NOVEL ONE-POT THREE - COMPONENT SYNTHESIS OF FUSED DIHYDROPYRIMIDO-THIADIAZOLE COMPOUNDS OF BIOLOGICAL INTEREST.

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF M.Phil. OF SCIENCE IN CHEMISTRY.

Submitted

by

SOMA MITRA

Student I.D: 1015033101

ORGANIC RESEARCH LABORATORY

DEPARTMENT OF CHEMISTRY

BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY(BUET),

DHAKA-1000, BANGLADESH.

June, 2019.

Dedicated

TO

My Mother

BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY (BUET)

DHAKA-1000, BANGLADESH

DEPARTMENT OF CHEMISTRY

THESIS ACCEPTANCE LETTER

A Thesis on

NOVEL ONE–POT THREE–COMPONENT SYNTHESIS OF FUSED DIHYDROPYRIMIDO–THIADIAZOLE COMPOUNDS OF BIOLOGICAL INTEREST

Submitted by

Soma Mitra

Roll No. 1015033101P, Session: October / 2015, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Masters of Philosophy (M.Phil) in Chemistry on June 22, 2019.

Board of Examiners

1. Dr. Md. Abdur Rashid
Professor
Department of Chemistry, BUET,
Dhaka-1000, Bangladesh

(Supervisor)

2. Dr. Md. Abdur Rashid
Professor & Head
Department of Chemistry, BUET,
Dhaka-1000, Bangladesh

Member (Ex-Officio)

3. Dr. Shakila Rahman
Professor
Department of Chemistry, BUET,
Dhaka-1000, Bangladesh

Member

4. Dr. Sharmeen Nishat
Assistant Professor
Department of Chemistry, BUET,
Dhaka-1000, Bangladesh

Member

5. Dr. Zinia Nasreen
Professor
Department of Chemistry, Dhaka University of Engineering & Technology, (DUET), Gazipur-1700

Member (External)

CANDIDATE'S DECLARATION

This thesis work has been done by the candidate herself and does not contain any material extracted from elsewhere or from a work published by anybody else . The work for this thesis has not been presented elsewhere by the author for any degree or diploma .

June 22 , 2019 .

Soma Mitra
M. phil student
Roll No. 1015033101
Department of Chemistry
BUET , Dhaka
Bangladesh.

ACKNOWLEDGEMENT

It is a great pleasure to express my gratitude to my honorable supervisor Dr. Md. Abdur Rashid , professor , Department of Chemistry , BUET , Dhaka to introduce me into research work . I am greatly indebted to him for his excellent supervision , inspiring guidance , enthusiastic encouragement , sagacious advice and affectionate surveillance throughout the execution of my research work .

I wish to express my gratitude and thanks to all other professors and teachers of BUET for their kind help and cooperation during the entire period of my research work .

I am also like to thanks to all staff in the Department of Chemistry , BUET , Dhaka for their instant help throughout the entire period of my work .

I would like to thank the authority of BUET to give me an opportunity to purse higher studies for M.phil Degree in this University and also give me financial support.

Finally , I would like to thanks my lab mates , my mother , relatives and friends for their inspirations , comments and suggestions during this research work.

Author

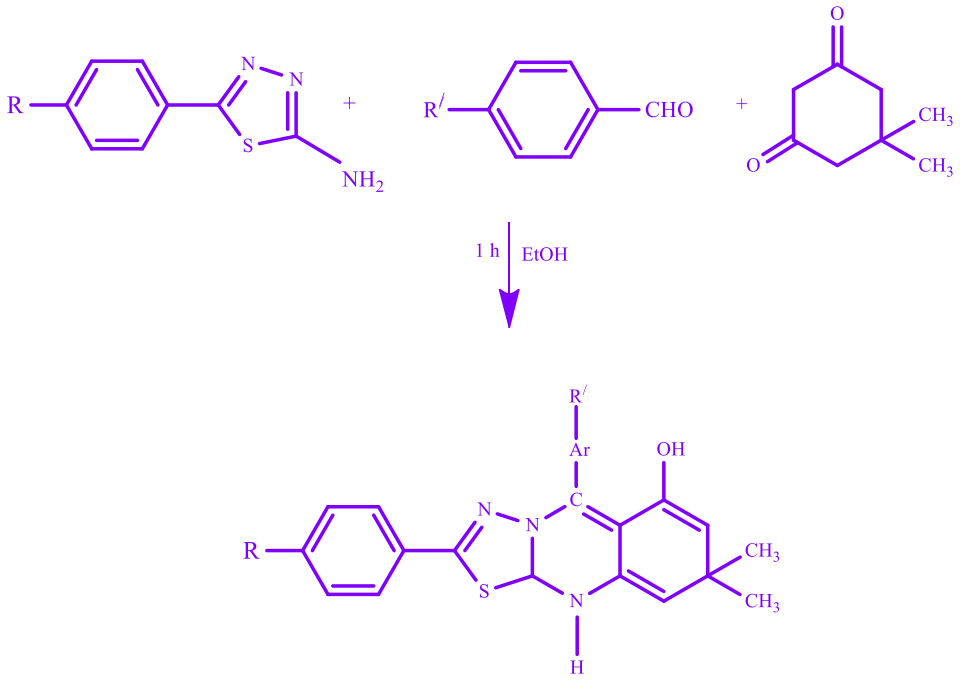
(Soma Mitra)

Contents

Chapter 3

ABSTRACT

Multi-component reaction allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the reaction of molecular diversity and complexity . Multi-component one-pot reaction is the simplest and the most economical methods for the synthesis of biologically important and pharmacologically useful dihydro-thiadiazol quinozoline derivatives . Without using catalyst under thermal condition is proven efficient method for a one-pot synthesis of dihydro-thiadiazole-quinazolin derivatives in excellent yields from thiadiazole , dimedone and aldehydes in presence of ethanol solvent . The present environmentally benign procedure for the synthesis of dihydro-thiadiazole-quinazolin derivatives is suitable for library synthesis and it will find application in the synthesis of biologically active molecules . The process presented here in operationally simple environmentally benign and has excellent yield . Furthermore , the reaction time is very short within an hour under steam bath reflux condition .



$R = NO_2, Cl$ $R^{/} = H, NO_2, Cl, OH, OCH_3$

Reaction scheme

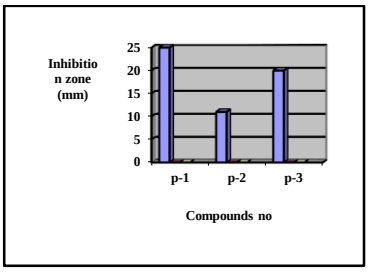
In Vitro Bactericidal Profiles of compounds in Terms of Zone of Inhibition

The P-2 compound showed bactericidal moderate activity against *S . aureus* , *B . subtilis* , *P. aeruginosa* . Noticeably , all the compounds showed the antibacterial activity against *B . subtilis* . *P . aeruginosa* *E . coli* , *S . aureus* , *C . freundii* . Among them P-1 showed very good activity against *B . subtilis* , *P . aeruginosa* , *E . coli* , *S . aureus* . P-3 compound showed very good activity against *C . freundii* .

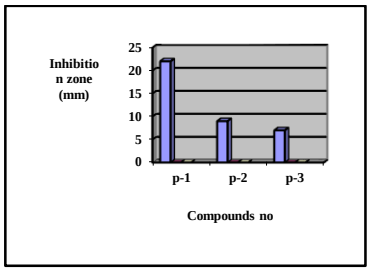
P-1 , P-2 and P-3 compounds showed the antifungal activity against both *T . harzianum* and *A . niger* .

Comp.	Bacterial species						Fungal Species	
	Gram positive	Gram negative						
	S.a	*B.s*	*E.c*	*P.a*	*S.t*	*C.f*	*T.h*	*A.n*
P-1	25	23	26	22	18	32	9	7
P-2	11	15	10	9	13	15	6	13
P-3	20	20	15	7	10	25	13	7

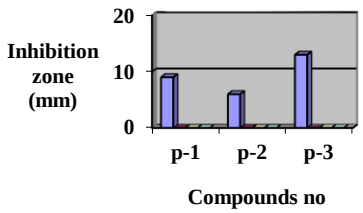
Antibacterial activity against *S .a*



Antibacterial activity against *P. a*



Antifungal activity aganist *T. h*



INTRODUCTION

Chapter 1

Multi-component reactions (MCR_s) are one-pot processes in which three or more reactants come together in a single reaction vessel to give a final product. Currently , multi-component reactions are an important part of numerous research work involved in the drug discoveries to achieve synthetic targets in effective way , because they are easy to carryout and provide rapid access to libraries of organic compounds with diverse substitution patterns [1-3] .

One pot reactions where several reaction sequences are conducted in the same reaction flask are one of the methods that can be used in order to conduct synthesis in a greener fashion . The chemistry is greener due to the reduction of work-up procedures and purification steps required compared to a more stepwise approach . In catalytic reaction it is possible to combine several catalytic processes in the same reaction vessel .

The most significant advantage , in the synthetic point of view is that it is less likely to lose material that would otherwise be lost during work up and purification .

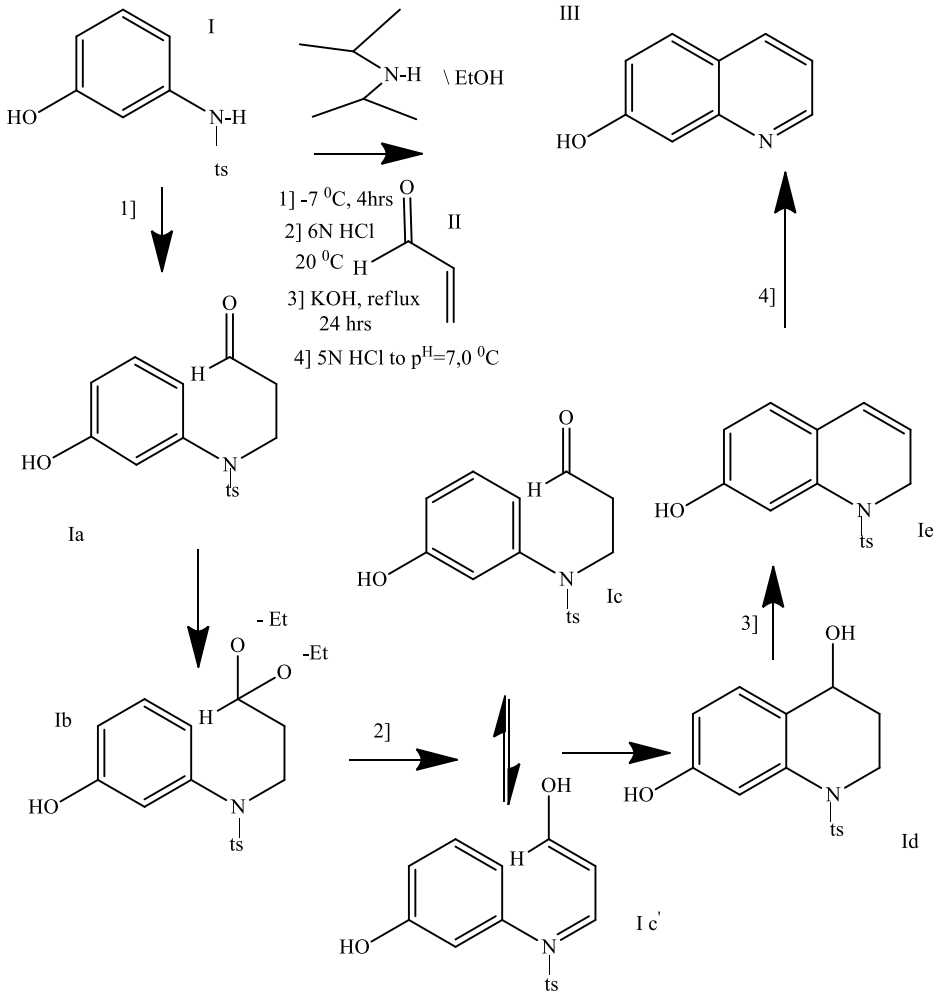
The second advantage is the economy of utilizing chemicals and solvents . To work up the reaction at each step , it always need to use some sort of solvents that would come to waste eventually . One-flask reaction , multicenter involving multiple steps would only requires final workup at the final step .

The third advantage is the minimal amount of work required , instead of working up each step of the synthesis involving , say , three steps , it only need to do one work up at the end.

In chemistry a one-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor . This is much desired by chemists because avoiding a lengthy separation process and purification of the intermediate chemical compounds would save time and resources while increasing chemical yield .

An example of a one-pot synthesis is the total synthesis of tropinone or the Gassman indole synthesis . Sequential one-pot synthesis can be used to generate even complex targets with multiple stereocentres , such as oseltamivir [4] , which may significantly shorten the number of steps required overall and have important commercial implications . A sequential one-pot

synthesis with reagents added to a reactor one at a time and without work-up is also called a telescoping synthesis . In one such procedure [5] the reaction of 3-*N*-tosylaminophenol **I** with acrolein **II** affords a hydroxyl substituted quinoline **III** through 4 sequential steps without workup of the intermediate products **(Scheme 1) .**



Scheme 1 (Synthesis of tropinone)

Multicomponent reactions are convergent reactions , in which three or more starting materials react to form a product , where basically all or most of the atoms contribute to the newly formed product . In an MCR , a product is assembled according to a cascade of elementary chemical reactions . Thus , there is a network of reaction equilibria , which all finally flow into an irreversible step yielding the product . The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions : solvent , temperature , catalyst , concentration , the kind of starting materials and functional groups .

In chemistry , a multi-component reaction (or MCR) , sometimes referred to as a "Multi-Component Assembly Process" (or MCAP) , is a chemical reaction where three or more compounds react to form a single product . By definition , multicomponent reactions are those reactions whereby more than two reactants combine in a sequential manner to give highly selective products that retain majority of the atoms of the starting material .

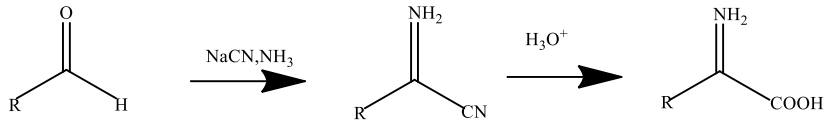
Multicomponent reactions have been known for over 150 years . First documented multicomponent reaction was the Strecker synthesis of α-amino cyanides in 1850 from which α-amino acids could be derived . A multitude of MCRs exist today , of which the isocyanide based MCRs are the most documented . Other MCRs include free-radical mediated MCRs , MCRs based on organoboron compounds and metal-catalyzed MCRs .

Multicomponent reaction (MCR) is a synthetic methodology in which three or more reactants come together in a single reaction vessel to form a new product . The characteristic aspect of MCRs is that the final products contain almost all portions of substrates , generating almost no by-products . That makes MCRs an extremely ideal and eco-friendly reaction system . Target compounds can be obtained in one pot with much fewer steps . Therefore , MCRs have been paid much attention in various research fields , such as discovery of lead compounds in medicinal chemistry or combinatorial chemistry . There have been a number of reports on MCRs so far , and typical examples are described as below .

Strecker reaction

(Three-component reaction: 3CR)

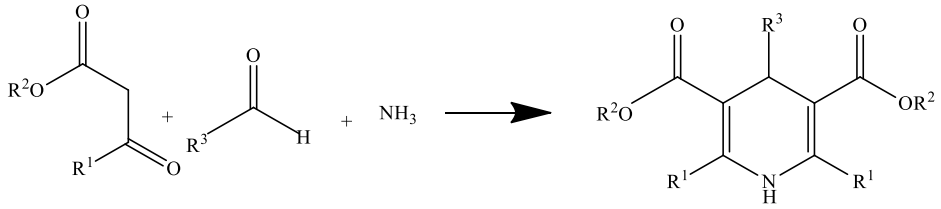
Strecker reaction (Amino acid synthesis)



Scheme 2 (Synthesis of α amino acid)

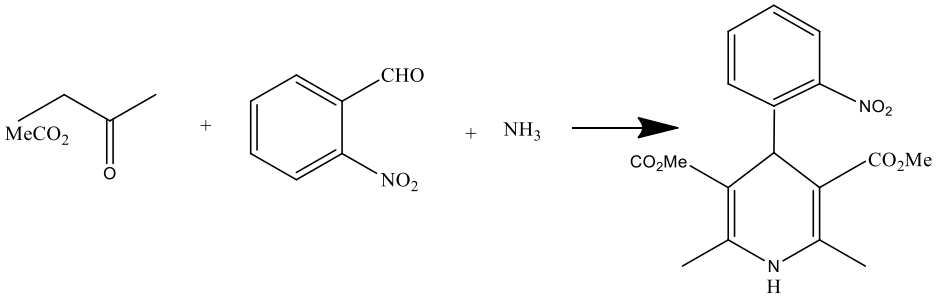
This reaction was reported by A . Strecker in 1850 , and is extremely famous as the synthesis of α-amino acids . This reaction is an MCR which comprises three components , aldehydes , hydrogen cyanide , and ammonia as substrates , and is recognized as the world's first MCR [6] .

Hantzsch dihydropyridine synthesis (3CR)



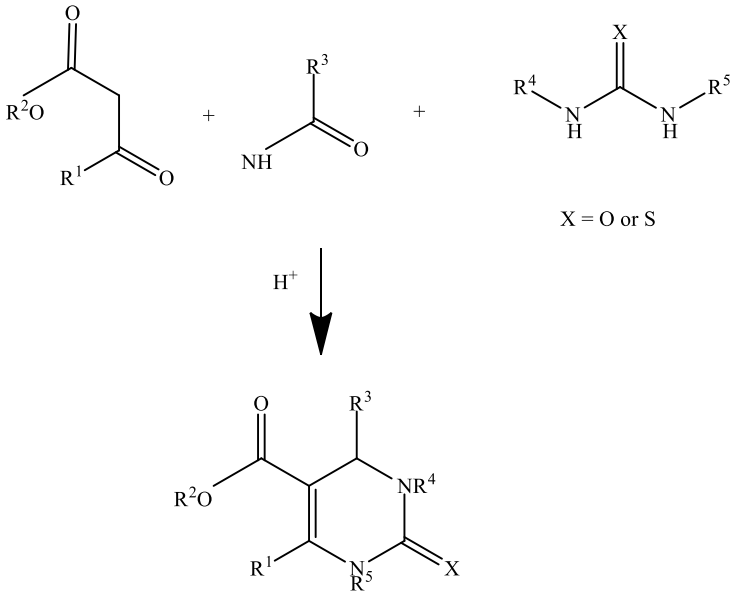
Scheme 3 (Synthesis of dihydropyridine)

This reaction was reported by A. R. Hantzsch in 1881 , and is the best-known three-component MCR , which affords 1,4-dihydropyridine derivatives using β-keto esters , aldehydes , and ammonia [7] . For an example , a calcium channel blocker "Nifedipine" is also synthesized by this reaction [8] .



Scheme 4 (Synthesis of Nifedipine)

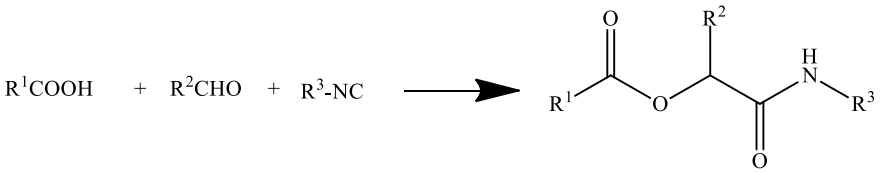
Biginelli reaction (3CR)



Scheme 5 (Synthesis of dihydropyrimidinone)

In 1891 , an Italian chemist , P. Biginelli has reported the three component MCR using β-keto esters such as ethyl acetoacetate , aromatic aldehydes such as benzaldehyde , and ureas (or thioureas) in the presence of acid catalyst (Brönsted or Lewis acids) , affording dihydropyrimidinone derivaties [9] . Dihydropyrimidinones have been paid much attention because of their various bioactivities such as antiinflammatory or anti-bacterial activities . For an example of pharmaceuticals developed by using the reaction , several antitubercular agents have been reported .

Passerini reaction (3CR)

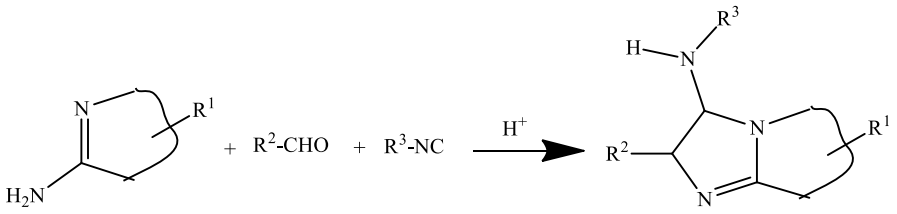


Scheme 6 (Synthesis of α – acyloxy amides)

In 1921 , an Italian chemist , M. Passerini et al. have reported the three-component reaction using carboxylic acids , aldehydes , and isonitriles , affording α-acyloxy amides [10] . The Passerini reaction also has been applied into pharmaceutical research , for example , Hulme et

al. have reported the library synthesis of novel norstatine derivatives bearing benzimidazole moieties [11] .

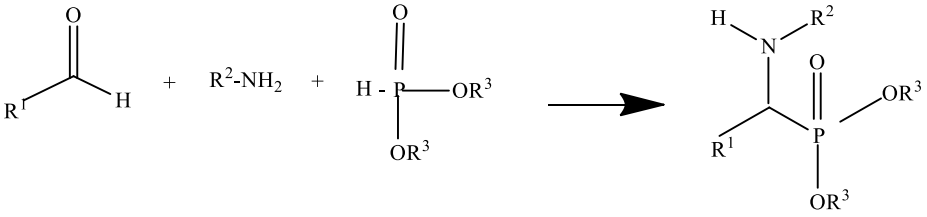
Gröbcke-Blackburn-Bienaymé reaction [12]



Scheme 7 (Synthesis of fused nitrogen – containing aromatic compounds)

This reaction is a three-component MCR using aldehydes , isonitriles , and α-aminoazines such as 2-aminoimidazole or 2-aminopyridine in the presence of acid catalyst . The reaction is applicable for the synthesis of fused nitrogen-containing aromatic compounds as below .

Kabachnik-Fields reaction (3CR)

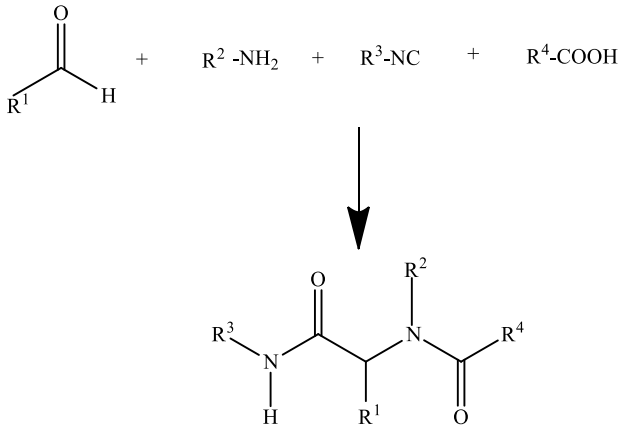


Scheme 8 (Synthesis of α aminophosphonates)

In 1952 , M. I. Kabachinik et al. have reported the three component MCR using aldehydes , amines , and dialkyl phosphites in the presence of acid catalyst (Brønsted or Lewis acids) , afforded α-aminophosphonates [13] .

In recent years , much attention has been paid to α-aminophoshonates since they can be considered as structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis . Thus , α-aminophoshonates have been applied into several research areas , such as development of renin inhibitors or HIV protease inhibitors [14] .

Ugi reaction (4CR)



Scheme 9 (Synthesis of Bis-amide)

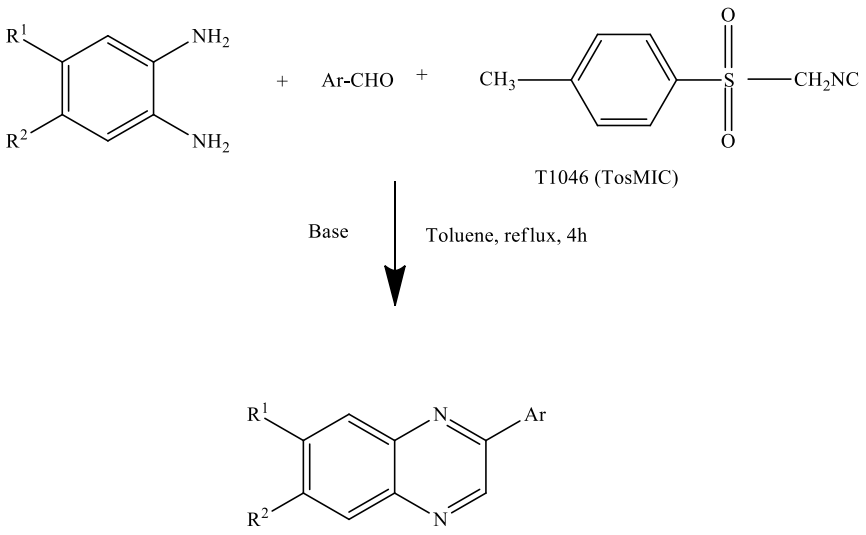
This reaction is the four-component MCR reported by I. K. Ugi et al. in 1962 for the first time . It enables one-pot condensation of four components (aldehydes , amines , isonitriles , and carboxylic acids) , thus , it can be said that the Ugi reaction is the most versatile among MCRs .

