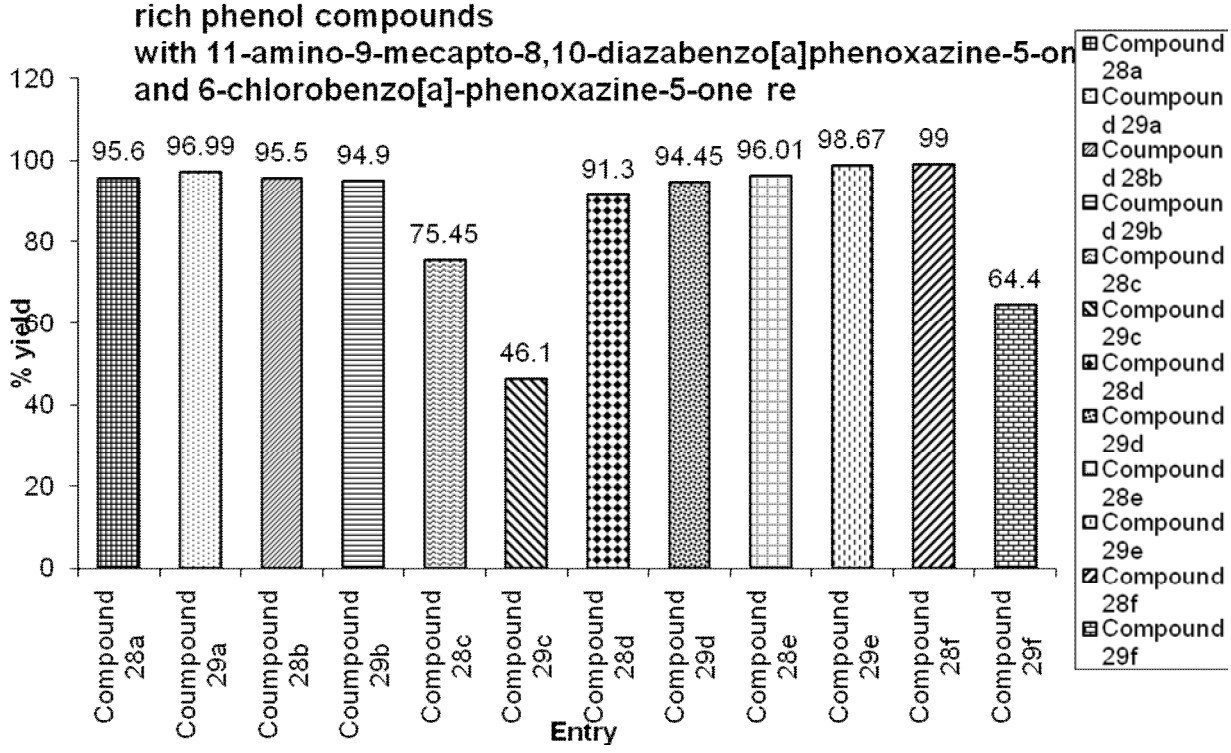


Fig 2: Graph of % yield of compound 25 with electron withdrawing and electron donating phenol

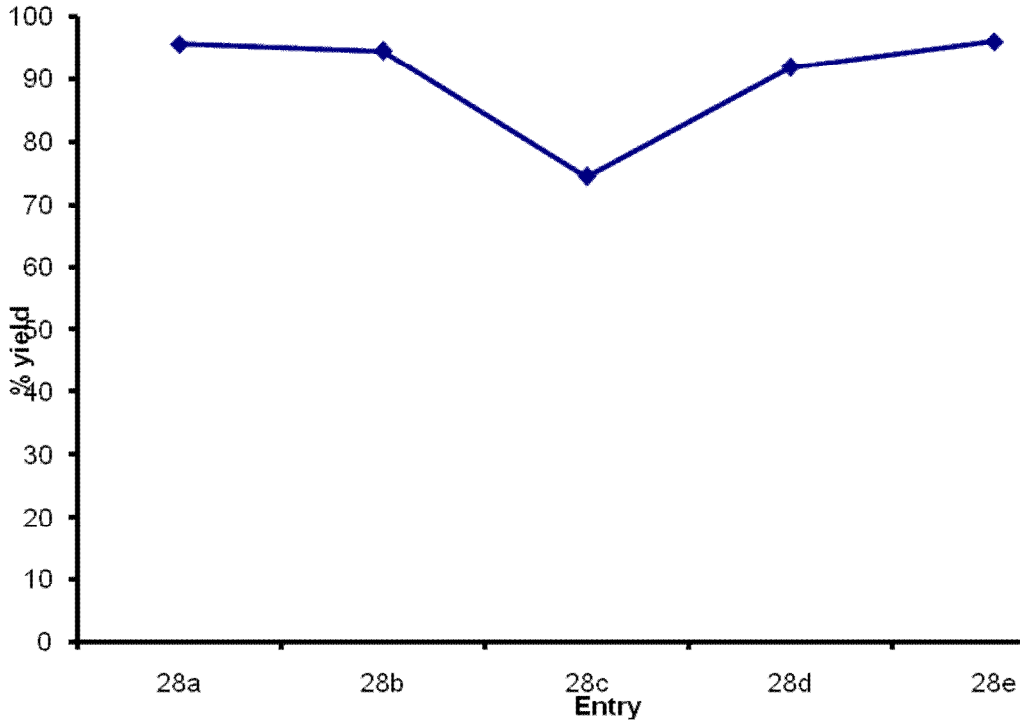
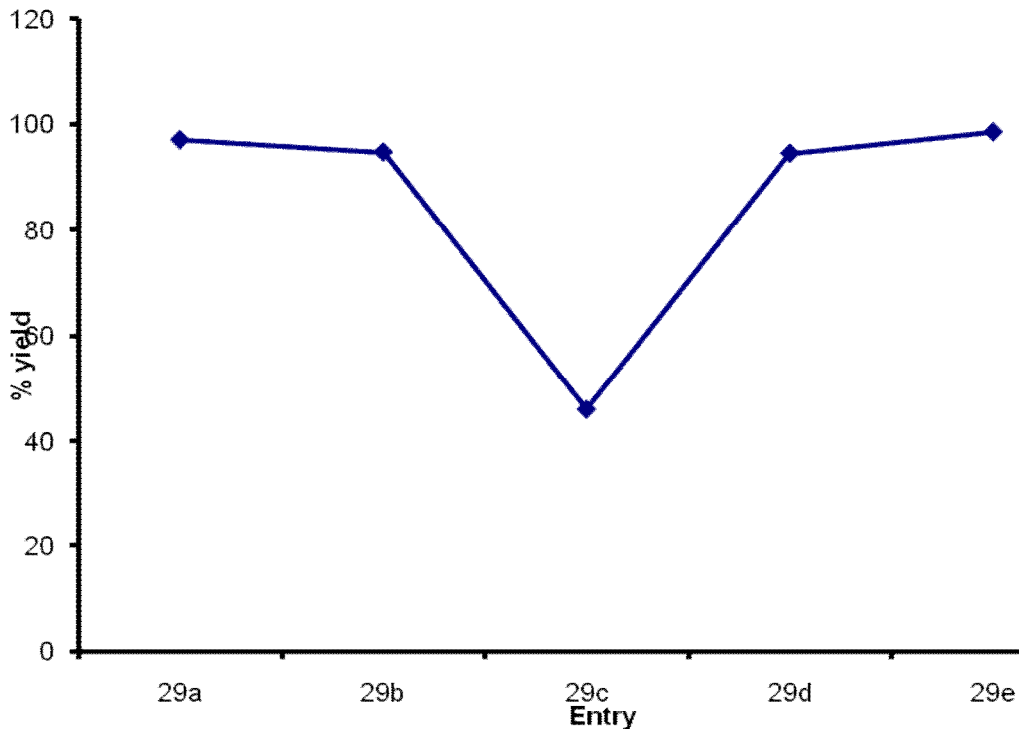


Fig 3: Graph of the % yield of compound 26 with electron withdrawing and electron donating phenols



The effect of this bulky and basic nature of the ligand (t- buxphos), is seen clearly in the entries 4 and 10. Under normal circumstances, it was expected that this will result in amination reaction because amine group in the 2- aminophenol is more electron donating than OH group and would release H- atom more easily to form the product. The result of the IR spectroscopy analysis showed no trace of amination reaction; instead, it proved the O-arylation in excellent yields. Also the base contributes to the easy formation of C-O-C bond. This is because it deprotonates OH group easily than amine group.

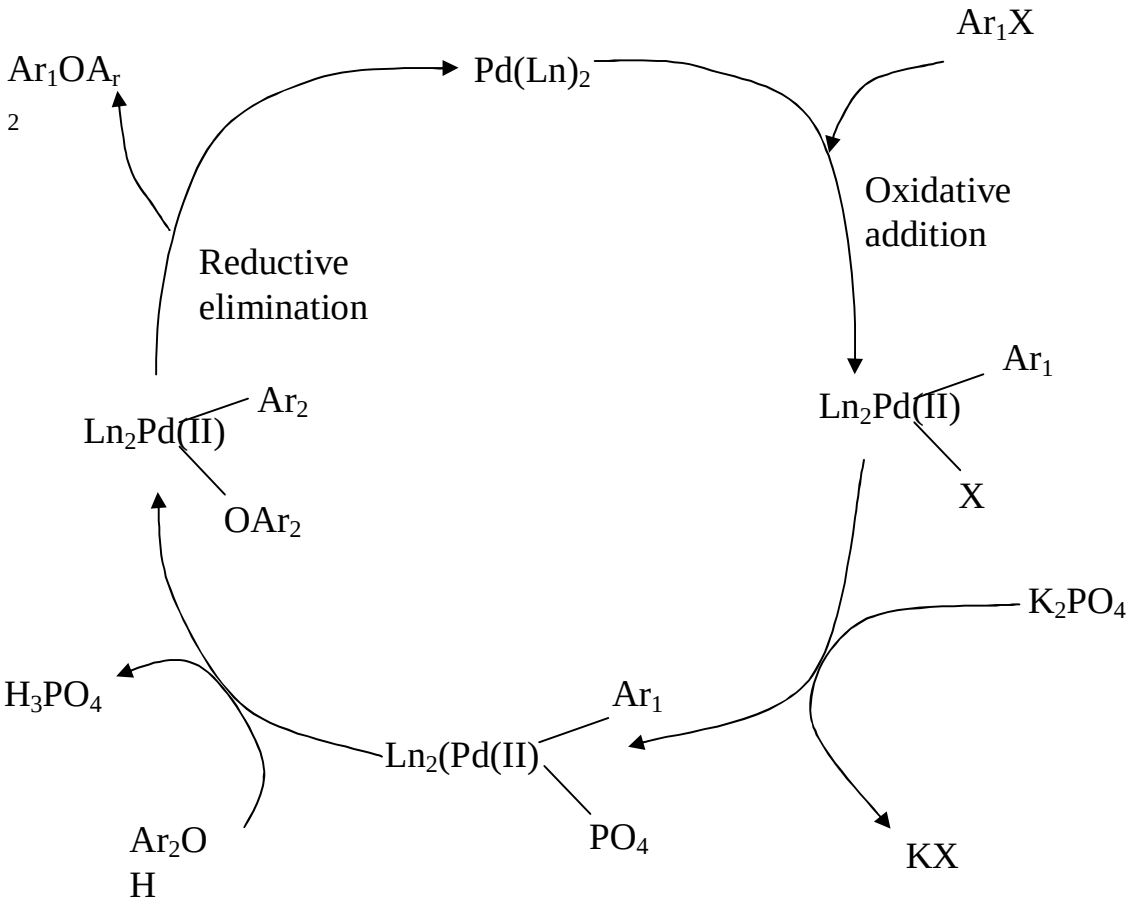
4.2 PROPOSED CATALYTIC CYCLE

Our proposed catalytic cycle for the aryl ether formation of these new phenoxazine derivatives is similar to that proposed for other palladium-catalyzed carbon-carbon and carbon-heteroatom bond forming process[117, 47, 138, 140, 141]. The catalytic cycle consists of three distinct stages:

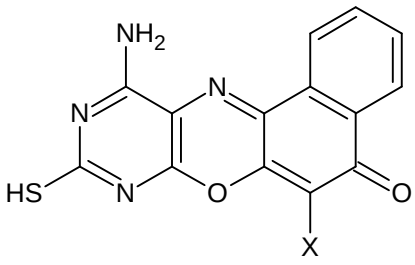
1. Oxidative addition of angular phenoxazine derivatives **26** and **25** to LnPd[0]
2. Formation of the Pd-phenoxazyloxide complex from the Pd- phenoxazine derivative adduct via transmetalation of a metal phenolate.
3. Reductive elimination of the aryl ether product (phenoxyl product), with concomitant regeneration of the active LnPd [0] species.

Bulkyl yet basic nature of the phosphine ligand is thought to be responsible for this transformation, which result in the increasing rate of reductive elimination of the aryl ether from the palladium. This is shown in the proposed catalytic cycle below.

Catalytic cycle



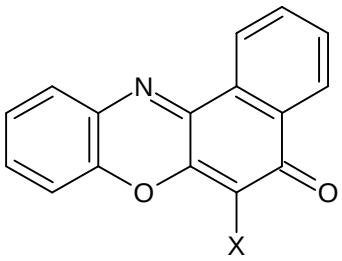
Ar$_1$X =



25

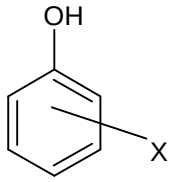
X = Cl

,



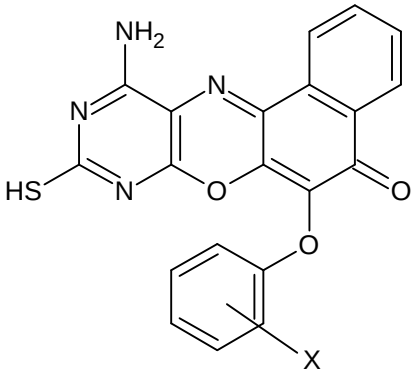
26

Ar^2OH =



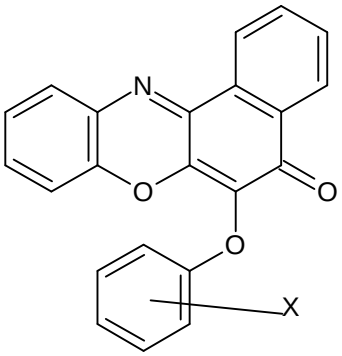
27

$Ar^1{-}O{-}Ar^2$ =



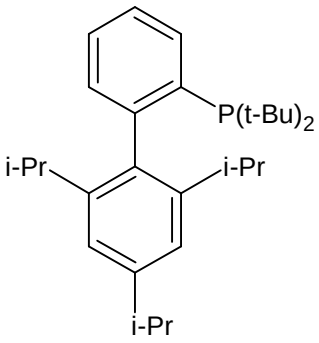
28

,



29

Ln =



133

4.3. UV/ VIS SPECTROSCOPY RESULTS OF THE SYNTHESIZED ANGULAR PHENOXAZINE DERIVATIVES

Most polynuclear aromatic and heterocyclic compounds show very characteristic intensity and band shape (fine structure) patterns, and may often be identified by comparing them with the spectra, which are available in the literature[137]. B and E bands are characteristic spectra of aromatic or heteroaromatic molecules. Substitution of the benzene ring by groups possessing non-bonding electrons (auxochromic groups ï NH_2) shifts the E and B bands to a longer wavelength frequency with intensification of the B band. A single band of low to medium intensity in which the novel angular diazaphenoxazine and phenoxazine derivatives have at wavelength less than 220nm indicates n - ů* transition of ethers and amines[137].

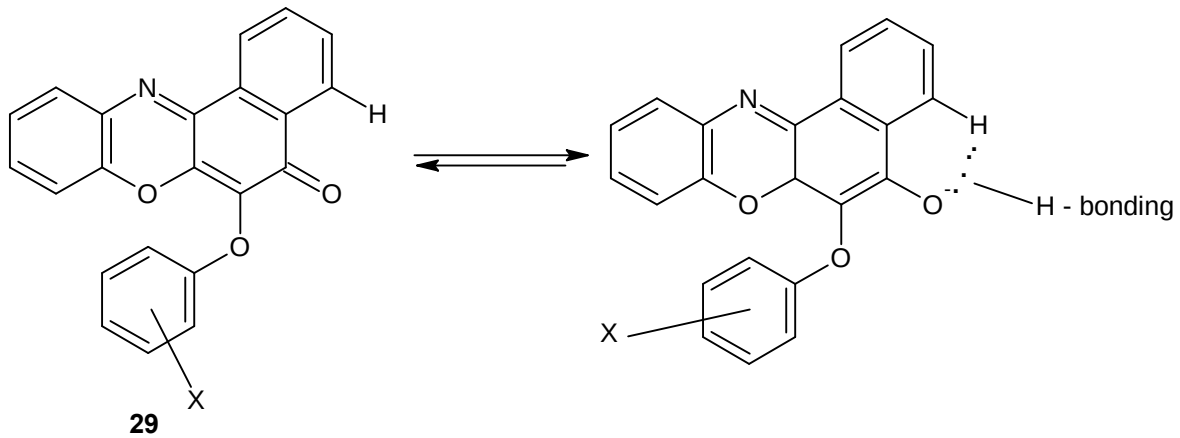
Below are the principal ɔ-$_{max}$ nm (Ɔmax) values for the bands E_2, B_2 and B_3 in various derivatives of angular diazaphenoxazines and the related carbocyclic analogue synthesized. (Table 4 below)

Table 4: Uv-Visible spectra data of synthesized compounds

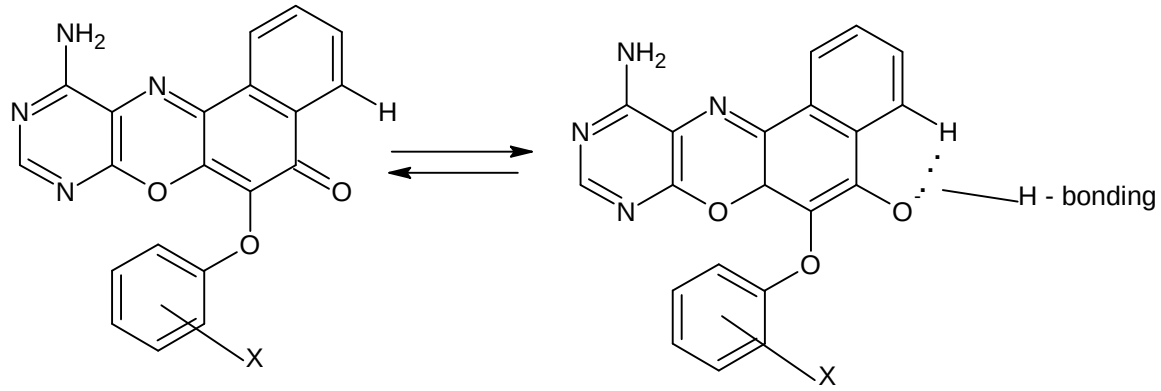
	BANDS E_2		**BANDS B_1**		**BANDS B_2**	
compounds	ɔ-max (nm)	Ɛ max	ɔ - max (nm)	Ɛmax	ɔ-max (nm)	Ɛmax
28a	224.20	5958	389.60	1563	480.00	1291
29a	269.60	670	389.90	396	450.60	348
28b	251.00	1458	481.40	265	-	-
29b	269.60	507	389.90	413	489.60	250
28c	258.00	342	382.60	158	484.00	71
29c	264.80	596	387.20	425	-	-
28d	-	-	388.00	632	-	-
29d	234.40	264	384.6	146	482.80	93
28e	263.40	1426	379.20	509	489.60	213
29e	260.00	1757	384.80	850	490.00	769
28f	216.80	7041	384.80	1292	-	-
29f	263.40	1018	384.60	270.30	-	-

4.4 CONFIRMATION OF THE STRUCTURES OF THE DIAZAPHENOXAZINE AND RELATED CARBOCYCLIC ANOLOGUE DERIVATIVES USING IR SPECTROSCOPIC DATA

Ethers are characterized by strong C-O-C stretching absorption in the range 1300-1000cm observed in other oxy-compounds such as alcohols, aldehydes, ketones, carboxylic acids etc. Therefore, the presence of an ether is confirmed only if the oxy-compound shows no absorption bond in the hydroxyl (3630 ï 3200cm^{-1}) or carboxyl (1870 ï 1650 cm^{-1}) region [137]. The system C-O-C is subjected to strong vibration coupling but in diakyl, alcyclic and diaryl ethers, one of the two resultant modes, symmetrical stretching is infrared in active and only the antisymmetric C-O-C stretching is observed near 1150 ï 1058 [137]. This particular pick was observed in IR spectra of all the phenoxazine derivatives synthesized. The peak 1631 ï 1620 or 3200 ï 2500 observed in all the spectra shows the absorption of C=O which forms O-hydroxyl aryl (intramolecular hydrogen bonding) as shown below.



29



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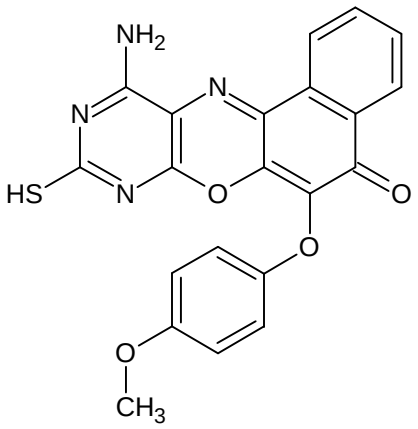
This may account for the delinquent nature of the phenoxazine derivatives synthesized. This particular peak was not observed in the intermediate. Below is the description of the IR spectroscopic data of the phenoxazine derivative synthesized (see appendix 2).



28a

3203 w, broad, conjugate chelation showing intramolecular H-bond with C=O, N-H bonding of primary amines(broad)

1634 C=O stretching forming O-hydroxyl aryl (intramolecular hydrogen bonding)

1581 Pyrimidine combination of C=C and C-H stretching

1501 C=C of the phenyl nucleus

1435 CH_3 bonding (sym) of CH_3 - O

1374 C=N stretching of the aryl primary amine. The higher value in this case of aromatic amine is due to the increase in the force constant of the C-N bond by resonance with the aromatic ring[137].

1267 C=N stretching of the aryl primary amine

1210 Aromatic ether R-O-Ar

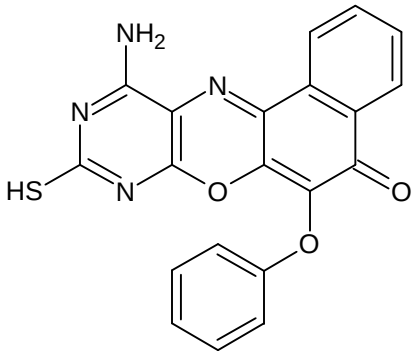
1059 C-O-C stretching of ether compounds

973 In plane bonding of the phenyl aryl (sharp absorption)

829 Benzene ring containing two adjacent H, atom, C-H stretching.

779 C-H out of plan bonding (three adjacent H ï atom) of the phenyl ring (variable intensity)

616 C-S stretching of the thiol group



28b

3183.02 Weak, broad conjugate chelation of intramolecular H-bonded with C-O, N-H bonding of primary amines(broad)

1632.05 C=O stretching forming O-hydroxyl aryl (intramolecular hydrogen bonding)

1581 Pyrimidine combination of C=C and C=N stretching

1513 Aromatic homocyclic compound

1432 (medium) aromatic multiple bond C=C stretching

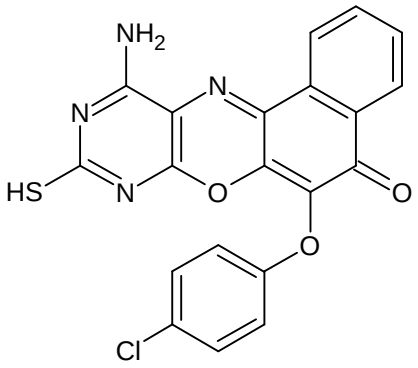
1378 Sharp, double absorption of C-N str of the aryl primary amine. The higher absorption value in this case is due to the increase in the force constant of C-N bond by resonance with the aromatic ring[137].

1060 Asymmetric C-O-C stretching of the ether compounds

976 C-H in plane binding of the phenyl ring

849 Benzene ring containing 2 adjacent H, C-H stretching

616 C-S stretching (weak absorption of the thiol group)



28c

3190 Weak, broad conjugate chelation of intramoleculr H-bonded with C=O, N-H bonding primary amins(broad).

1636 C=O str. form O-hydroxyl aryl (intramolecular hydrogen bonding)

1580 Pyrimidine combination of C=C and C=N stretching

1501 Aromatic homocyclic compound C=C

1432 Aromatic multiple bond C ï C str.

1266 Sharp double absorption of C-N stretching of the aryl primary amine

1222 Aromatic ethers R-O-R str.

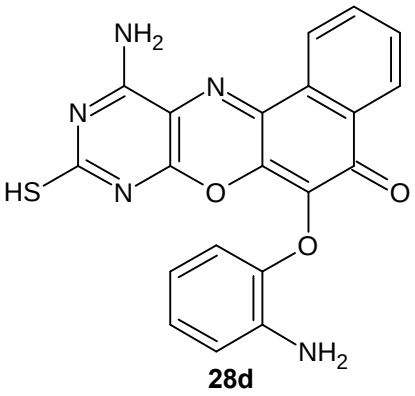
1060 Asymmetric C-O-C stretching of ether compounds

973 (Strong), C-H in plane bonding of the phenyl ring

830 Benzene ring containing two adjacent H. C-H stretching

780 C-Cl stretching of monochlorinated aromatic bond.

616 C-S stretching of the thiol groups.



28d

3205 Weak broad conjugate chelaton of intramolecular H-bonded with C=O. N-H bonding of primary amines (broad)

1631 C=O str. Forms O-hydroxyl aryl (intramolecular hydrogen bonding)

1582 Pyrimidine combination of C=C and C=N stretching

1433 Aromatic multiple bond C=C stretching

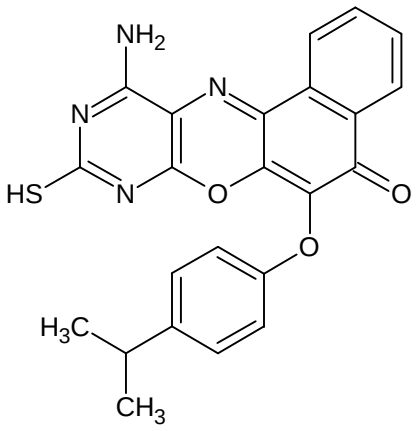
1307 C-N stretching of the aryl primary amine

1059 Asymmetric C-O-C stretching of ether compounds

979 C-H in plan bonding of the phenyl ring

847 Benzene ring containing two adjacent H, C-H stretching

616 C-S - stretching of the thiol group.



28e

3175 Weak, broad conjugated chelation of intramolecular H-bond with C=O, N-H bonding primary amines (broad)

1635 C=O Stretching forms O ï Hydroxyl (aryl intramolecular hydrogen bonding)

1564 Pyrimidine combination of C =C and C = N structure.

1513 C ï C of the phenyl nucleus

1409 C ï H bending vibration of isolated isopropyl

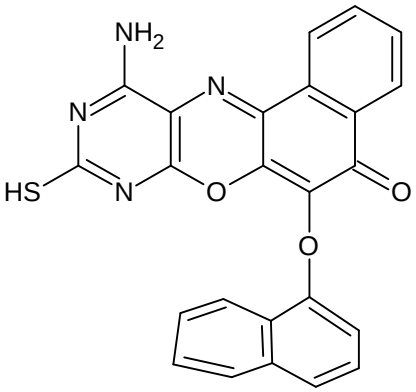
1378 C ï N stretching of the aryl primary amine

1058 Asymmetric C ï O - C stretching of ethers compounds

974 Cï H in plane bending of the phenyl ring

848 Benzene ring containing 2 adjacent H, C ï H stretching

616 C ï S stretching of the thiol group



28f

3190 Weak, broad conjugate chelation of intramolecular H-bonded with C=O, N-H bonding of primary amines (broad)

1640 C=O stretching forms O-Hydroxyl aryl (intramolecular hydrogen bonding)

1581 Pyrimidine combination of C=N and C=C stretching

1513 C ï C stretching of the phenyl nucleus

1441 Aromatic multiple bond C=C stretching

1366 C-N stretching of the aryl primary amine

1226 Aromatic ethers R-O-Ar

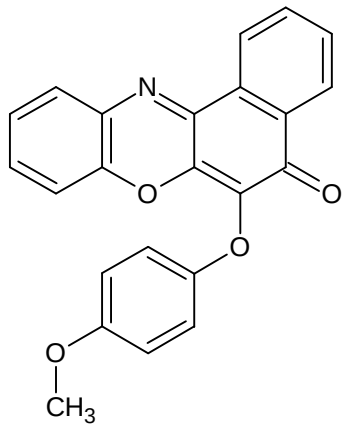
1059 Asymmetric C-O-C stretching of ether compounds

971 C-H in plane bonding of the phenyl ring

814 Benzene ring with three adjacent Hydrogen

742 C-H out of plane bonding (4-adjacent H-atoms) of the Ŭï substituted naphthalene ring

617 C-S stretching of the thiol group



29a

3163 weak, broad, conjugate chelation of intramolecular H bonded with C=O.

1626 C=O stretching forming O-hydroxyl aryl (intramolecular hydrogen bonding)

1583 Nitrogen heterocyclic combination of C=C and C-N stretching

1483 m, CH_3 bonding of R-O-CH_3

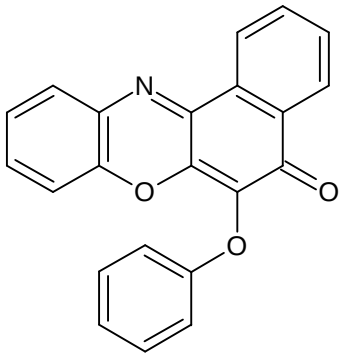
1208 Aromatic ethers R-O-Ar stretching.

1060 Asymmetric (strong) C-O-C stretching of the saturated ether, compound.

977 C-H in plan bonding of the phenyl ring (s)

844 Benzene ring containing two adjacent, H, C-H stretching.

747 Benzene ring (variable intensity) with three adjacent hydrogen



29b

3181 Weak, (broad) conjugage chelation of intramolecular H-bonded with C=O.

1632 Absorption of C=O forming O-hydroxyl aryl (intramolecular) hydrogen bonding.

1563 Nitrogen heterocycle combination of C=C and C=N

1449 (m) Aromatic multiple and C=C str.

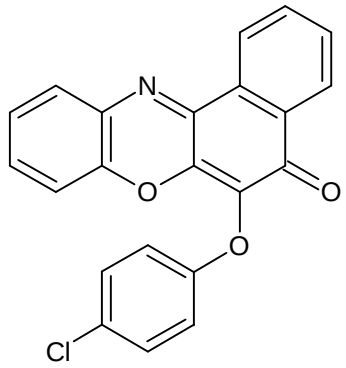
1265 Aromatic ethers R-O-Ar str.

1058 C-O-C Asymmetric stretching of the ethers compounds

979 C-H in plane bending of the phenyl ring.

847 Benzene ring containing two adjacent H-atom, C-H stretching

743 Benzene ring (variable intensity) with three adjacent hydrogen C-H out of plane bonding.



29c

3172 Weak, broad conjugate chelation of intramolecular H-bonded with C=O

1631 Absorption of C=O forming O-hydroxyl aryl (intramolecular) hydrogen bonding.

1563 Nitrogen heterocycles combination of C=C and C-N stretching

1410 Aromatic multiple bond C=C stretching.

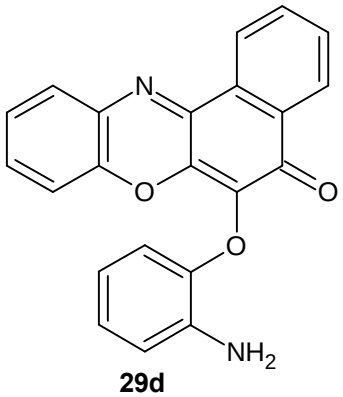
1263 Aromatic ethers R-O-Ar

1059 Asymmetric C-O-C stretching of ether compounds

976 C-H in plane bonding of the phenyl ring

848 Benzene ring containing two adjacent H, C-H stretching

740 C-Cl stretching of monochlorinated aromatic compound.



29d

3197 Weak, broad conjugate chelaton of intramolecular H-bonded with C=O, N-H bonding of primary amines

1632 C=O stretching, forms O-hydroxyl aryl (intramolecular hydrogen bonding)

1561 Nitrogen heterocycles combination of C=C and C=N stretching

1459 Aromatic multiple bond C=C stretching

1378 C-N Stretching of the aryl primary amine

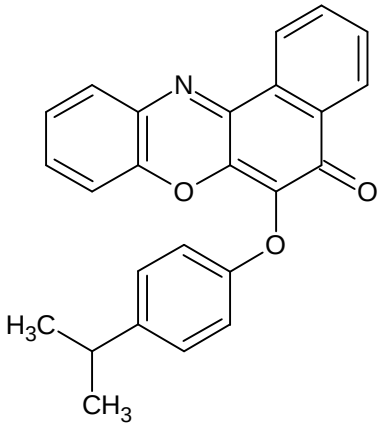
1269 Aromatic ethers R-O-Ar stretching

1065 Asymmetric C-O-C stretching of ether compounds

983 C-H in plane blending of the phenyl ring

848 Benzene ring containing two adjacent hydrogen, H and C-H stretching

746 Benzene ring with three adjacent hydrogen



29e

3194 Weak, broad conjugate chelation of intramolecular H-bonded with C=O

1640.98 C=O stretching forms O-hydroxyl aryl (intramolecular hydrogen bonding)

1563 Nitrogen heterocycles combination of C=C and C=N stretching

1483 C-C stretching of the phenyl nucleus

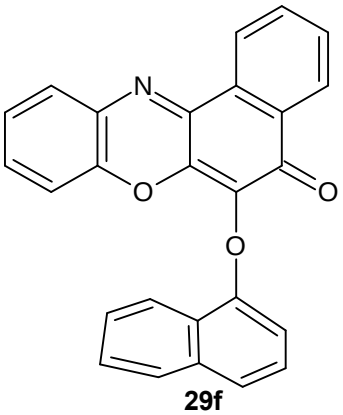
1410 C-H bonding vibration of the isolated ï Cï H (isopropyl)

1266 Aromatic ethers R-O-Ar stretching

1059 Asymmetric C-O-C stretching of an ether compound

979 C-H in plane bonding in the phenyl ring

846 Benzene ring containing 2 adjacent H, C-H stretching



29f

3171 Weak, broad conjugate chelation of intramolecular H-bonded with C=O

1626 C=O stretching forms O-Hydroxyl aryl (intramolecular hydrogen bonding)

1585 Nitrogen heterocycles combination of C=C and C=N stretching

1059 Asymmetric C-O-C stretching of ether compounds

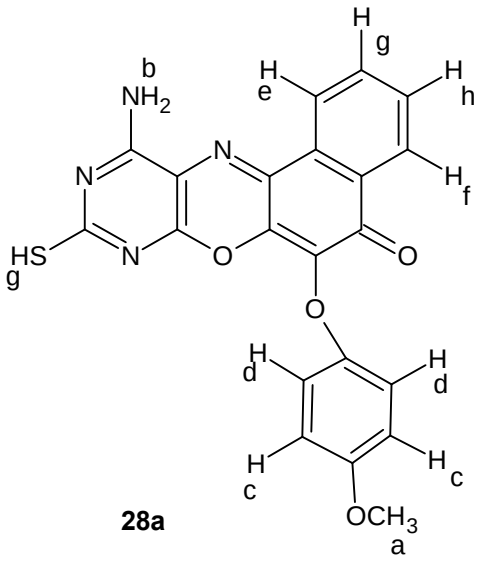
973 C-H in plane bonding of the phenyl ring

850 Benzene ring containing two adjacent H, atom C-H stretching

746 C-H out of plane bonding (4-adjacent H-atoms) of the Ŭ-substituted naphthalene ring

677 m, C-C out of plane bonding (wagging) ring puckering three adjacent H-atom of benzene ring (or 1,3-disubstituted benzene ring)

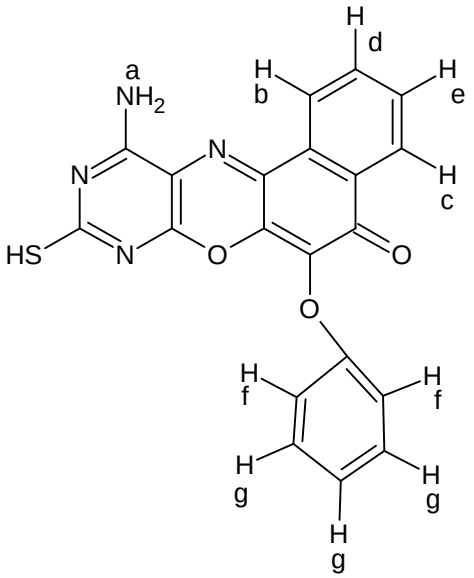
4.5. NMR INTERPRETATION OF ANGULAR DIAZAPHENOXZINES AND RELATED CARBOCYCLIC ANALOGUES SYNTHESIZED.



28a

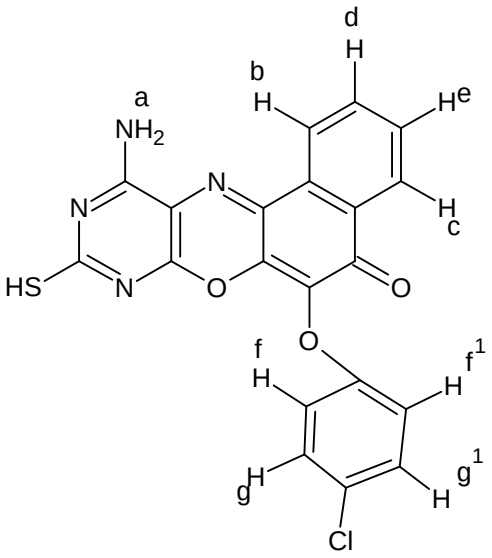
1. A singlet at ŭ 1.73 equivalent to 1H, is due to SH proton ógô.
2. A peak at ŭ 3.65 equivalent to 3H represents the Methyl group óaô. It is shifted down field because it is bonded to oxygen, an electronegative element.
3. A singlet at ŭ 5.47 equivalent to 2H, is due to two protons óbô.
4. A doublet at ŭ 7.76-7.77 equivalent to 2H, due to two protonsódô othor to the ether group bonded to the fused aromatic ring. This is because methyl group has more shielding effect at ortho and para position as compared to that at meta positions.
5. A doublet at ŭ 7.84 ï 7.85, equivalent to 2H is due to two protons ócô meta to the ether group bonded to the fused aromatic ring

6. Peak at ŭ 8.98, ŭ 8.18, ŭ 7.65 and ŭ 7.51 equivalent to 1H exhibits respectively the aromatic protons e, f, g and h due to chemical shift on fused aromatic ring.



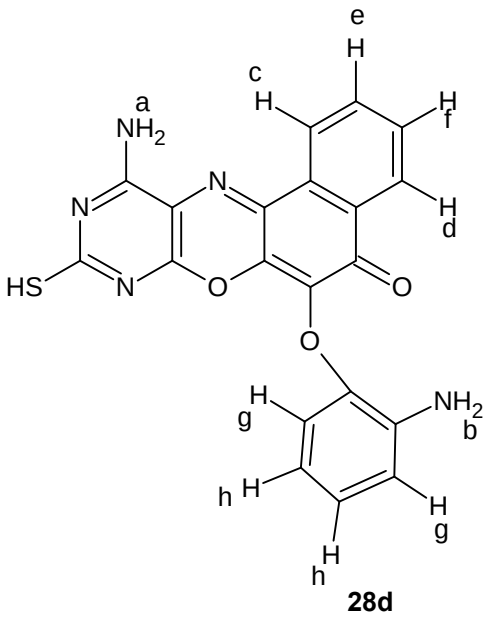
28b

1. A singlet at ŭ 1.64 equivalent to 1H, is due to SH proton.
2. A singlet at ŭ 5.99 is due to NH_2 proton óaô.
3. Peaks at ŭ 8.52, ŭ 8.16, ŭ 7.94 and ŭ 6.92 equivalent to 1H exhibits aromatic protons b, c, d and e respectively, due to chemical shift of proton on fused aromatic ring.
4. A doublet at ŭ 7.78-7.77 equivalent to 1H, is due to two protons at ófô attached to the aromatic ether.
5. A triplet at ŭ 7.65-7.67 equivalent to 3H represents the three aromatic protons ócô attached to the aromatic ether.



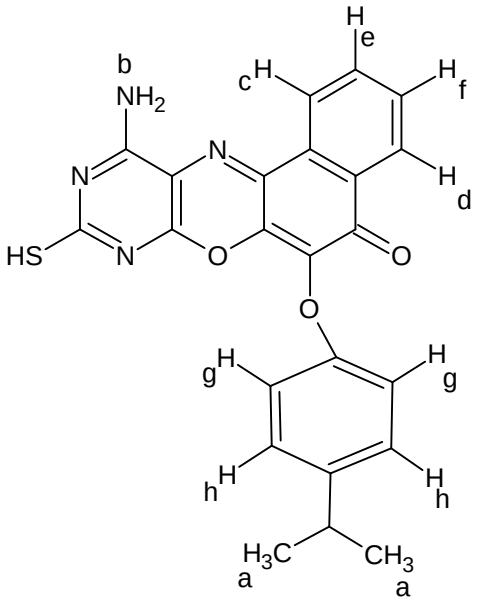
28c

1. A singlet at ŭ 5.47 is due to NH_2 protons óNH_2ô.
2. Peaks at ŭ 7.86, ŭ 7.85 , ŭ 7.77, and ŭ 7.66 equivalent to 1H exhibit the aromatic protons b, c, d and e respectively, due to chemical shift of protons on fused aromatic ring.
3. A peak at ŭ 1.66 equivalent to 1H is due to SH proton.
4. The peaks at ŭ 6.77-6.82 and ŭ 7.16-7.20 is due to protons on para-disubstituted benzene ring. Since this has a plane of symmetry (a plane passing through the ether and chloro group), one would expect the proton H_F and H_F^I and also Hg andHg^1 to have the same chemical shift (chemically equivalent protons). Thus, the proton H_f is split by the proton Hg into a doublet. Magnetically, however they are not equivalent because the coupling from H_f to H_g is not the same as coupling from H_f^1 and H_g^1. What this means in practical terms is that the doublet we observe will have a slight distortions at their bases. An expansion of the ppm scale exhibits that the pattern resembles quadruplet. This pattern is an f f^1 and g g^1.



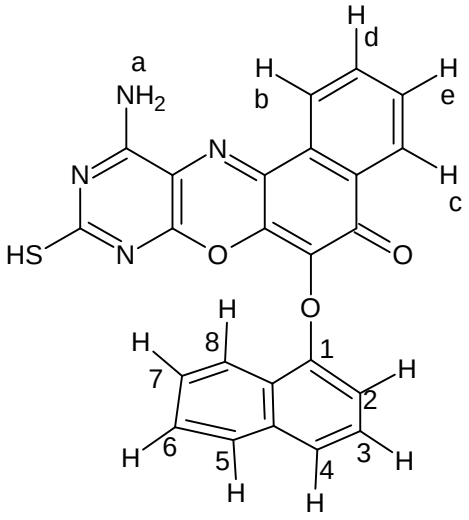
28d

1. A singlet peak at ŭ 1.67 equivalent to 1H is due to SH proton.
2. A singlet at ŭ 5.99 and ŭ 5.46 is due to NH_2 protons óaô and ôbô respectively.
3. The peaks at ŭ 8.96, ŭ 8.17, ŭ 8.06 and ŭ 7.25 equivalent to 1H exhibit the four aromatic protons c, d, e and f respectively due to the chemical shift of the protons on fused aromatic ring.
4. A doublet at ŭ 7.71- ŭ 7.72 equivalent to 1H, is due to two protons ódô on the aromatic rings
5. A triplet at ŭ 7.402 equivalents to 1H is due to two protons ôhô on the aromatic ring.



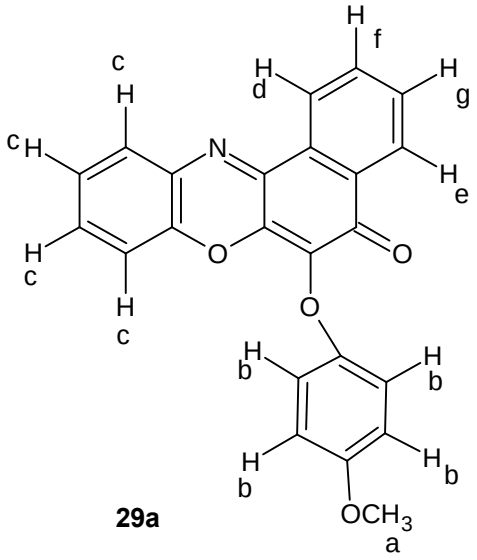
28e

1. The quadruplet at ŭ 3.64-3.71 equivalent to 3H is due to the protons of the two methyl group óaô caused by the omega splitting.
2. A singlet at ŭ 5.54 equivalents to 2H, is due to NH_2 proton óbô.
3. Peaks at ŭ 8.996, ŭ 8.12, ŭ 7.66 and ŭ 7.52 equivalent to 1H exhibit respectively the four aromatic proton c, d, e and f due to chemical shift of protons on fused aromatic ring.
4. A doublet at ŭ 7.78-7.77 equivalent to 1H is due to two protons óhô on the aromatic ring.
5. A singlet at 2.78 ŭ equivalent to 1H, is due to SH proton.



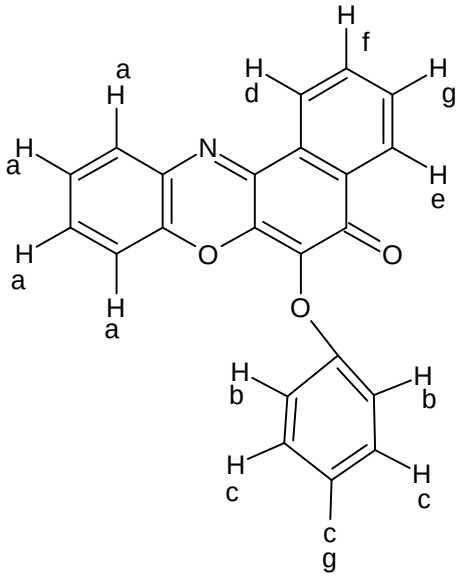
28f

1. A singlet at ŭ 5.47 equivalent to 2H, is due to NH_2 proton óaô.
2. Peaks at ŭ 8.47, ŭ 8.16, ŭ 8.00 and ŭ 7.86 equivalent to 1H exhibit the four aromatic protons c, d, e and f respectively due to chemical shift on fused aromatic ring.
3. A doublet of doublet at ŭ 7.50 ï ŭ 7.65 exhibits the proton C_2-H which is split by C_3 ï H proton into a quartet by C_4 ï H protons
4. A multiplet at ŭ 6.67 ï 7.12, equivalent to 4H, is due to the aromatic protons C_3-H, C_4-H, C_6-H and C_7-H.
5. A doublet at ŭ 7.74-7.86 represents the peri-proton C_5-H.
6. A doublet at ŭ 8,78 ï 8.79 exhibits the peri ï proton C_8-H.
7. A singlet at ŭ 2.30 equivalents to 1H is due to SH proton.



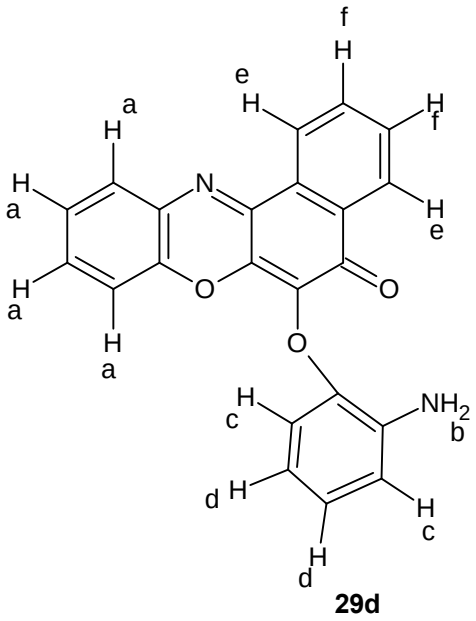
29a

1. A singlet at ŭ 2.56 equivalent to 3H represents the methoxy proton óaô.
2. A multiplet at ŭ 7.40 ï 7.44 equivalents to 4H, is due to four protons ôbô.
3. A multiplet at ŭ 7.08 ï 7.29 equivalents to 4H, is due to four protons ôCô.
4. Peaks at ŭ 7.50, ŭ 6.99, ŭ 6.79 and ŭ 6.47 equivalent to 4H exhibit respectively the four aromatic protons d, e, f, g due to chemical shift of proton on fused aromatic ring.



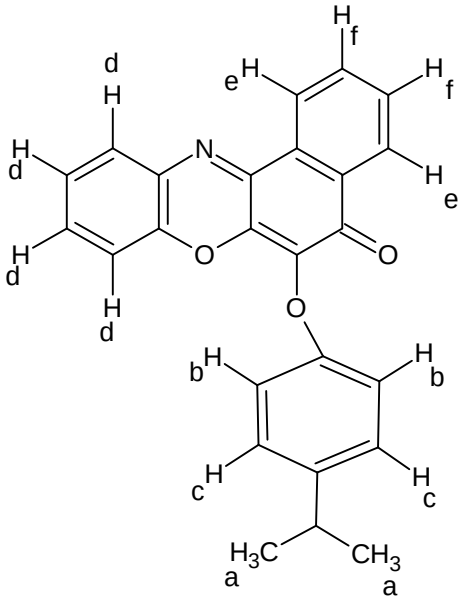
29b

1. A multiplet at ŭ 6.38 ï 6.56 equivalents to 4H, is due to four protons óaô.
2. A doublet at ŭ 7.97 ï 7.98 equivalents to two protons at óbô.
3. A triplet at ŭ 7.23 ï 7.25 equivalents to 1H, is due to three protons at ócô.
4. A peak at ŭ 8.55, ŭ 8.53 , ŭ 7.53 and ŭ 7.51 equivalent to 4H exhibit respectively the four aromatic protons d, e, f and g due to chemical shift of proton on fused aromatic ring.



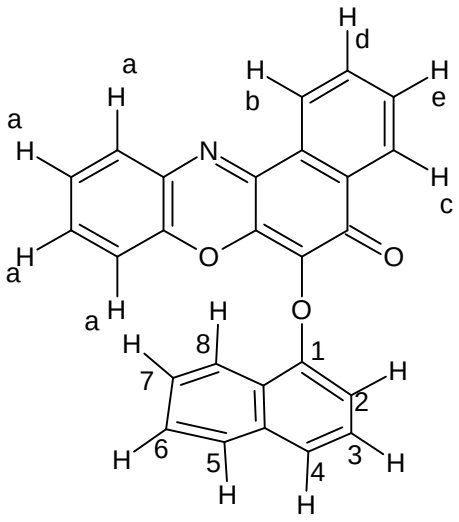
29d

1. A singlet at ŭ 6.92 equivalents to 1H, is due to NH_2 proton b.
2. A multiplet at ŭ 7.45 ï 7.50 equivalent to 4H, is due to four protons a.
3. A doublet at ŭ 6.77 ï 6.78 equivalents to 1H, is due to proton c.
4. A triplet at ŭ 6.77 ï 6.78 equivalents to 1H, is due to proton d.
5. A doublet at ŭ 7.17 ï 7.18 equivalents to 1H is due to proton e.
6. A triplet at ŭ 7.24 ï 7.26 equivalents to 1H, is due to proton f.



29e

1. A singlet at ŭ 3.54 equivalents to 3H, is due to three protons óaô of the methyl group.
2. A doublet at ŭ 7.89 ï 7.91 equivalents to 1H, is due to two protons b.
3. A doublet at ŭ 7.78 ï 7.79 equivalent to 1H is due to two protons c
4. A multiplet at ŭ 6.65 ï 6.68 equivalent to 4H,is due to four protons d
5. A doublet at ŭ 7.47 ï 7.48 equivalents to 1H, is due to proton e.
6. A triplet at ŭ 6.49 ï 6.51 equivalents to 1H, is due to protons f.



29f

1. A doublet at ŭ 6.37 ï 6.39, exhibits the proton C_2-H.
2. A multiplet central at ŭ 7.66 ï 7.72 equivalent to 4H,is due to 4H,is due to aromatic protons C_3-H,C_4-H,C_6-H and C_7-H.
3. A doublet at ŭ 7.24 ï 7.25 represent the peri ï proton C_5-H.
4. A doublet at ŭ 7.53 ï 7.55 exhibits the peri ï proton C_8-H.
5. A multiplet at ŭ 7.66 ï 7.71 equivalent to 4H¸ is due to proton a.
6. The peak at ŭ 8.27, ŭ 7.39, ŭ 7.34 and ŭ 7.18 equivalent to 4H, exhibit respectively the aromatic proton b, c,d and e , due to chemical shift on fused aromatic ring.

4.6 BIOLOGICAL ACTIVITY OF THE NOVEL ANGULAR DIAZAPHENOXAZINE AND BENZOPHENOXAZINE DERIVATIVES.

The novel angular diazaphenoxazine and related carbocyclic analogue derivatives were screened for their antibacterial and antifungal activities against some pathogenic bacteria via *Bacillus subtilis, staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella;* and fungi *Candida albicans* and *Aspergillus nigger* using agar diffusion method (table 5 and 6). The antibacterial activity investigation of the new derivatives when compared with the intermediates **25** and **26** showed that the coupling improved the antibacterial activity. This is because intermediate **25** and **26** was inactive against all the tested bacterial but most of the new derivatives (see tables 5) were very active to the extent that the MIC result shows that some of the novel angular phenoxazines were more active than the standard antibacterial agent ciprofloxacin (table 7, compound **29c** and **29e**). The antifungal activity investigation showed that some of the new derivatives (see table 5) were active except in *Aspergillus nigger* in which all the novel compounds were inactive. The novel compounds were not as active as the standard ketoconazole. Compounds **28a**, **28e** and **29f** were inactive in all cases but they can be used as dyes since they absorb in UV- visible region. These inactive compounds can also open up a new area of research in other to make them active.

Table 5: The inhibition zone diameter of the novel angular diazaphenoxazine derivatives and the related carbocyclic analogues (mm)

Compounds	B.S	S.a	E.c	Ps.a	Sal	C.alb	A.m
28a	0	0	0	0	0	0	0
29a	9	12	7	0	0	0	0
28b	0	0	0	0	0	14	0
29b	0	17	0	0	0	12	0
28c	0	19	9	7	0	0	0
29c	0	20	9	7	0	0	0
28d	0	0	0	4	0	0	0
29d	0	14	0	5	0	14	0
28e	0	0	0	0	0	0	0
29e	0	14	9	8	0	0	0
28f	0	6	0	0	0	0	0
29f	0	0	0	0	0	0	0
25 **26**	0 0	0 0	0 0	0 0	0 0	32 28	29 19
Ciprofloxazine	22	20	25	18	20	-	-
Ketoconazole	-	-	-	-	-	30	25

Key

Test Organisms

B.s	*Bacillus subtilis*
S.a	*Staphylococcus aureus*
E.c	*Eschericha coli*
Ps.a	*Pseudomorias aeruginosa*
Sal	*Salmonella*
C.alb	*Candida albicans*
A.n	*Aspergillus nigger*

ACTIVITY RANGE

High	12 ï 32
Moderate	5 ï 9.
Low	4
No growth	0

Table 6: The result of various inhibition zone diameter (IZD) concentrations of the new angular phenoxazine derivatives and some standard drugs ((20 mg/ml)

COMPOUNDS	**C.alb**						**Sa**						
	1	2	3	4	5	6		1	2	3	5	5	6
29a								12	9	6	+	+	+
28b	14	11	10	+	+	+							
29b	17	14	9	+	+	+							
28c								19	16	12	8	+	+
29c								20	16	12	9	+	+
29d	14	11	6	+	+	+							
29e								14	11	7	4	+	+
25	32	27	20	16	12	+							
26	28	21	18	13	10	+							
Ciprofloxazine	-	-	-	-	-	-		31	25	20	14	+	+
Ketoconazole	43	32	21	16	10	+		-	-	-	-	-	-

Table 7: Minimum inhibitory concentration (MIC) mg/ml of the novel phenoxazine derivatives and some standard drugs**.**

COMPOUNDS/ DRUGS	**Sa**	**C.alb**
29a	2.14	-
28b	-	3.24
29b		17 78
28c	1.58	-
29c	1.03	
29d	-	1.41
29e	1.03	-
25	-	1.20
26	-	1.02
Ciprofloxazine	1.12	-
Ketoconazole	-	1.26

- = not dictated

Conclusion

This study has shown that palladium based electron rich, bulky aryl diarylphosphine ligand in which the alkyl group is tert-butyl (t-buxphos), offers excellent routes to the synthesis of O-arylated angular diazabenzo[a]phenoxazine and related carbocycle analogue. These base (K_3PO_4) mediated coupling reactions proceeded excellently in toluene in excellent yields and require short reaction time.

Due to extended conjugation on these new water-soluble diazaphenoxazines and related carbocycle analogue scaffolds, they are intensely coloured, their colours are black and dark brown respectively. The compounds could likely meet the requirements to be considered as dyes since they show absorption maxima in the visible region. Besides, their biological activity proves them to be of pharmaceutical interest as they effectively controlled the growth of *Escherichia coli, staphylococcus aureus, and pseudomonas aeruginosa* and *Candida albicans*

This study has thus opened up a new and facile route for possible synthesis of aryl ether based diazaphenoxazines and benzophenoxazine nuclei using Buchwald catalyst (palladium-based t-buxphos).