Other examples of MCR

MCR using *p*-toluenesulfonylmethyl isocyanide

(TosMIC) (3CR)

p-Toluenesulfonylmethyl isocyanide (TosMIC) (T1046) is a synthetic reagent , developed by Leusen et al., and has both an isonitrile group and a tosyl group (leaving group) in one molecule , [15] . Different from other isonitrile compounds with odor character , TosMIC is an odorless and solid compound . Because of its easy-handling property , TosMIC has been widely used for the synthesis of nitrogen-containing aromatic heterocyclic compounds , such as oxazoles [16] . TosMIC also has been used for MCRs , for example , Tsoleridis et al. reported the synthesis of quinoxaline derivatives via the three-component condensation of o-phenylenediamines , aromatic aldehydes and TosMIC [17] .



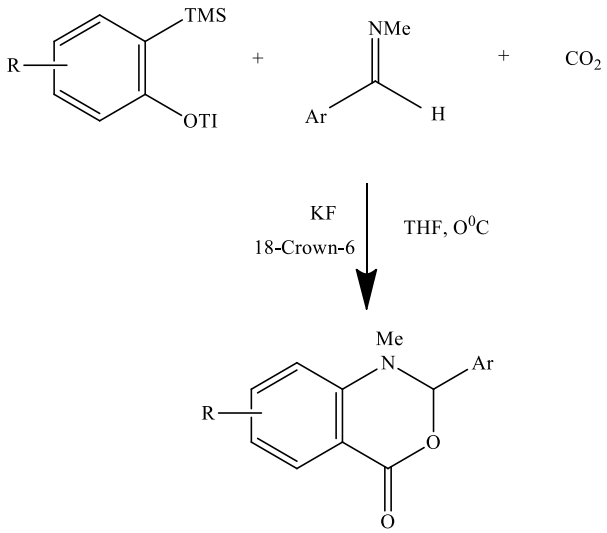
Scheme 10 (Synthesis of quinoxaline)

Entry	R^1	R^2	Ar	Base	Quinoxaline(Y.%)
1	H	H	Phenyl	DABCO	91%
2	H	H	2,4-dimethylphenyl	DABCO	81%
3	H	H	4-chlorophenyl	DABCO	84%
4	Me	Me	Phenyl	DBU	86%
5	Me	Me	2-methylphenyl	DBU	85%

MCR using benzynes (3CR)

Recently , there also have been several reports on MCRs using benzynes . For example , Yoshida et al. have reported the three-component MCR using in situ generated benzynes , imines , and carbon dioxide , affording benzoxadinones [18] .

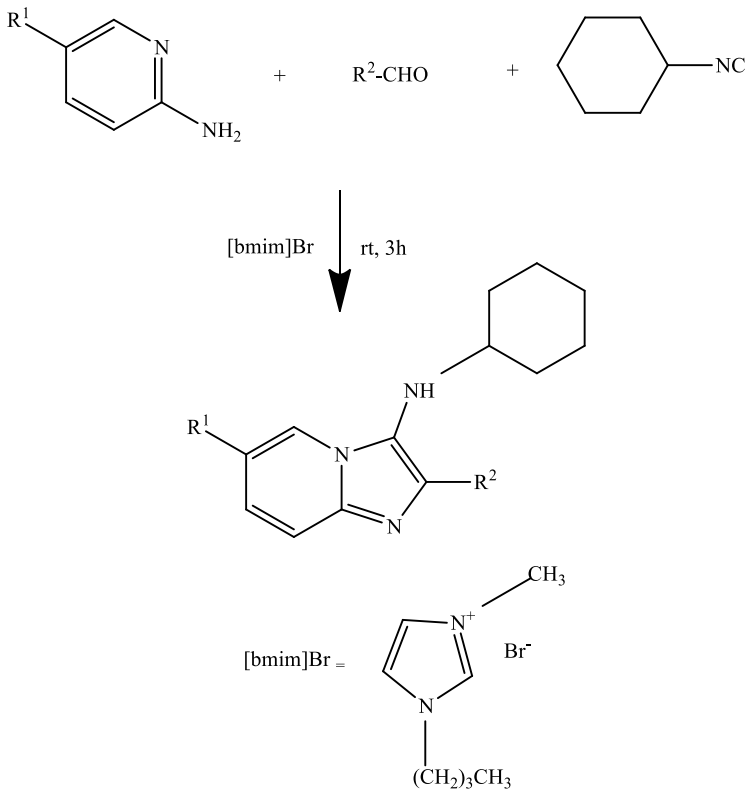
Recently , much attention has been paid on organic synthesis using carbon dioxide as a carbon source from the ecological point of view , thus , the reaction above is an extremely useful and eco-friendly MCR .



Ar = 2,4,6 – trimethylphenyl

Scheme 11 (Synthesis of benzoxadinones)

Thus, MCR is a strong synthetic methodology to enable condension of various substrates in one pot , however , in some cases , reactions require long times for completion or result in undesired side reactions even after optimization of reaction conditions such as solvents or Lewis acid catalysts . For resolving these problems , there have been successful reports on accelerating MCRs . For example , Shaabani et al. have reported the ionic liquid promoted Grobcke – Blackburn – Bienayme reaction . As indicated in the table below , in the case of using ionic liquids as solvents , reactions proceed smoothly to afford the desired products in excellent yields . On the other hand , the yield of product is poor even in the prolonged reaction time . Moreover , as indicated in Entry 1 , the ionic liquid can be reused for the same reactions but maintain the high yields .



Scheme 12 (Example of undesired side reaction)

Entry	R^1	R^2	Yield(%)
1	Br	Ph	98
2	Me	Ph	98
3	Me	Ph	25
4	Me	4-$CH_3C_6H_4$	99
5	Me	4-$O_2NC_6H_4$	92
6	Me	4-Pyridly	97

All of the newly synthesized compounds were evaluated for their in vitro growth inhibitory activities against a panel of standard strains of pathogenic microorganisms including three Gram-positive bacteria , three Gram-negative bacteria , and three strains of fungi . The antimicrobial studies were assessed by minimum inhibitory concentration (MIC) using the broth dilution method [19 , 20] . MIC is the highest dilution of a compound which shows clear fluid with no development of turbidity .

Multi-component reactions (MCRs) are convergent reactions , in which three or more starting materials react to form a product , where basically all or most of the atoms contribute to the

newly formed product . In an MCR , a product is assembled according to a cascade of elementary chemical reactions . Thus , there is a network of reaction equilibria , which finally flow into an irreversible step yielding the product . The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products . The result is clearly dependent on the reaction conditions : solvent , temperature , catalyst , concentration , the kind of starting materials and functional groups . Such considerations are of particular importance in connection with the design and discovery of novel MCRs . In the drug discovery process, MCR offers many advantages over traditional approaches . With only a limited number of chemists and technicians , more scaffold synthesis programs can be achieved within a shorter time . With one pot reactions , each synthetic procedure (weighing of reagents , addition of reagents , reaction time , control) and work-up procedure (quenching , extraction , distillation , chromatography , weighing , and analysis) needs to be performed only once , in contrast to multistep synthesis . MCRs are compatible with a solution phase approach , thus enabling a simple monitoring and they are easily amenable to automation . Moreover , each scaffold is expandable from a low number of compounds (scouting library) to a larger library. Thus, "hit-to lead" transitions are normally accomplished easily and promptly . Certain physicochemical properties can be built into a library , e.g. lipophilicity and aqueous solubility , molecular weight , numbers of hydrogen donors and acceptors and the number of rotatable bonds , as well as the polar surface area . Finally , scale-up is often possible from a preclinical lab-scale (mg, gram) to clinical exploratory amounts (kg) using the same type of chemistry [21] . Drug molecules derived from MCR are very cost effective which , is the need of the hour . MCRs have received considerable attention because of the complexity of the molecules that can be easily achieved from readily available starting materials in one reaction sequence [22] . MCRs generally occur in one pot and exhibit high atom economy and product selectivity . In most of the cases , they yield a single product and thus MCRs are advantageous over linear stepwise synthesis because of operational simplicity , reduction in reaction time , ecological friendliness , saving of money and raw materials , inexpensive purification , and avoidance of protection and deprotection processes [23] .

A simple , economical and one-pot protocol is developed for construction of multiple carbon–carbon bonds having C(sp2)-C(sp2) and C(sp2)-C(sp) hybridization , as these intriguing molecular architectures exhibit significant optoelectronic and medicinal properties. To this end , a sequential reaction is devised that allows one-pot three-component reactions of

hydroxybenzaldehydes (C_6–C_1 unit) , halo-phenylacetic acids (C_6–C_2 unit) and arylacetylenes (C_6–C_3 unit) resulting in the formation of highly π-conjugated complex arylethenyl-arylethynyl-arenes (C_6–C_2–C_6–C_2–C_6 unit) bearing a hydroxyl group via sequential perkin condensation–decarboxylation–Sonogashira coupling in polyethylene glycol with microwave irradiation . The process avoids protection–deprotection manipulations , generates CO_2 and H_2O as by-products and is successfully extended for the efficient construction of a wide series of novel aliphatic/alicyclic/hetero/aromatic arylethenyl-arylethynyl-arenes with pendant hydroxy functionality , which could undergo further chemical modification to achieve target biological and physical properties .

Synthetic methods that rapidly generate molecular complexity from simple starting materials in a tandem (consecutive or sequential) manner are highly attractive for the pot-economic synthesis of bioactive organic molecules , natural products and functional materials . Such methods preclude the isolation or purification of intermediates and are more efficient and sustainable . Thus , one-pot tandem [24] reactions have become innovative protocols for the construction of several bonds, including carbon–carbon bonds . In this way , construction of multiple carbon–carbon single bonds with double and triple bonds in one pot for the synthesis of privileged arylethenyl-arylethynylarenes with C(sp2)-C(sp2) and C(sp2)-C(sp) hybrid orbitals would be highly advantageous because such extended *p*-conjugated [25,26] scaffolds (with enyne bonds) are of considerable interest for their wide range of optoelectronic and medicinal properties .

Conventionally , construction [27] of these highly significant C(sp2)-C(sp2) and C(sp2)-C(sp) hybridized molecules has been mainly achieved either by Sonogashira coupling between halostilbenes and phenylacetylenes or by Cadiot–Chodkiewicz [28] coupling . Furthermore , Heck–Sonogashira sequences or the Suzuki–Miyaura [29] reaction (between potassium alkynyl-aryltrifluoroborates and aryl halides) are also useful for synthesizing such p-conjugated molecules . The synthesis of similar polyaromatic molecules can also be achieved by Sonogashira coupling followed by Wadsworth–Emmons reaction using diethyl (4-cyanobenzyl) phosphonate [30] . The Heck–Sonogashira reaction sequence has also been reported but this yielded only non-hydroxylated arylethenyl-arylethynyl-arene products [31] . Furthermore , use of expensive and unstable substrates , multistep synthesis and generation of waste , as well as protecting group manipulations [32] in the case of hydroxy-substituted arylethenyl-arylethynyl-arenes are of concern from green chemistry and economical

perspectives . Highly p-conjugated hydroxylated aromatic molecules [33] have gained importance for their biological activities and applications as advanced materials , as the presence of hydroxy groups allows further chemical modification to achieve desired properties .

In recent years , dihydropyrimidine-2 (1H) one derivatives have gained much interest for their biological and pharmaceuticals properties such as HIV gp-120-CD4 inhibitors [34] , calcium channel blockers [35] , α-adrenergic and neuropeptide Y antagonists [36] , as well as antihypertensive , antitumor , antibacterial , anti-inflammatory [37] agent . The scope of this pharmacophore has been further increased by the identification of the Monostrol a novel as a cell-permeable lead compound for the development of the new anticancer drugs [38] bearing the dihydropyrimidones core . Thus the development of facile and environmental friendly synthetic method towards dihydropyrimidines constitute active area of investigation of in organic synthesis , the first synthetic method for the preparation of dihydropyrimidine-2(1H) ones (DHPMs) was recorded by Biginelli [39] , that involves the one pot three component condensation of aldehyde, 1, 3-dicarbonyl compounds and urea or thiourea in ethanol under strongly acidic conditions producing DHPMs , albeit in low yields . In the view of the pharmaceuticals importance of these compounds many improved catalytic methods have been developed [40-44] . Although these methods have their long reaction time , harsh reaction conditions , unsatisfactory yield and use of large quantity of catalyst .

Dihydropyrimidine dehydrogenase (DPD) is an enzyme that is involved in pyrimidine degradation that in humans is encoded by the DPYD gene [45-46] . It is the initial and rate-limiting step in pyrimidine catabolism . It catalyzes the reduction of uracil and thymine [47] . It is also involved in the degradation of the chemotherapeutic drugs 5-fluorouracil and tegafur [48] .

The protein is a pyrimidine catabolic enzyme and the initial and rate-limiting factor in the pathway of uracil and thymidine catabolism . Genetic deficiency of this enzyme results in an error in pyrimidine metabolism associated with thymine-uraciluria and an increased risk of toxicity in cancer patients receiving 5-fluorouracil chemotherapy [49] .

Dihydropyridine is a molecule based upon pyridine , and the parent of a class of molecules that have been semi-saturated with two substituents replacing one double bond.

They are particularly well known in pharmacology as L-type calcium channel blockers , used in the treatment of hypertension . Compared with certain other L-type calcium channel blockers (for example those of the phenylalkylamine class such as verapamil) that have significant action at the heart, they are relatively vascular selective in their mechanism of action in lowering blood pressure .

Dihydropyridine (DHP) calcium channel blockers are derived from the molecule dihydropyridine and often used to reduce systemic vascular resistance and arterial pressure . Sometimes when they are used to treat angina , the vasodilation and hypotension can lead to reflex tachycardia , which can be detrimental for patients with ischemic symptoms because of the resulting increase in myocardial oxygen demand . Dihydropyridine calcium channel blockers can worsen proteinuria in patients with nephropathy [50] .

DHP act by binding to a site that is formed by amino acid residues in two adjacent S6 segments plus the intervening S5 segment .

They gain access to this site from the extracellular side of the membrane , possibly via a sidewalk pathway similar to that postulated for local anesthetics . DHP bind preferentially to the open/inactivated state of the VGCC and binding results in modification of channel gating. All DHP used clinically act by promoting transition of VGCC into a nonconducting inactivated state as envisaged by the “modulated receptor” hypothesis . Agonist forms of DHP also exist , although they have no clinical role . Agonist DHP bind to the same region of the VGCC as antagonist DHP (although they may not have identical molecular targets) and increase the likelihood of the channel adopting a long open state that occurs only rarely under normal conditions . In some cases enantiomers of the same chemical entity act as agonist and antagonist , respectively , and agonists can be converted to antagonists or vice versa following site-specific mutation of the channel or by modified experimental conditions .

The mechanism by which DHP reduce Ca^{2+} entry has been studied extensively . A recent model suggests that DHP stabilize an impermeable state which binds a single Ca^{2+} ion . The preferential binding of DHP to channels in the open or inactivated state means that the affinity of DHP is influenced by the membrane potential (i.e., voltage dependence) . DHP show higher affinity for VGCC under more depolarized conditions because in these conditions the probability of the open or inactivated state is favored . The voltage-dependence

of DHP partially explains why these drugs act preferentially on VGCC in vascular smooth muscle compared with cardiac muscle because vascular smooth muscle cells generally maintain a more depolarized membrane potential than cardiac myocytes . However , other factors also contribute to the preferential action of DHP on the vasculature . These factors include the lower DHP sensitivity of $Ca_V1.3$ and $Ca_V1.4$ subtypes in the heart , and the higher expression of splice variants of $Ca_V1.2$ in vascular smooth muscle that show greater affinity for DHP .

DHP can be further subclassified into first- , second- , and third-generation agents . Initially this was based on the sequence of drug development , however just because a drug is developed later does not necessarily imply superiority . A more recent and persuasive classification is based on the pharmacokinetic and pharmacodynamic properties of DHP. Other classifications based on vascular: cardiac selectivity and duration of action have also been proposed .

Dihydropyridines (DHP_S) have attracted increasing interest due to their diverse therapeutic and pharmacological properties such as insecticidal , bactericidal and herbicidal effects [51] . DHP drugs , namely nifedipine , nicardipine and amlodipine, are cardiovascular agents for the treatment of hypertension [52] . A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure [53] . In addition , dihydropyridines find applications in stereo specific hydrogen transfer reduction of phenylglyoxylic and pyruvic acid to biomimetic models of lactase dehydrogenase [54] . Recently , DHPs are used as organocatalysts for asymmetric reactions such as hydrogenation of quinolines in the synthesis of alkaloids [55] , asymmetric reductive amination of aldehydes [56] and hydrogenation of α, β-unsaturated aldehydes and ketones [57] .

Additionally , dihydropyrimidinones ($DHPM_s$) have exhibited important therapeutic and pharmacological properties as the integral backbone of several calcium channel blockers [58], antihypertensive agents [59] , and α1a-antagonists [60] . A broad range of biological effects including antiviral , antitumor , antibacterial and anti-inflammatory activities has been described for these compounds [61-63] . Some of the representative compounds of this class possess antiviral , antibacterial , antihypertensive and antitumor activities [64 , 65] . Several alkaloids isolated from marine sources also exhibit interesting biological activities , molecular structures of which contain the dihydropyrimidinone moiety [66] . Therefore ,

their synthesis has been the focus of great interest for organic and medicinal chemists [67] . The original Biginelli protocol for the preparation of $DHPM_s$ consisted of heating a mixture of three components which included β- ketoester , aldehyde and urea in ethanol containing a catalytic amount of HCl [68] .

The treatment of infectious disease caused by bacteria , fungi and viruses still remains an important and challenging problem because of a combination factors including newly emerging infectious diseases and increasing number of multi-drug resistant gram-positive pathogens [69] , such as methicillin-resistant Staphylococcus aureus (MRSA) , penicillin resistant Streptococcus pneumoniae (PRSP) , and vancomycin-resistant Enterrococci (VRE) , compounded problems in the therapeutics [70] . Thus it is still necessary to search for new antimicrobial agents .

In chemistry thiadiazoles are a sub-family of azole compounds . Structurally they are five-membered heterocyclic compounds containing two nitrogen and a sulfur atoms , and two double bonds , to give an aromatic ring ; with the name thiadiazole originating from the Hantzsch–Widman nomenclature . Four possible structures exist depending on the relative positions of the heteroatoms ; these forms do not interconvert and hence are structural isomers and not tautomers . The compounds themselves are rarely synthesized and possess no particular application , however compounds bearing them as a structural motif are fairly common in pharmacology [71-73] .

Five membered aromatic systems having three hetero atoms at symmetrical position have interesting physiological properties [74] . During recent years there has been intense investigation of different classes of thiadiazole compounds , many of which known to possess interesting biological properties such as antimicrobial [75-77] , anti-inflammatory [78 , 79-81] , anticonvulsants [82 , 83-86] , antioxidant [87] , anticancer [88] and antifungal [89] activities . The activity of 1,3,4- thiadiazoles is possibly due to the presence of the, N–C–S moiety [90] . In view of these facts , synthesized several new 1,3,4-thiadiazole derivatives of 2-(4-formyl-2-methoxyphenoxy) acetic acid moiety in order to study their biodynamic behavior [91] .

Derivatives of 1,2,3-thiadiazoles is known to exhibit antiviral [92 , 93] , analgesic [94 , 95] and antidepressant activity [96] . Among the pharmacological profiles of 1,2,3-thiadiazoles

and derivatives , their antimicrobial , anticonvulsant and antidepressant properties seem to be the best documented. 1,2,3-thiadiazoles and related compounds are of great interest in chemistry owing to their bioactivity of certain plant growth regulating effect as well as antimicrobial activity [97 , 98] . In spite of the obvious attraction of P and Sheterocycles , only a few preparative routes have been described . Antitubercular activities of thiadiazoles linked with aromatic cycles through the methyleneoxy group have also been reported and compounds of this type have shown inhibition on both cycloxygenase and 5-lipoxygenase activities [99] . Lee and coworkers have synthesized some thiadiazoles with antihelminthic activities [100] . More recently , sulfonamide derivatives of 1,3,4-thiadiazoles have been reported to behave as a modulator of anticancer therapies in combination with some cytotoxic compounds [101-104] . Lalezari et al. [105-107] . were the first to report the synthesis of 1,2,3-thiadiazole system , which had been prepared previously by Hurd and Mori .

Aromatic five-membered nitrogen heterocycles have been potential targets of investigations by several research groups owing to their interesting biological activities and medicinal properties [108 , 109] . Furthermore , 1,3,4-thiadiazoles is also important classes of azoles endowed with significant biological properties as there are several examples in the literature including antifungal [110 , 111] , anti-inflammatory [112 , 113], antimicrobial [114 , 115] , antiviral [116 , 117] and anticancer [118 , 119] activities . Additionally , many investigations showed that the clubbing of two or three heterocyclic units may significantly potentiate the antimicrobial activities [120–122] . In addition , Schiff bases have been the focus of numerous studies due to their wide spectrum of biological activities [123] . Moreover , thiosemicarbazaide Schiff bases linkages , as attractive connecting units that could bind two pharmacophores to generate an innovative bifunctional drugs , have rapidly emerge as one of the most challenging and attractive topics in drug design for the constructing of novel bioactive molecules . Based on all above considerations and as an extension of our studies on the developments of novel azoles antimicrobial agents [124 , 125] , The synthesis of new polyheterocyclic ring systems with anticipated antimicrobial and antiproliferative activities , by clubbing 1,3,4-thiadiazole with Schiff base moiety in one frame work . Cancer is a leading cause of death worldwide . Lung , stomach , liver , colon and breast cancer cause the most cancer deaths each year [126] . Based on type and stage of cancer , treatments include surgery, radiation therapy , chemotherapy and targeted therapies [127] . Management of cancer still represents a major challenge in medicine despite of significant progress achieved in anticancer therapy . Therefore , the development of novel effective anticancer drugs and

strategies is eagerly being pursued . 1,3,4-Thiadiazole derivatives possessed a wide range of therapeutic activities like antimycobacterial [128] , antileshmanial [129] , analgesic , antipsychotic [130] and anticonvulsant [131 , 132] . 1,3,4-Thiadiazole derivatives exhibited interesting in vitro [133-136] and in vivo [137-139] antitumor activities. Different mechanisms of action were attributed to antitumor activity of 1,3,4-thiadiazole ring such as inhibited DNA and RNA syntheses specifically without appreciably affecting protein synthesis [140] , inhibition of carbonic anhydrase [141] , phosphodiesterase-7 (PDE7) [142] , histone deacetylase [143] or as adenosine A_3 receptor antagonists [144] . 2-Amino-1,3,4-thiadiazole and structurally related compounds had antitumor and uricogenic activity that can be prevented or reversed by nicotinamide [145-149] . In addition , phenyl-1,3,4-thiadiazole derivatives were found to have anticancer activity against different human cell lines [150 , 151] . Substitution of 1,3,4- thiadiazole ring with both amino and phenyl groups resulted in compounds with promising anticancer activity against several cell lines [152 , 153] . 2-(4-Fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (FABT) , IIa , is one of the most promising derivatives [154] , in addition to FABT IIa were not toxic to normal cells [155 , 156] .

In view of the above mentioned facts , the 1,3,4-thiadiazole scaffold is selected as a building block for the design and synthesis of new potent antitumor agents . All the newly synthesized compounds were evaluated for the antitumor properties of the prepared compounds against human tumor cell line A549 “Non-small cell lung cancer cell line” [157] .

A survey of the literature revealed that differently substituted 1,3,4-thiadiazoles and annelated 1,3,4-thiadiazoles have wide range of pharmacological activities such as antibacterial , antifungal , antituberculosis , antihepatitis B viral , antileishmanial , anti-inflammatory , analgesic , CNS depressant , anticancer , antioxidant , antidiabetic , molluscicidal , antihypertensive , diuretic , analgesic , antimicrobial , antitubercular , and anticonvulsant activities [158–168] . These important biological activities encouraged several research groups to find out different methods for synthesis of new thiadiazoles using different synthones , such as thiosemicarbazides , thiocarbazides , dithiocarbazates , thioacylhydrazines , acylhydrazines and bithioureas [161 , 164] .