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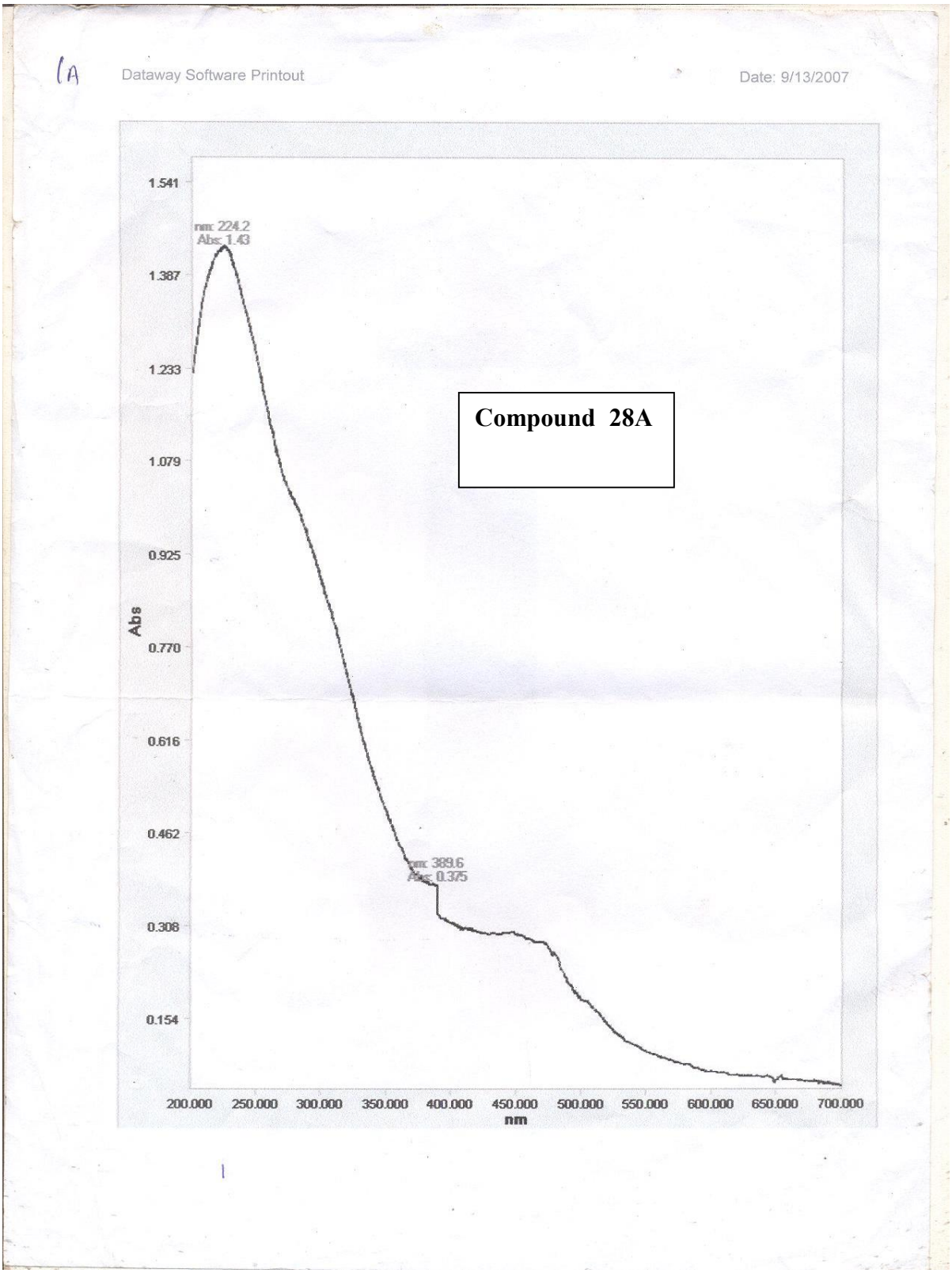
APPENDIX 1 (UV SPECTRA OF THE NEW DERIVATIVES)



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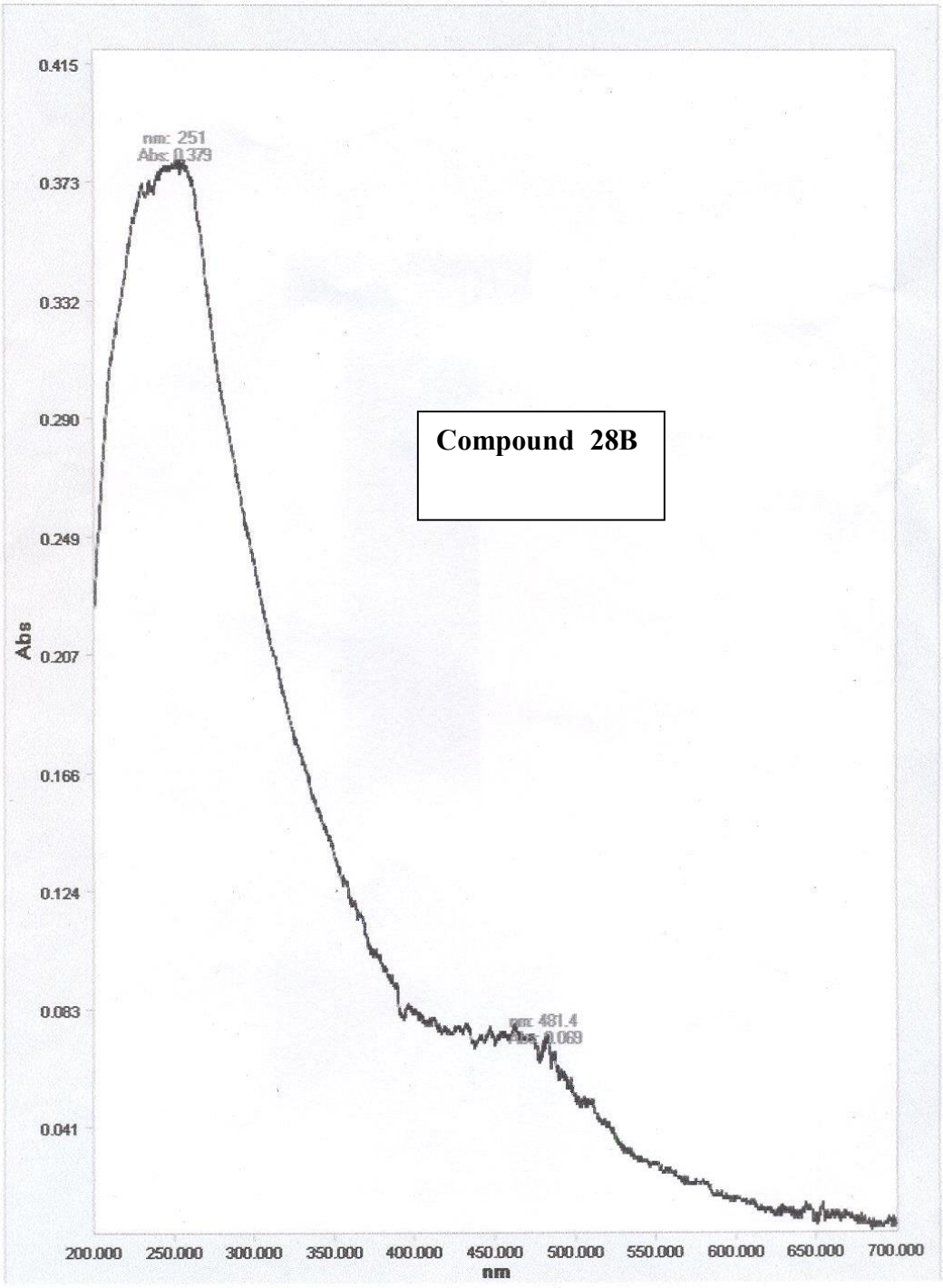

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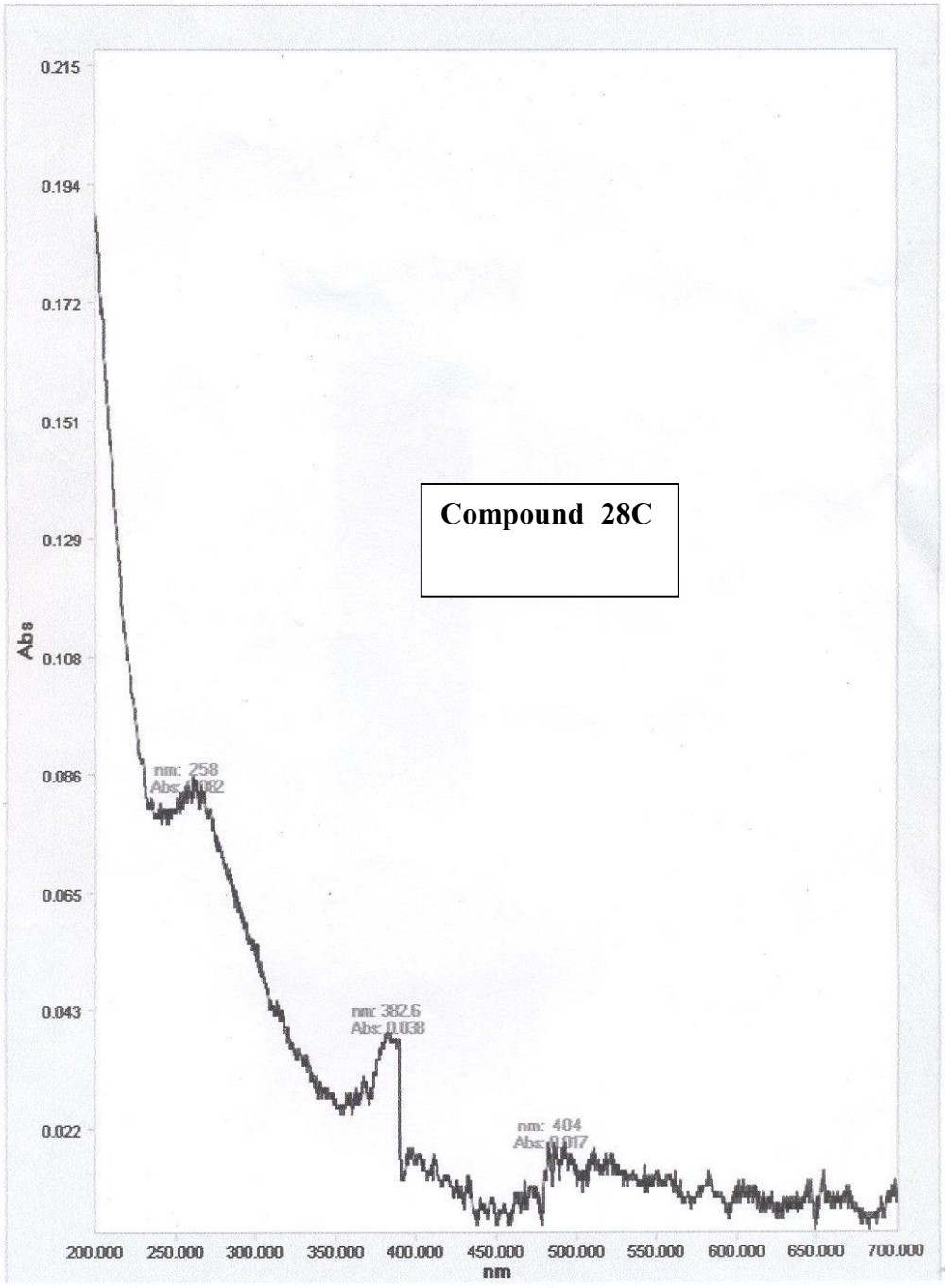

Compound 28C

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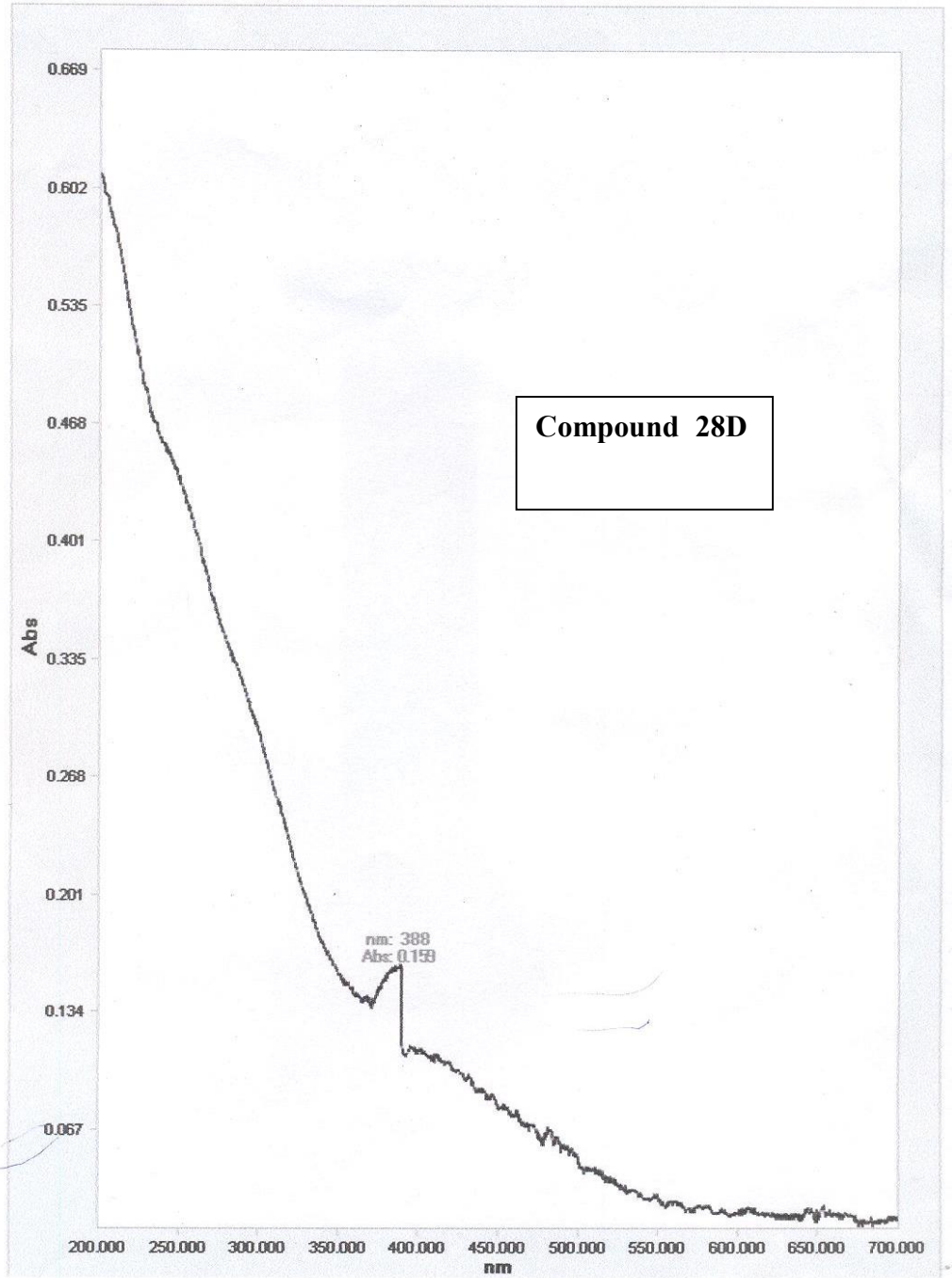

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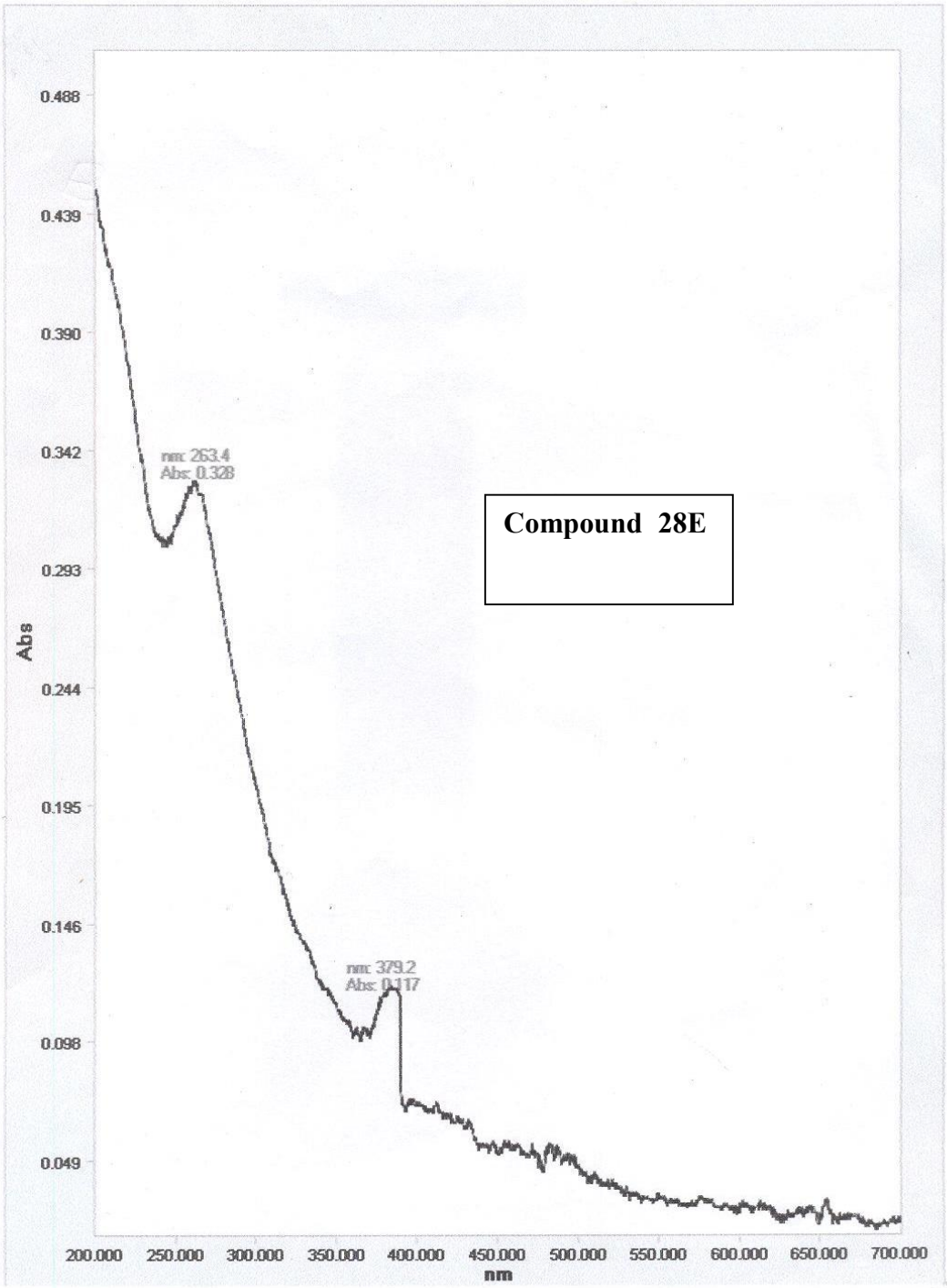

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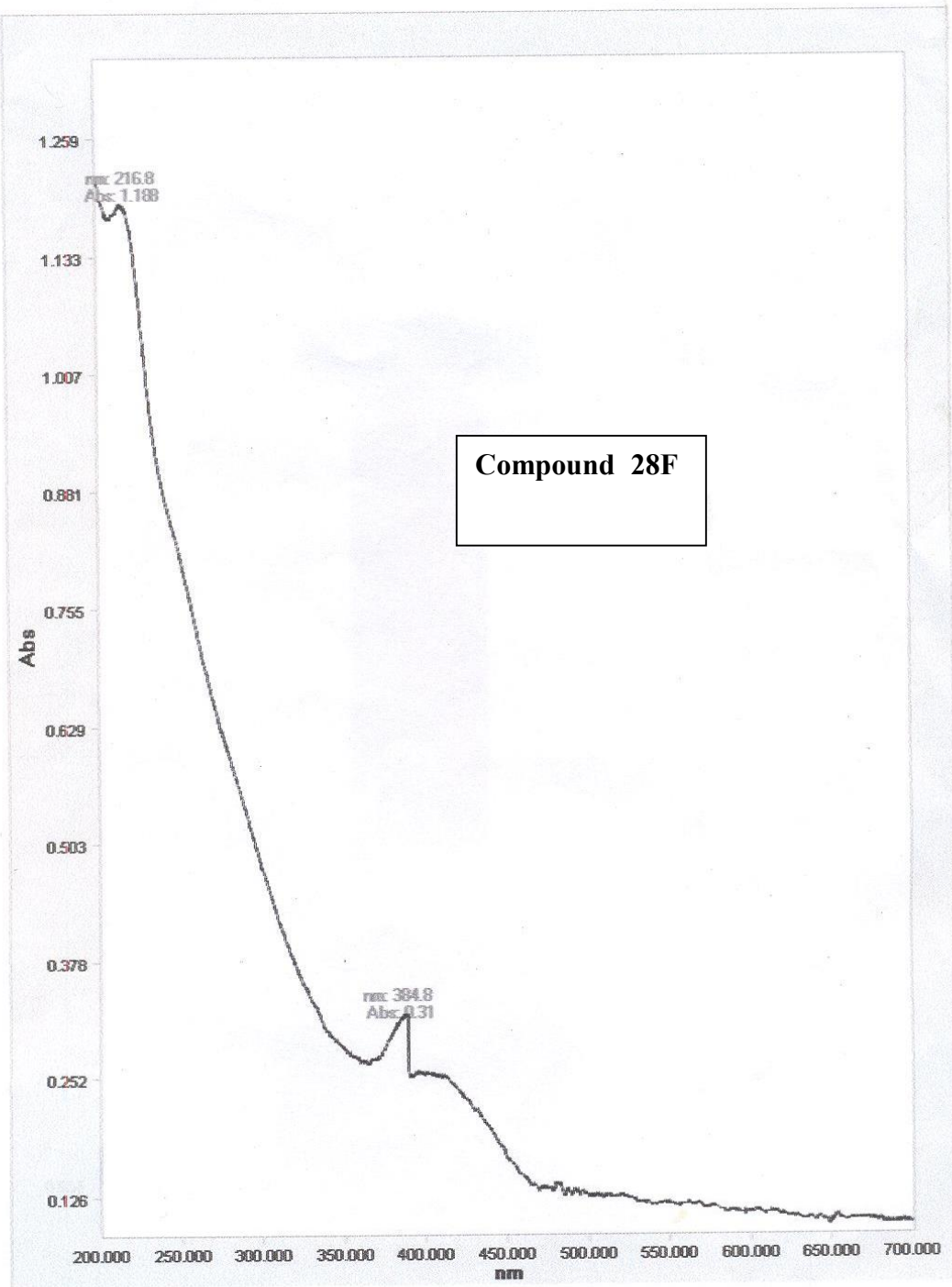

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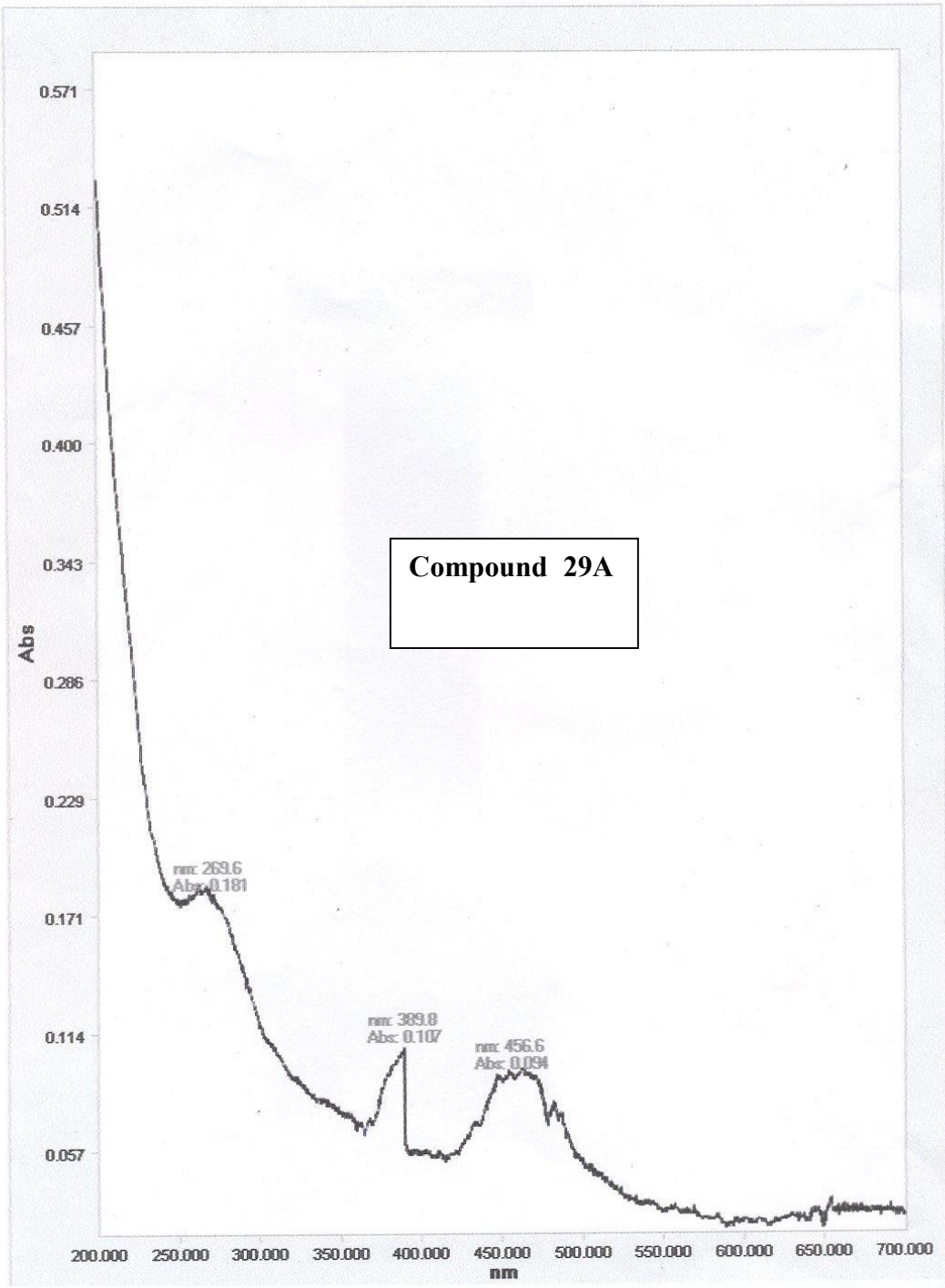

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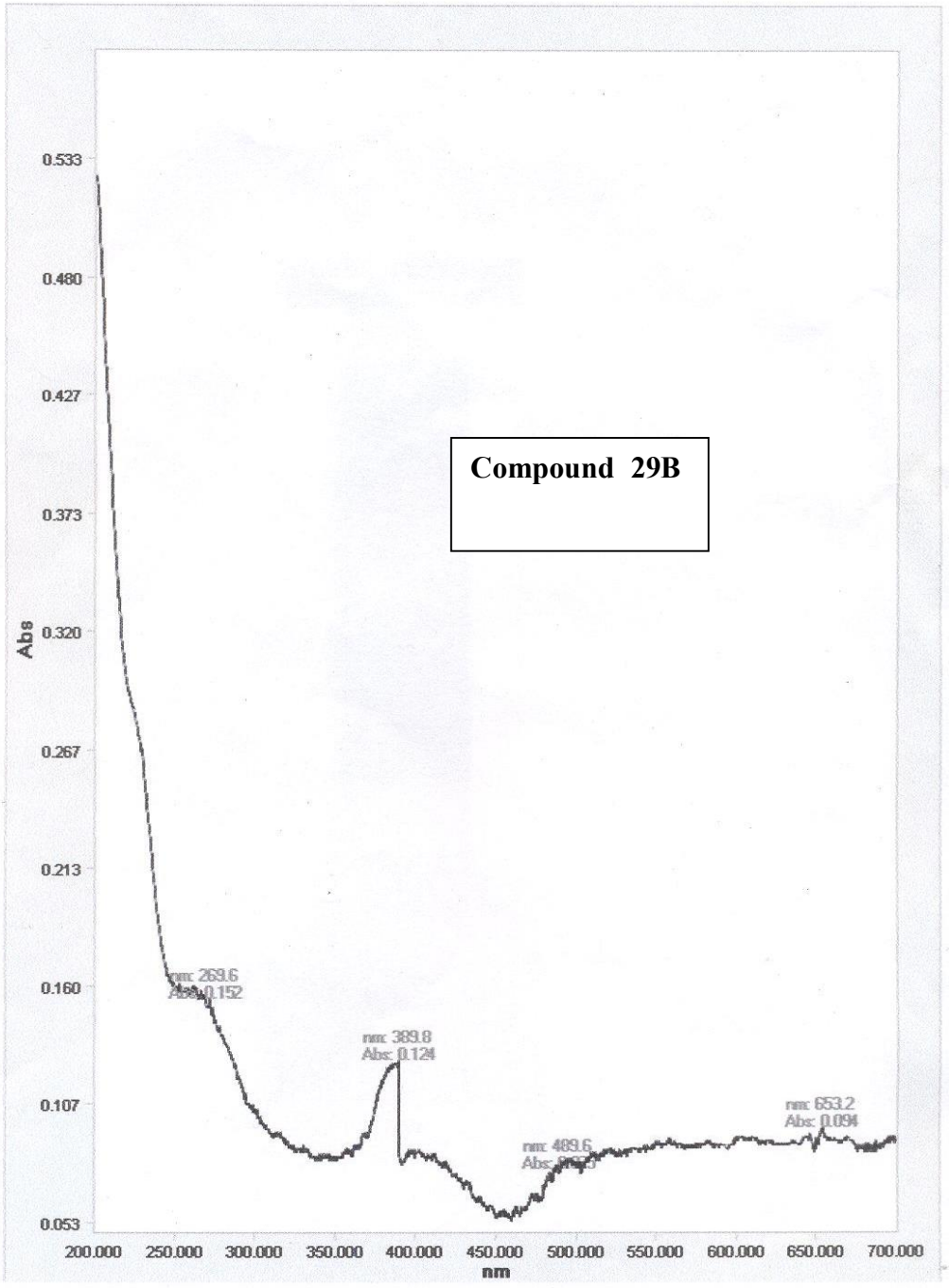

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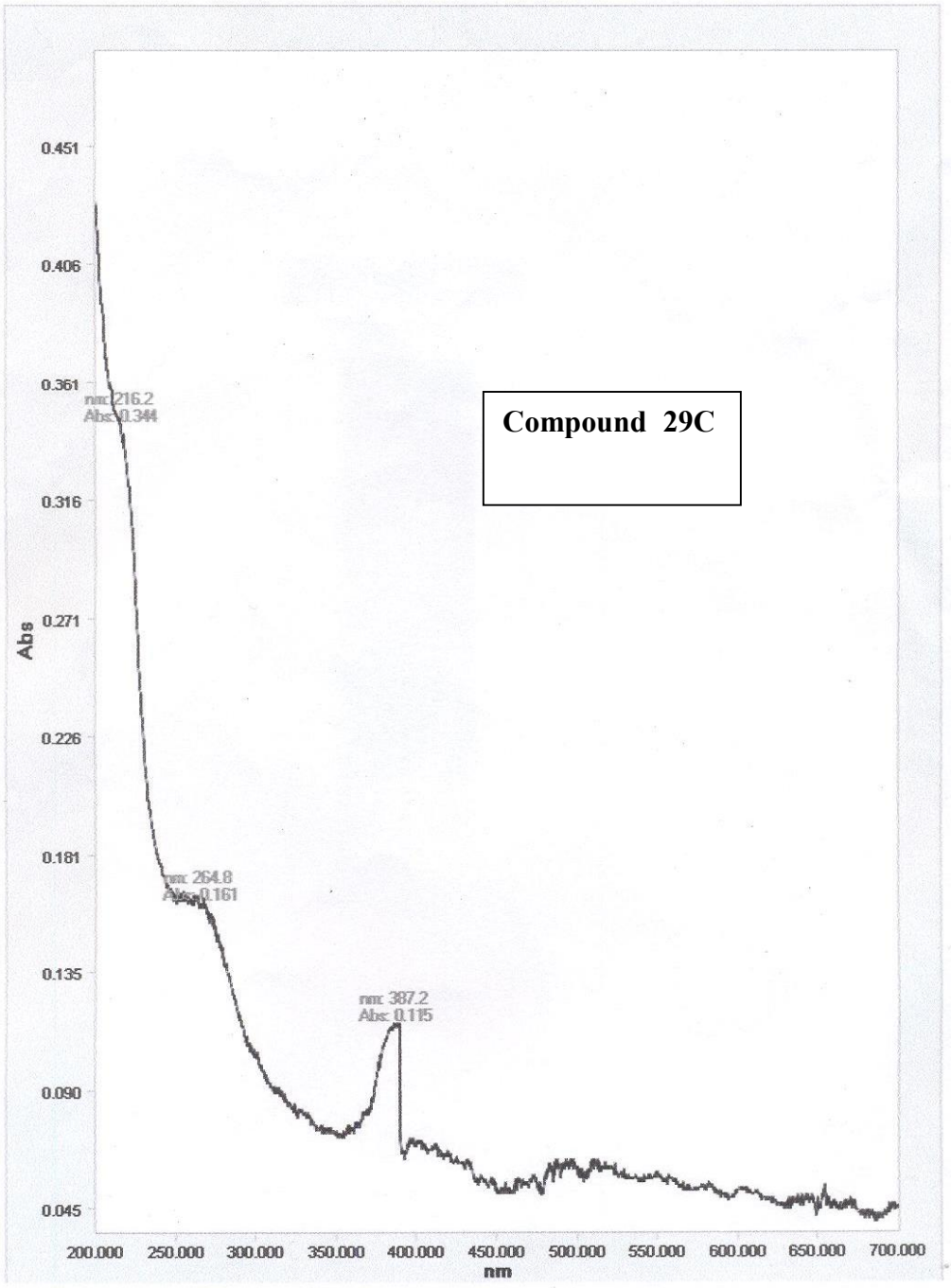

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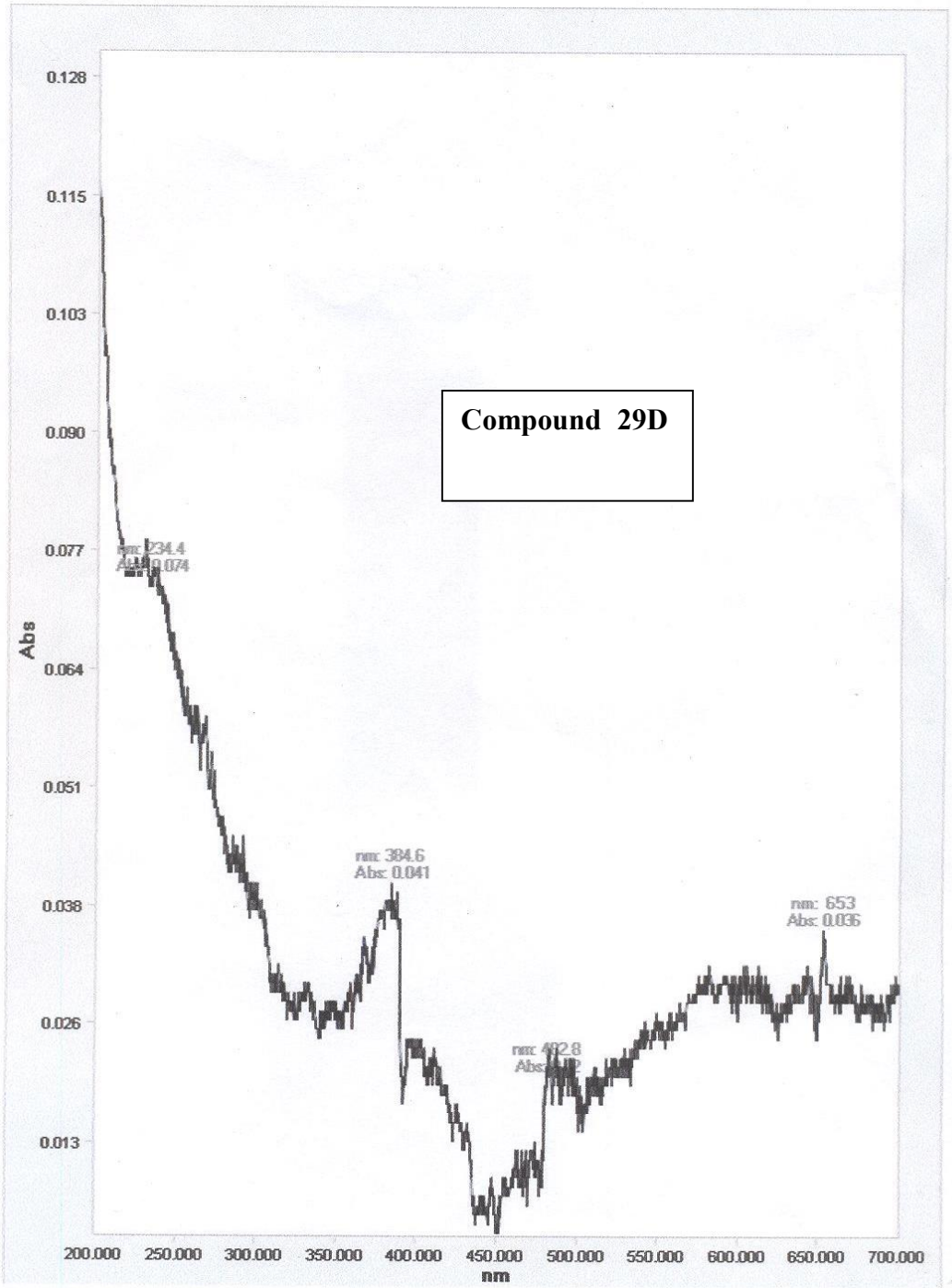

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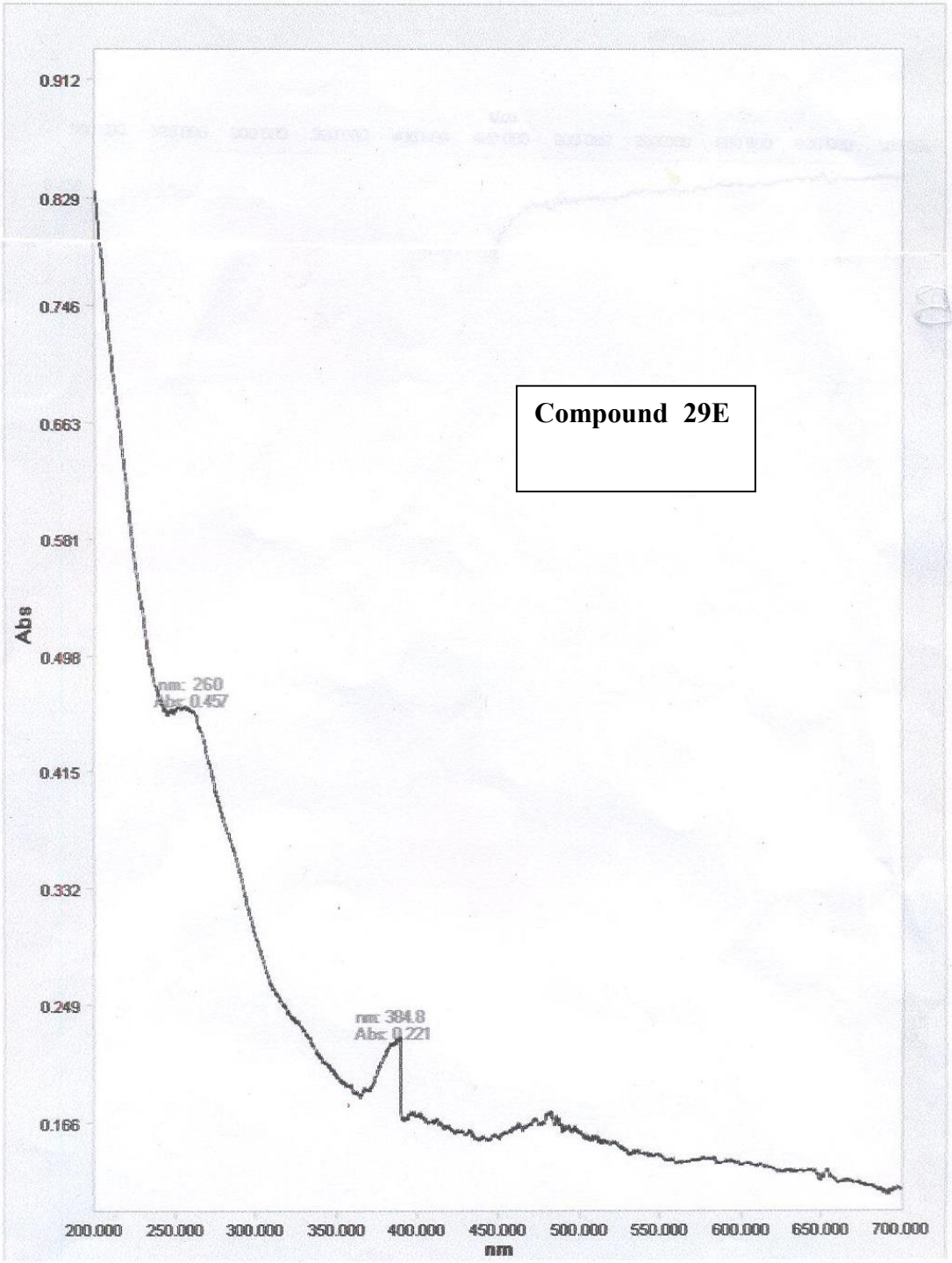

Compound 29E

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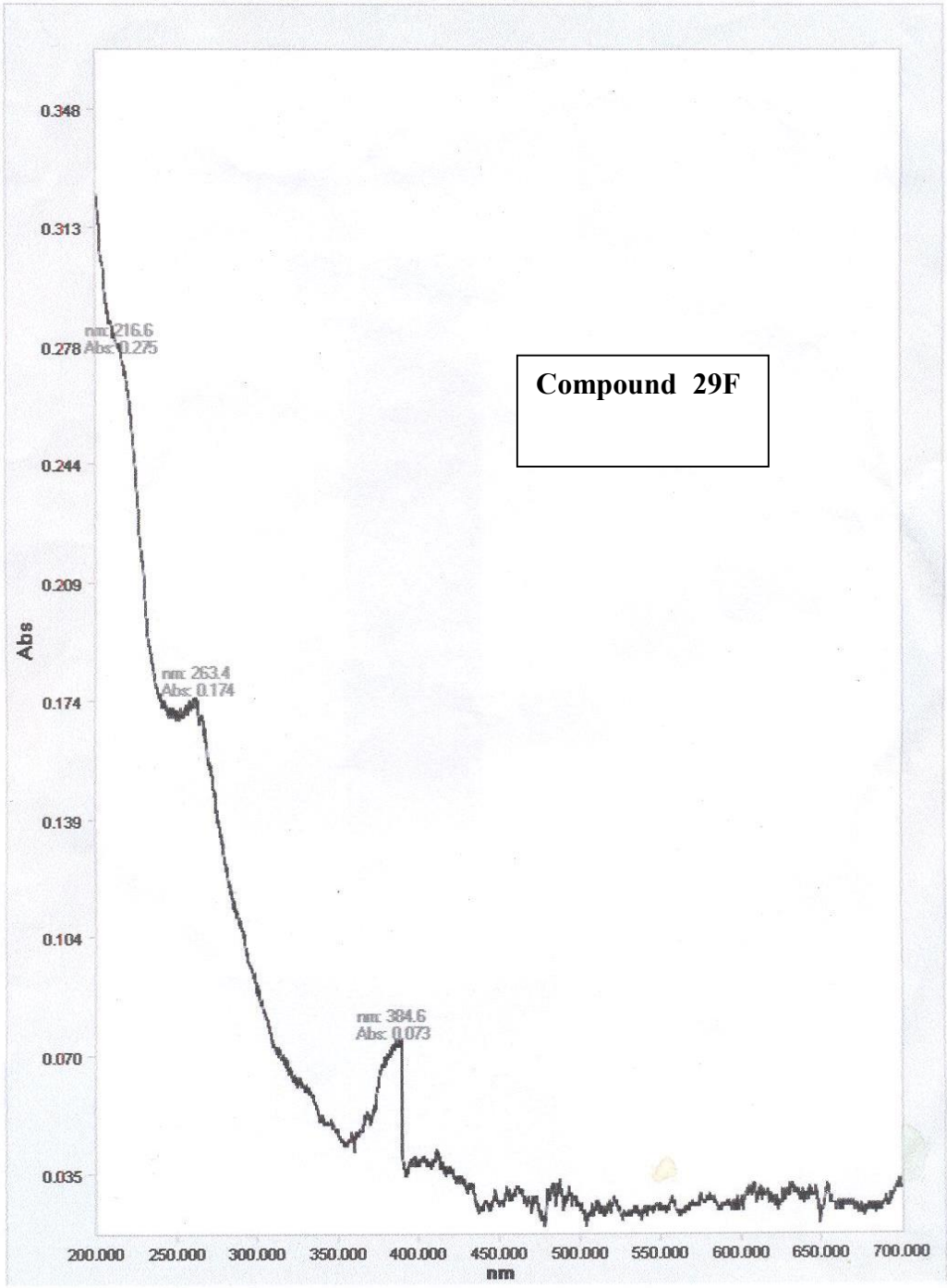
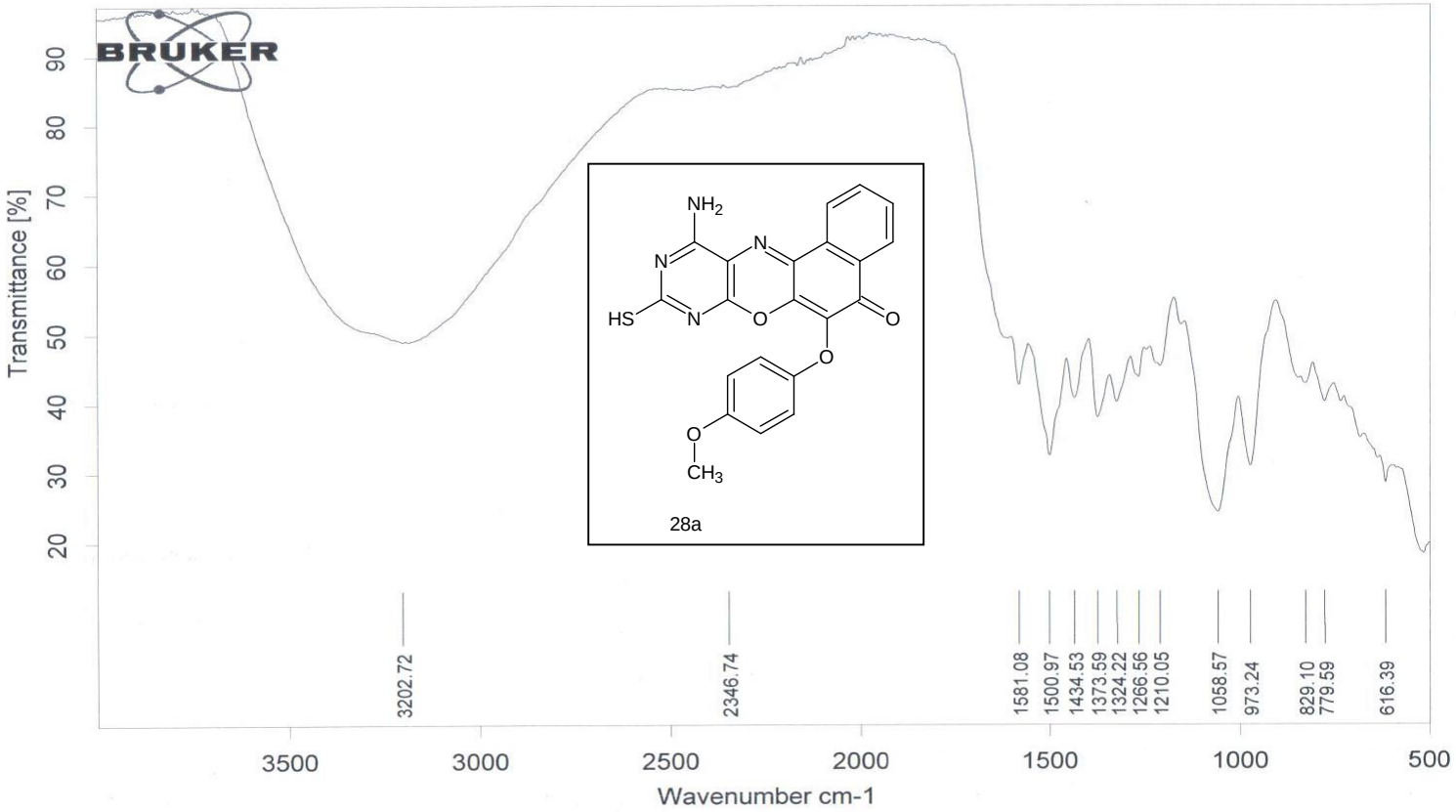


Compound 29F

APPENDIX 2 (IR SPECTRA OF THE NEW DERIVATIVES)



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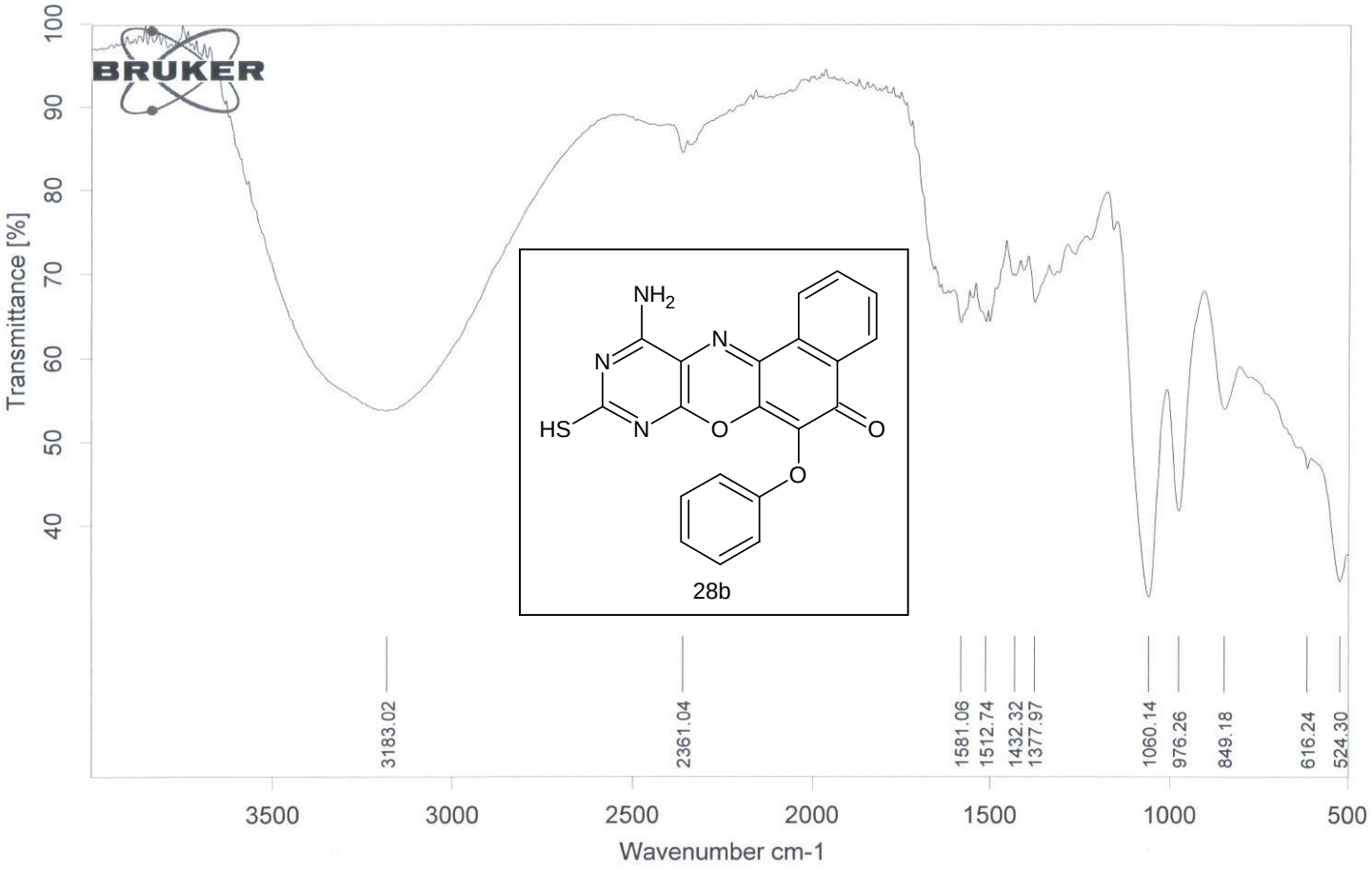

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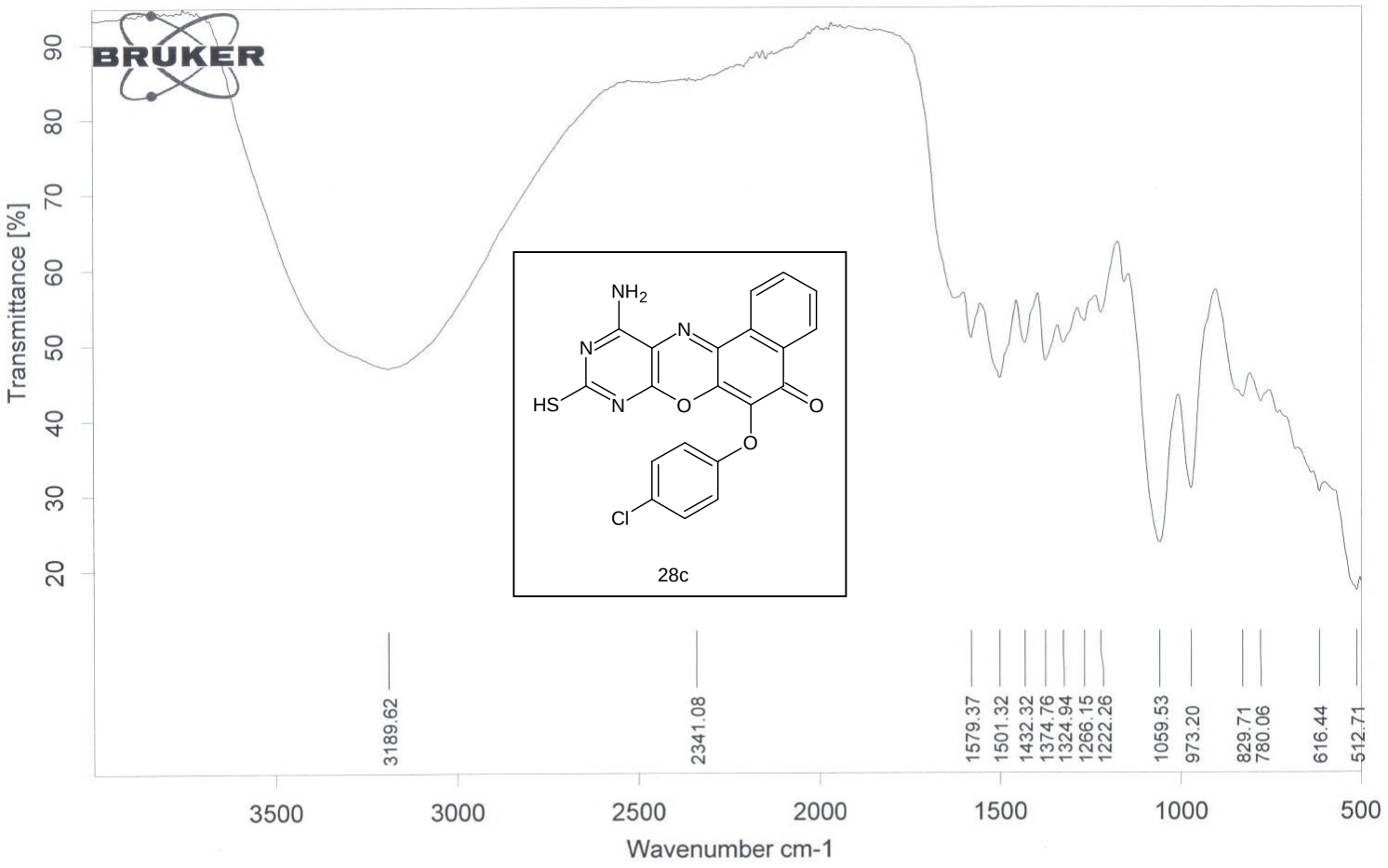

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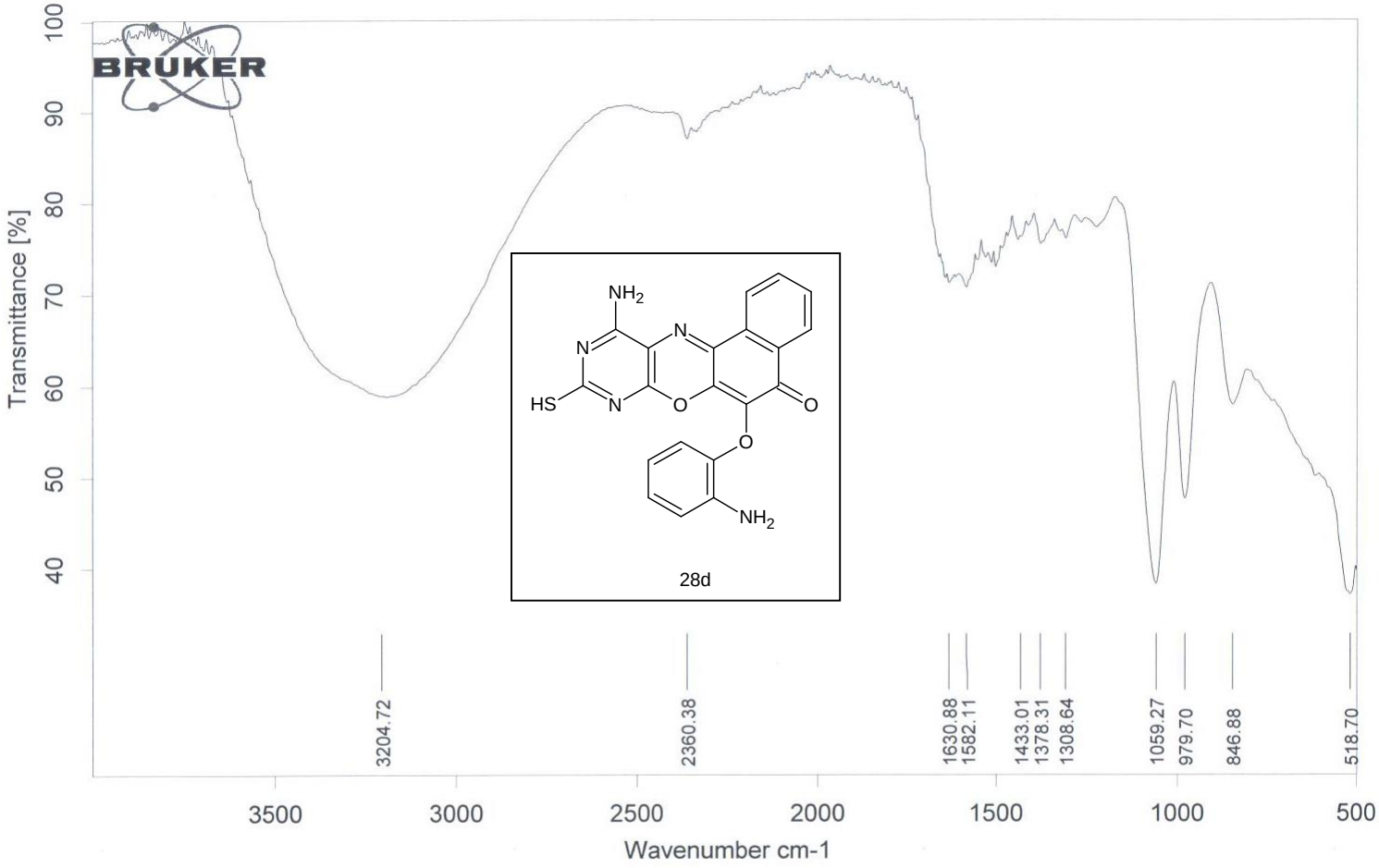