Many of the thiadiazole derivatives that have been prepared by the foregoing reactions , proved to possess wide range of pharmaceutical activities like antimicrobial , antivirus , anticancer , and molluscicidal effectiveness .

Thiadiazole and its derivatives are important organic reaction intermediates and they have been widely used as anticonvulsant , antidepressant , analgesic , anti-inflammatory , antiplatelet , antimalarial , antimicrobial , antimycobacterial , antitumoral , antiviral , diuretic and muscles relaxant activity . Generally , synthesis of the thiadiazole derivations needs high temperature (≥ 1000C) or low temperature (< 00C) or high pressure (at least higher than 1 atmospheric pressure) , and the yields of those reactions are low . Otherwise , they could be synthesized by reacting thiocarbonyl dichloride with dithizone .

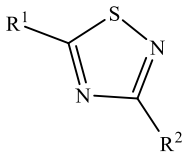
The resistance towards available drugs is rapidly becoming a major worldwide problem . The need to design new compounds to deal with this resistance has become one of the most important areas of research today . Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities . Thiadiazole moiety acts as “hydrogen binding domain” and “two-electron donor system”. It also acts as a constrained pharmacophore . Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide , methazolamide , sulfamethazole , etc . Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety . So it acts like third and fourth generation cephalosporins , hence can be used in antibiotic preparations . Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms viz. 1,2,3-thiadiazole ; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole . Thiadiazole derivatives possess interesting biological activity probably conferred to them by the strong aromaticity of this ring system , which leads to great in vivo stability and generally , a lack of toxicity for higher vertebrates , including humans . When diverse functional groups that interact with biological receptors are attached to this ring , compounds possessing outstanding properties are obtained .

Chemistry of Thiadiazole moiety :

A series of thiadiazole have been synthesized using an appropriate synthetic route and characterized by elemental analysis and spectral data. There are various types of thiadiazole rings are present :

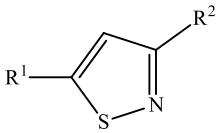
1, 2, 4-Thiadizole moiety

1,2,4 – Thiadiazole moiety contain sulfur at position-1 , and two nitrogen atom at position-2 and position-4 .

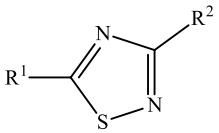


1 , 2 , 4 thiadiazole

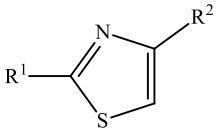
The photochemistry of 1,2,4-thiadiazoles is of interest because the ring system can be viewed as a combination of a thiazole and isothiazole .



Isothiazole



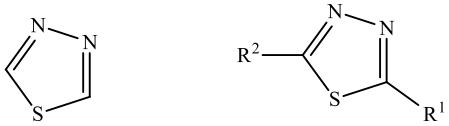
1,2,4-thiadiazole



thiazole

1, 3, 4-Thiadizole moiety

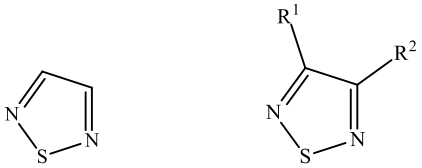
1,3,4- Thiadiazole moiety contain a heterocyclic nucleus in which sulfur present at position -1 and two nitrogen atom at position-3 and position-4 .



1 , 3 , 4 - thiadiazole

1, 2, 5-Thiadizole moiety

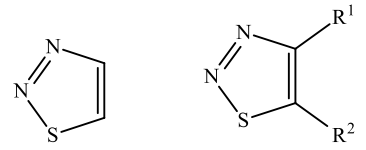
1,2,5- Thiadiazole moiety contain a heterocyclic nucleus in which sulfur present at position -1, and two nitrogen atom at position -2 & position -5 .



1 , 2 , 5 - thiadiazole

1, 2, 3-Thiadizole moiety

1,2,3- Thiadiazole moiety contain a heterocyclic nucleus in which sulfur present at position -1, and two nitrogen atom at position -2 & position -3 .

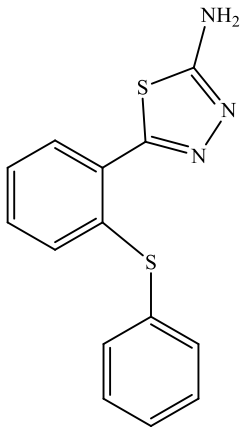


1 , 2 , 3 Thiadizole moiety

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities .

All of the newly synthesized compounds were evaluated for their in vitro growth inhibitory activities against a panel of standard strains of pathogenic microorganisms including three Gram-positive bacteria , three Gram-negative bacteria , and three strains of fungi . The antimicrobial studies were assessed by minimum inhibitory concentration (MIC) using the broth dilution method . MIC is the highest dilution of a compound which shows clear fluid with no development of turbidity . Antibacterial and antifungal screening revealed that some of the tested compounds exhibited good to excellent activities at concentrations ranging between 4–62.5 μg/mL. Diethyl 4,4′-[(1,3,4-thiadiazol-2,5-diyl) bis (sulfanediyl)] dibutanoate and its hydrazide derivative displayed good activity against Gram-positive and Gram-negative bacterial strains at MIC 16–31.25 μg/mL and moderate activity towards fungal strains at MIC 31.25–62.5 μg/mL . Evaluating the antimicrobial activity of the synthesized 2,2′- (2,2′- (3,3′- (1,3,4- thiadiazol – 2 , 5 – diyl) bis - (sulfanediyl)bis-(propane-3,1-diyl)bis-(hydrazine-2,1-diyl)bis-(N-aryl/alkyl-2-oxoethanethioamide) , revealed that compounds exhibited good to moderate antibacterial activity at 16–31.25 μg/mL while their antifungal activity was significantly diminished . On other hand , the antimicrobial activity of the thiadiazoles 2,5-Bis[(2-phenylamino-1,3,4-thiadiazol-5-yl)propylthio]-1,3,4-thiadiazole, 2,5-Bis[(2-methylamino-1,3,4-thiadiazol-5-yl)propylthio]-1,3,4-thiadiazole and 2,5-Bis[(2-ethylamino-1,3,4-thiadiazol-5-yl)propylthio]-1,3,4-thiadiazole revealed that all the tested compounds showed comparatively good activity against all bacterial and fungal strains at 8–31.25 μg/mL . Moreover , 2-amino-1,3,4-oxadiazole derivatives 2,5-Bis[(2-phenylamino-1,3,4-oxadiazol-5-yl)propylthio]-1,3,4-thiadiazole , 2,5-Bis[(2-methylamino-1,3,4-oxadiazol-5 - yl) propylthio] - 1 , 3 , 4 - thiadiazole and 2 , 5 – Bis [(2 – ethylamino - 1,3,4-oxadiazol-5-yl) propylthio]-1,3,4-thiadiazole showed good and greater antibacterial activity against

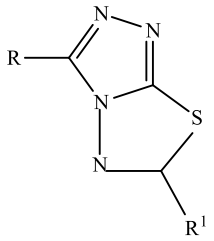
Gram-positive at MIC 8–16 μg/mL . Furthermore , compounds exhibited moderate antifungal activity at MIC 31.25–62.5 μg/mL . Among the oxadiazoles 2,5-Bis[(3H-1,3,4-oxadiazole-2-thione-5-yl)propylthio]-1,3,4-thiadiazole , oxadiazole functionalized with thiol group at position 2 exhibited excellent antibacterial activities against all bacterial strains at MIC 4–8 μg/mL and good activity towards fungal strains at MIC 16–31.28 μg/mL . The incorporation of amino and thiol group into 1,2,4-triazole ring as 2,5-bis[(4-amino-2,4-dihydro1,2,4-triazol-3-thione-5-yl)propylthio]-1,3,4-thiadiazole resulted in enhancing the antimicrobial activities against all examined bacterial and fungal strains at MIC 4–16 μg/mL.Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent , abnormal electrical activity in the brain . The pharmacotherapy of epilepsy has been archived during the last decade. Furthermore , although for the last twenty years new antiepileptic drugs have been introduced into clinical practice , the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity . A series of 5-[2-(phenylthio) phenyl] - 1, 3, 4-thiadiazole derivatives were synthesized . Compounds were evaluated in vivo for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests , ED50 of this synthesized compound was found to be greater than 100 .



5- [2- (phenylthio) phenyl] – 1 , 3 , 4 – Thiadiazole derivatives

Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus system (triazolothiadiazoles) were found to have diverse pharmacological activities such as fungicidal , bactericidal , insecticidal , herbicidal , anticancer , antiinflammatory and CNS stimulant properties . They also find application as dyes , lubricants and analytical reagents . The compounds that exhibited the most potent anti-MES activity included which have a

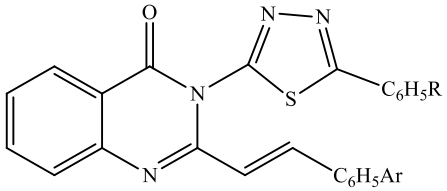
thiadiazole with styryl and quinazoline are reported to exhibit wide range of anticonvulsant , sedative , tranquilizer , analgesic , antimicrobial , anesthetic , anticancer , antihypertensive , anti-inflammatory , diuretic and muscle relaxant propertictivity comparable with phenytoin and carbamazepine .



triazolothiadiazoles

R= $C_6H_5CH_2$,$C_6H_5OCH_2$, 2-OHC_6H_4

R_1= $C_6H_5CONHCH_2$, 2-BrC_6H_4, 3-BrC_6H_4,4-BrC_6H_4



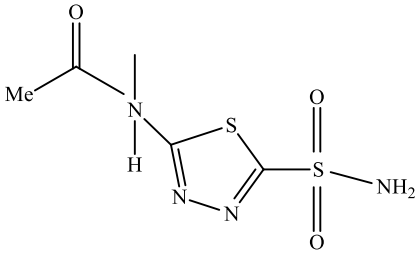
thiadiazole with styryl and quinazolin

R= $N(CH_3)_3$, ρ-F,3-NO_2,4-OH,

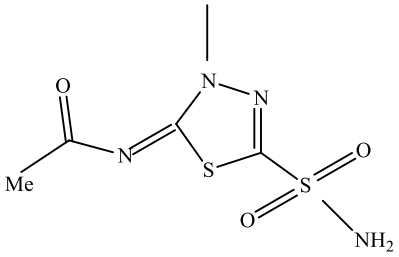
Ar = 3-NO_2,$N(CH_3)_3$,4-Br,4-FC_6H_4.

Anticonvulsant Sulfonamides Incorporating Valproyl and Other Lipophilic Moieties

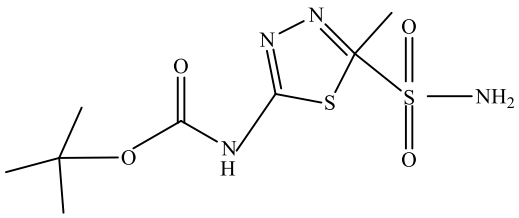
The valproyl derivative of acetazolamide (5-valproylamido-1, 3, 4-thiadiazole-2-sulfonamide) was one of the best CA I and CA II inhibitor in the series and exhibited very strong anticonvulsant properties in an MES test in mice . In consequence , other 1,3,4-thiadiazolesulfonamide derivatives possessing potent CA inhibitory properties and substituted with different alkyl/ arylcarboxamido/sulfonamido/ureido moieties in the 5 position have been investigated for their anticonvulsant effects in the same animal model . It was observed that some lipophilic derivatives , such as 5- benzoylamido-, 5-toluenesulfonylamido-, 5-adamantylcarboxamido, and 5 – pivaloylamido – 1 , 3 , 4 - thiadiazole -2- sulfonamide , show promising in vivo anticonvulsant properties and that these compounds may be considered as interesting leads for developing anticonvulsant or selective cerebrovasodilator drugs .



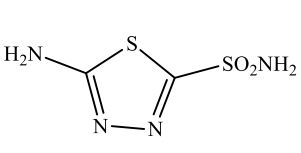
Acetazolamide



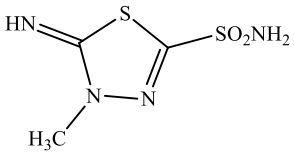
Methazolamide



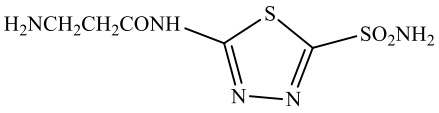
Sulfonamido



i



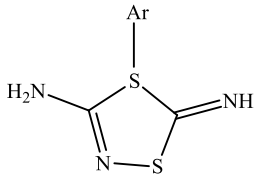
ii



iii

Series of 5- cyclohexylamino – 1 , 3 , 4 –thiadiazole (i , ii , iii)

Recently , compound containing thiourea and urea groups have emerged as structurally novel anticonvulsants . Thus , a series of novel thiourea derivatives carrying the 5-cyclohexylamino-1, 3, 4-thiadiazole moiety were synthesized and their anticonvulsant activity was evaluated [165] . A series of 3-aryl amino/amino-4-aryl-5-imino-Delta (2)-1, 2, 4-thiadiazoline compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (ScPTZ) induced seizure models in mice [166] .

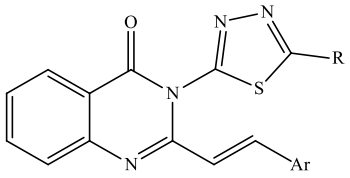


Ar= p-OC_2H_5-C_6H_4

3 aryl amino

Antidepressant agent

A series of novel 3-[5-substituted phenyl-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones were synthesized and evaluated for anticonvulsant , sedative-hypnotic and CNS depressant activities [167] .



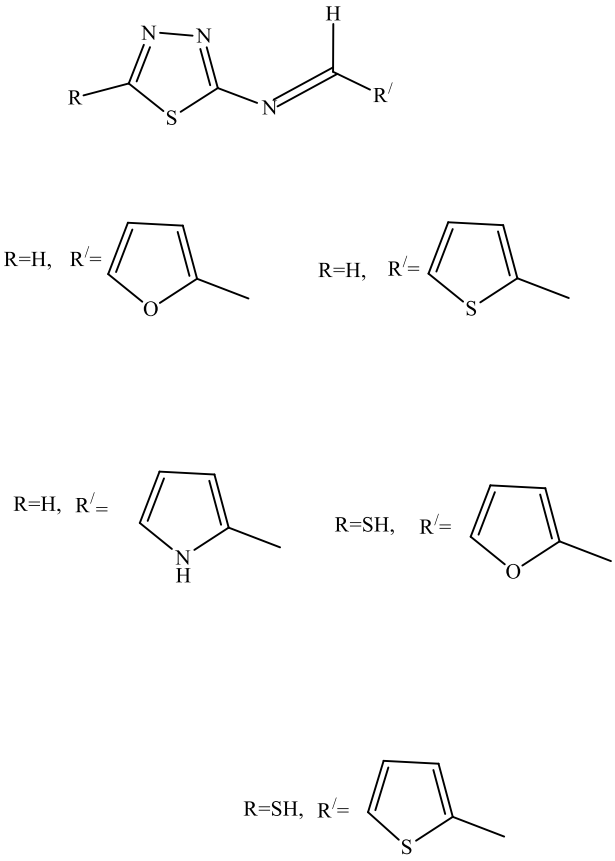
3 – [5- substitudes phenyl – 1 , 3 , 4 thiadiazolo -2 yl] -2 styryl quinazoline

Anti- microbial agent

Synthetic antibacterial compounds are divided into two major classes, topical agents and systemic agents . The topical agents or local anti-infective agents may be classified as antiseptics and disinfectants and constitute as important , if under appreciated , group of drugs . The topical are termed as disinfectants , antiseptics and preservatives based on how they are used . Several five member aromatic systems having three hetero atoms at symmetrical position have been studied because of their interesting physiological properties . It is also well established that various derivatives of 1,2,4-triazole, 1,3,4-thiadiazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal activities . The available therapeutically important medicines are terconazole , itraconazole , fluconazole, cefazoline and ribavirin etc. are some of the examples which contain one of these heterocyclic nucleus [168] .

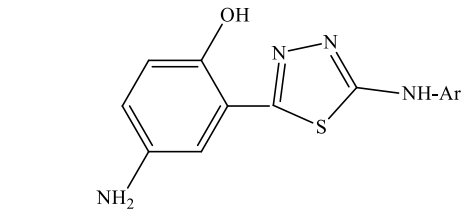
Schiff bases of Thiadiazole

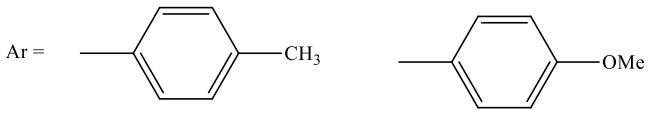
Replacement of the morpholine C-ring of linezolid with a 1,3,4- thiadiazolyl ring leads to oxazolidinone analogues having potent antibacterial activity against both gram-positive and gram-negative organism Conversion of the C5 acetamide group to a thioacetamide further increases the potency of these compounds [169] .

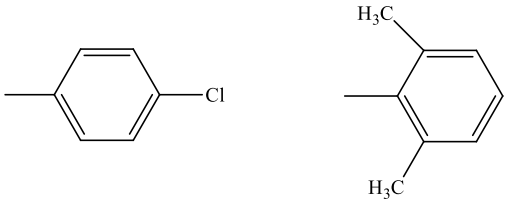


1 , 3 , 4 – thiodiazoly ring

Various 4-amino-2-{5-[(4- substituted phenyl) amino]-1, 3, 4- thiadiazole-2-yl} phenol were synthesized and evaluated for their antibacterial and antifungal activity . The compounds showed significant antibacterial activity against S. aureus (gram-positive) and E.coli (gram-negative) bacteria and antifungal activity against A. niger fungi using cup plate technique . Compounds were found to be very good antibacterial activity against S. aureus (gram-positive) and E.coli (gram-negative) bacteria and antifungal activity against A. niger (MIC value 25µg/ml) [169] .



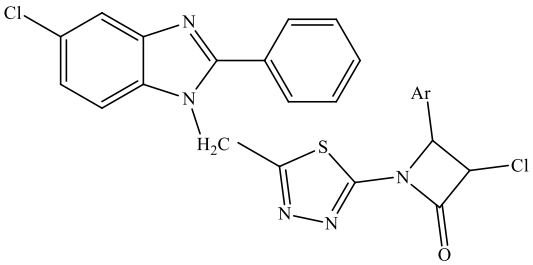




4– amino – 2- { 5- [4- substituted phenyl) amino] – 1 , 3 , 4 – thiadiazole – 2- yl } phenol

Potent Antimicrobial agent

A variety of azetidine derivatives have been successfully synthesized in appreciable yields and screened in vitro for their antimicrobial activities against both strains of Gram-positive and Gram-negative bacteria . Good antibacterial activity was observed in below compound against *B. Subtilis* compounds showed good activity against *S. aureus* compounds showed significant activity against *A. niger*.

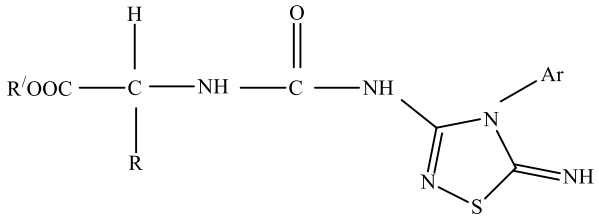


Azetidine derivatives

Ar= a. 2-hydroxy-4-methoxy, b. 4-clorophenyl, c. 2-nitrophenyl, d. 4-nitrophenyl, e. 4-chloro-2-nitrophenyl, f. 2- ethoxyphenyl, g. 4-ethoxyphenyl, h. 2, 4-diclorophenyl, i. 2-clorophenyl, j. phenyl, k. 2-hydroxyphenyl, l. 4- methoxyphenyl, m. 4-hydroxyphenyl.

The antimicrobial activity of synthesized compound was determined by paper disc method . The organisms selected for antimicrobial activity were *Bacillus substilis , Escherichia coli , Sachromyces cerviceae , Staphylococcus aureus , Pseudomonas aeruginosa ,*

Corynebacteriun diphtheria , *Bacillus megaterium* . The synthesized compound give good antimicrobial response against the selected organisms .

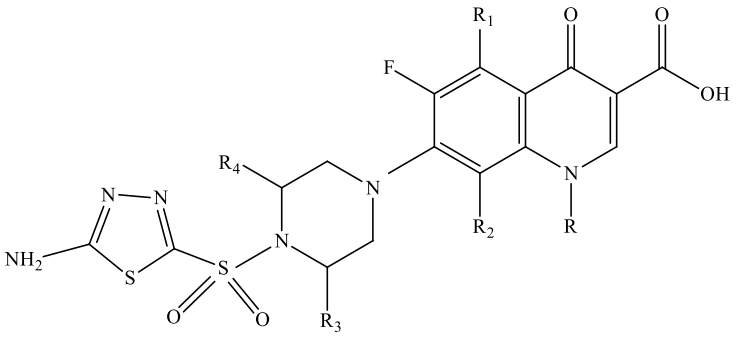


Alkyl {5–imino–4–aryl–4,5–dihydro–1,2,4–thiadiazol–3–yl)carbonyl] amino} acetate

Ar	R	R′
$C_6H_5NH_2$	CH_3	CH_3
p-Cl-$C_6H_4NH_2$	CH_3	CH_3
p-NO_2-C_6H_4-NH_2	CH_3	CH_3
p-CH_3-C_6H_4-NH_2	CH_3	CH_3

Anti-tubercular agents

7-[4-(5-amino-[1,3,4] thiadiazole-2-sulfonyl)-piperazin-1-yl] fluoroquinolones have been synthesized by the reaction of appropriate N-piprazinyl FQs and 5-acetylamino-[1,3,4] thiadiazole-2-sulfonyl chloride . Compound tested exhibited pronounced antibacterial activity against the Gram-(+) ve bacteria atrimethoxyphenyl , o. dimethylaminophenyl and moderate poor activity against Gram-(-)ve bacteria and Mycobacterium tuberculosis strain H37Rv .



R=Cyclopropyl/Ethyl

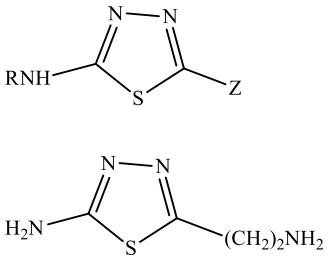
R_1=H.H.NH_2H. R_2=H.H.R$COCH_3$

R_3=H.H.CH_3H, R_4=H.H CH_2CH_3

7-[4-(5-amino-[1,3,4]thiadiazole-2sulfonyl)-piperazin-1-yl]fluoroquinolones

Anti-tumor agents

5-amino-l,3,4-thiadiazole-derivatives such as the thiol a compound used as radioprotective agent , as well as an investigational antitumor and gastroprotective drug ; acetazolamide which was the first nonmercurial diuretic drug , used clinically thereafter as antiglaucoma , antiepileptic or antiulcer drug , together with a large series of its congeners derived from 5-amino-1,3,4-thiadiazole-2-sulfonamide .



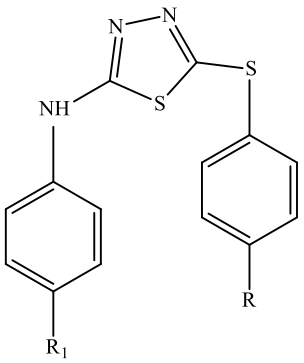
5 – amino – 1,3,4 – thiadiazole derivatives

Analgesic and anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthiritis , soft tissue and oral cavity lesions , respiratory tract infections and fever . The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively , besides COX-2 , leading to gastrointestinal injury , suppression of TXA2 formation and platelet aggregation . The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs . Some evidences suggest that the thiadiazole moiety present in some compounds possess a pharmacophoric character for the inhibition of COX. More recently , researchers reported 1, 3, 4-thiadiazole derivatives that exhibited analgesic and anti-inflammatory activities . 5-Arylamino substituted 3-nicotinoyl/isonicotinoyl-1,3,4-thiadiazol-2(3H)-one, 5-arylamino-1,3,4-thiadiazol-2(3H)-one,3-(5-bromo-2-thienyl)-1-phenyl-4-[3-acetyl-5-(N-substitutedacetamido) - 2 , 3 – dihydro – 1 , 3 , 4 – thiadiazol – 2 – yl] - 1H – pyrazol , and 2-(2 naphthyloxymethyl) -5 - substituted amino-1, 3, 4 - thiadiazole derivatives showed anti-inflammatory and analgesic activities .

2-Amino-5-sulfanyl-1, 3, 4-thiadiazoles

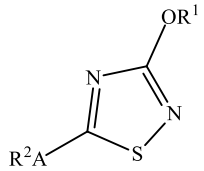
A series of diaryl substituted 2-amino-5-sulfanyl-1, 3, 4-thiadiazole derivatives , and perform their pharmacological testing .