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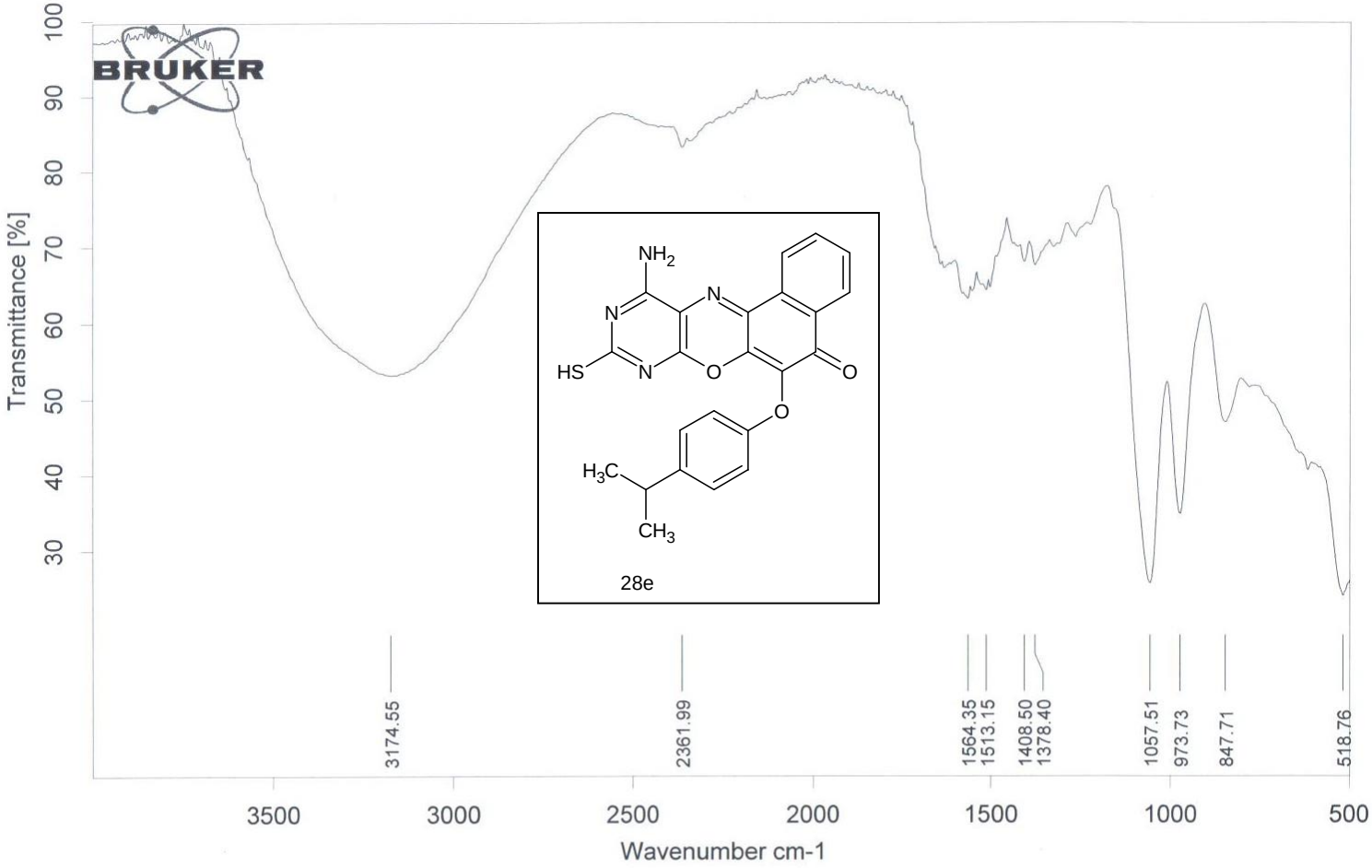

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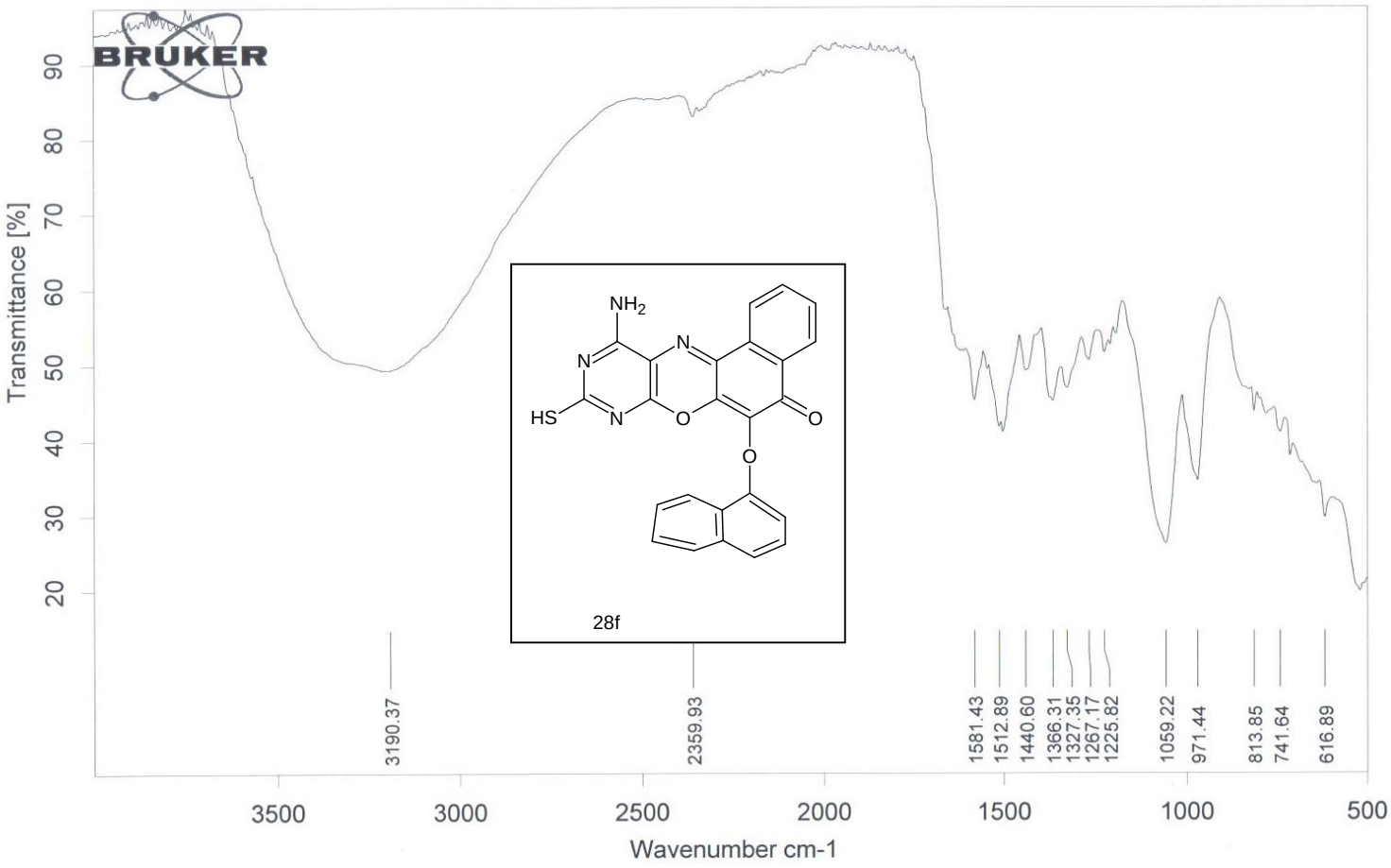
Page 1/1



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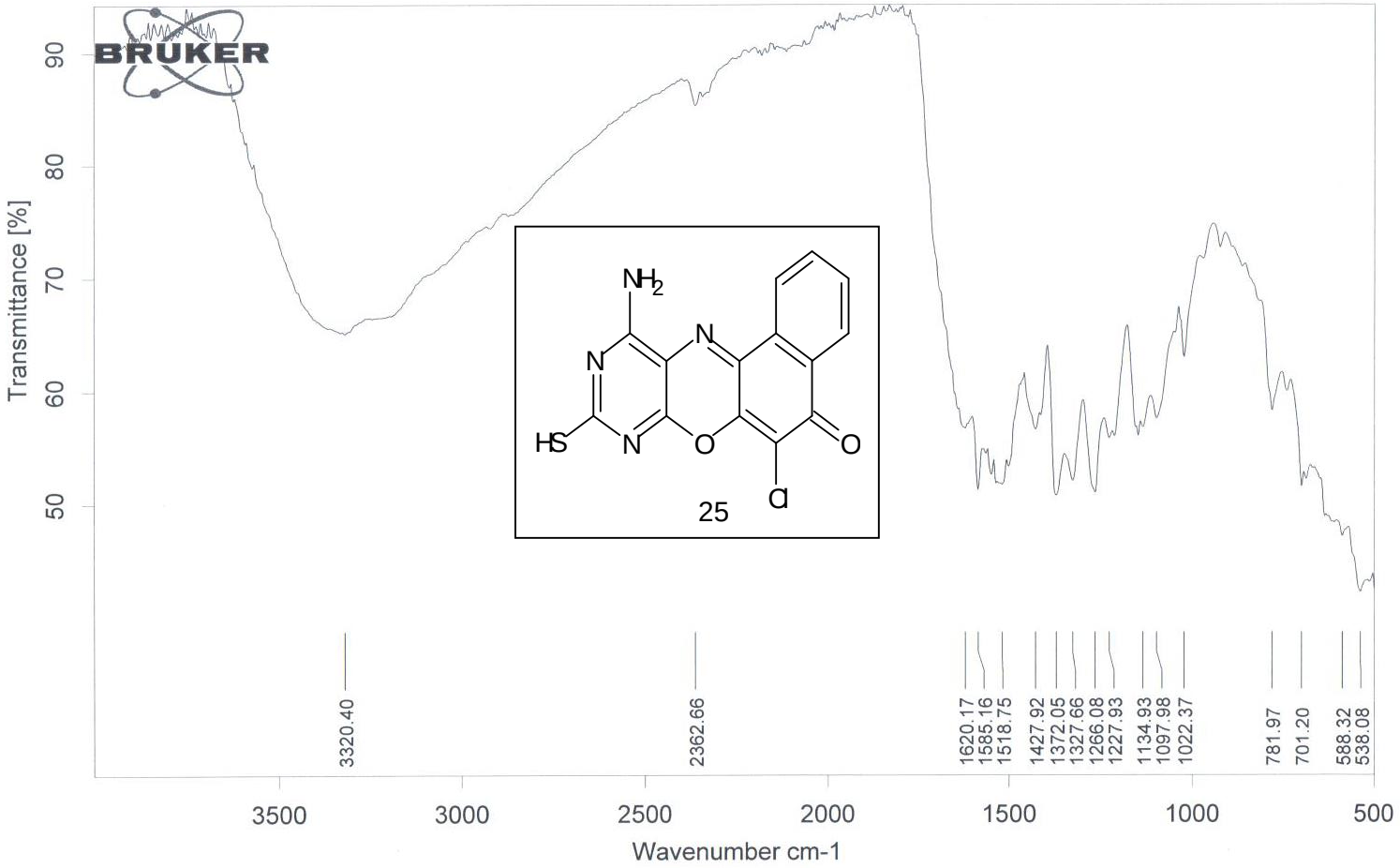

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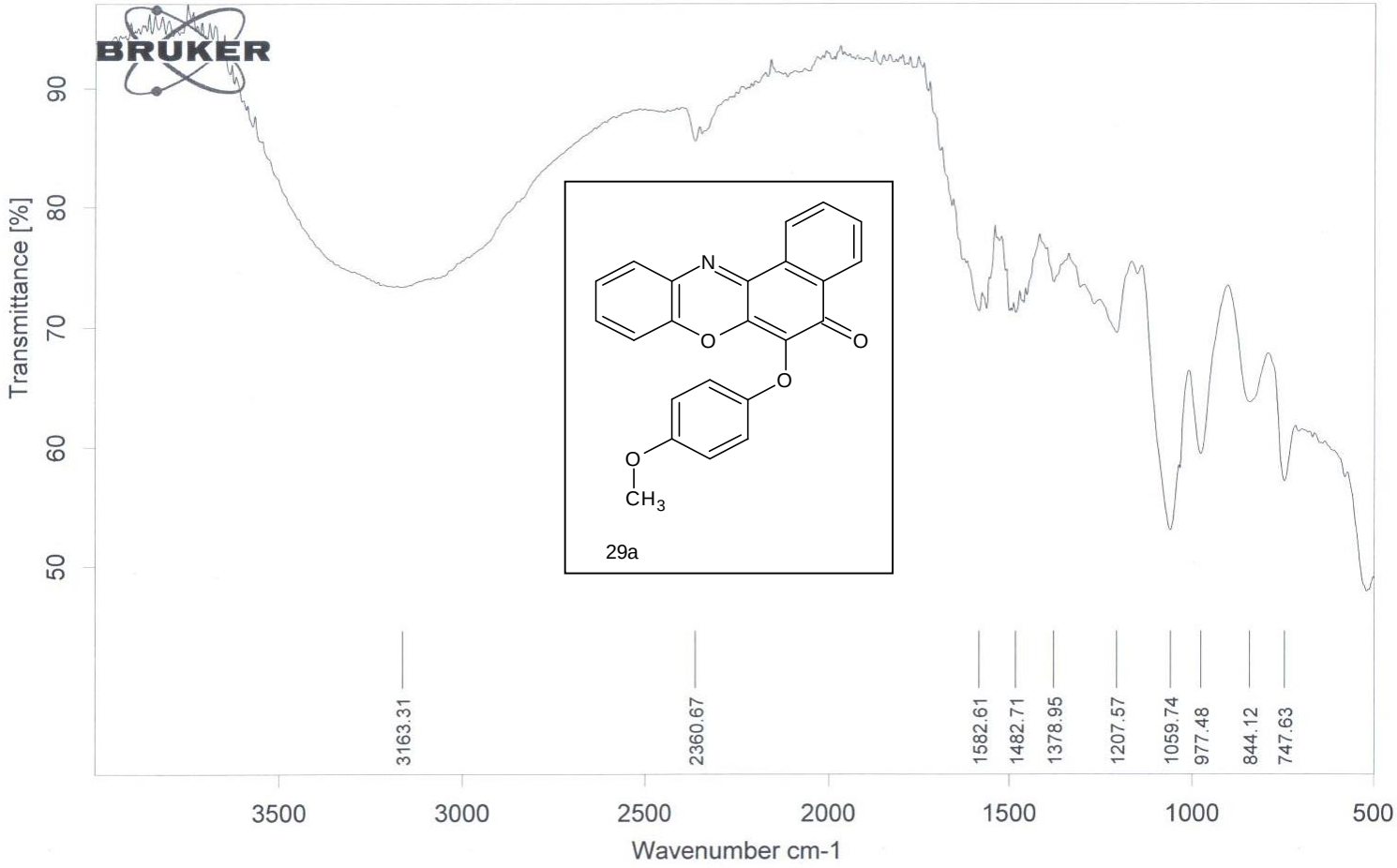
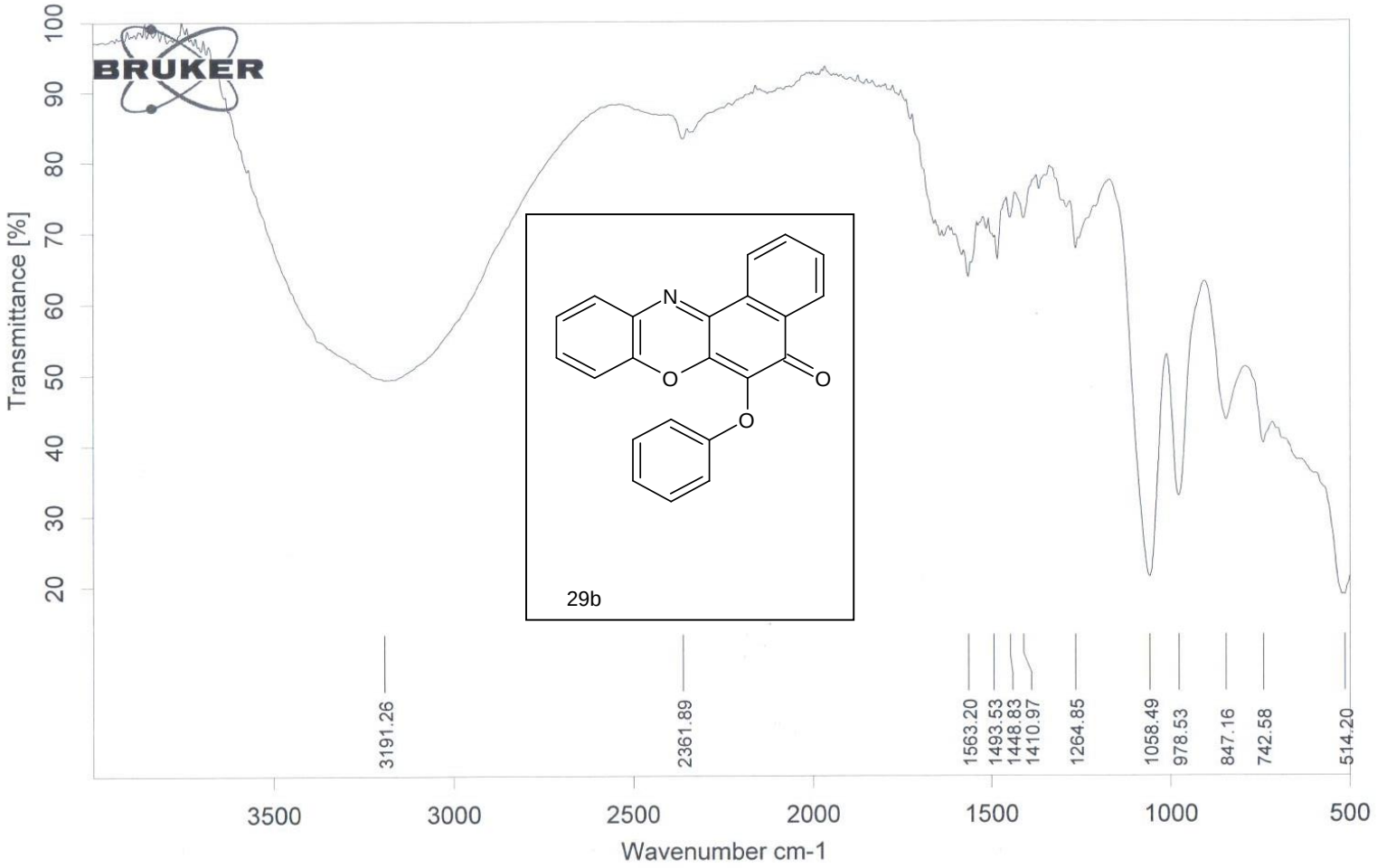
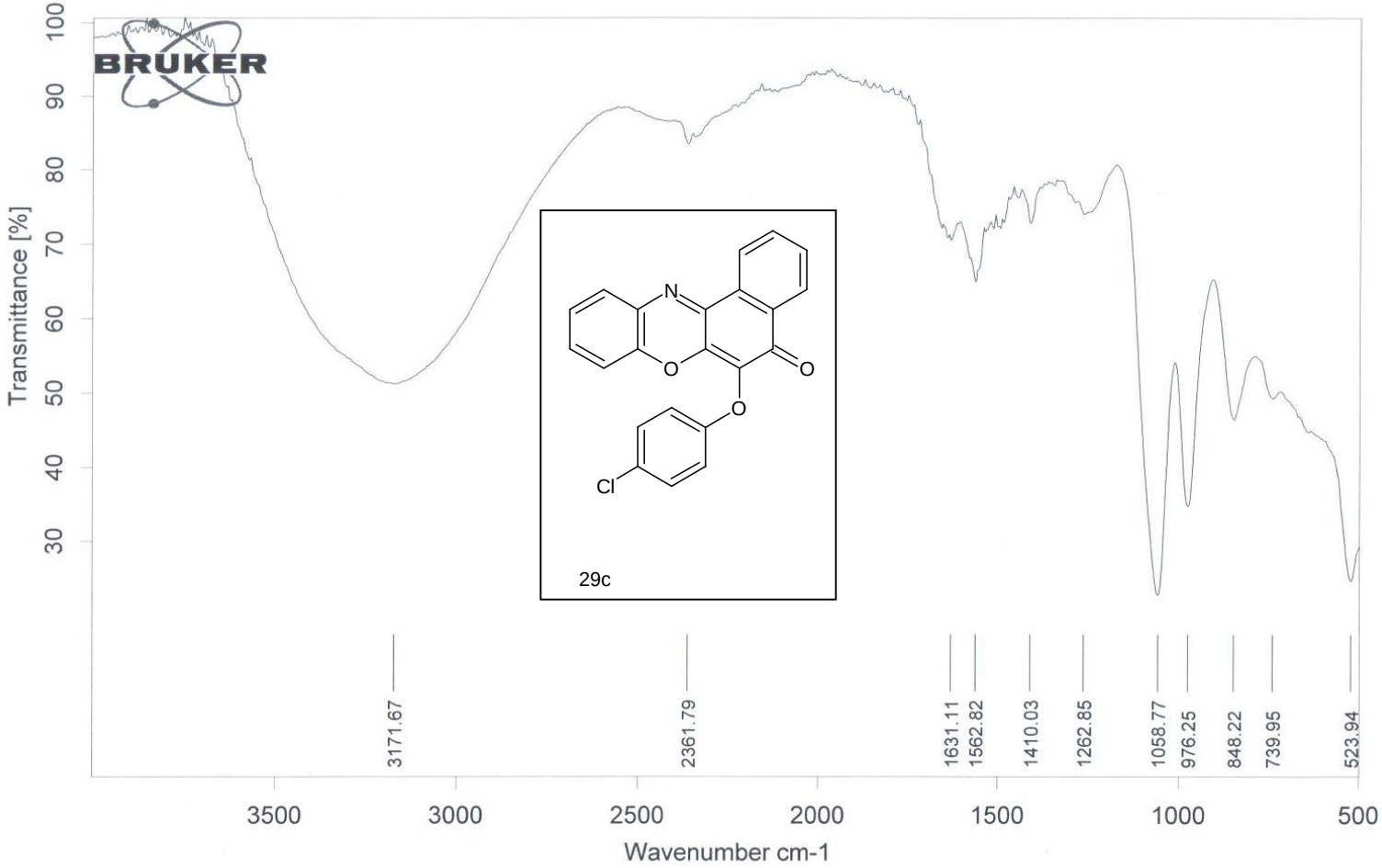


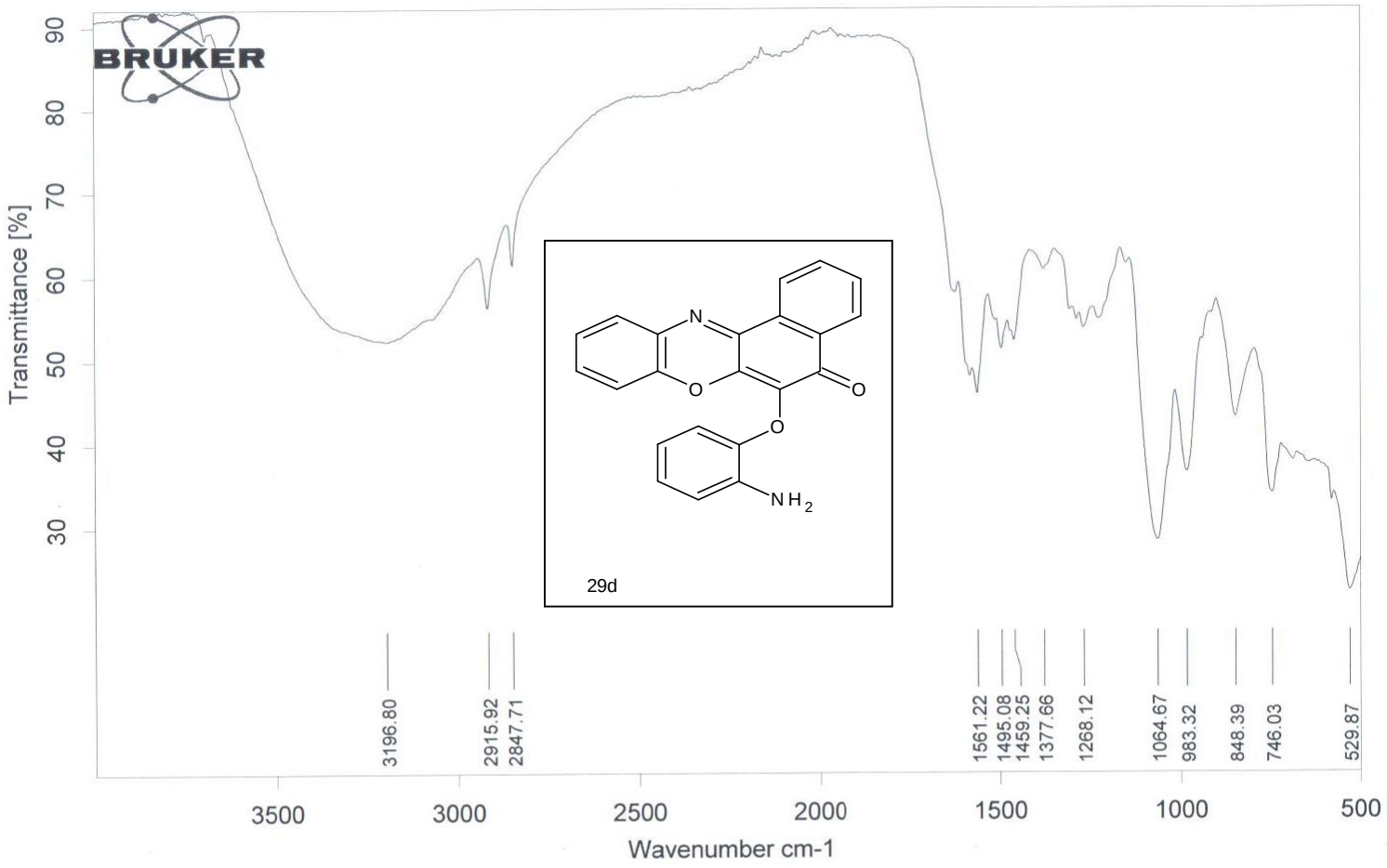
C:\Unilag\.635	Dr. (Mrs) Ezeokonkwo - 1B	Instrument type and / or accessory	31/03/2015



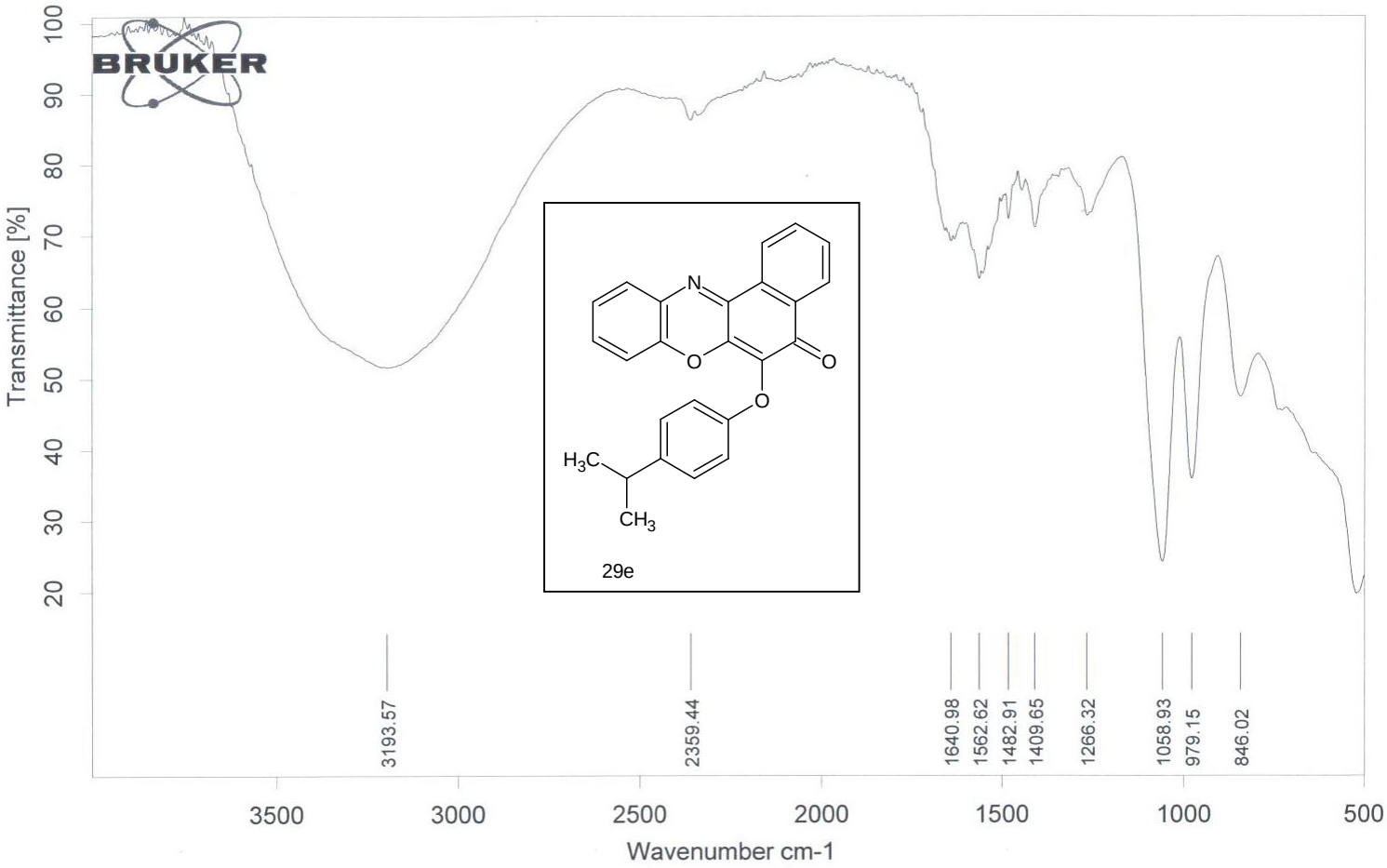
C:\Unilag\.640	Dr. (Mrs) Ezeokonkwo - 2B	Instrument type and / or accessory	31/03/2015



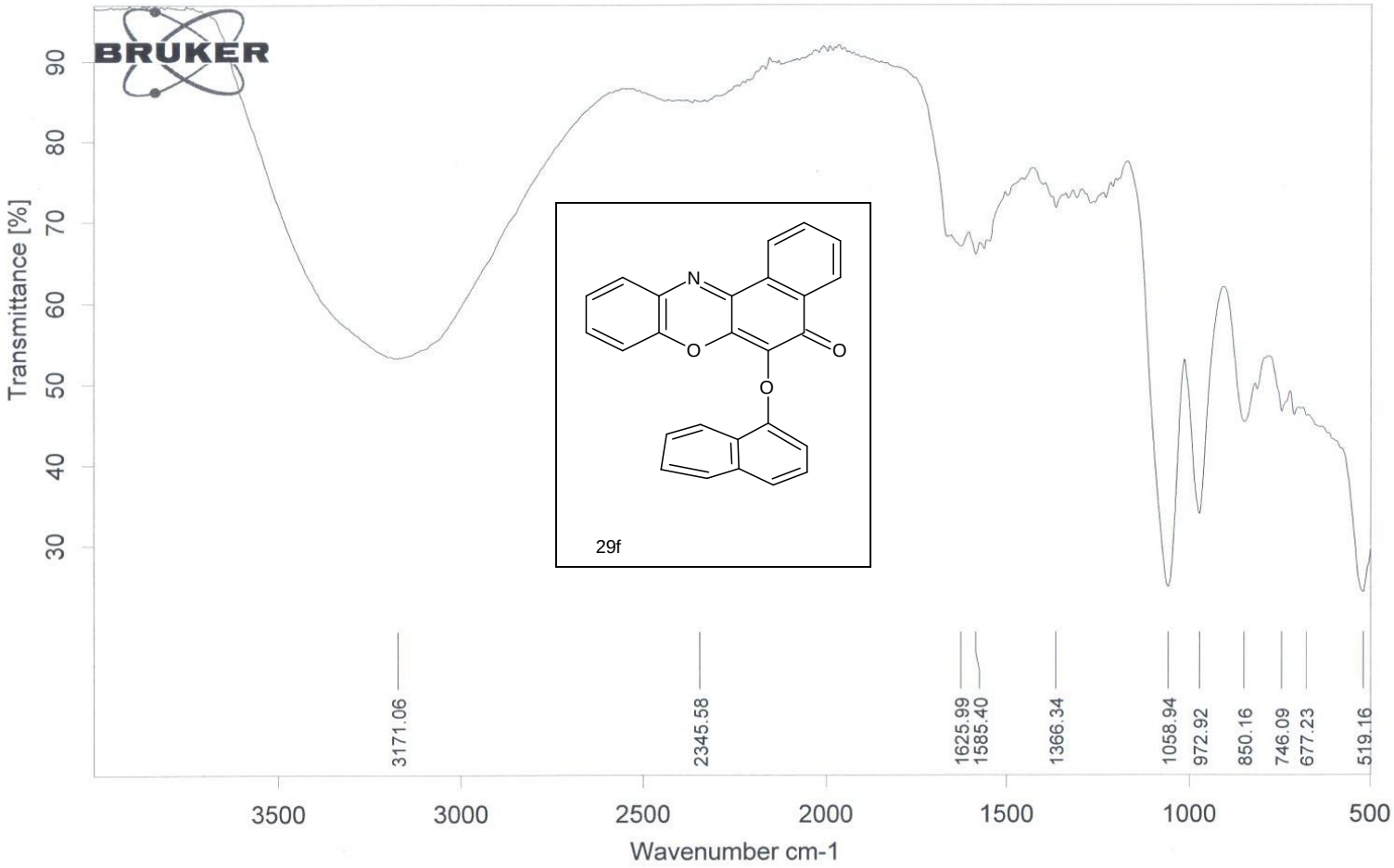
C:\Unilag\.636	Dr. (Mrs) Ezeokonkwo - 3B	Instrument type and / or accessory	31/03/2015



C:\Unilag\.643	Dr. (Mrs) Ezeokonkwo - 4B	Instrument type and / or accessory	01/04/2015

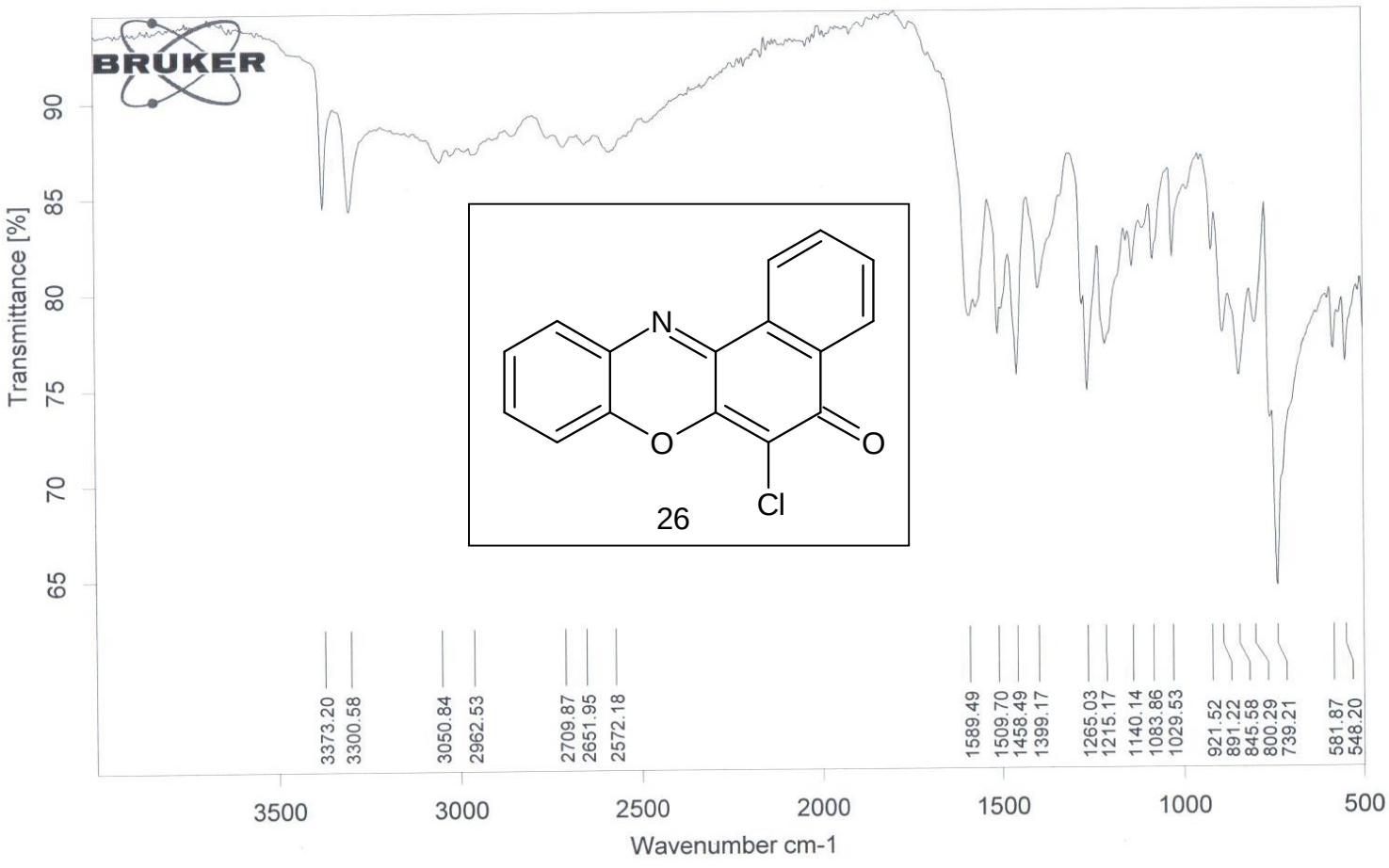


C:\Unilag\.634	Dr. (Mrs) Ezeokonkwo - 5B	Instrument type and / or accessory	31/03/2015



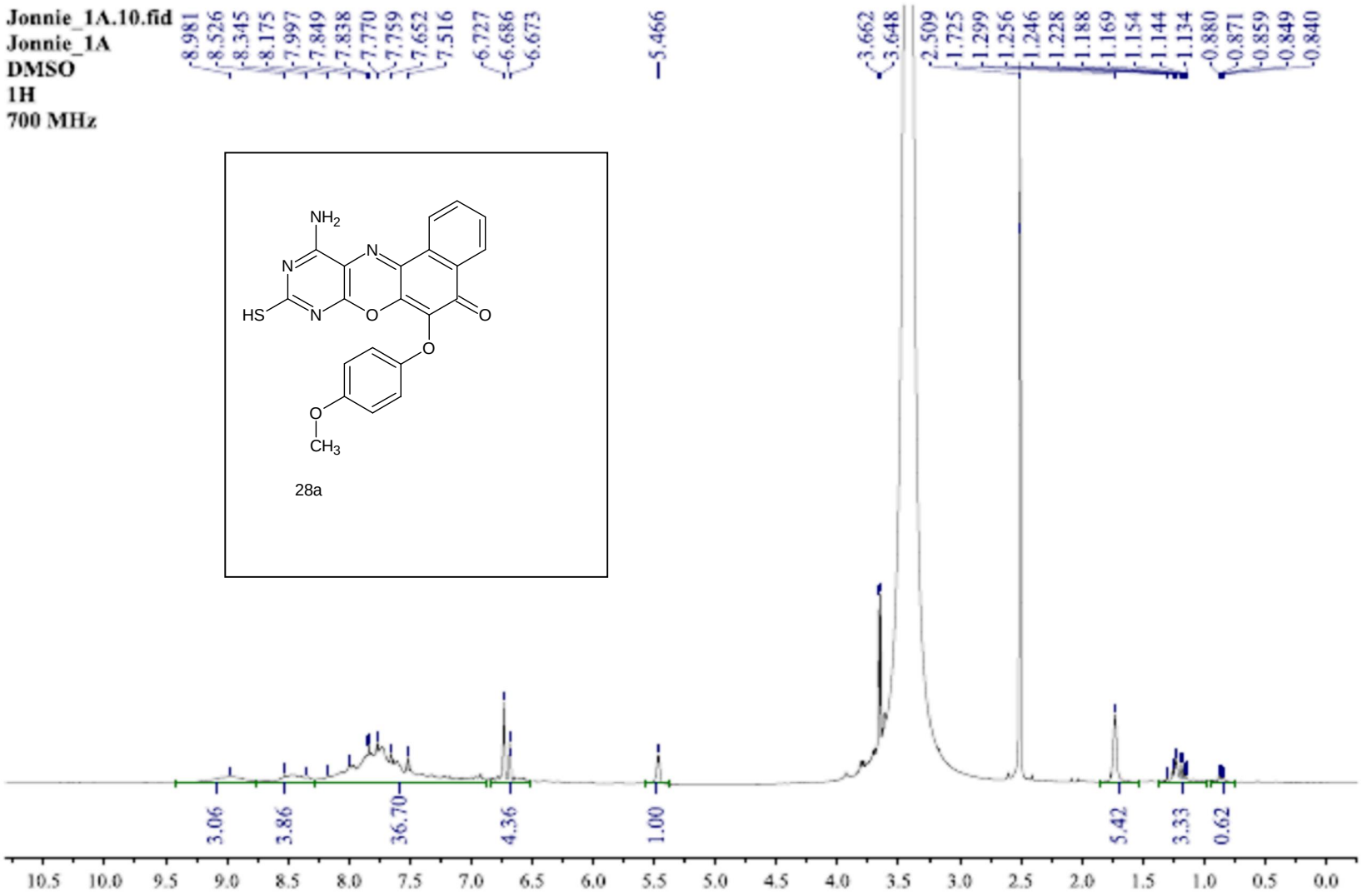
C:\Unilag\.644	Dr. (Mrs) Ezeokonkwo - 6B	Instrument type and / or accessory	01/04/2015

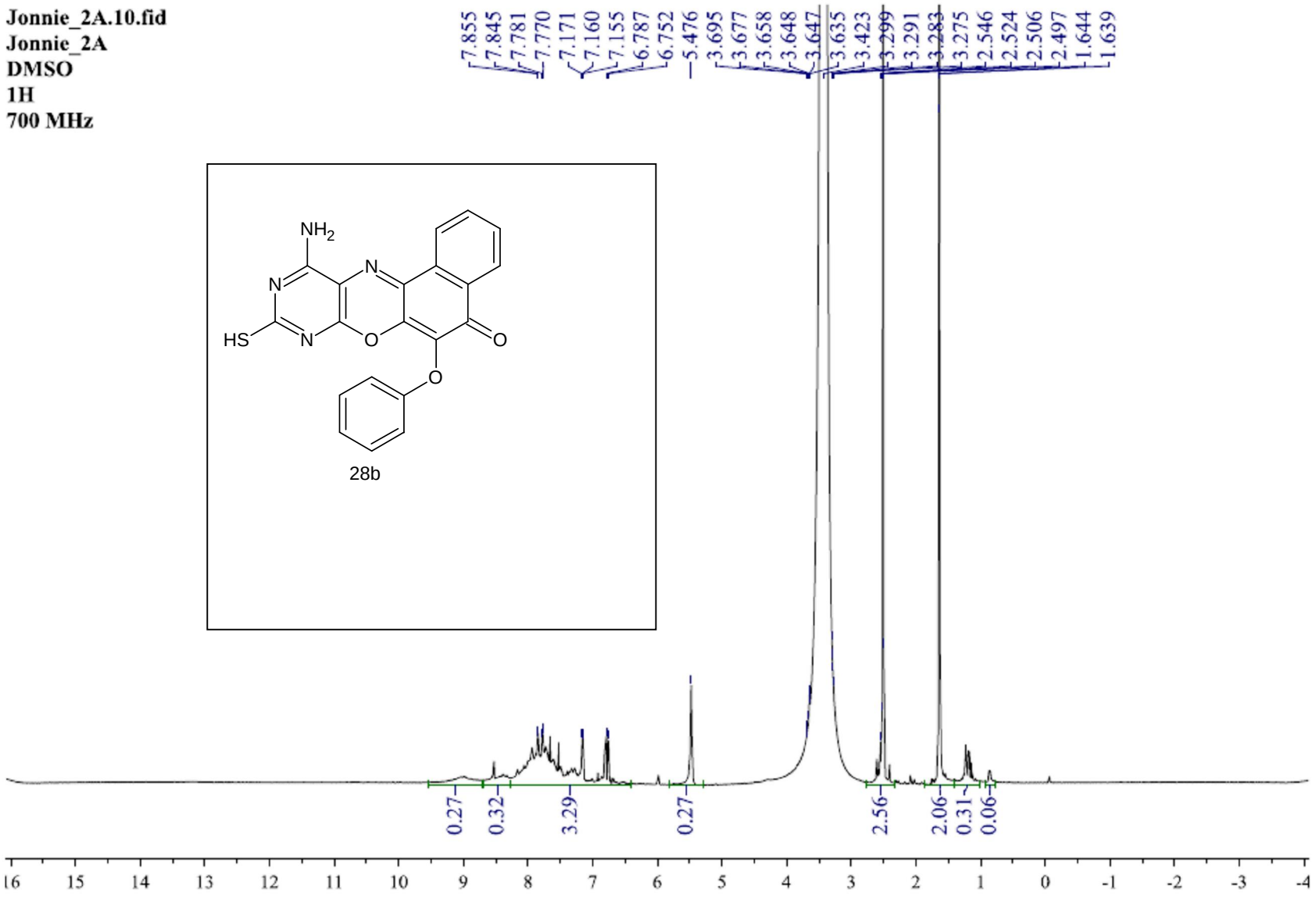
Page 1/1

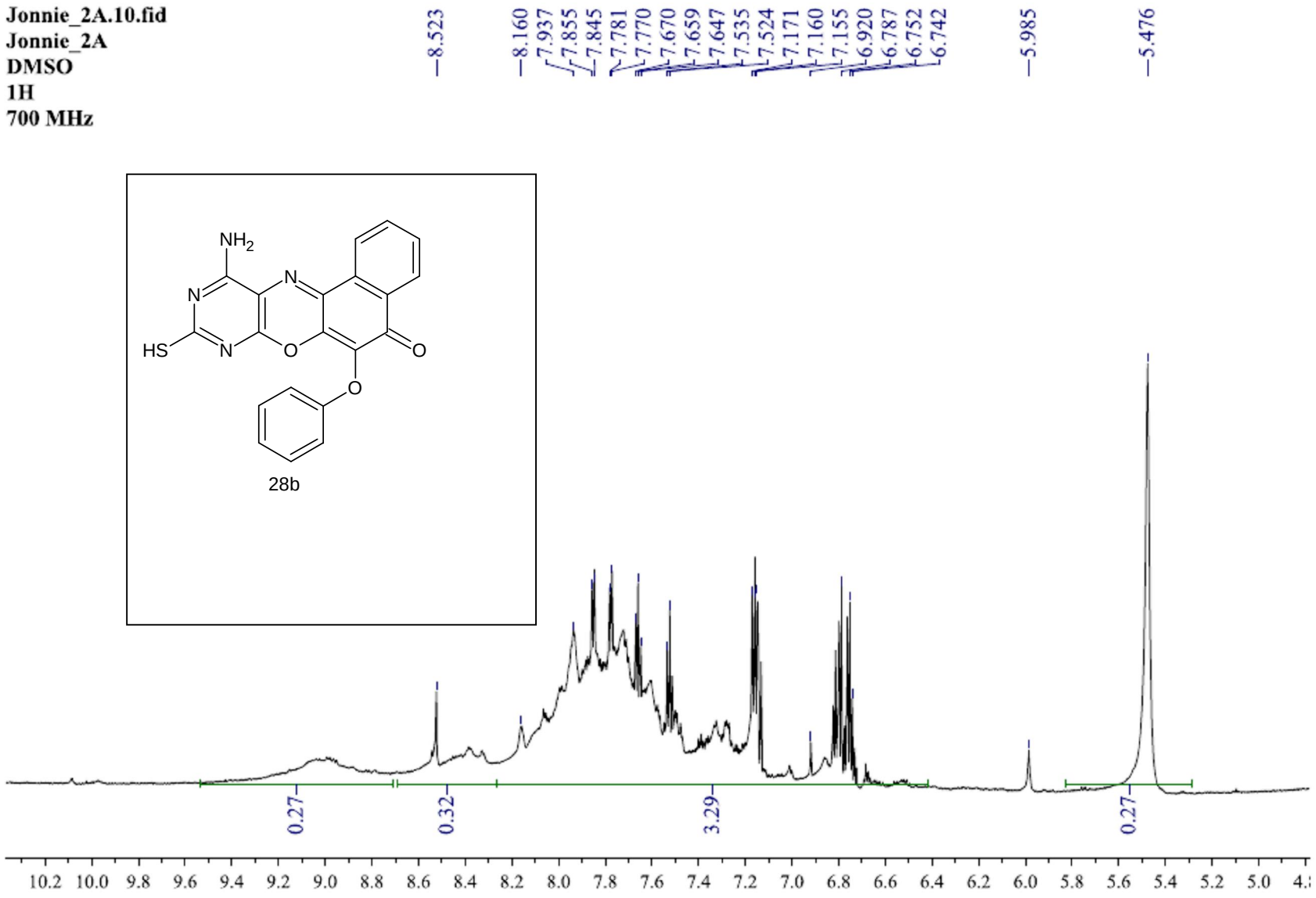


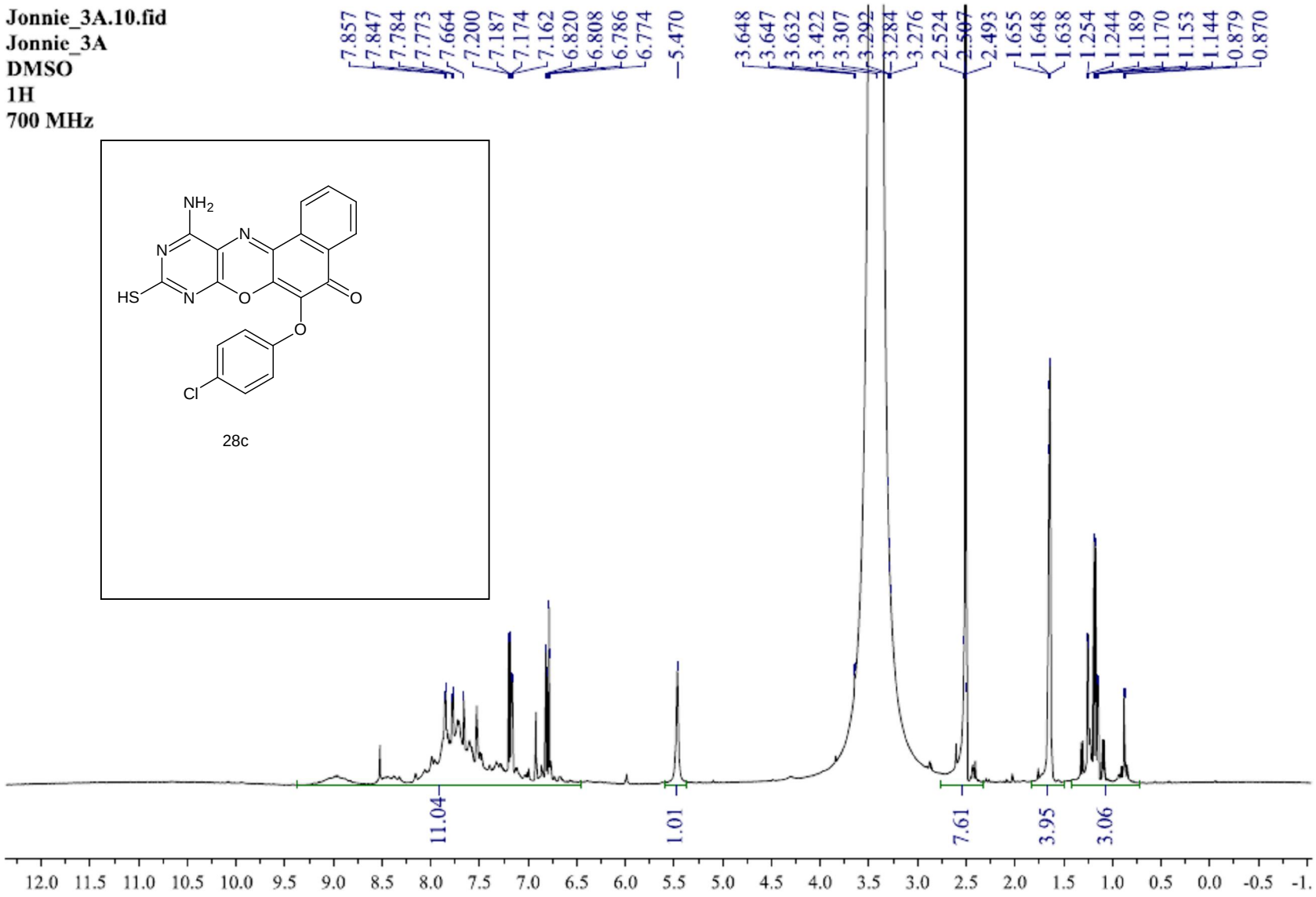
C:\Unilag\.642	Dr. (Mrs) Ezeokonkwo - MB	Instrument type and / or accessory	01/04/2015

APPENDIX 3(NMR SPECTRA OF NEW DERIVATIVES)



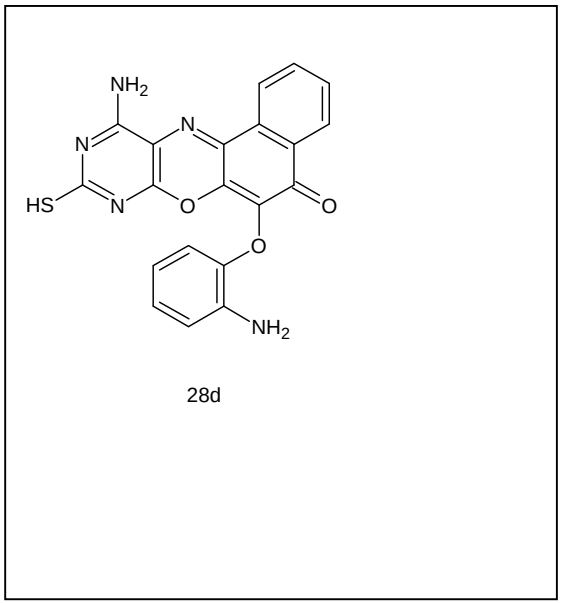

Jonnie_2A.10.fid
Jonnie_2A
DMSO
1H
700 MHz
7.855
7.845
7.781
7.770
7.171
7.160
7.155
6.787
6.752
5.476
3.695
3.677
3.658
3.648
3.647
3.635
3.423
3.299
3.291
3.283
3.275
2.546
2.524
2.506
2.497
1.644
1.639
NH2
N
N
HS
N
O
O
O
28b
0.27
0.32
3.29
0.27
2.56
2.06
0.31
0.06
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4


Jonnie_2A.10.fid
Jonnie_2A
DMSO
1H
700 MHz
8.523
8.160
7.937
7.855
7.845
7.781
7.770
7.670
7.659
7.647
7.535
7.524
7.171
7.160
7.155
6.920
6.787
6.752
6.742
5.985
5.476
NH2
N
N
HS
N
O
O
O
28b
0.27
0.32
3.29
0.27
10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0


Jonnie_3A.10.fid
Jonnie_3A
DMSO
1H
700 MHz
7.857
7.847
7.784
7.773
7.664
7.200
7.187
7.174
7.162
6.820
6.808
6.786
6.774
5.470
3.648
3.647
3.632
3.422
3.307
3.292
3.284
3.276
2.524
2.507
2.493
1.655
1.648
1.638
1.254
1.244
1.189
1.170
1.153
1.144
0.879
0.870
NH2
N
N
HS
N
O
O
O
Cl
28c
11.04
1.01
7.61
3.95
3.06
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.