Di aryl substituted 2-amino – 5 sulfonyl – 1 , 3 , 4 - thiadiazole

Anti-diabetic agent

1, 2, 4- thiadiazole compound for the treatment of type-II diabetes mellitus Orally administrate pharmaceutical compositions in the form of tablets, comprising glibenclamide and metformin, or pharmaceutically acceptable salts thereof , as active ingredients , maintained separate from one another within the same composition , are described for the treatment of type-II diabetes mellitus .

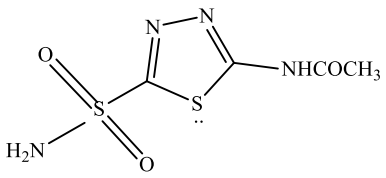


1 , 2 , 4 – thiadiazole compound

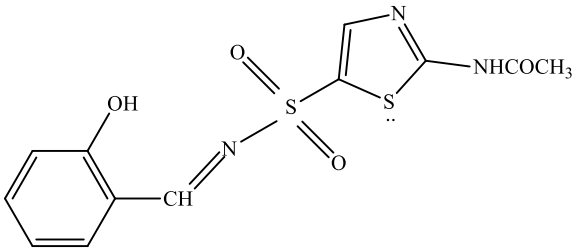
Where in , R1 represents C3-C7 alkynyl that may he substituted with halogen ; R2 represents C3-C8 cycloalkyl which may be substituted with C1-C4 alkyl , halogen atom and tritluoromethyl or the like ; A1 represents a single bond , C1-C2 alkylene or C2-C3 alkylidene . The 1, 2, 4-thiadiazole compound has an excellent arthropod controlling activity , and can effectively control an arthropod pests such as insect pests , acarine pests and the like. Sulfonylureas are the most widely used antidiabetic agents . These agents act on pancreatic ß-cells stimulating insulin secretion. 1, 3, 4-Thiadiazole , is a versatile pharmacophore which exhibits a wide variety of biological activities . A few of them which are worthy of mention are diuretic , CNS depressants , hypoglycemic , anti-inflammatory , and anti-microbial activities . It was planned to suitably incorporate the sulfonylurea moiety into the 1, 3, 4-thiadiazole ring system and to explore the possibilities of some altered biological action; hence , the following sulfonylurea derivatives were synthesized and screened for antidiabetic and antibacterial activity .

Diuretic agents

Reaction of 3- and 4-carboxybenzenesulfonyl chloride with 5-amino-1,3,4-thiadiazole-2-sulfonamide/5- imino-4-methyl-2-1,3,4-thiadiazoline-2-sulfonamide afforded two series of benzolamide analogues to which the carboxyl moiety has been derivatized as esters or amides, in order to reduce their very polar character . The new derivatives showed low nanomolar affinity for three carbonic anhydrase (CA) isozymes , CA I , II and IV, and were effective as topical antiglaucoma agents in normotensive rabbits . Efficacy of several of the new sulfonamides reported was better than that of the standard drugs dorzolamide and brinzolamide , whereas their duration of action was prolonged as compared to that of the clinically used drugs . Schiff base metal chelates are widely applicable because of their industrial and biological importance .

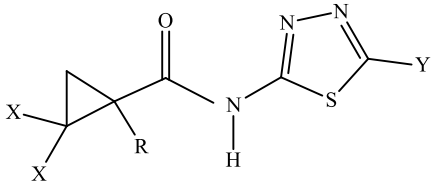


acetazolamide

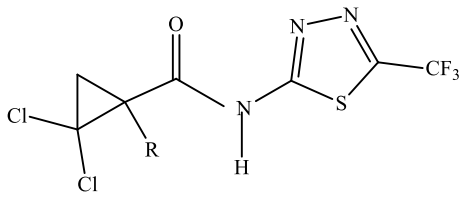


Schiff base

Thiadiazole compounds useful as Pesticides

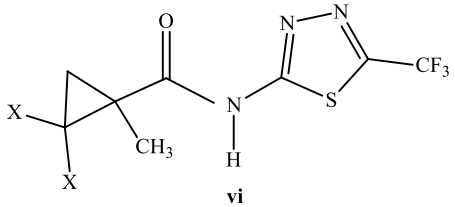


iv



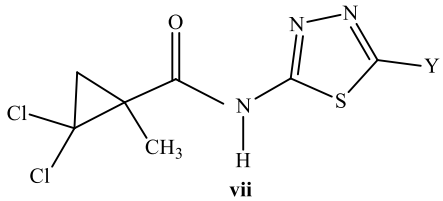
v

R= CH_3 was found to be most active against Tetranychus uriticase.



vi

X= Cl was found to be most active against Tetranychus urticae.

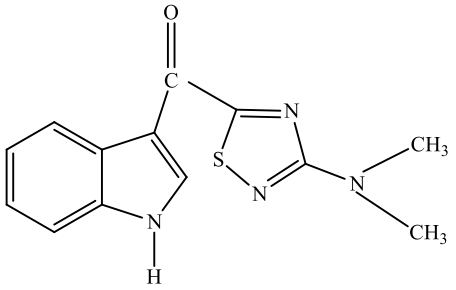


vii

Y= $CF_3CF_2CF_3$,$(CF_2)_2CF_3$ was found to be most active against Tetranychus urticase.

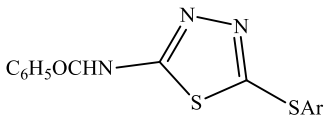
Thiadiazole compounds use for various pesticides (iv, v, vi, vii)

Antioxidant



Dendrodoine

Dendrodoine (5-[(3-N-dimethylamino)-1, 2, 4- thiadiazolyl]-3-indanyl methanone) is an alkaloid extracted from the marine algae Dendrodoa grossularia . It possesses a 1, 2, 4-thiadiazole unit , a rarity among natural products . It is use as antioxidant . Some novel 5-[(2-(substituted phenyl)-1H-benzimidazole-1-yl) methyl]-N-methyl-1, 3, 4- thiadiazole-2- amines were synthesized and tested for antioxidant properties by using various invitro systems . Compound which is the most active derivative inhibited lipid peroxidation slightly at 10-3 M concentration .

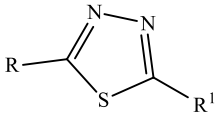


Ar = 4-$C_6H_4SO_2Cl$, Ar = 4-$C_6H_4SO_2NH_2$

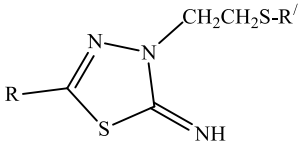
Ar = 4-$C_6H_4CF_3$.

[1, 3, 4] thiadiazole derivatives

Thiol and aminothiol compounds are among the most efficient chemical radioprotectors [184] . Synthesized thiol and aminothiol compounds derived from thiadiazole structures . They examined them for their ability to scavenge free radicals (DPPH·, ABTS·+, ·OH). Thiol derivatives with a thiadiazole structure are the most active compounds scavenging DPPH· and ABTS·+ free radicals, with an IC50 of 0.053 ± 0.006 and 0.023 ± 0.002 mM, respectively , for the derivative . Moreover compound at 60 mM gave 83% protection against 2- deoxyribose degradation by ·OH . In both the test thiol derivatives were most efficient . Compound totally inhibits DNA strand breaks at the concentration of 50 mM .



R= -SCH_2CH_3.CH_2CH_3 , R/= -SH,-$NHCH_2CH_2SH$



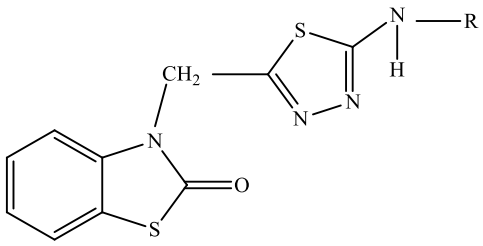
R= -SCH_2CH_3,-CH_2CH_3

R/ = -SO_3H, -$PO(OH)_2$

Amino thiol compounds

Antihistaminic agents

2-Oxobenzothiazoline derivatives bearing substituents at position 3 with thiadiazole moiety have reported to exhibit antihistaminic activity . Compounds were more potent than others and the standards in tail flick test .



2- oxobenzothiazoline derivatives

Antiplatelet agents

Twenty 1, 3, 4-thiadiazole-2-nitrosimines and two 1, 2, 4-thiadiazole-5-nitrosimines were synthesized and assayed in the Born-test for their antiplatelet activity . Only two 1, 3, 4-thiadiazoles inhibited the aggregation at IC50 < 10 mumol/L . In an in vivo thrombosis model only in arterioles a small inhibition of thrombus formation was observed . The poor test results correspond to a very high chemical stability of the titel nitrosamines .

AIM OF THE PROJECT

Thiadiazole based synthetic organic compounds display a broad spectrum application in the field of synthetic organic chemistry and also immence importance in medicinal chemistry . Recently , some literature reported the potential anti-microbial agents of certain thiodiazole derivatives . Drugs which are based on dihydropyromidine , have also been used clinically to treat patient of HIV and antitumor conditions . Very recently some researcher reported that the dihydropyrimidine derivatives is the causative agent for antihypertensive , antitumor , antibacterial , anti-inflammatory . Since synthetic thiadiazole based organic compounds are being widely designed now a days in parallel with the development of combinatorial chemistry and compound libraries , they could be exploited for the development of new drugs. This factor has attracted researchers to evaluate thiodiazole based compounds for their safety point of view and potential medical properties .

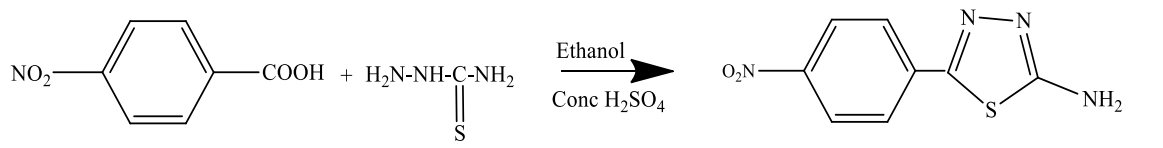
The proposed research project is undertaken with the following objectives

a) To prepare 1,3,4-thiadiazole precursor .
b) To develop a method for the synthesis of fused pyrimido-thiadiazole compounds .
c) To optimize the reaction condition to get the target compounds .
d) To establish the structures of the fused pyrimido-thiadiazole products by different physical , chemical and spectroscopic methods .
e) To evaluate the antibacterial property of the synthesized products .

EXPERIMENTAL

Chapter 2

2.1 Synthesis of [5-amino-1,3,4-thiadiazol-2-yl]4-nitro benzene

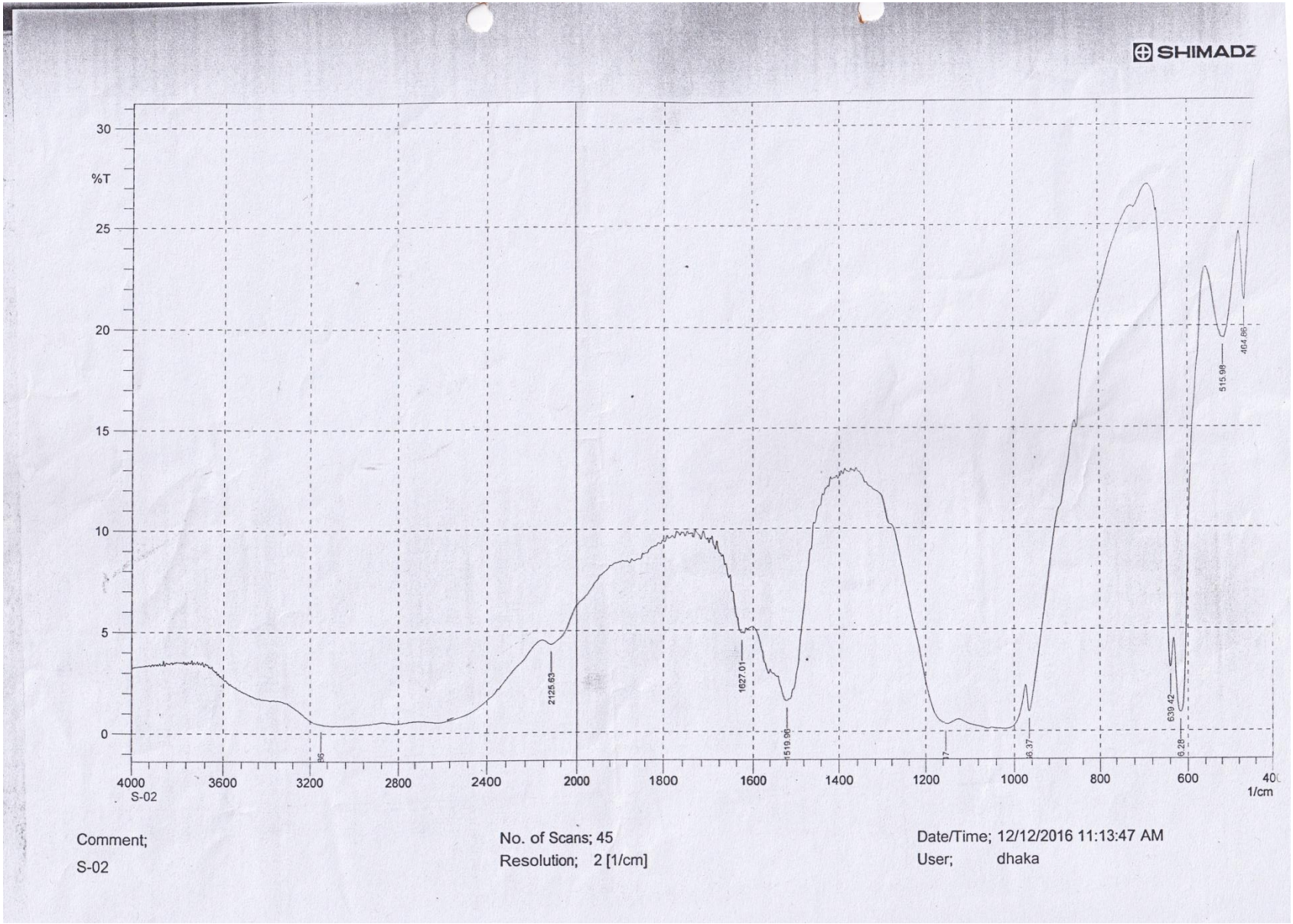


[5-amino-1,3,4, thiodiazol-2-yl] 4-nitro benzene

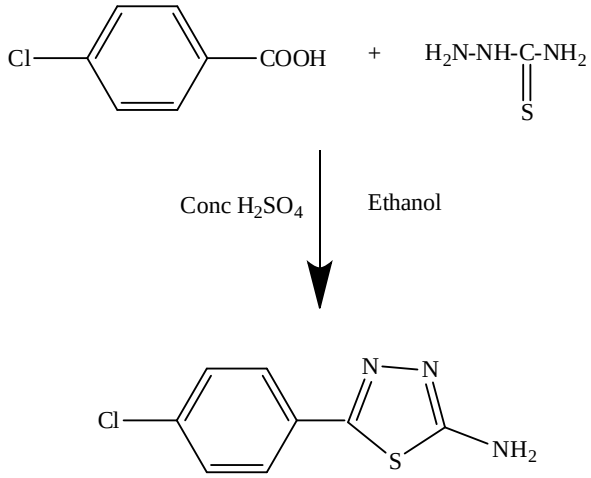
A mixture of thiosemicarbazide (0.01 mol), para nitrobenzoic acid (0.01 mol) and concentrated sulphuric acid 1 ml in 10 ml ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one and half hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a white crude product was obtained . The crude product was separated out by filtration . The crude product was then purified by recrystallization from 10% aqueous ethanol to yield 81% as a white solid . The melting point was recorded as 220-222 ºC .

IR (KBr, cm^{-1}, Fig. 1) : 3394 (N-H, symmetric stretching) , 3290 (N-H, asymmetric stretching) , 3193 (C-H, aromatic) , 1621 (C=N) , 1600 , 1580 , 1536 (C=C , aromatic) ,719 (C-S-C linkage of thiadiazole) .

Figure -1


SHIMADZ
%T
30
25
20
15
10
5
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
1/cm
S-02
2125.63
1627.01
1519.99
639.42
515.98
464.86
Comment;
S-02
No. of Scans; 45
Resolution; 2 [1/cm]
Date/Time; 12/12/2016 11:13:47 AM
User; dhaka

2.2 Synthesis of [5-amino-1,3,4-thiadiazol-2-yl] 4-chloro benzene

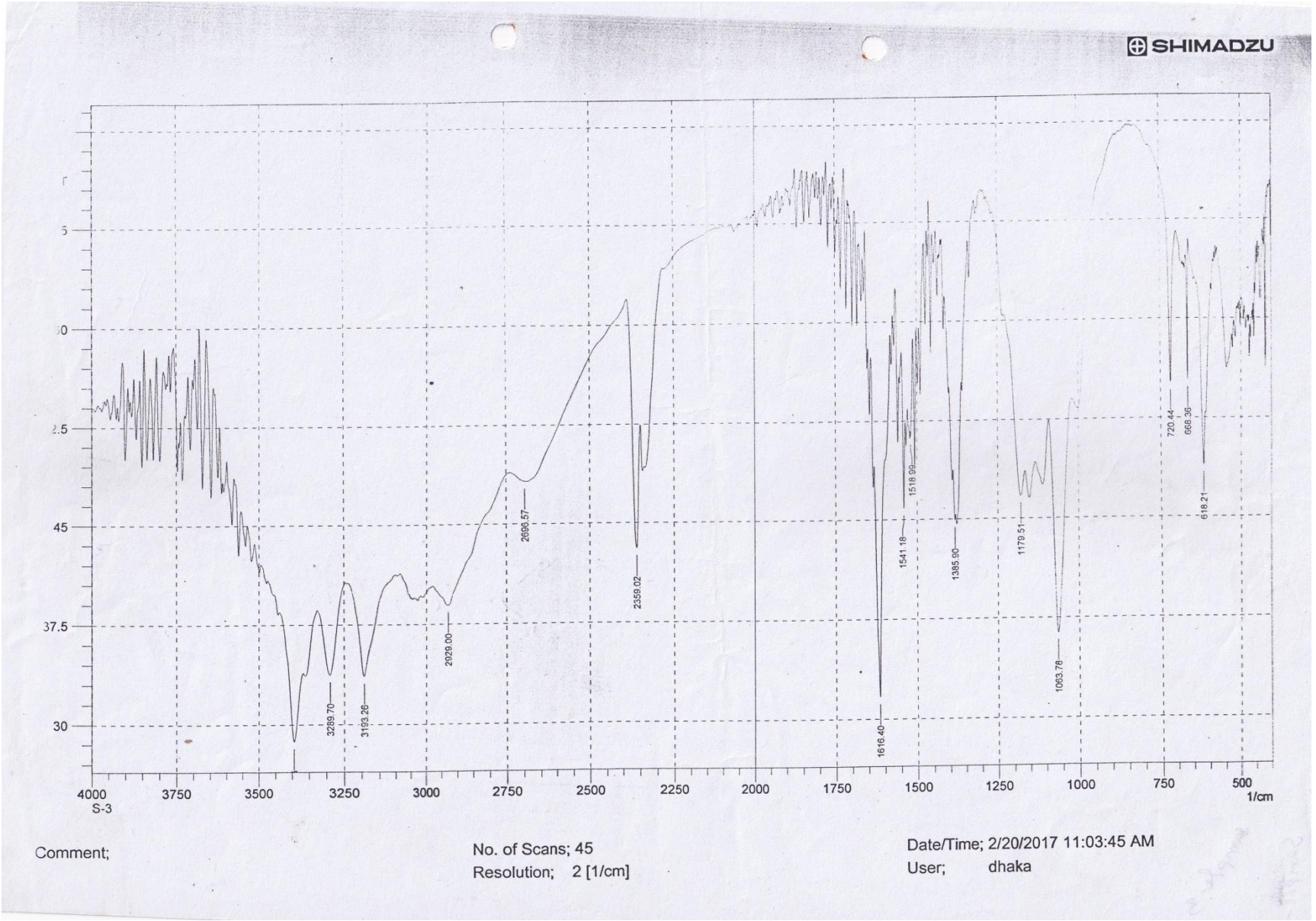


[5-amino-1,3,4 thiodiazol-2-yl] 4-chloro benzene

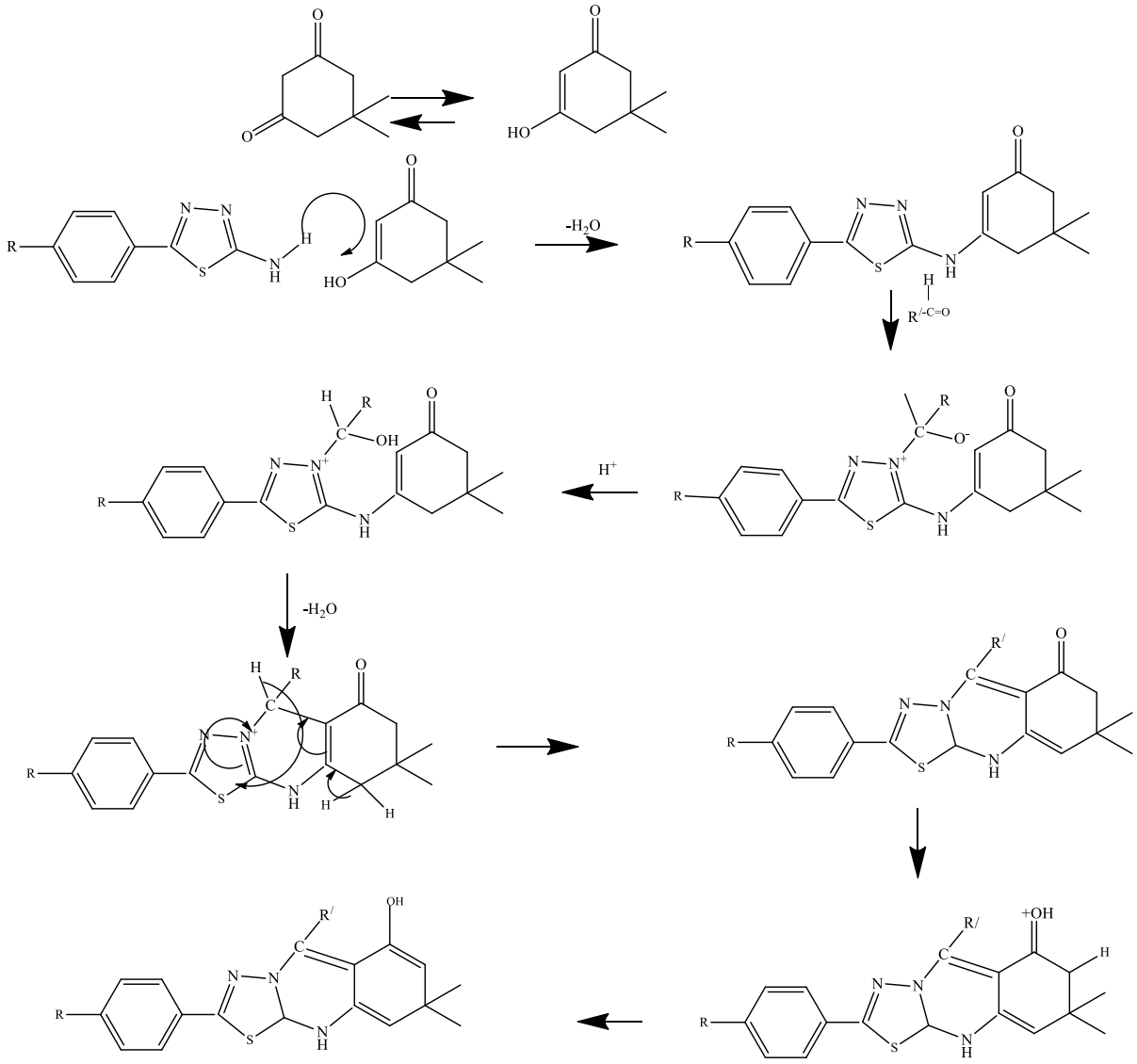
A mixture of thiosemicarbazide (0.01 mol, 0.912 gm) , para chloro benzoic acid (0.01 mol, 1.221gm) and concentrated sulfuric acid 1 ml in 10 ml ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for two hours and 45 minutes under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a white crude product was obtained. The crude product was then purified by recrystallization from 10% aqueous ethanol to yield 78% as white solid. The melting point was recorded as 210-215 ºC .

IR (KBr, cm^{-1}, Fig.2) : 3391 (N-H , symmetric stretching) , 3292 (N-H , asymmetric stretching) , 3190 (C-H , aromatic) , 1620 (C=N) , 1600 , 1570 , 1530 (C=C , aromatic) ,720 (C-S-C linkage of thiadiazole) .

Figure - 2

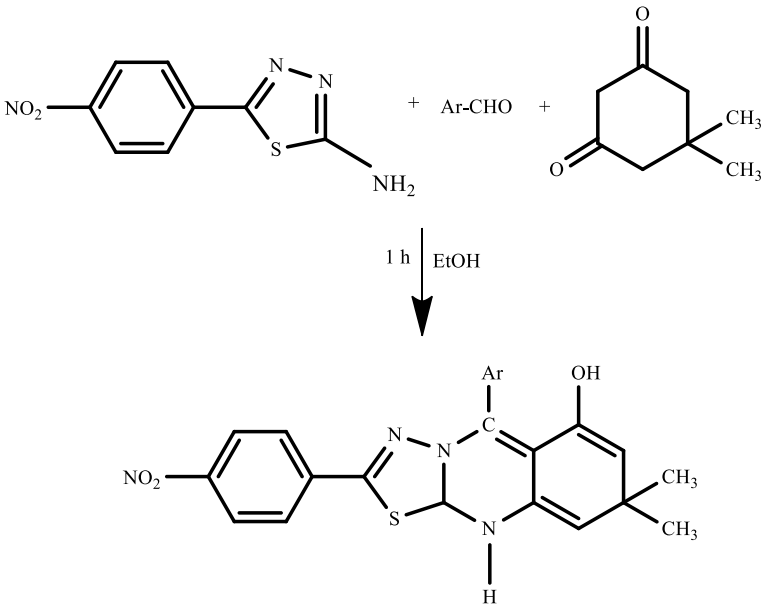

SHIMADZU
3289.70
3193.26
2929.00
2696.57
2359.02
1616.40
1541.18
1518.99
1385.90
1179.51
1063.78
720.44
668.36
618.21
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
S-3
Comment;
No. of Scans; 45
Resolution; 2 [1/cm]
Date/Time; 2/20/2017 11:03:45 AM
User; dhaka

Mechanism



Scheme 13 Mechanism for the formation of dihydro-pyrimido thiadiazole.

2.3 Synthesis of 5-(phenyl)– 8,8-dimethyl-2-(4-nitrophenyl)-10, 10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol. (1)



Compound 1

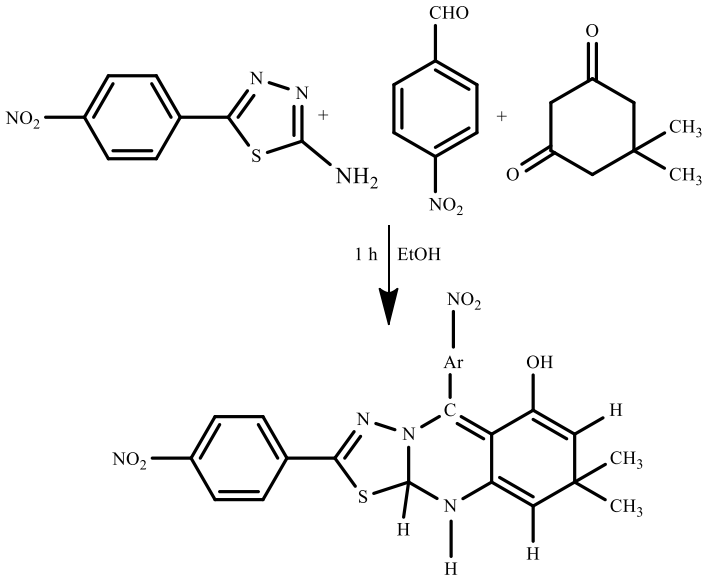
A mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01 mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and benzaldehyde (0.01 mol , 1.0613 gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration an orange crude product was obtained . The crude product was then purified by recrystallization from absolute ethanol to yield 75% as orange solid . The melting point was recorded as 195-198 ^{0}C .

IR (KBr, cm^{-1}, Fig. 3) : 3400-3475 (O-H) , 3346 (N-H) , 3123 (C-H , aromatic) , 2975 (C-H, aliphatic) , 1600 (C=N) , 1572 , 1540 , 1520 (C=C , aromatic and aliphatic) , 693 (C-S-C) .

^{1}H NMR (400 MH$_z$, DMSO-d$_6$, δ ppm , fig. 4-5) : 1.051(s , 6H , 2CH$_3$) , 6.90 (d , 1H , J=8.00 Hz , =CH) , 7.18 (bd , s , 1H , SCHN) , 7.27 (m , 5H , Ar-H) , 7.43 (m ,4H , Ar-H) , 7.71 (d , 1H , J=8 Hz , C=CH) , 8.120 (s ,1H , O-H) , 11.651 (s , 1H , N-H) .

^{13}C NMR (100 MH$_z$, DMSO-d$_6$, δ ppm , fig. 6-8) : 176.86 (1C , C=N) , 143.31 , 142.50 (2C, C=C) , 134.57 , 130.46 (2C , C=C) , 129.39 , 129.11 (2C , C=C) , 128.45 (4C , Ar) , 127.33 (2C , Ar) , 126.77 (1C , Ar) , 126.39 (5C , Ar) , 113.79 (1C , S-C-N) , 51.48 (1C , aliphatic) , 32.35 (1C , aliphatic) , 28.31 (1C , aliphatic) .

2.4 Synthesis of 5-(4-nitrophenyl)–8,8-dimethyl-2-(4-nitrophenyl)-10, 10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol. (2)



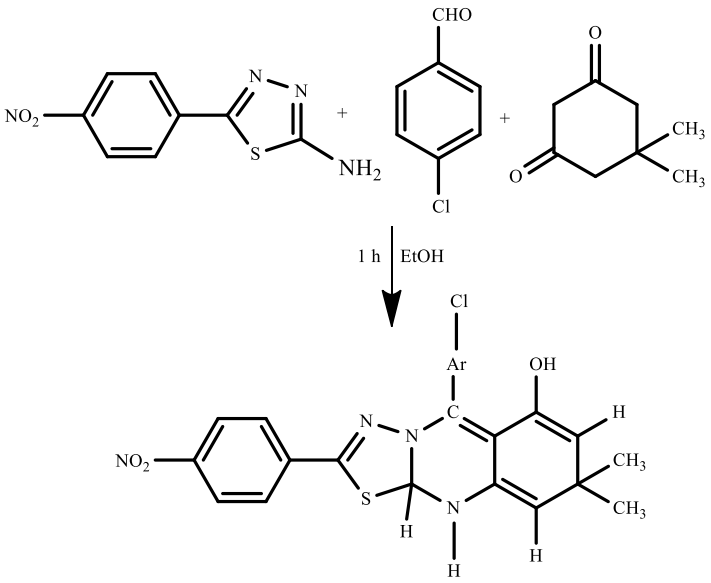
Compound 2

A mixture of [5-amino-1,3,4-thiodiazol-2-yl] 4-nitro benzene (0.01 mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and para nitro bezaldehyde (0.01 mol , 1.511 gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a yellow crude product was obtained . The crude product was then purified by recrystallization from absolute ethanol to yield 73% as yellow solid . The melting point was recorded as 198 – 200 ^{0}C .

IR (KBr, cm^{-1}, fig. 9) : 3450-3500 (O-H) , 3337 (N-H) , 3085 (C-H , Ar) , 2963 (C-H , aliphatic) , 1607 (C=N) , 1604 ,1580 ,1527 ,1510 (C=C , Aromatic and aliphatic) , 720 (C-S-C) .

^{1}H NMR (400 MH$_z$, CDCl$_3$, δ ppm , fig.10-11) : 1.013 (s , 3H , CH_3) , 1.096 (s , 3H , CH_3), 7.49 (d , 1H , J=8.0 Hz , =CH) , 8.11 (m , 2H , -CH , O-H) , 8.246 (m , 4H , Ar-H) , 8.297 (m, 4H , Ar-H) , 8.42 (d ,1H , J=8.0 Hz , C=H) , 10.185 (s , 1H , N-H) .

2.5 Synthesis of 5-(4-chlorophenyl)– 8,8-dimethyl-2-(4-nitrophenyl)-10,10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol. (3)



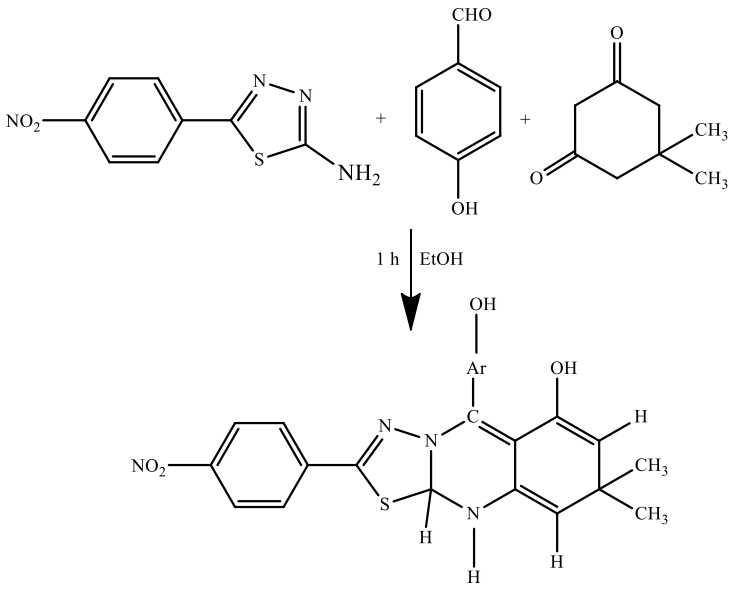
Compound 3

A mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and para chloro bezaldehyde (0.01 mol , 1.4 gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a yellow crude product was obtained . The crude product was then purified by recrystallization from absolute ethanol to yield 74% as a light yellow solid . The melting point was recorded as 194-195 ^{0}C .

IR (KBr , cm^{-1}, fig. 12) : 3446 (O-H) , 3288 (N-H) , 3150 (C-H , Ar) , 2997 (C-H , aliphatic), 1601 (C=N) , 1525 , 1490 , 1450 (C=C , Aromatic and aliphatic) , 816 (C-S-C) .

^{1}H NMR (400 MH$_z$, CDCl$_3$, δ ppm , fig.13-14) : 1.136 (s , 3H , CH_3) , 1.654 (s , 3H , CH_3), 6.388 (bd , s , 1H , =CH) , 7.212 (bd , s , 1H , =CH) , 7.414 (d , 4H , J=8.0 Hz , Ar-H) , 7.61 (d , 4H , J= 8.0 Hz , Ar-H) , 7.842 (s ,1H , S-CH) , 9.400 (s , 1H , O-H) , 10.012 (s , 1H , N-H) .

2.6 Synthesis of 5-(4-hydroxyphenyl)– 8,8-dimethyl-2-(4-nitrophenyl)-10, 10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol. (4)



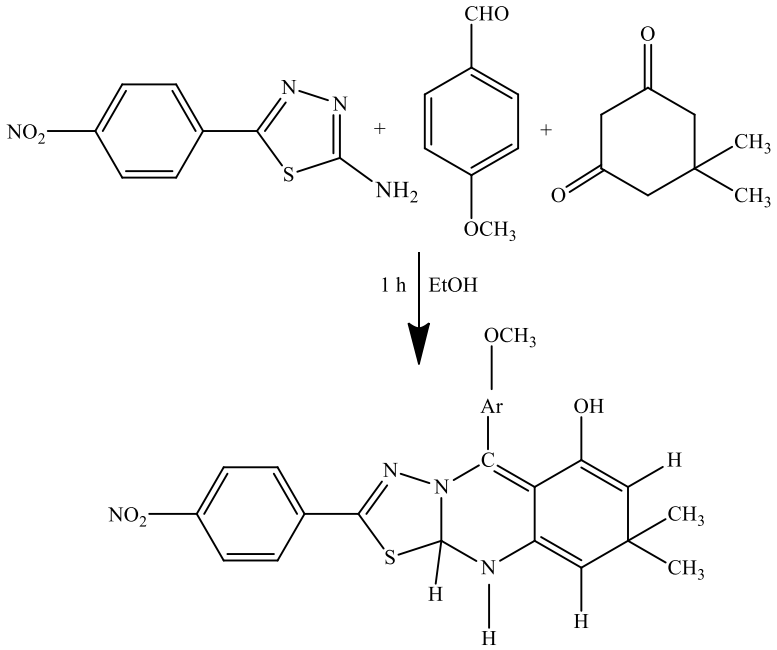
Compound 4

A mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01 mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and para hydroxy bezaldehyde (0.01 mol , 1.0613 gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration an orange crude product was obtained . The crude product was then purified by recrytallization from absolute ethanol to yield 73% as orange solid . The melting point was recorded as 201-204 ^{0}C .

IR (KBr , cm^{-1}, fig.15) : 3400-3460 (O-H , phenolic) , 3340-3360 (O-H , enolic) , 3100 (C-H, Ar) , 2961 (C-H , aliphatic) , 1609 (C=N) , 1590 , 1550 , 1511 , 1490 (C=C , Aromatic and aliphatic) , 850 (C-S-C) .

^{1}H NMR (400 MH$_z$, CDCl$_3$, δ ppm , fig.16) : 1.12 (d , 6H , J=2.0 Hz , 2CH$_3$) , 7.44 (d , 4H, J=12.0 Hz , Ar) , 7.83(d , 4H , J=8.0 Hz , Ar) , 8.032(s , 2H , =CH) , 8.066 (bd , s , 1H , O-H , enolic) , 8.029 (bd , s ,1H , OH , phenolic) , 11.407 (s , 1H , NH) .

2.7 Synthesis of 5-(4-methoxyphenyl)– 8,8-dimethyl-2-(4-nitrophenyl)-10,10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol. (5)



Compound 5

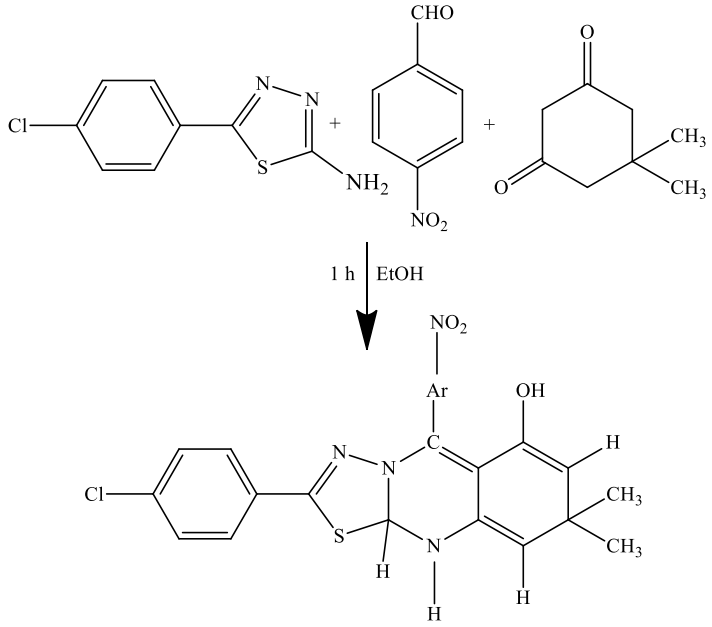
A mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01 mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and para methoxy bezaldehyde (0.01 mol , 1.36gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a yellow crude product was obtained . The crude product was then purified by recrystallization from absolute ethanol to yield 72% as a yellow solid . The melting point was recorded as 190-195 ^{0}C .

IR (KBr , cm^{-1} , fig. 17) : 3400-3410 (O-H) , 3293 (N-H) , 3159 (C-H , Ar) , 2961 (C-H , aliphatic) , 1607 (C=N) , 1595 , 1510 , 1450 , 1452 (C=C , Aromatic and aliphatic) , 842 (C-S-C) .

^{1}H NMR (400 MHz , $CDCl_3$, δ ppm , fig.18-19) : 1.103 (s , 3H , -CH_3) , 1.117 (s , 3H , -CH_3) , 3.375 (s , 3H , OCH_3) , 6.76 (d , 2H , J=8.0 Hz , Ar-H) , 6.91 (d , 1H , J=8.0 Hz , C=C-H) , 7.02(d , 1H , J=8.0 Hz , C=C-H) , 7.24 (d , 2H ,J =8.0 Hz , Ar-H) , 7.61 (bd , s , 1H ,- S-CH) , 7.875 (d , 1H , J=8.0 Hz , O-H) , 8.243 , 8.332 (m , 4H , Ar-H) .

^{13}C NMR (100 MH$_z$, DMSO-d$_6$, δ ppm , fig. 20) : 162.183(1C , C=N) , 158.00 (1C , SCN) , 136.459 , 135.184 , 132.360 , 132.024 , 131.217 (6C , Aromatic) , 130.665 , 129.315 , 129.202 , 125.588 , 123.567 , 123.494 (6C , C=C) , 115.840 , 114.425 , 114.351 , 113.800 , 113.012 (6C , Ar) , 50.766 (1C , NCS) , 40.898 (1C , OCH_3) , 32.195 (1C , -CCH_3) , 30.969 , 27.349 (2C , $C(CH_3)_2$) .

2.8 Synthesis of 5-(4-nitrophenyl)– 8,8-dimethyl-2-(4-chlorophenyl)-10,10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol. (6)



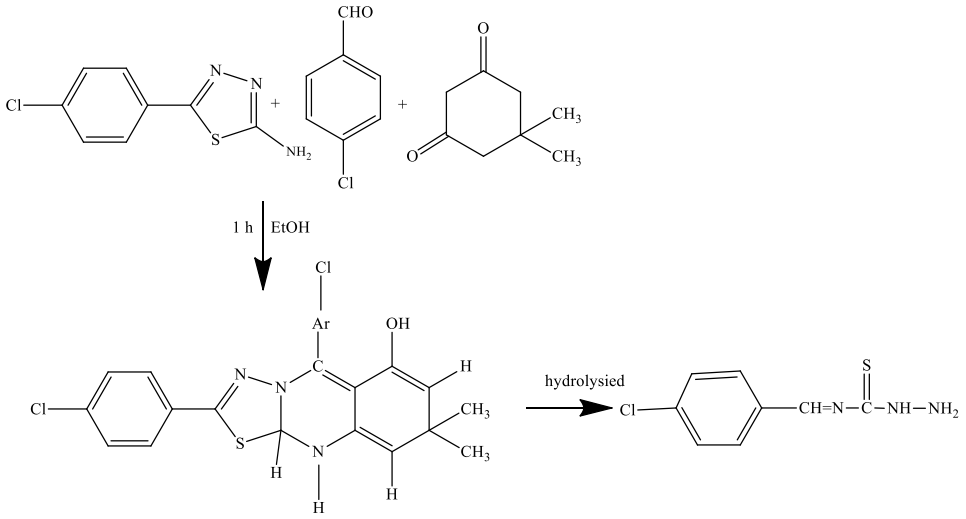
Compound 6

A mixture of [5-amino-1,3,4- thiadiazol-2-yl] 4-chloro benzene (0.01mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and para nitro bezaldehyde (0.01 mol , 1.511gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a orange crude product was obtained . The crude product was then purified by recrystallization from absolute ethanol to yield 73% as a orange solid . The melting point was recorded as 210-212 ^{0}C .

IR (KBr , cm^{-1} , fig. 21) : 3500-3510 (O-H) , 3386 (N-H) , 3145 , 3096 (Ar -H) , 2996 (C-H , aliphatic) , 1600 (C=N) , 1590 , 1540 , 1452 (C=C , Aromatic) , 820 (C-S-C) .

^{1}H NMR (400 MHz , $CDCl_3$, δ ppm , fig.22) : 1.266 (s , 3H , -CH_3) , 1.283 (s , 3H , -CH_3) , 6.75 (1H , S-CH) , 6.90 (1H , C=C) , 7.02 (1H , C=C) , 7.24 (2H , Ar-H) , 7.62 (2H , Ar-H) , 7.87 (2H , Ar-H) , 8.06 (2H , Ar-H) , 8.2 (1H , O-H) , 9.96 (1H , NH) .

2.9 Synthesis of 5-(4-chlorophenyl)– 8,8-dimethyl-2-(4-chlororophenyl)-10, 10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol . (7)



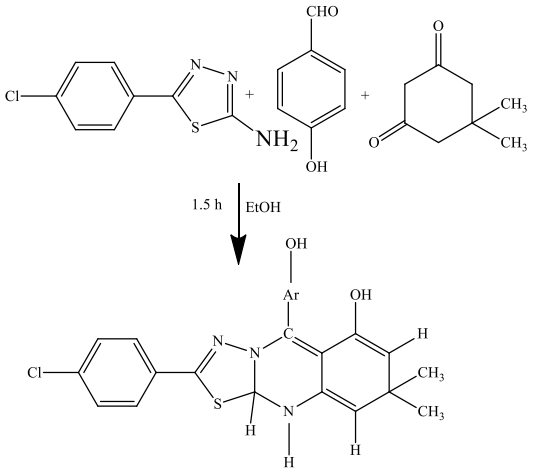
Compound 7 **7a**

A mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-chloro benzene (0.01 mol , 2.22 gm) , dimedone (0.0 mol ,1.4 gm) and para chloro bezaldehyde (0.01 mol , 1.405 gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product was separated out by filtration . After filtration a white crude product was obtained . The crude product was then purified by recrystallization from absolute ethanol to yield 60% as a white solid . The melting point was recorded as 150-152 ^{0}C .

IR (KBr , cm^{-1}, fig. 23) : 3445 (N-H) , 3300 (NH_2) , 3122 (C-H , Ar) , 1600 (C=N) , 1550 , 1502 , 1455 (C=C) , 1283 (C=S) .

^{1}H NMR (400 MH$_z$, DMSO-d$_6$, δ ppm , fig. 24-25) : 7.45 (d , 2H , J=8.0 Hz , Ar-H) , 7.83 (d , 2H , J=8.0 Hz , Ar-H) , 8.032 (s , 1H , C=C-H) , 8.066 (bd , s , 1H , NH_2) , 8.229 (bd , s , 1H , NH_2) , 11.477 (s ,1H , N-H) .

2.10 Synthesis of 5-(4-hydroxyphenyl)– 8,8-dimethyl-2-(4-chlorophenyl)-10, 10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol . (8)



Compound 8

A mixture of [5-amino-1,3,4- thiadiazol-2-yl] 4-chloro benzene (0.01mol , 2.22 gm) , dimedone (0.0 mol , 1.4 gm) and para hydroxy bezaldehyde (0.01 mol , 1.22gm) in 5 ml of ethanol was taken in a round bottomed flux . The flux was then placed on water-bath with constant stirring for one hour under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The solid product separated out by filtration . After filtration a white crude product was obtained . The crude product was not possible to purify .

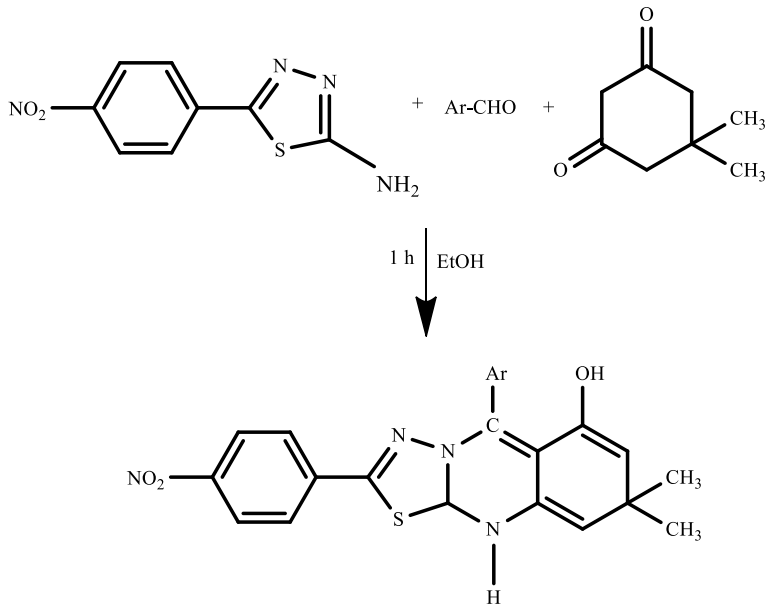
IR (KBr , cm^{-1} , fig. 26) : 3400-3450 (N-H) , 3275-3315 (NH_2) , 3190 (C-H , Ar) , 1611 (C=N) , 1610 , 1563 , 1515 (C=C , aromatic) , 1225 (C=S) .

RESULTS AND DISCUSSION

Chapter 3

3.1 Characterization of the compound 5-(phenyl)-8,8-dimethyl-2-(4-nitrophenyl)-10,10$_a$-dihydro-8H [1,3,4] thiadiazolo [2,3-b] quinazolin-6-ol . (1)

The desired product **1** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01 mol) , dimedone (0.01 mol) and benzaldehyde (0.01 mol) in ethanol under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The soild product was separated out by filtration . After filtration an orange crude product was obtained . The crude product was then purified by recrystallisation from ethanol to yield 75% as orange solid . The melting point was recorded as 195-198 $^{\circ}$C .