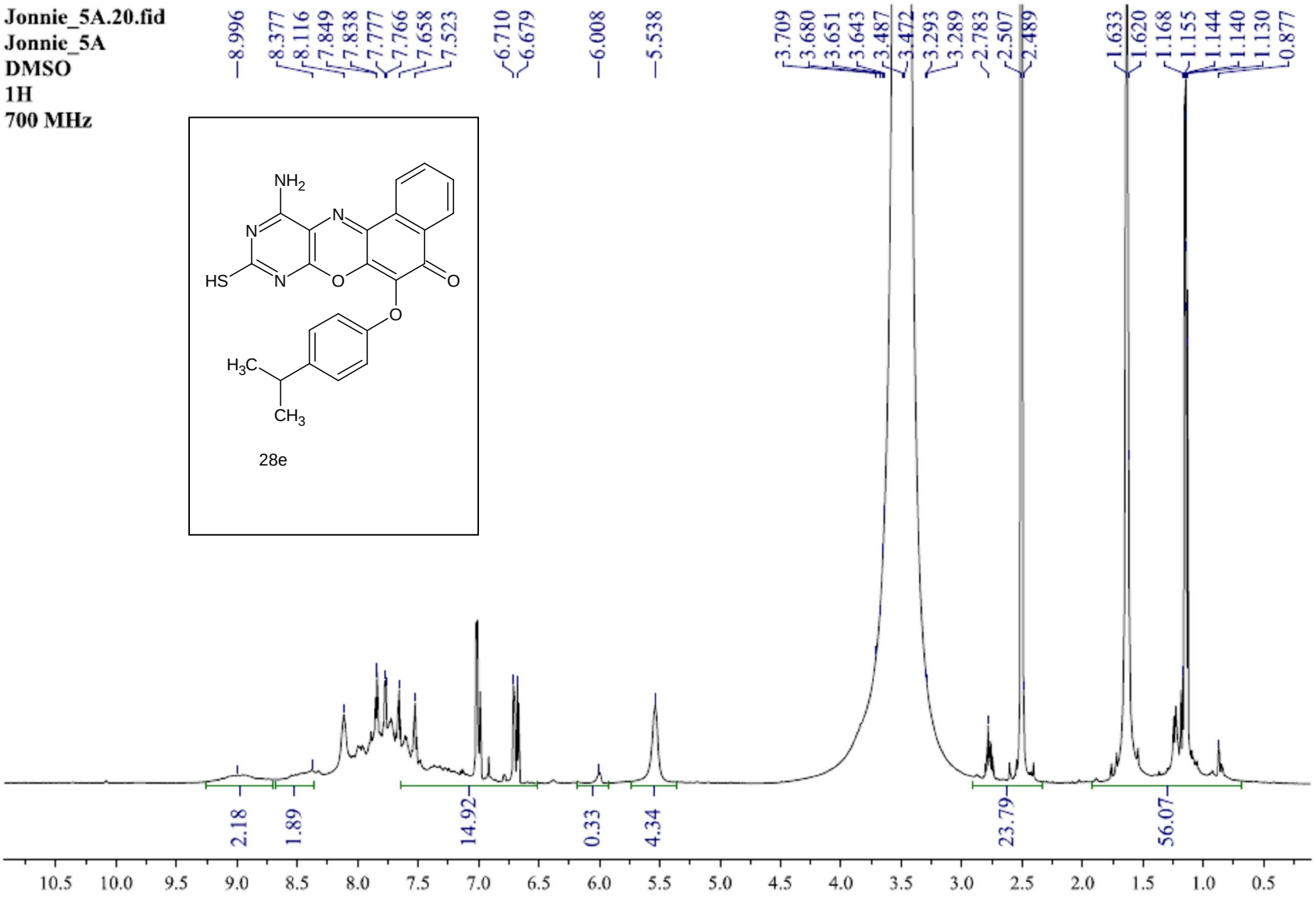
Jonnie_4A.10.fid
Jonnie_4A
DMSO
1H
700 MHz

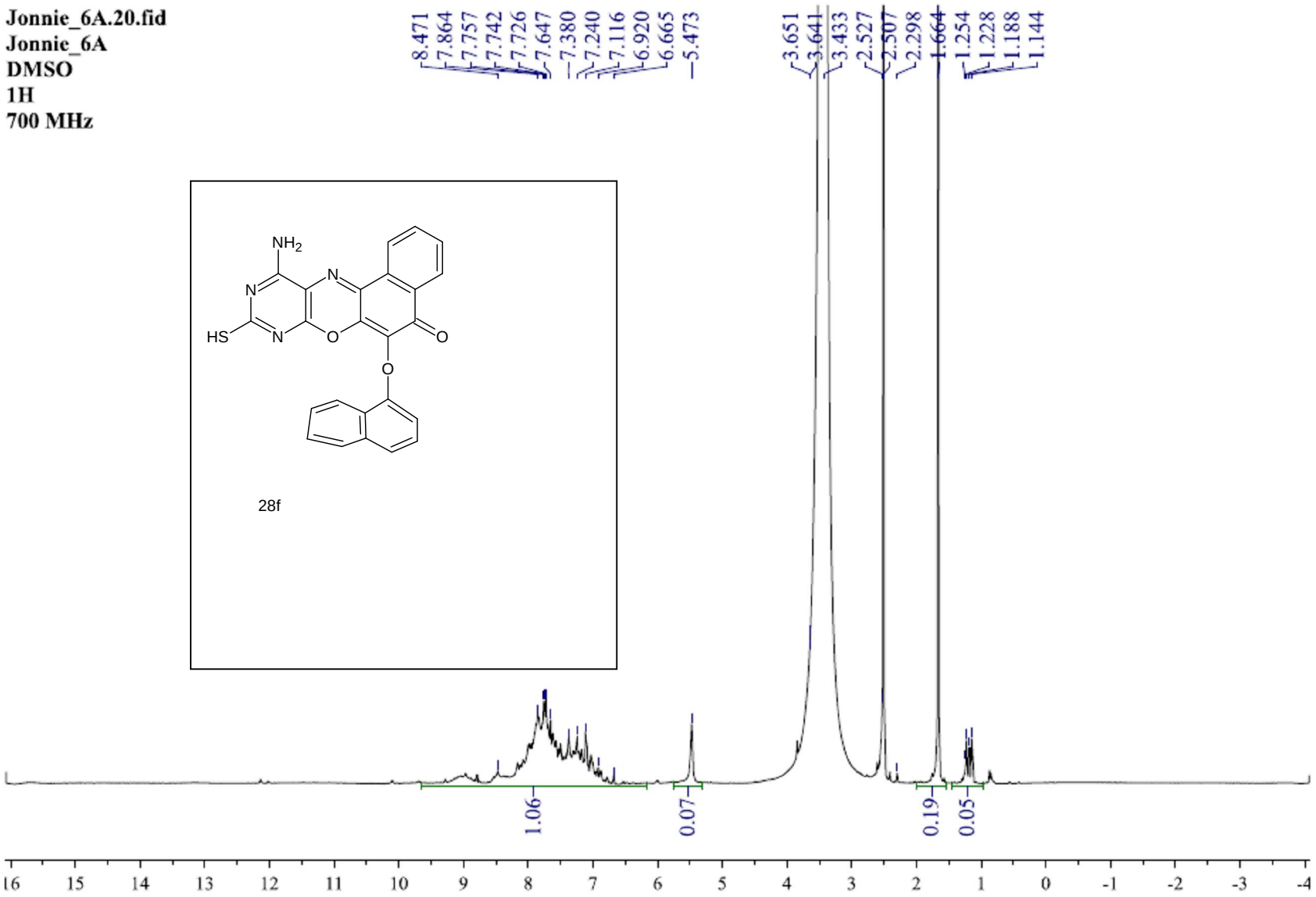
10.090
9.091
9.057
8.962
8.520
8.442
8.383
8.326
8.169
8.064
7.720
7.709
7.506
7.471
7.402
7.250
7.181
7.146
7.064
6.920
6.844
6.380
5.992
5.457

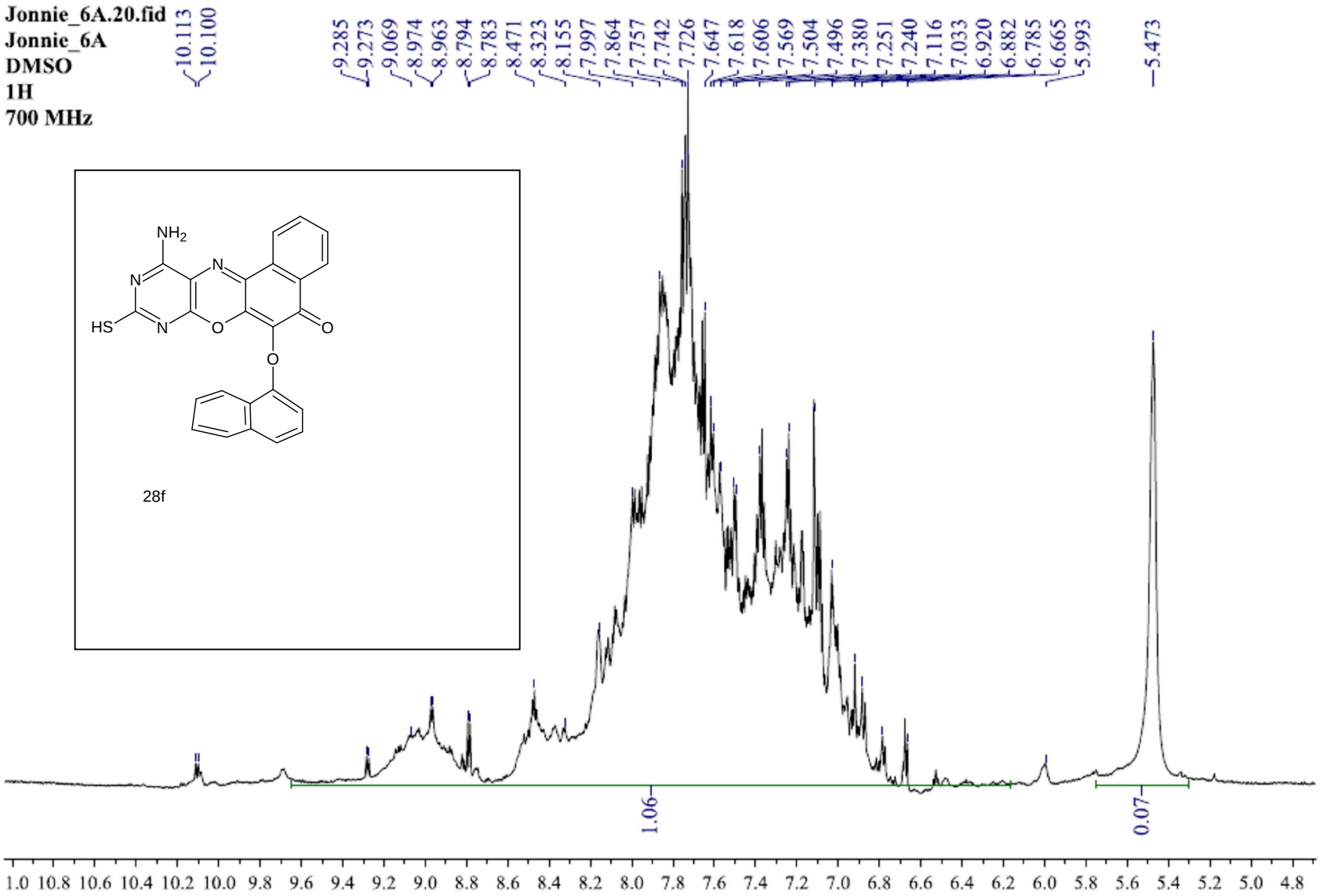


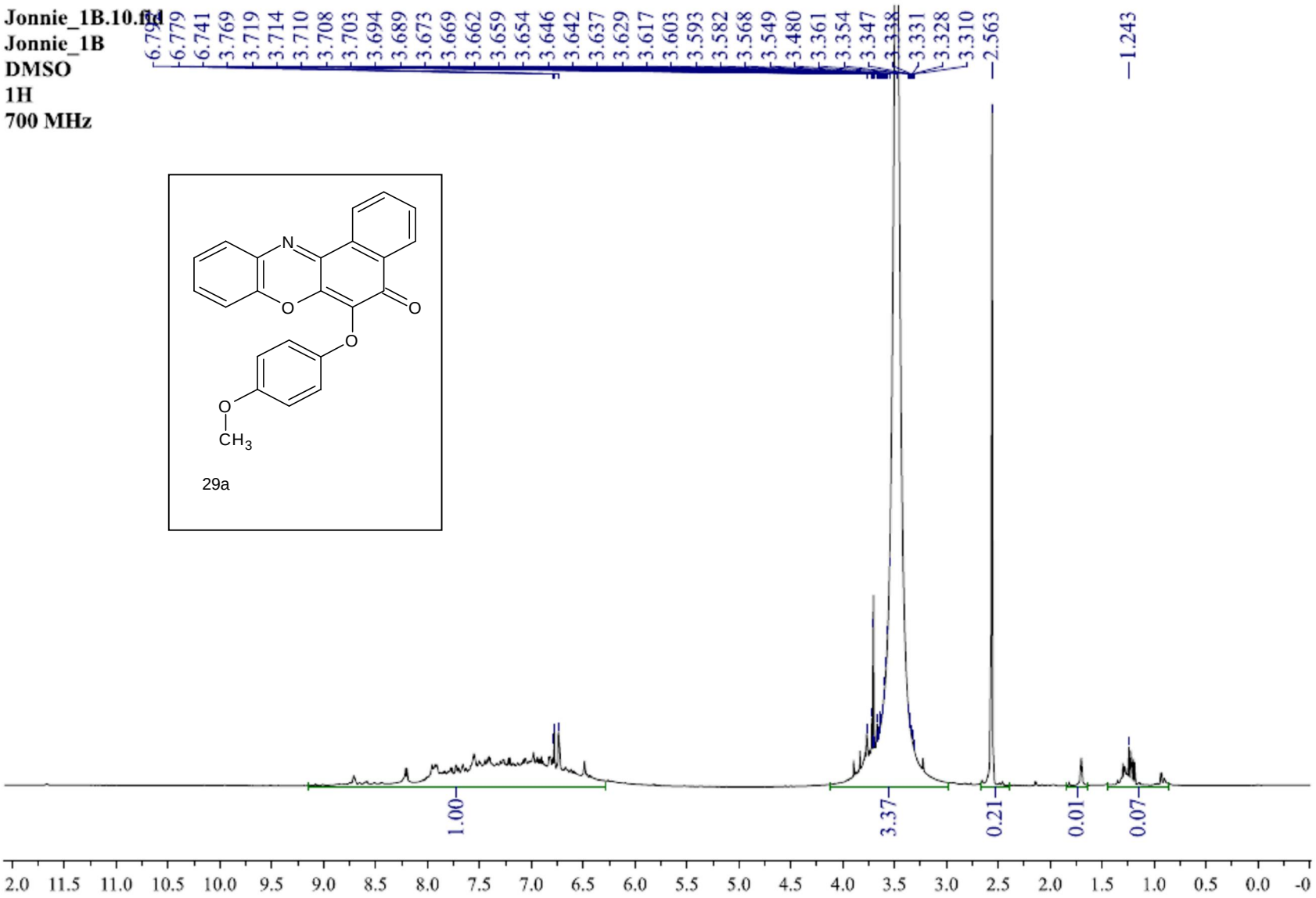
28d

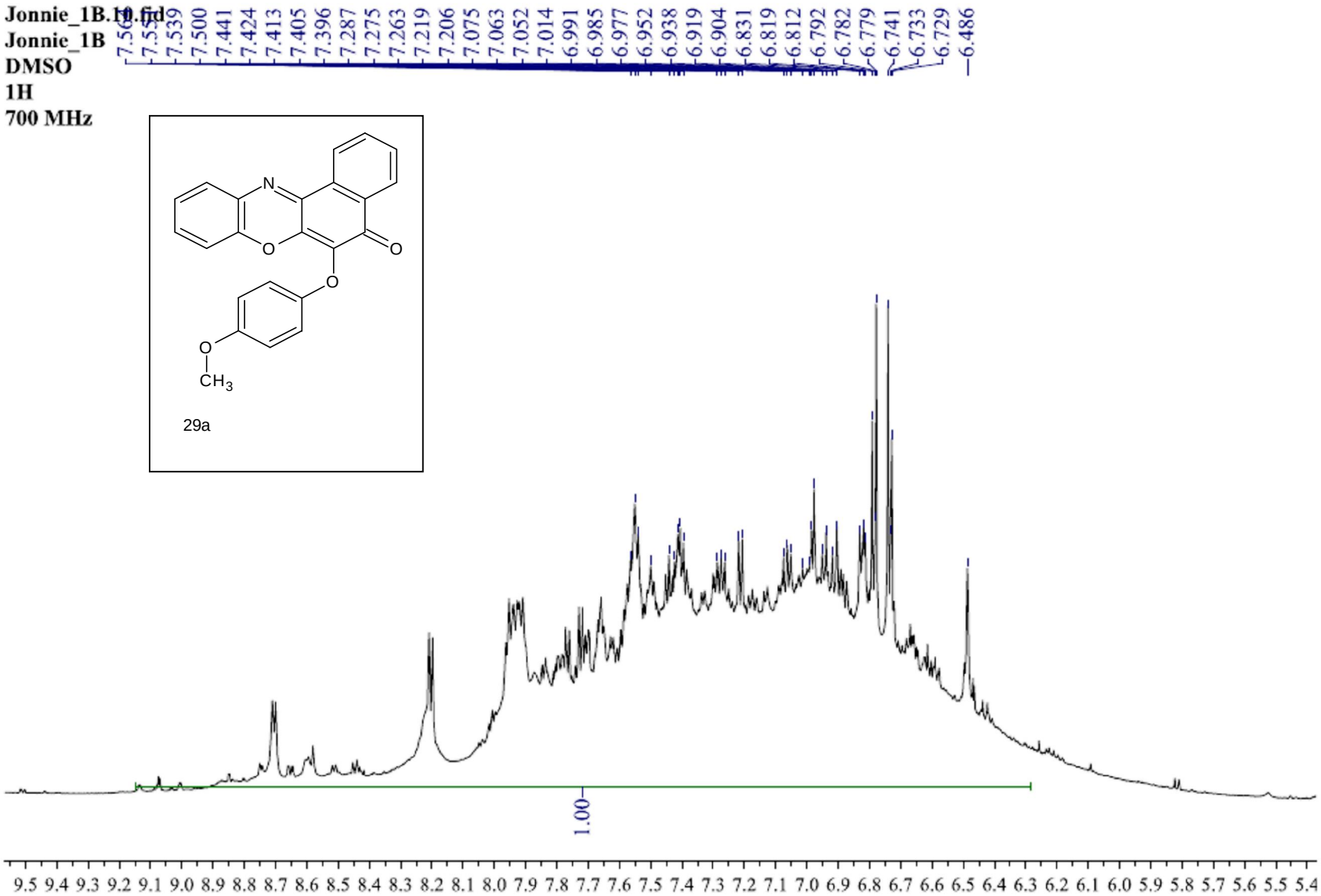
1.4 11.2 11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8

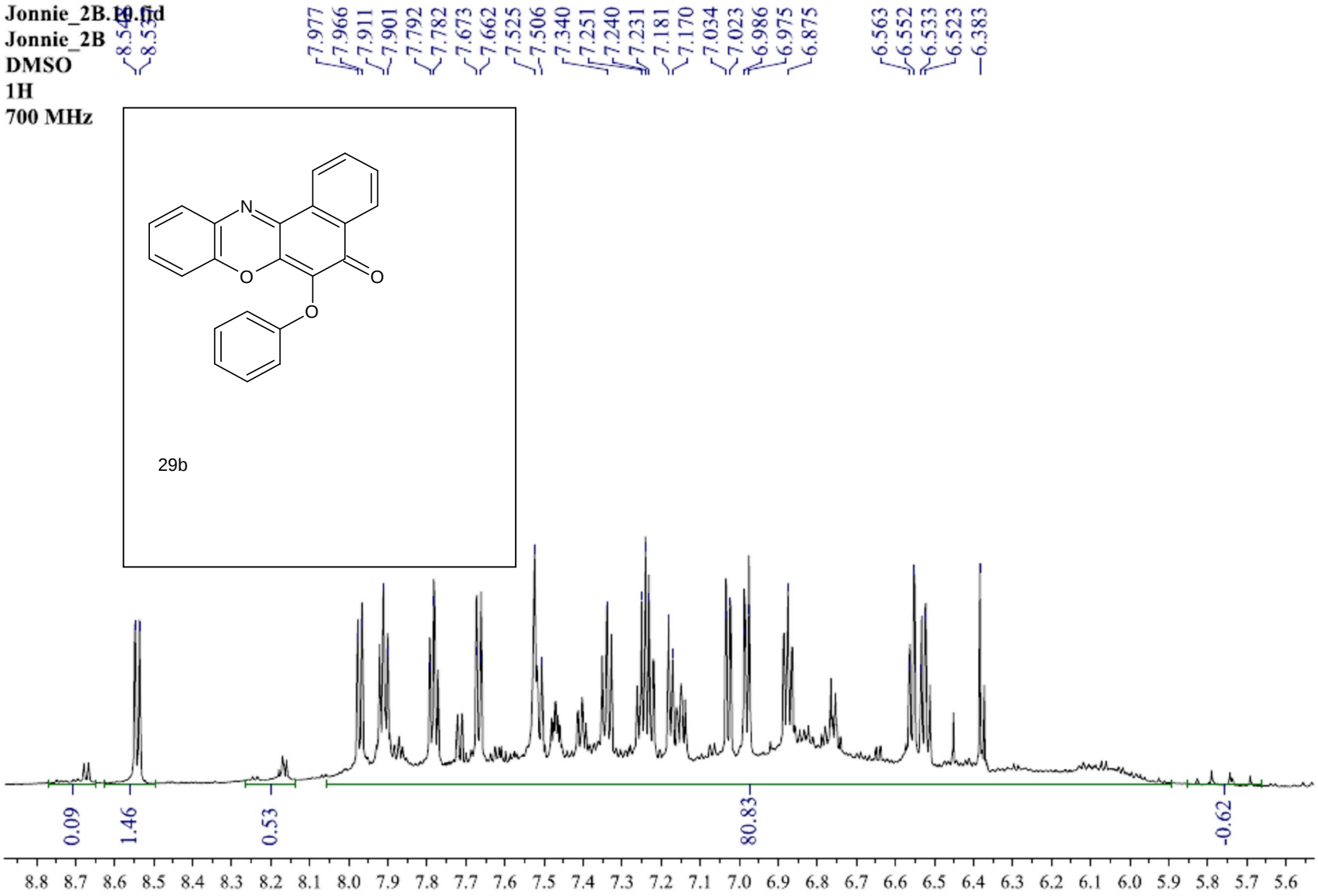

Jonnie_5A.20.fid
Jonnie_5A
DMSO
1H
700 MHz
8.996
8.377
8.116
7.849
7.838
7.777
7.766
7.658
7.523
6.710
6.679
6.008
5.538
3.709
3.680
3.651
3.643
3.487
3.472
3.293
3.289
2.783
2.507
2.489
1.633
1.620
1.168
1.155
1.144
1.140
1.130
0.877
NH2
N
N
HS
N
O
O
O
H3C
CH3
28e
2.18
1.89
14.92
0.33
4.34
23.79
56.07
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

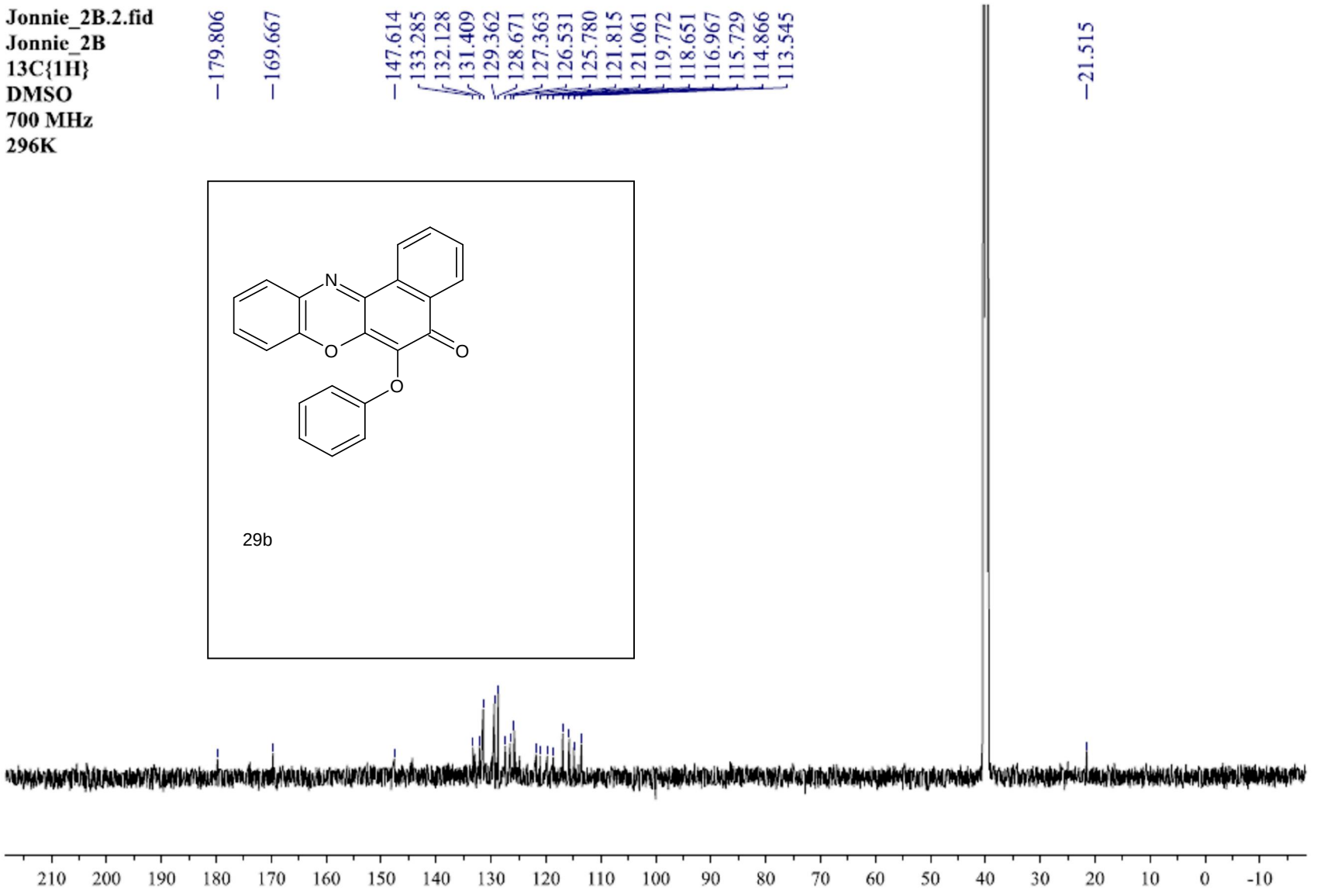

Jonnie_6A.20.fid
Jonnie_6A
DMSO
1H
700 MHz
8.471
7.864
7.757
7.742
7.726
7.647
7.380
7.240
7.116
6.920
6.665
5.473
3.651
3.641
3.433
2.527
2.507
2.298
1.664
1.254
1.228
1.188
1.144
NH2
N
N
HS
N
O
O
O
28f
1.06
0.07
0.19
0.05
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4

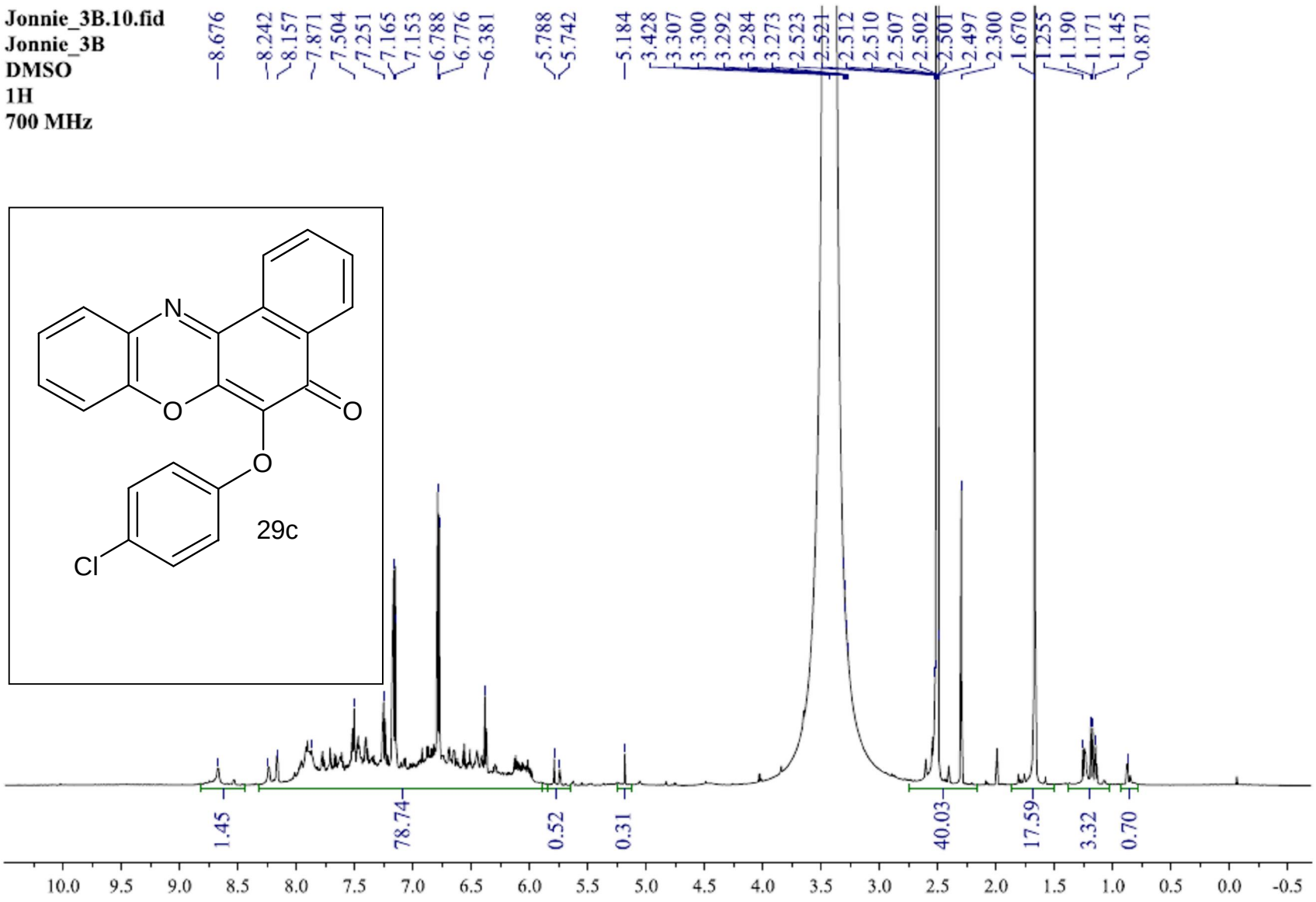

Jonnie_6A.20.fid
Jonnie_6A
DMSO
1H
700 MHz
10.113
10.100
9.285
9.273
9.069
8.974
8.963
8.794
8.783
8.471
8.323
8.155
7.997
7.864
7.757
7.742
7.726
7.647
7.618
7.606
7.569
7.504
7.496
7.380
7.251
7.240
7.116
7.033
6.920
6.882
6.785
6.665
5.993
5.473
NH2
N
N
HS
N
O
O
O
28f
1.06
0.07
1.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8