Compound 1

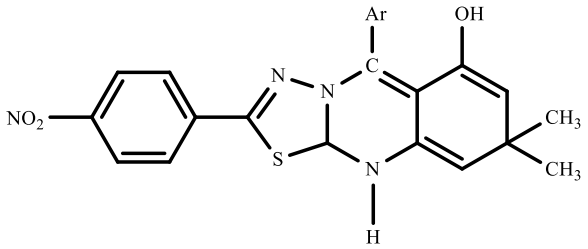
The IR spectra (**Fig.3**) of the compound **1** showed a wide absorption band at the range 3400-3475 cm^{-1} for enolic O-H group . The peak at 3346 cm^{-1} was designated for N-H . The aromatic C-H stretching was assigned at 3123 cm^{-1}. The aliphatic C-H stretching band was indicative at 2975 cm^{-1} . The characteristic C=N moiety was distinctive at 1600 cm^{-1} . The peaks at 1572 , 1540 and 1520 cm^{-1} were distinguished for aromatic and aliphatic C=C bonds. The C-S-C linkage was identified at 693 cm^{-1} .

The ^{1}H NMR spectra (**Fig. 4-5**) of the compound **1** showed a sharp singlet for six protons of two gem dimethyl group at 1.051 . The doublet with the coupling constant J=8.0 Hz at 6.90 was designated for olefinic one proton . The broad singlet at 7.18 was assigned for single proton of S-CH-N . The multiplet at 7.27 was distinguished for five aromatic protons . The

second multiplet was altributed for four aromatic protons at 7.43 . The doublet with the coupling constant J=8.0 Hz was ascribed for one olefinic proton at 7.71 . The sharp singlet at 8.120 was assigned for one enolic O-H proton . The sharp downfielded singlet at 11.651 was characterized for one N-H proton .

The ^{13}C NMR spectra (**Fig. 6-8**) of the compound **1** showed a signal at 176.86 for 1C of C=N. The signals 143.31 , 142.50 , 134.57 , 130.46 , 129.39 and 129.11 were distinctive for six olefinic protons . The aromatic 12C showed the characteristics signals at 128.45 , 127.33 , 126.77 and 126.39 . The signal at 113.79 was identified for 1C of S-C-N . The aliphatic three carbons were ascribed at 51.48 , 32.35 and 28.31 .

All the spectral evidences express harmony with the structure of the compound 1 as



Compound 1

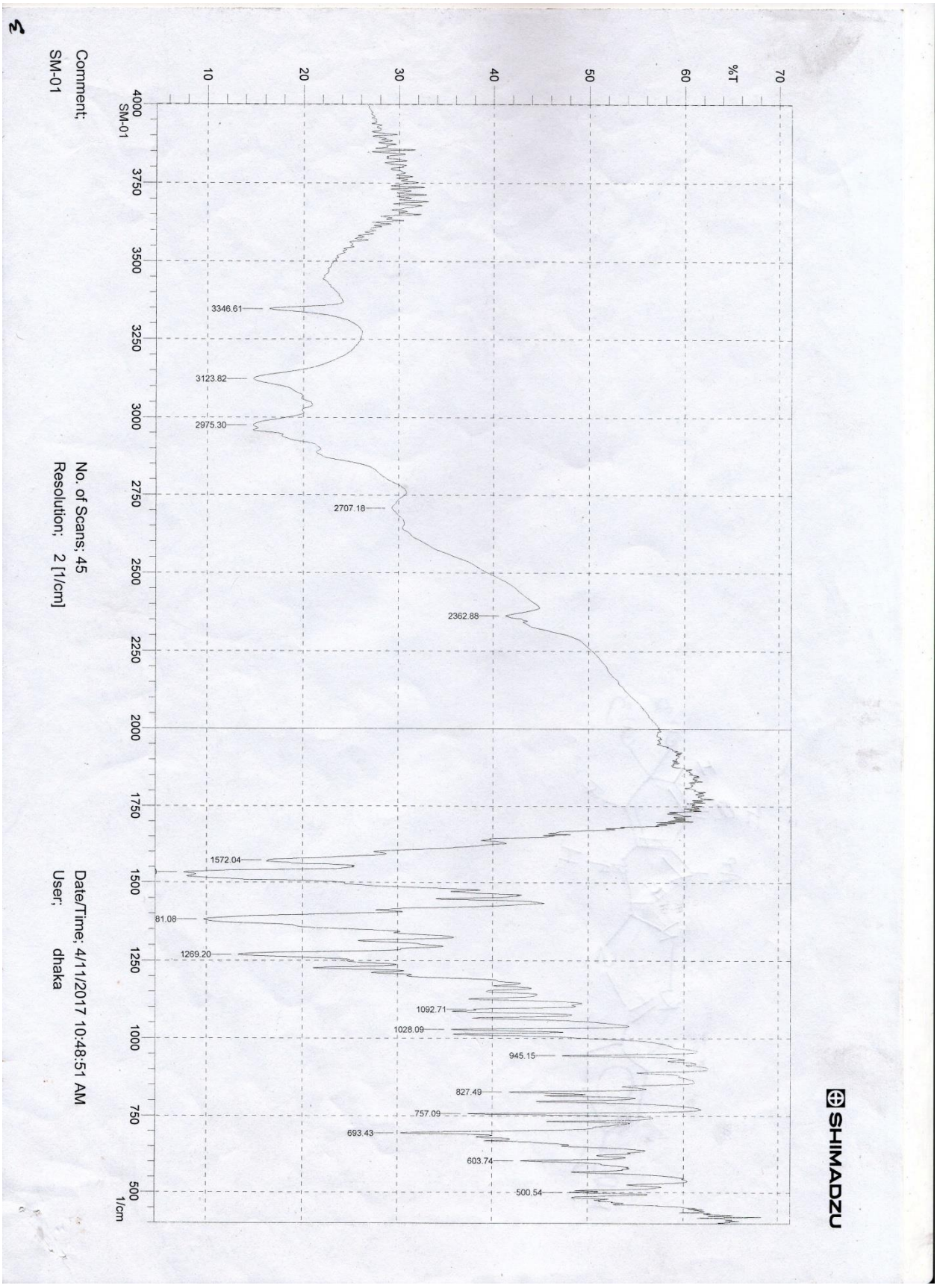

SHIMADZU
%T
10
20
30
40
50
60
70
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
SM-01
3346.61
3123.82
2975.30
2707.18
2362.88
1572.04
81.08
1269.20
1092.71
1028.09
945.15
827.49
757.09
693.43
603.74
500.54
Comment;
SM-01
No. of Scans; 45
Resolution; 2 [1/cm]
Date/Time; 4/11/2017 10:48:51 AM
User; dhaka

Figure-3

Figure-4

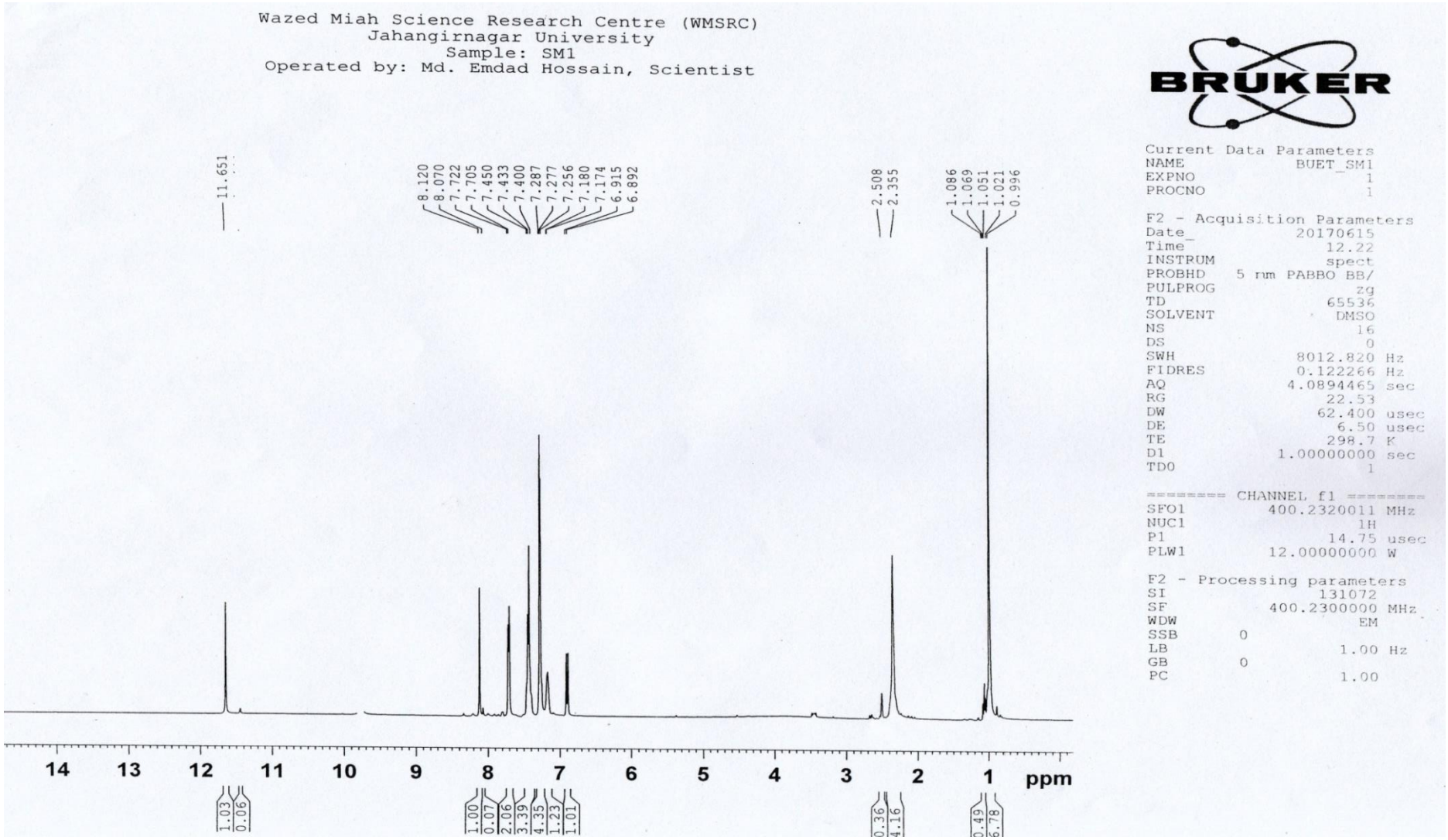

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM1
Operated by: Md. Emdad Hossain, Scientist
11.651
8.120
8.070
7.722
7.705
7.450
7.433
7.400
7.287
7.277
7.256
7.180
7.174
6.915
6.892
2.508
2.355
1.086
1.069
1.051
1.021
0.996
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.03
0.06
1.00
0.07
2.06
3.39
4.35
1.23
1.01
0.36
4.16
0.49
6.78
BRUKER
Current Data Parameters
NAME BUET_SM1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170615
Time 12.22
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT DMSO
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 22.53
DW 62.400 usec
DE 6.50 usec
TE 298.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 14.75 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure-5

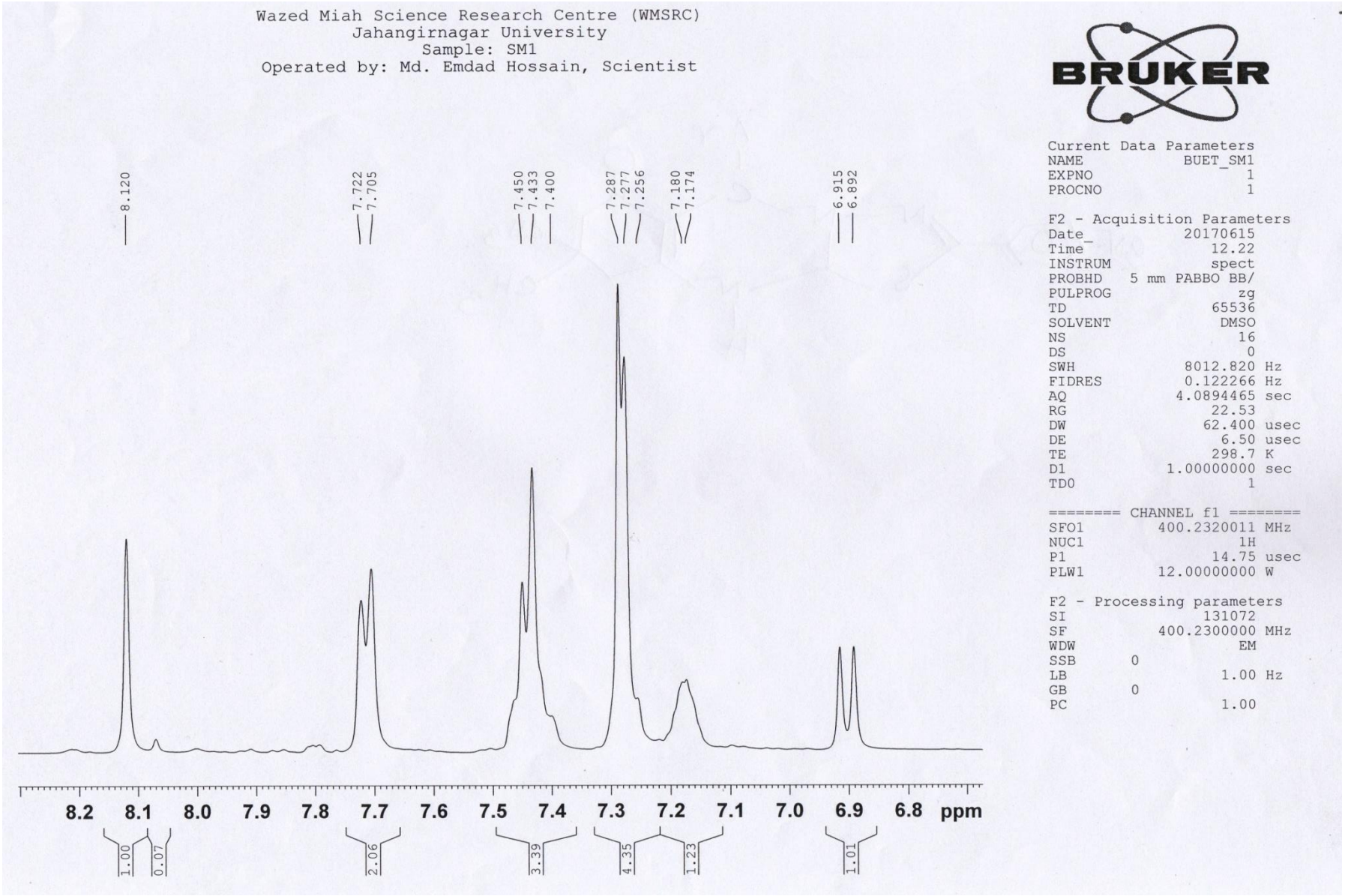

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM1
Operated by: Md. Emdad Hossain, Scientist
8.120
7.722
7.705
7.450
7.433
7.400
7.287
7.277
7.256
7.180
7.174
6.915
6.892
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
1.00
0.07
2.06
3.39
4.35
1.23
1.01
BRUKER
Current Data Parameters
NAME BUET_SM1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170615
Time 12.22
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT DMSO
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 22.53
DW 62.400 usec
DE 6.50 usec
TE 298.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 14.75 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure-6

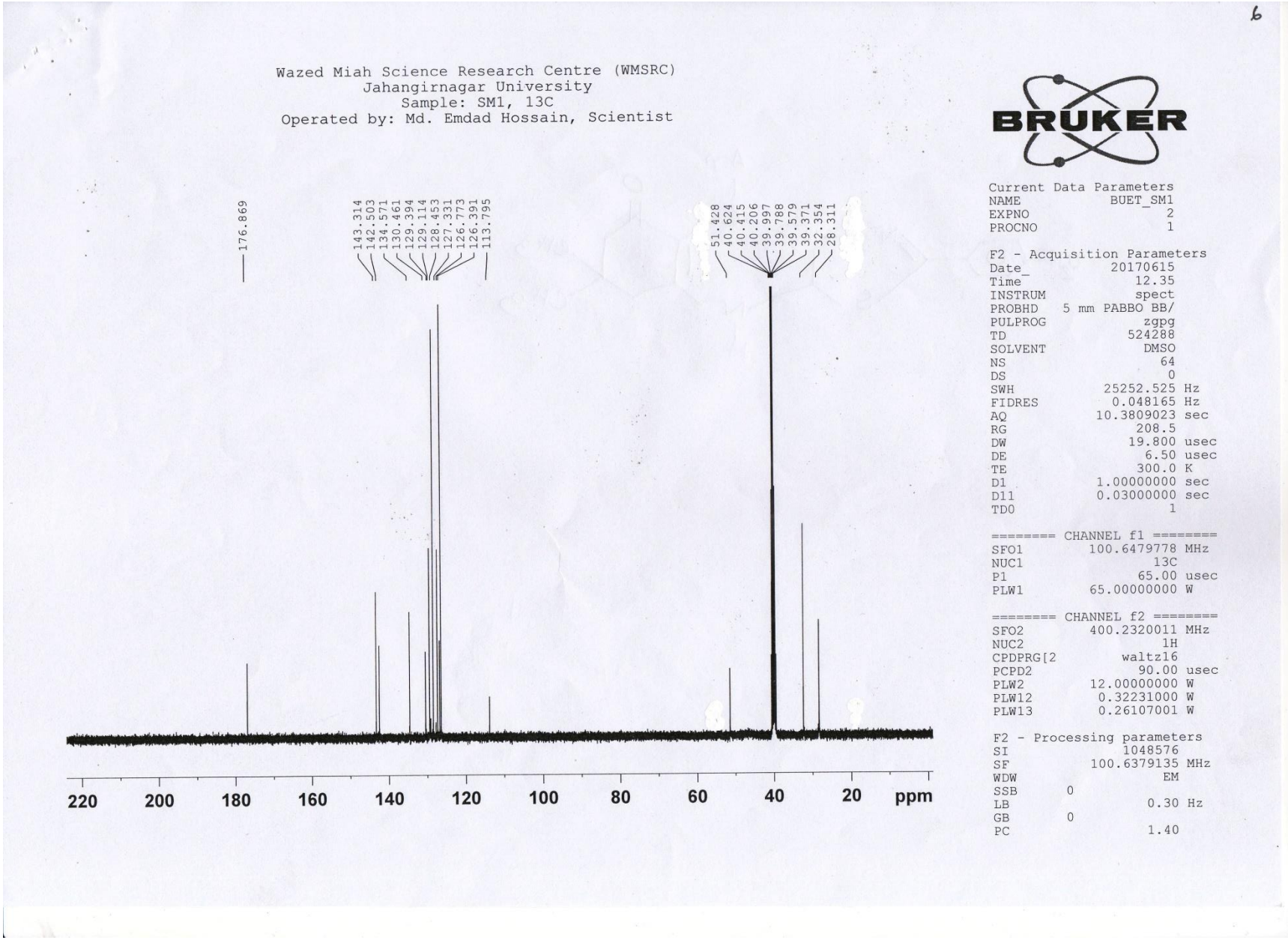
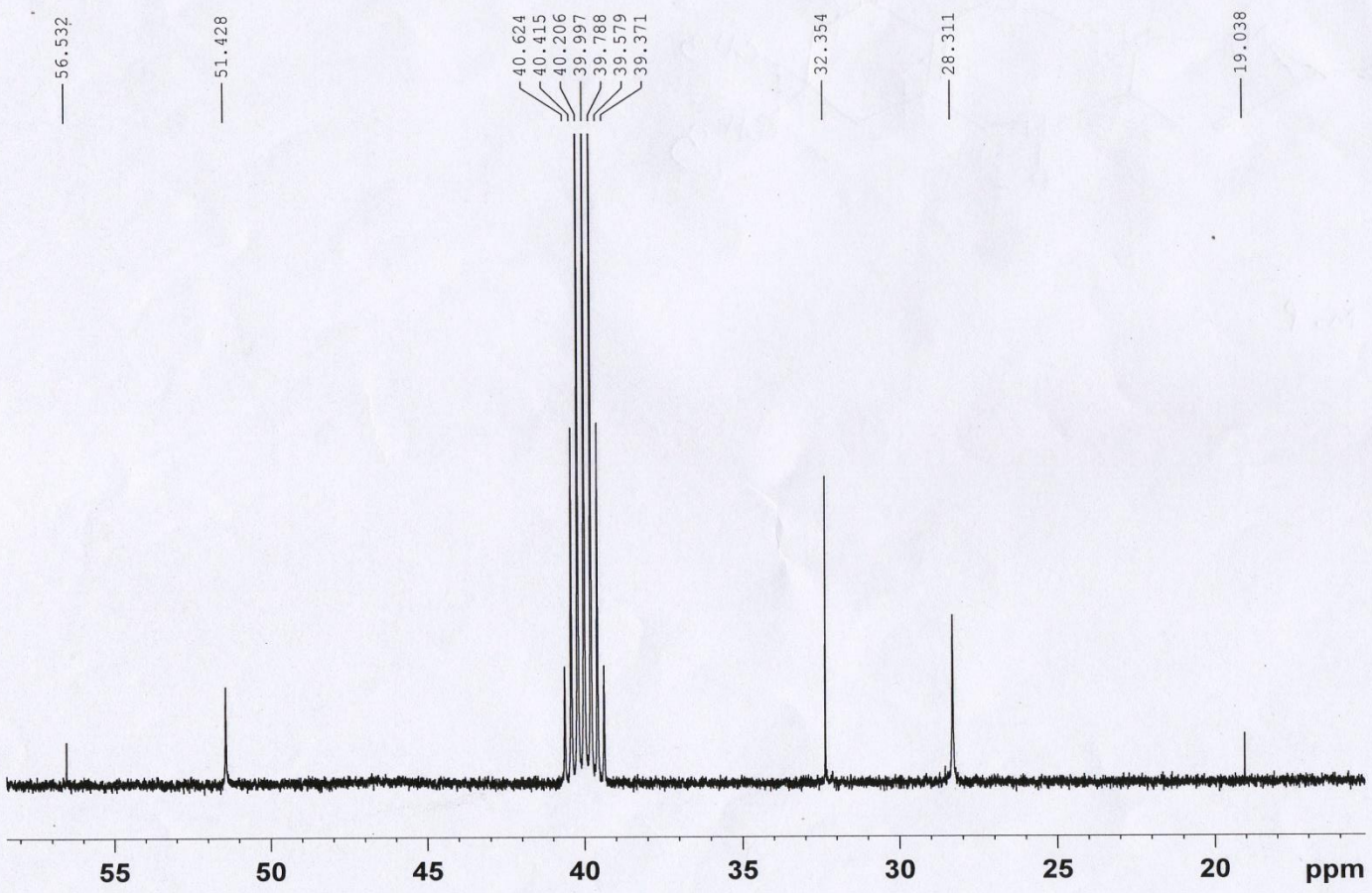

6
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM1, 13C
Operated by: Md. Emdad Hossain, Scientist
176.869
143.314
142.503
134.571
130.461
129.394
129.114
128.453
127.331
126.773
126.391
113.795
51.428
40.624
40.415
40.206
39.997
39.788
39.579
39.371
32.354
28.311
220
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME BUET_SM1
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170615
Time 12.35
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg
TD 524288
SOLVENT DMSO
NS 64
DS 0
SWH 25252.525 Hz
FIDRES 0.048165 Hz
AQ 10.3809023 sec
RG 208.5
DW 19.800 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6479778 MHz
NUC1 13C
P1 65.00 usec
PLW1 65.00000000 W
======== CHANNEL f2 ========
SFO2 400.2320011 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.32231000 W
PLW13 0.26107001 W
F2 - Processing parameters
SI 1048576
SF 100.6379135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

Figure -7

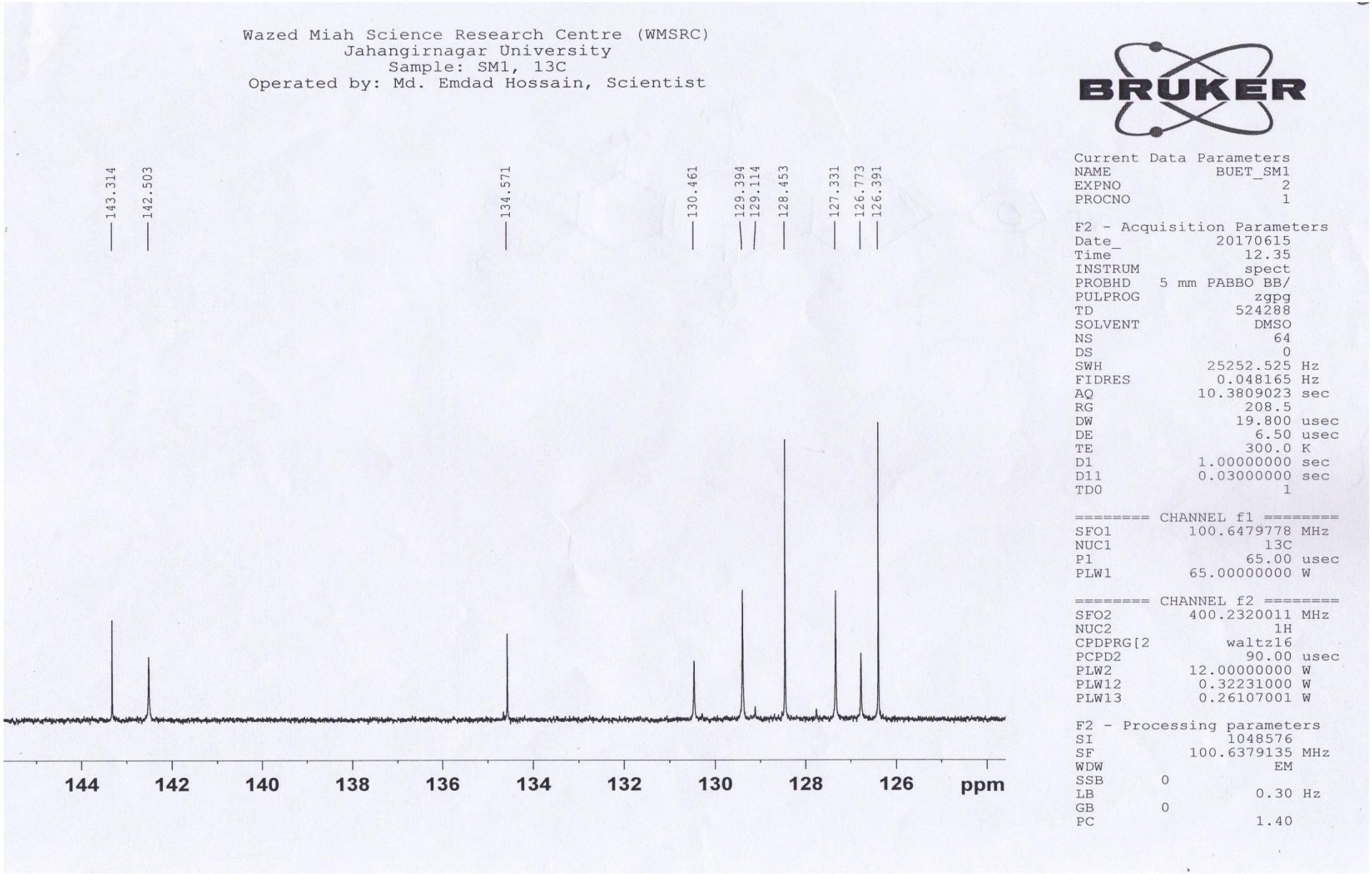
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM1, 13C
Operated by: Md. Emdad Hossain, Scientist



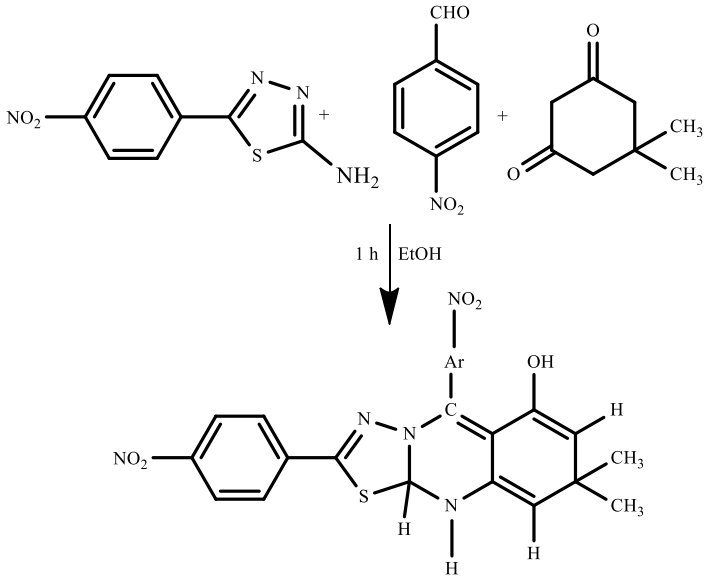

```
Current Data Parameters
NAME                  BUET_SM1
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170615
Time                     12.35
INSTRUM                  spect
PROBHD    5 mm PABBO BB/
PULPROG                  zgpg
TD                     524288
SOLVENT                   DMSO
NS                          64
DS                           0
SWH                25252.525 Hz
FIDRES              0.048165 Hz
AQ                 10.3809023 sec
RG                      208.5
DW                     19.800 usec
DE                      6.50 usec
TE                     300.0 K
D1                 1.00000000 sec
D11                0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1            100.6479778 MHz
NUC1                     13C
P1                     65.00 usec
PLW1           65.00000000 W

======== CHANNEL f2 ========
SFO2            400.2320011 MHz
NUC2                     1H
CPDPRG[2              waltz16
PCPD2                  90.00 usec
PLW2           12.00000000 W
PLW12           0.32231000 W
PLW13           0.26107001 W

F2 - Processing parameters
SI                     1048576
SF              100.6379135 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.40
```

64

Figure - 8


Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM1, 13C
Operated by: Md. Emdad Hossain, Scientist
143.314
142.503
134.571
130.461
129.394
129.114
128.453
127.331
126.773
126.391
144
142
140
138
136
134
132
130
128
126
ppm
BRUKER
Current Data Parameters
NAME BUET_SM1
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170615
Time 12.35
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg
TD 524288
SOLVENT DMSO
NS 64
DS 0
SWH 25252.525 Hz
FIDRES 0.048165 Hz
AQ 10.3809023 sec
RG 208.5
DW 19.800 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6479778 MHz
NUC1 13C
P1 65.00 usec
PLW1 65.00000000 W
======== CHANNEL f2 ========
SFO2 400.2320011 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.32231000 W
PLW13 0.26107001 W
F2 - Processing parameters
SI 1048576
SF 100.6379135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

3.2. Characterization of the compound 5-(4-nitrophenyl)-8,8-dimethyl-2-(4-nitrophenyl)-10,10$_a$-dihydro-8H-[1,3,4] thiadiazole [2,3-b] quinazolin-6-ol . (2)



Compound 2

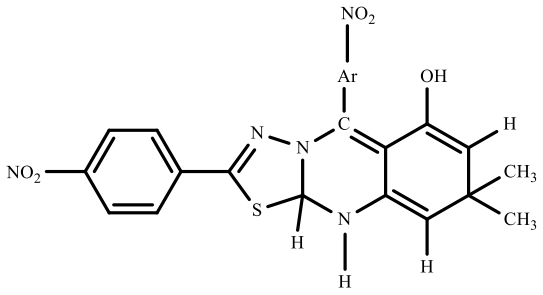
The desired product **2** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01 mol) , dimedone (0.01 mol) and para nitro benzaldehyde (0.01 mol) in ethanol under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The soild product was separated out by filtration . After filtration a yellow crude product was obtained . The crude product was then purified by recrystallisation from ethanol to yield 73% as yellow solid . The melting point was recorded as 198-200 $^{\circ}$C .

The IR spectra (**Fig.9**) of the compound **2** showed a very weak absorption broad band at 3450-3500 cm^{-1} for enolic O-H . The peak at 3337 cm^{-1} was assigned for N-H . The aromatic C-H stretching was designated at 3085 cm^{-1} . The peak at 2963 cm^{-1} was distinctive for aliphatic C-H stretching . The band at 1607 cm^{-1} was distinctive for C=N . The characteristic peaks at 1604 , 1580 , 1527 at 1510 cm^{-1} were assigned for C=C of aliphatic and aromatic . The C-S-C bridge was identified at 720 cm^{-1} .

The ^{1}H NMR spectra (**Fig. 10-11**) of the compound **2** showed a sharp singlet at 1.013 for three protons of one of the gem methyl group . The another sharp singlet for the rest of the three protons of methyl was ascribed at 1.096 . The doublet with the coupling constant J=8.0 Hz for one olefinic proton was identified at 7.490 . The multiplet at 8.11 was for one proton

of S-CHN and another one proton for enolic O-H . The multiplet for four aromatic protons was distinguished at 8.246 . The another multiplet at 8.297 was attributed for four aromatic protons . The doublet with the coupling constant J=8.0 Hz at 8.42 was distinctive for another olefinic proton . The sharp downfielded singlet at 10.185 was designated for one proton of N-H .

All the spectral evidences support in favour of the structure of the compound **2** as



Compound 2

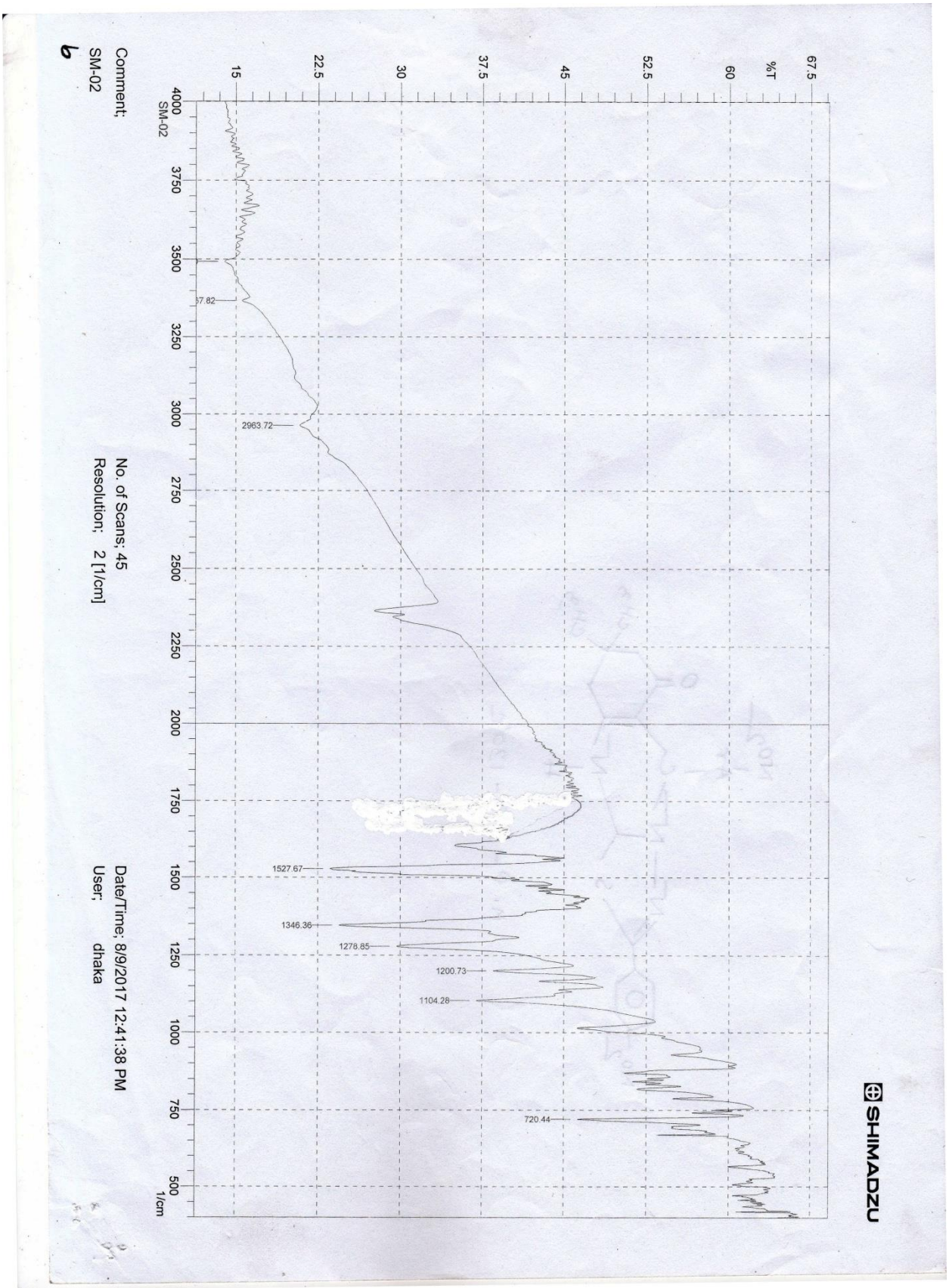

SHIMADZU
%T
67.5
60
52.5
45
37.5
30
22.5
15
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
SM-02
3437.82
2963.72
1527.67
1346.36
1278.85
1200.73
1104.28
720.44
Comment;
SM-02
6
No. of Scans; 45
Resolution; 2 [1/cm]
Date/Time; 8/9/2017 12:41:38 PM
User; dhaka

Figure - 9

Figure - 10

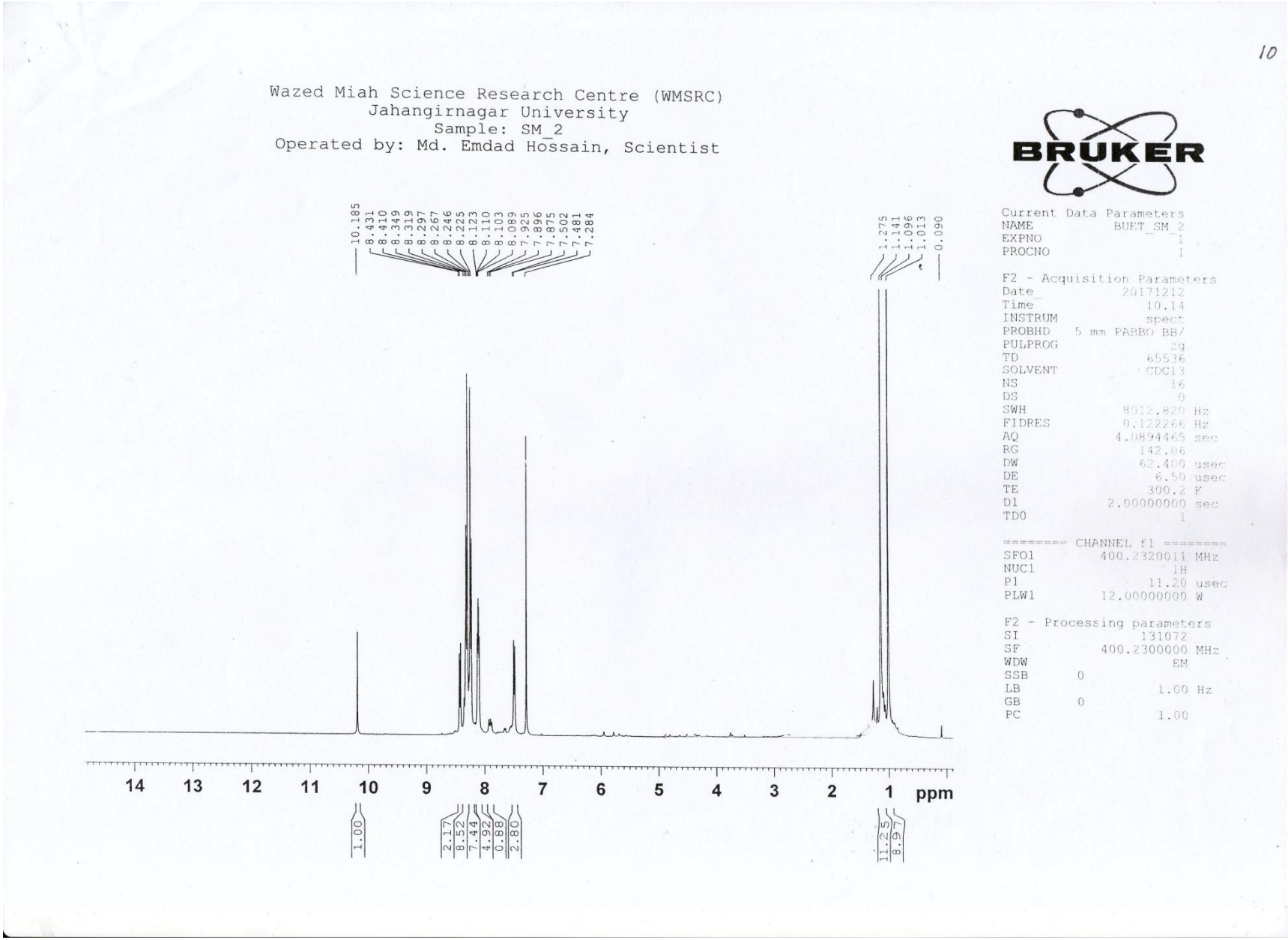
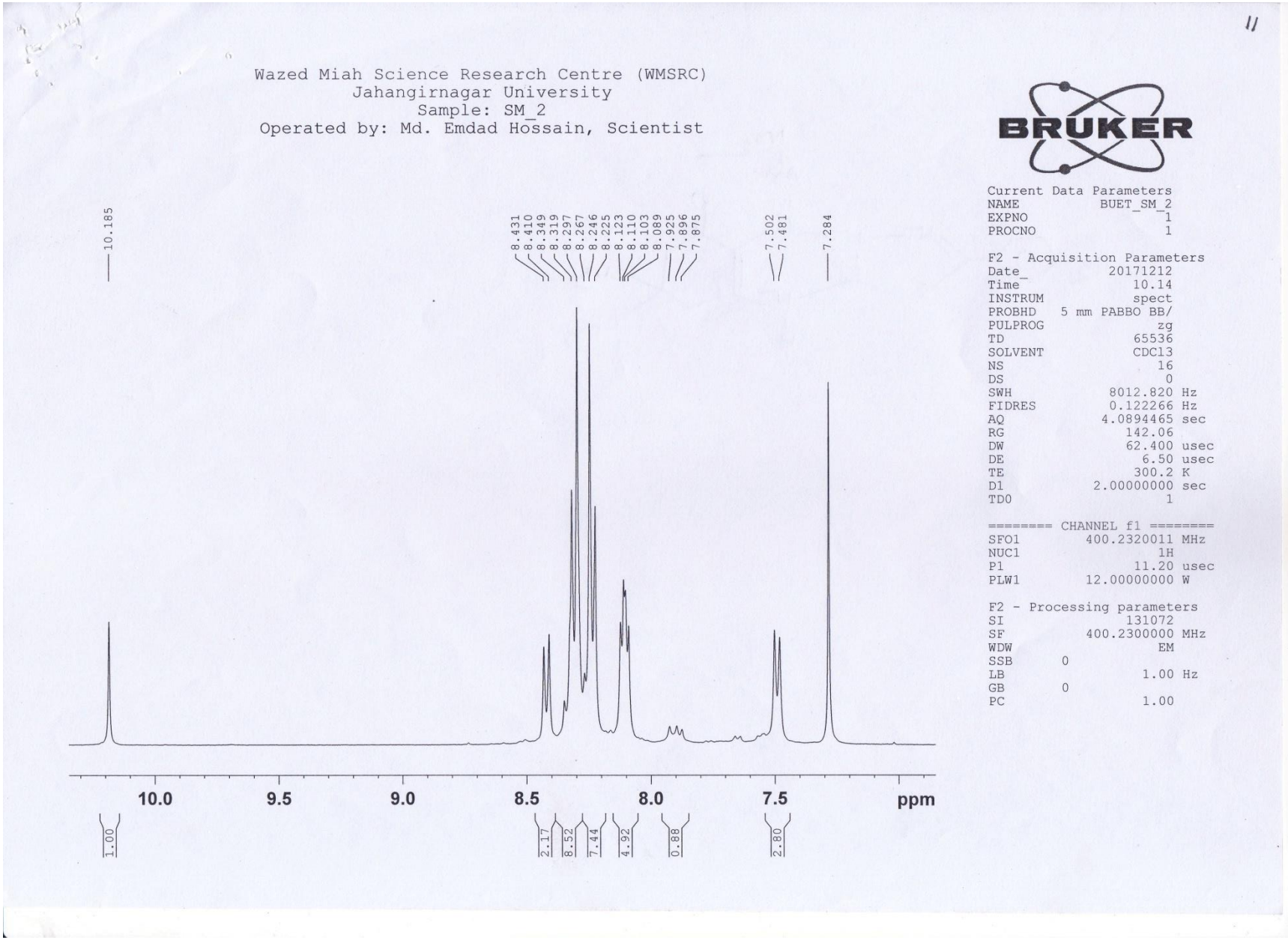
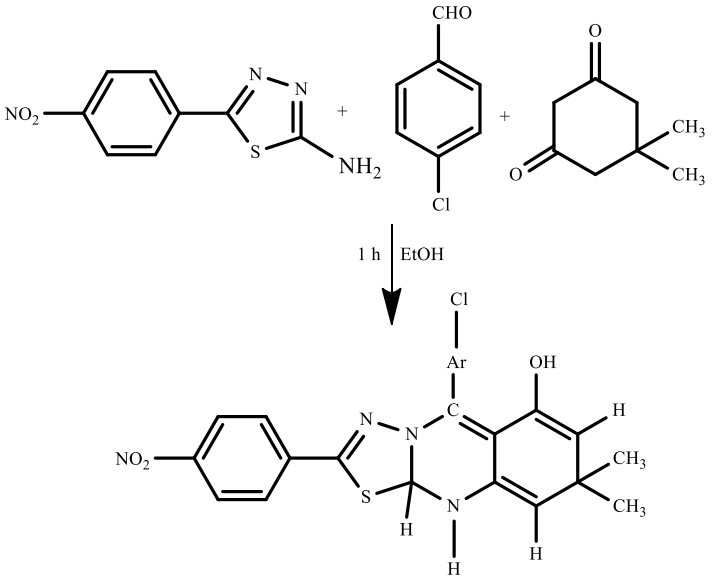

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_2
Operated by: Md. Emdad Hossain, Scientist
10.185
8.431
8.410
8.349
8.319
8.297
8.267
8.246
8.225
8.123
8.110
8.103
8.089
7.925
7.896
7.875
7.502
7.481
7.284
1.275
1.141
1.096
1.013
0.090
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
2.17
8.52
7.44
4.92
0.88
2.80
11.25
8.97
BRUKER
Current Data Parameters
NAME BUET_SM_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 10.14
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122286 Hz
AQ 4.0894465 sec
RG 142.06
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure -11


Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_2
Operated by: Md. Emdad Hossain, Scientist
10.185
8.431
8.410
8.349
8.319
8.297
8.267
8.246
8.225
8.123
8.110
8.103
8.089
7.925
7.896
7.875
7.502
7.481
7.284
10.0
9.5
9.0
8.5
8.0
7.5
ppm
1.00
2.17
8.52
7.44
4.92
0.88
2.80
BRUKER
Current Data Parameters
NAME BUET_SM_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 10.14
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 142.06
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

3.3. Characterization of the compound 5-(4-chlorophenyl)-8,8-dimethyl-2-(4-nitrophenyl)-10 , 10_a-dihydro-8H-[1,3,4] thiadiazole [2,3-b] quinazolin-6-ol . (3)

The desired product **3** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl]4-nitro benzene (0.01 mol) , dimedone (0.01 mol) and para chloro benzaldehyde (0.01 mol) in ethanol under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The soild product was separated out by filtration . After filtration an yellow crude product was obtained . The crude product was then purified by recrystallisation from ethanol to yield 74% as light yellow solid . The melting point was recorded as 194-195 $^{\circ}$C .



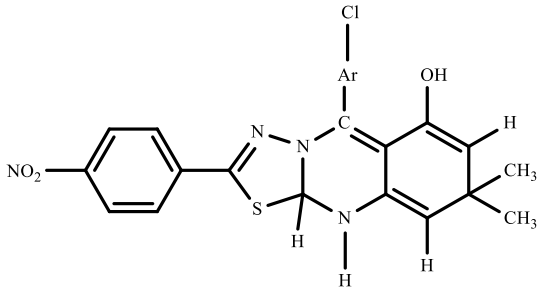
Compound 3

The IR spectra **(Fig . 12)** of the compound **3** showed a peak at 3446 cm^{-1} for enolic O-H . The peak at 3288 cm^{-1} was assigned for N-H . The aromatic C-H stretching was designated at 3150 cm^{-1} . The aliphatic C-H stretching was indicative at 2997 cm^{-1} . A distinctive peak at 1601 cm^{-1} was assigned for C=N moiety . The characteristics peaks at 1525 , 1490 and 1450 cm^{-1} were distinguished for C=C . A weak peak at 816 cm^{-1} was identified for bridge C-S-C .