Jonnie_1B.10.fid
Jonnie_1B
DMSO
1H
700 MHz
6.779
6.741
3.769
3.719
3.714
3.710
3.708
3.703
3.694
3.689
3.673
3.669
3.662
3.659
3.654
3.646
3.642
3.637
3.629
3.617
3.603
3.593
3.582
3.568
3.549
3.480
3.361
3.354
3.347
3.338
3.331
3.328
3.310
2.563
1.243
N
O
O
O
O
CH3
29a
1.00
3.37
0.21
0.01
0.07
2.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0


Jonnie_1B.10.fid
Jonnie_1B
DMSO
1H
700 MHz
7.566
7.553
7.539
7.500
7.441
7.424
7.413
7.405
7.396
7.287
7.275
7.263
7.219
7.206
7.075
7.063
7.052
7.014
6.991
6.985
6.977
6.952
6.938
6.919
6.904
6.831
6.819
6.812
6.792
6.782
6.779
6.741
6.733
6.729
6.486
N
O
O
O
O
CH3
29a
1.00
9.5 9.4 9.3 9.2 9.1 9.0 8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4


Jonnie_2B.10.fid
Jonnie_2B
DMSO
1H
700 MHz
8.547
8.535
7.977
7.966
7.911
7.901
7.792
7.782
7.673
7.662
7.525
7.506
7.340
7.251
7.240
7.231
7.181
7.170
7.034
7.023
6.986
6.975
6.875
6.563
6.552
6.533
6.523
6.383
N
O
O
O
29b
0.09
1.46
0.53
80.83
-0.62
8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6


Jonnie_2B.2.fid
Jonnie_2B
13C{1H}
DMSO
700 MHz
296K
179.806
169.667
147.614
133.285
132.128
131.409
129.362
128.671
127.363
126.531
125.780
121.815
121.061
119.772
118.651
116.967
115.729
114.866
113.545
21.515
N
O
O
O
29b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


Jonnie_3B.10.fid
Jonnie_3B
DMSO
1H
700 MHz
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8.242
8.157
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7.504
7.251
7.165
7.153
6.788
6.776
6.381
5.788
5.742
5.184
3.428
3.307
3.300
3.292
3.284
3.273
2.523
2.521
2.512
2.510
2.507
2.502
2.501
2.497
2.300
1.670
1.255
1.190
1.171
1.145
0.871
N
O
O
O
Cl
29c
1.45
78.74
0.52
0.31
40.03
17.59
3.32
0.70
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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1.0
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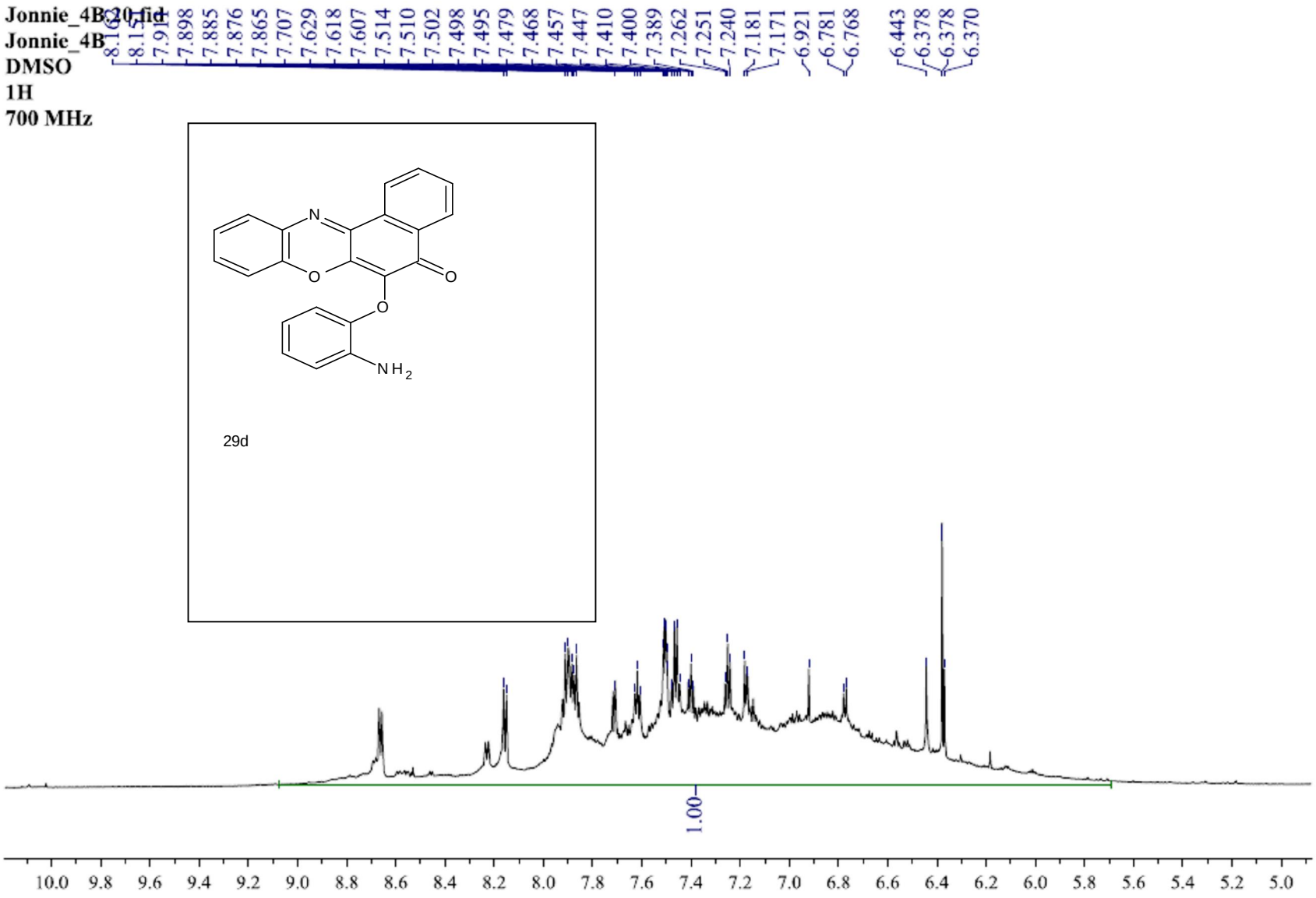
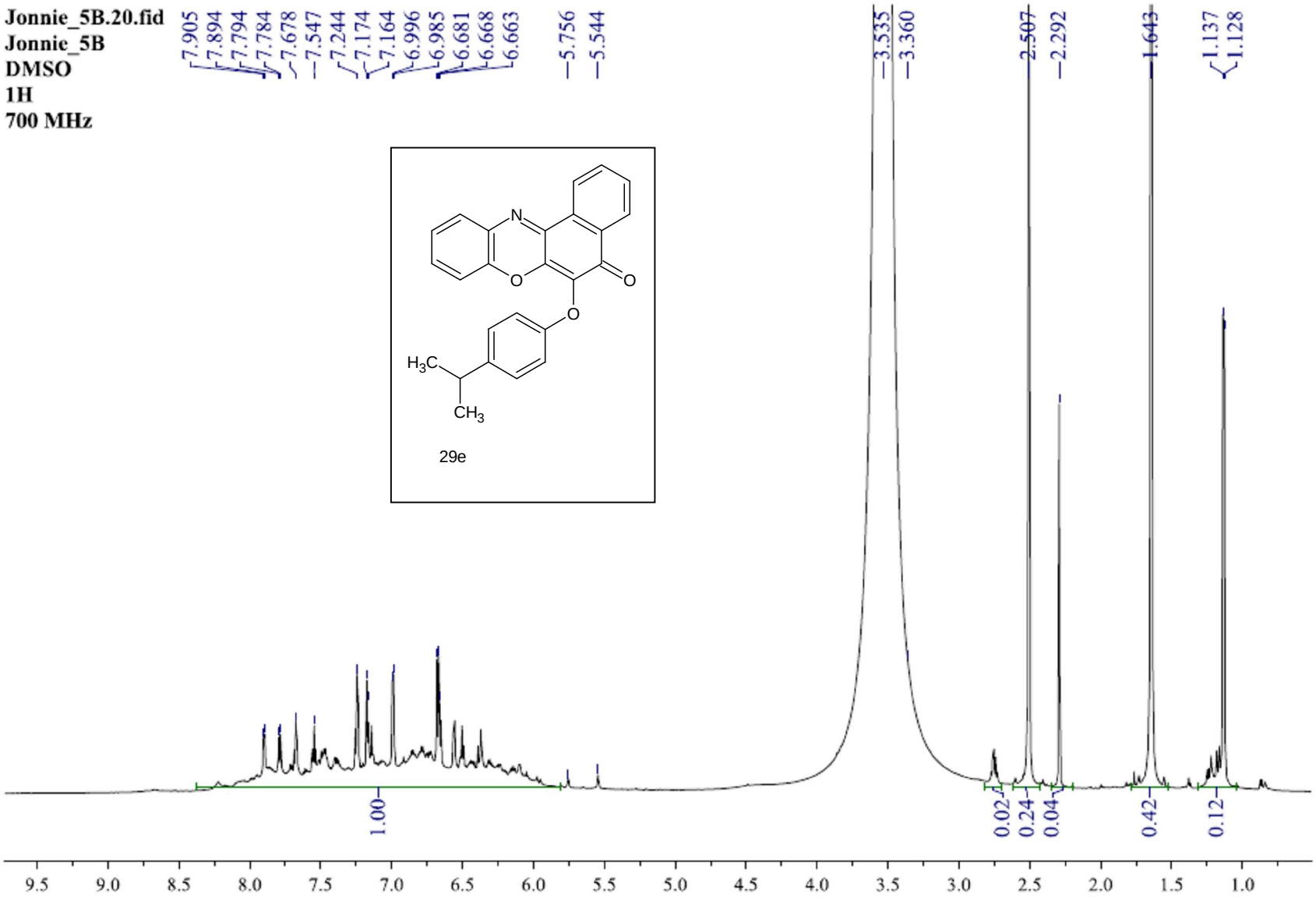
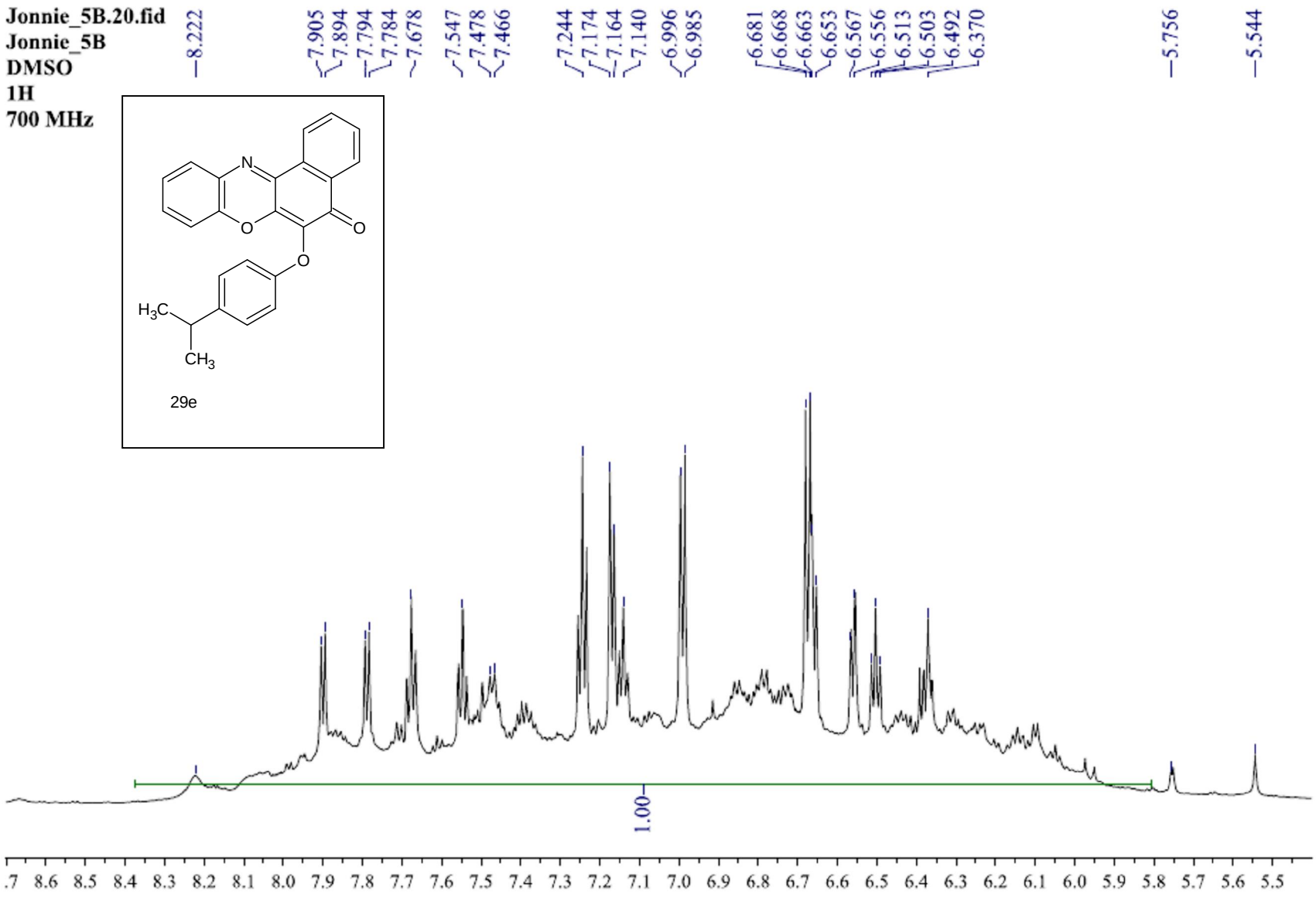
-0.5


Jonnie_4B_20_fid
Jonnie_4B
DMSO
1H
700 MHz
8.157
8.154
7.911
7.898
7.885
7.876
7.865
7.707
7.629
7.618
7.607
7.514
7.510
7.502
7.498
7.495
7.479
7.468
7.457
7.447
7.410
7.400
7.389
7.262
7.251
7.240
7.181
7.171
6.921
6.781
6.768
6.443
6.378
6.378
6.370
N
O
O
O
NH2
29d
1.00
10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0


Jonnie_5B.20.fid
Jonnie_5B
DMSO
1H
700 MHz
7.905
7.894
7.794
7.784
7.678
7.547
7.244
7.174
7.164
6.996
6.985
6.681
6.668
6.663
5.756
5.544
3.535
3.360
2.507
2.292
1.643
1.137
1.128
N
O
O
O
H3C
CH3
29e
1.00
0.02
0.24
0.04
0.42
0.12
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0


Jonnie_5B.20.fid
Jonnie_5B
DMSO
1H
700 MHz
8.222
7.905
7.894
7.794
7.784
7.678
7.547
7.478
7.466
7.244
7.174
7.164
7.140
6.996
6.985
6.681
6.668
6.663
6.653
6.567
6.556
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6.503
6.492
6.370
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5.544
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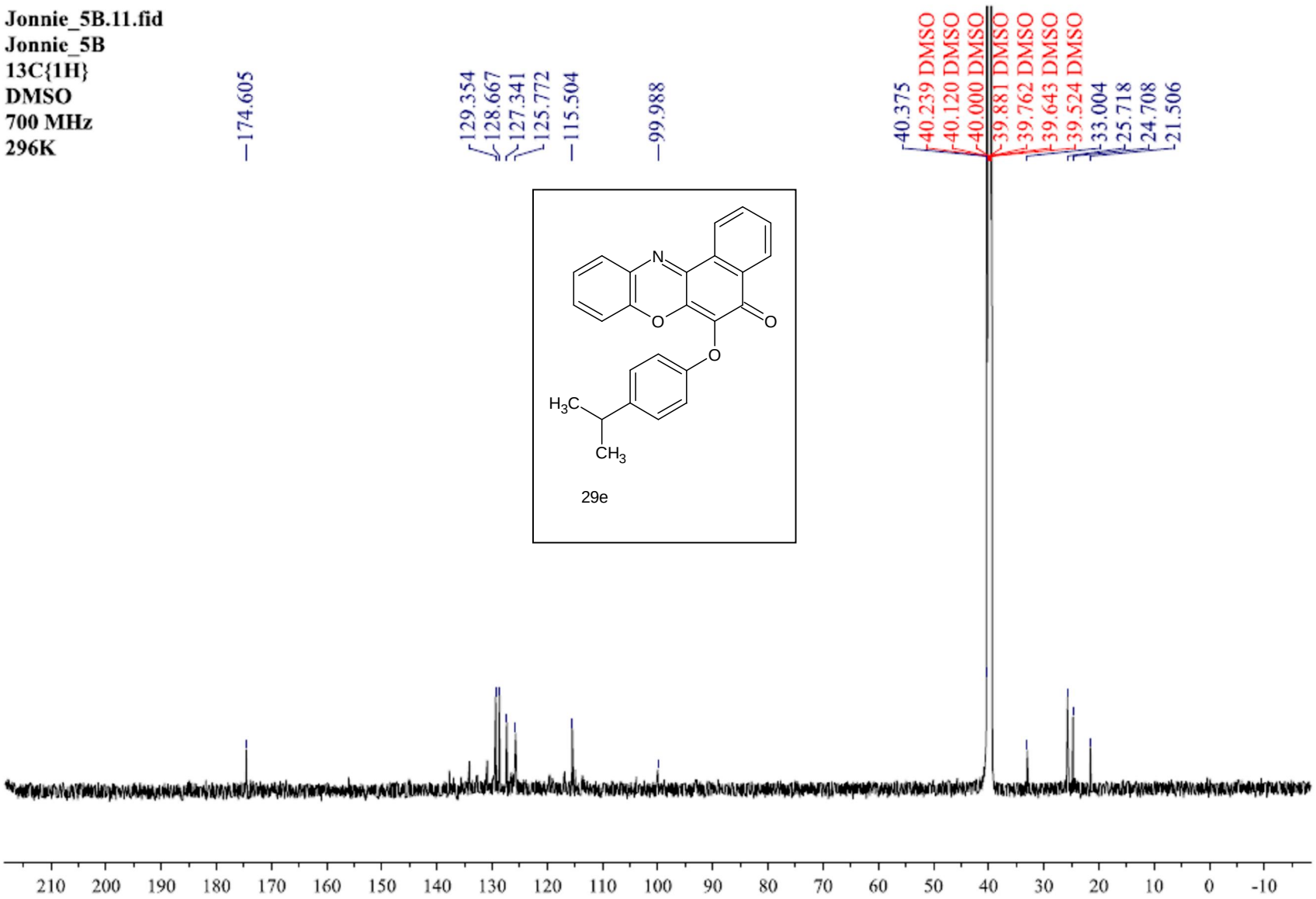
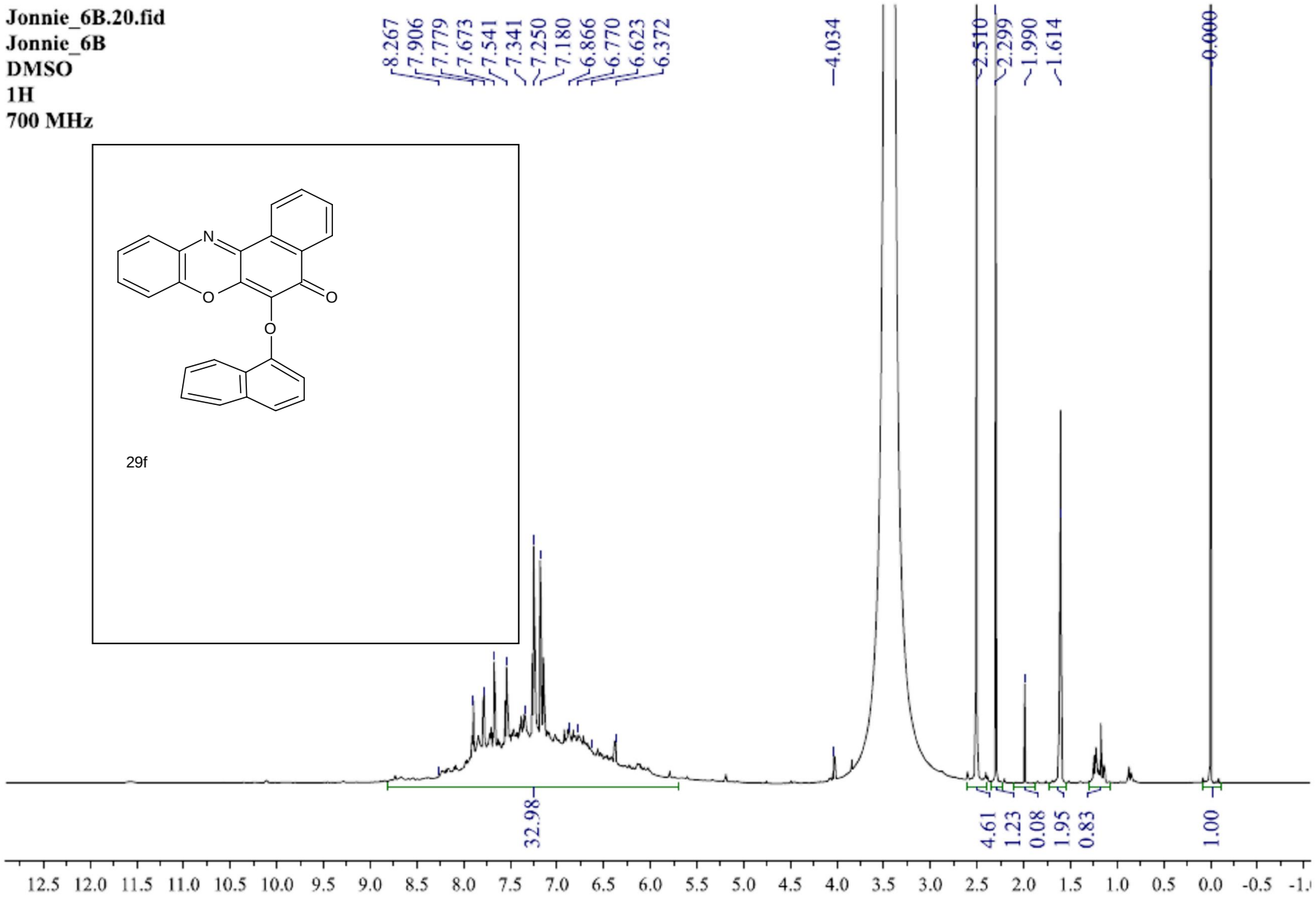
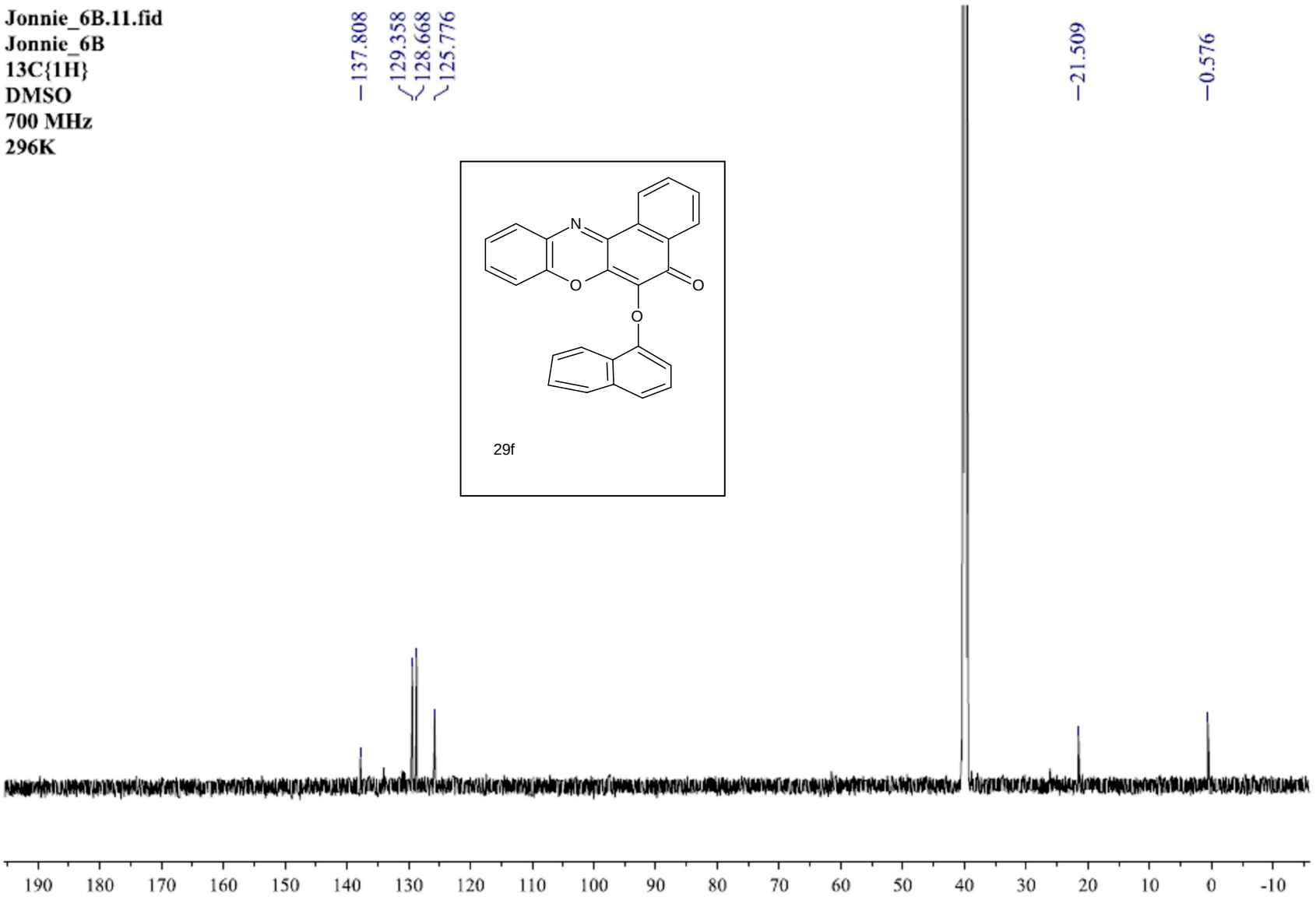
O
O
O
H3C
CH3
29e
1.00
.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5


Jonnie_5B.11.fid
Jonnie_5B
13C{1H}
DMSO
700 MHz
296K
174.605
129.354
128.667
127.341
125.772
115.504
99.988
40.375
40.239 DMSO
40.120 DMSO
40.000 DMSO
39.881 DMSO
39.762 DMSO
39.643 DMSO
39.524 DMSO
33.004
25.718
24.708
21.506
N
O
O
O
H3C
CH3
29e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


Jonnie_6B.20.fid
Jonnie_6B
DMSO
1H
700 MHz
29f
8.267
7.906
7.779
7.673
7.541
7.341
7.250
7.180
6.866
6.770
6.623
6.372
4.034
2.510
2.299
1.990
1.614
0.000
32.98
4.61
1.23
0.08
1.95
0.83
1.00


Jonnie_6B.11.fid
Jonnie_6B
13C{1H}
DMSO
700 MHz
296K
137.808
129.358
128.668
125.776
21.509
0.576
N
O
O
O
29f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10