The ^{1}H NMR spectra (**Fig 13-14**) of the compound **3** showed a sharp singlet at 1.136 for three protons of gem methyl and another sharp singlet at 1.654 was distinguished for three protons of gem methyl group . The broad singlet at 6.388 was designated for one olefinic proton . The another olefinic proton was assigned at 7.212 . The doublet with the coupling contant J=8.0 Hz at 7.414 was attributed for four aromatic protons, the another doublet with the coupling

constant J=8.0 Hz was ascribed for four aromatic protons at 7.61 . The sharp singlet at 7.842 was distinctive for one proton of S-C-H . The sharp singlet at 9.400 was indicative for one proton of enolic O-H. The downfielded sharp singlet at 10.012 was identified for one proton of N-H .

All the spectral evidences express harmony with the structure of the compound **3** as



Compound 3

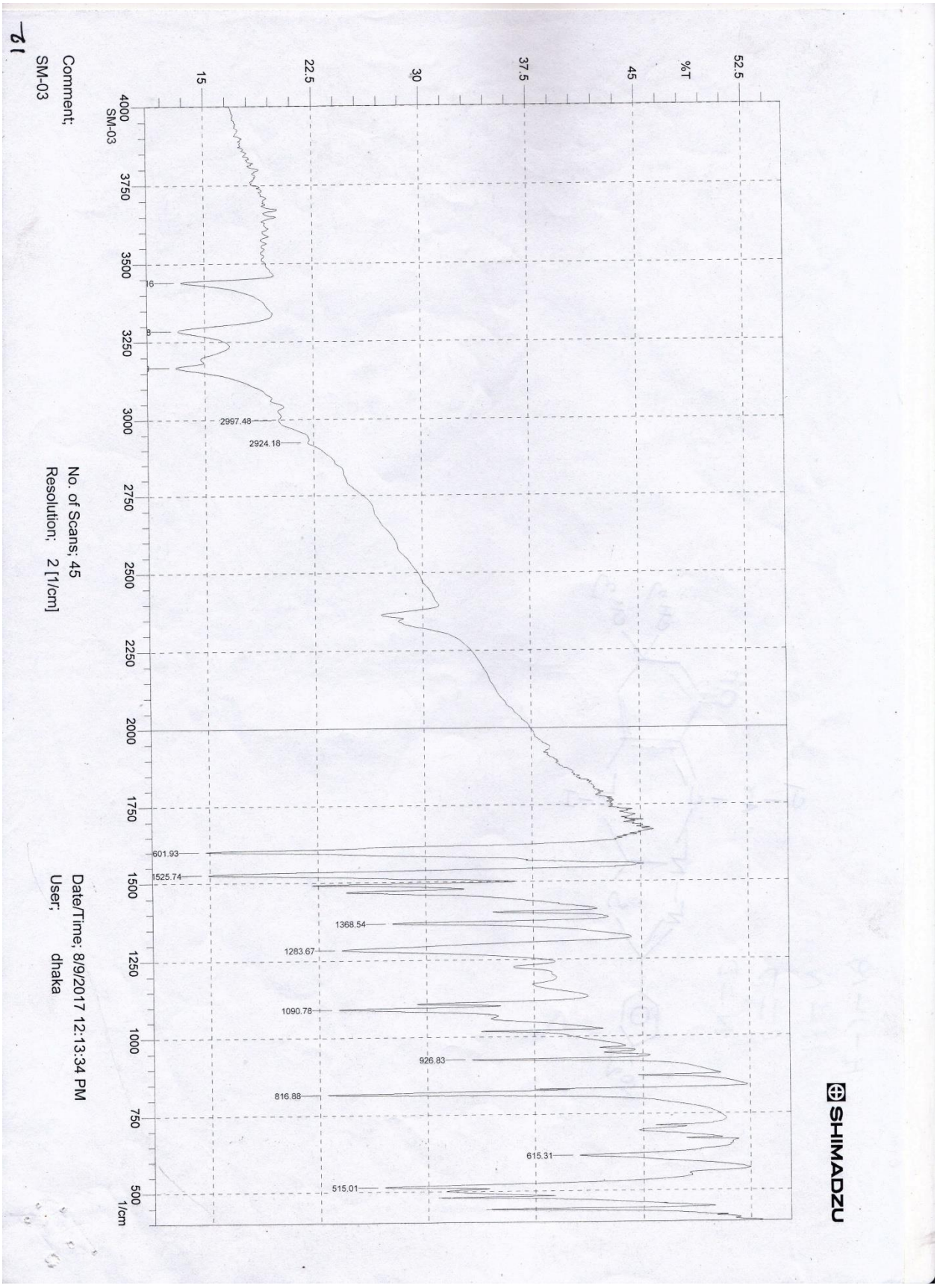

SHIMADZU
%T
52.5
45
37.5
30
22.5
15
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
SM-03
2997.48
2924.18
601.93
1525.74
1368.54
1283.67
1090.78
926.83
816.88
615.31
515.01
Comment;
SM-03
No. of Scans; 45
Resolution; 2 [1/cm]
Date/Time; 8/9/2017 12:13:34 PM
User; dhaka

Figure - 12

Figure - 13

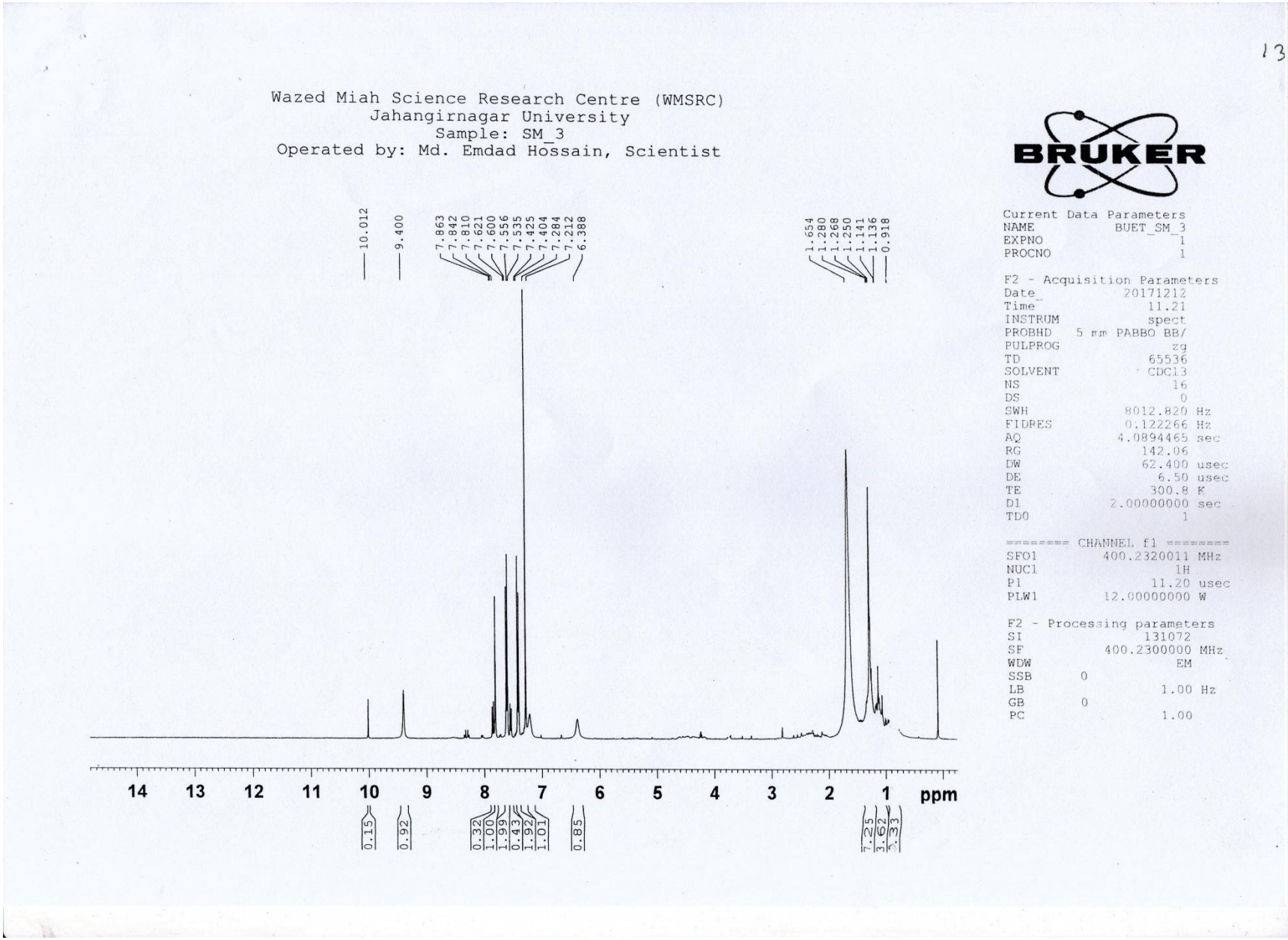
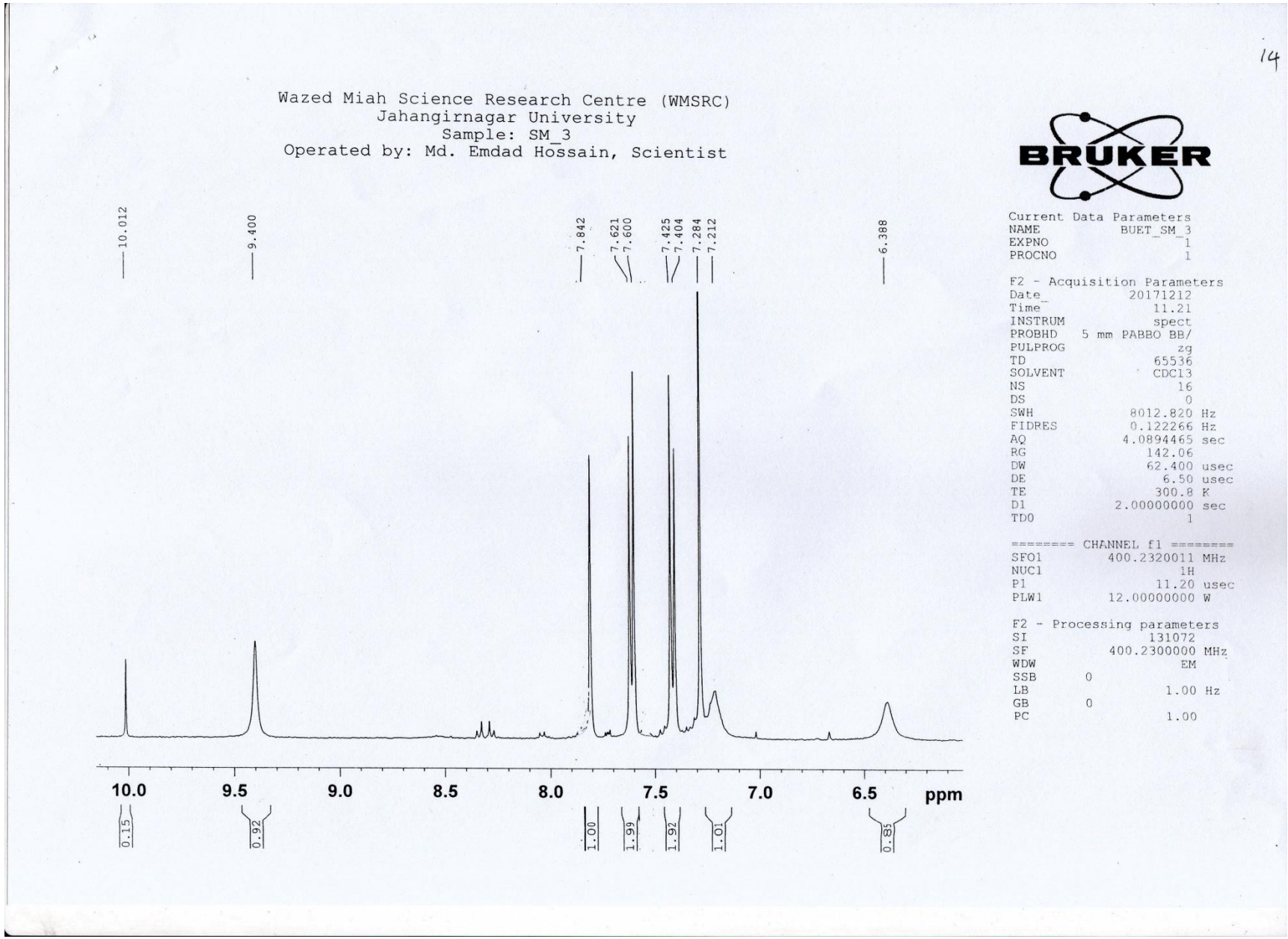
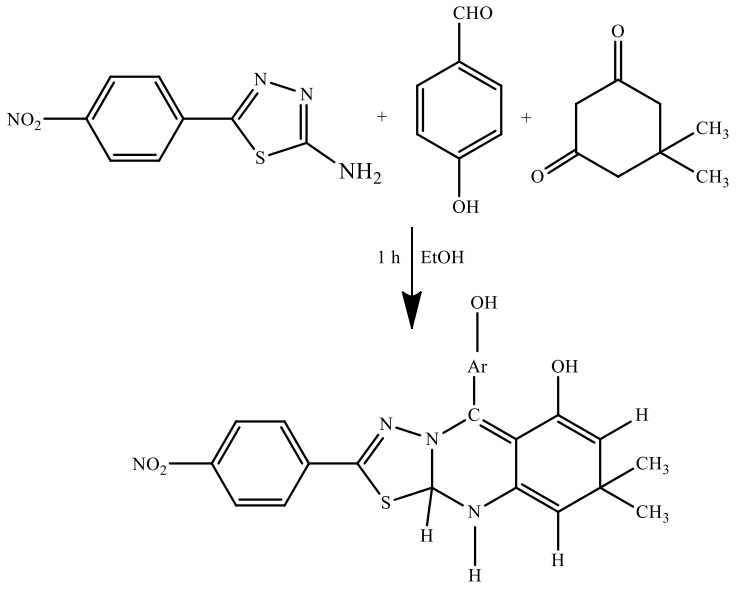

13
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_3
Operated by: Md. Emdad Hossain, Scientist
10.012
9.400
7.863
7.842
7.810
7.621
7.600
7.556
7.535
7.425
7.404
7.284
7.212
6.388
1.654
1.280
1.268
1.250
1.141
1.136
0.918
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.15
0.92
0.32
1.00
1.99
0.43
1.92
1.01
0.85
7.25
3.62
3.33
BRUKER
Current Data Parameters
NAME BUET_SM_3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 11.21
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 142.06
DW 62.400 usec
DE 6.50 usec
TE 300.8 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure - 14


14
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_3
Operated by: Md. Emdad Hossain, Scientist
10.012
9.400
7.842
7.621
7.600
7.425
7.404
7.284
7.212
6.388
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
ppm
0.15
0.92
1.00
1.99
1.92
1.01
0.85
BRUKER
Current Data Parameters
NAME BUET_SM_3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 11.21
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDC13
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 142.06
DW 62.400 usec
DE 6.50 usec
TE 300.8 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

3.4 Characterization of the compound 5-(4-hydroxyphenyl)-8,8-dimethyl-2-(4-nitrophenyl)-10,10$_a$-dihydro-8H-[1,3,4] thiadiazole [2,3-b] quinazolin-6-ol . (4)



Compound 4

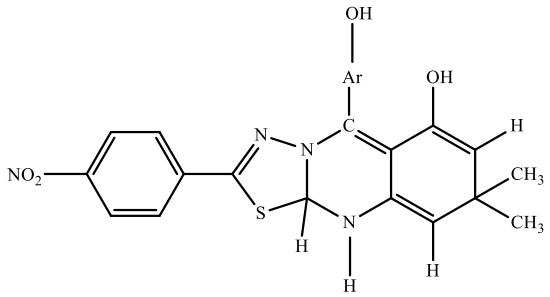
The desired product **4** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl]4-nitro benzene (0.01 mol) , dimedone (0.01 mol) and para hydroxy benzaldehyde (0.01 mol) in ethanol under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The soild product was separated out by filtration . After filtration an orange crude product was obtained . The crude product was then purified by recrystallisation from ethanol to yield 73% as orange solid . The melting point was recorded as 201-204 $^{\circ}$C .

The IR spectra (**Fig. 15**) of the compound **4** showed a wide absorption band at 3400-3460 cm^{-1} for phenolic OH group . The band at 3340-3380 cm^{-1} was identified for enolic O-H . The aromatic and aliphatic C-H stretching were distinctive at 3100 and 2961 cm^{-1} respectively . The peak at 1609 cm^{-1} was designated for C=N . The characteristics peaks at 1590 , 1550 , 1511 and 1490 cm^{-1} were distinguished for aromatic and aliphatic C=C .The peak at 850 cm^{-1} was identified for C-S-C bridge linkage .

The ^{1}H NMR spectra **(Fig 16**) of the compound **4** showed a doublet with the coupling constant J=2.0 Hz for six proton of two methyl groups . The doublet with the coupling constant J=12.0 Hz at 7.44 was assigned for four aromatic protons . The other aromatic four protons showed as doublet with the coupling constant J=8.0 Hz at 7.83 . The singlet at 8.037

was assigned for two olefinic protons . The broad singlet at 8.066 was designated for one proton of enolic O-H. The other singlet of one phenolic proton was attributed at 8.029 . The sharp downfielded singlet was distinctive for one proton of N-H at 11.407 .

All the spectral evidences support in favour of the structure of the compound **4** as



Compound 4

Figure - 15

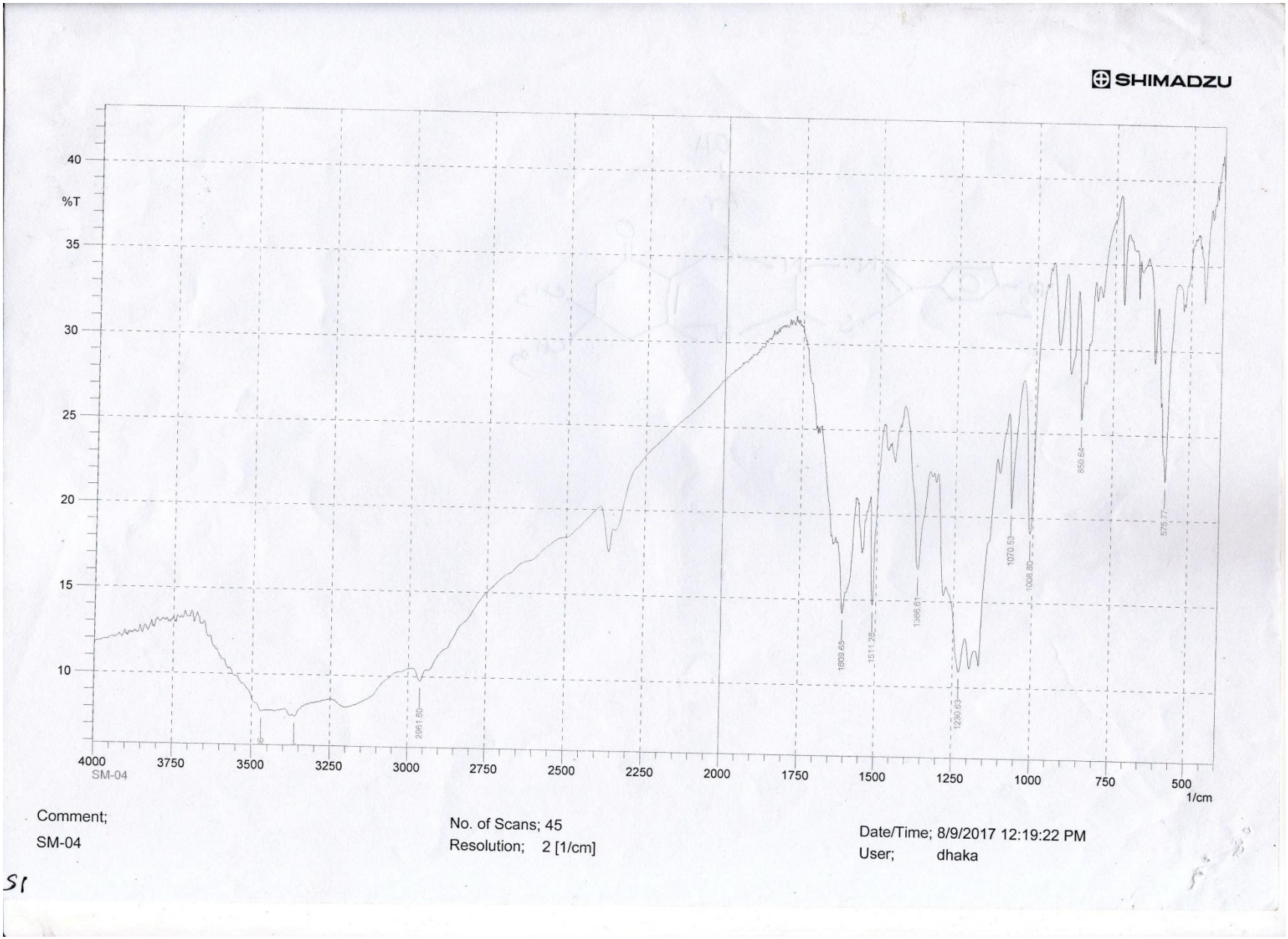
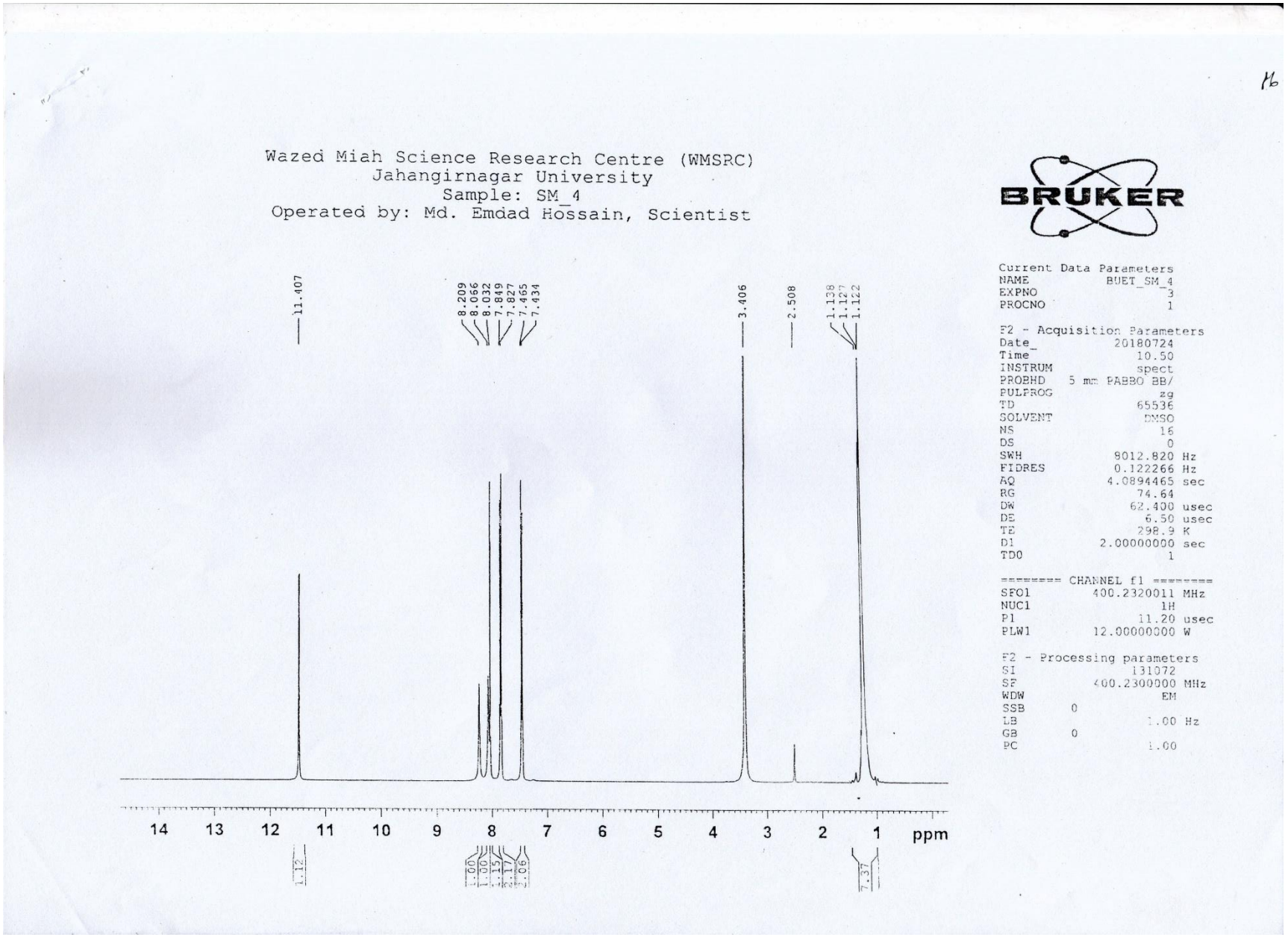
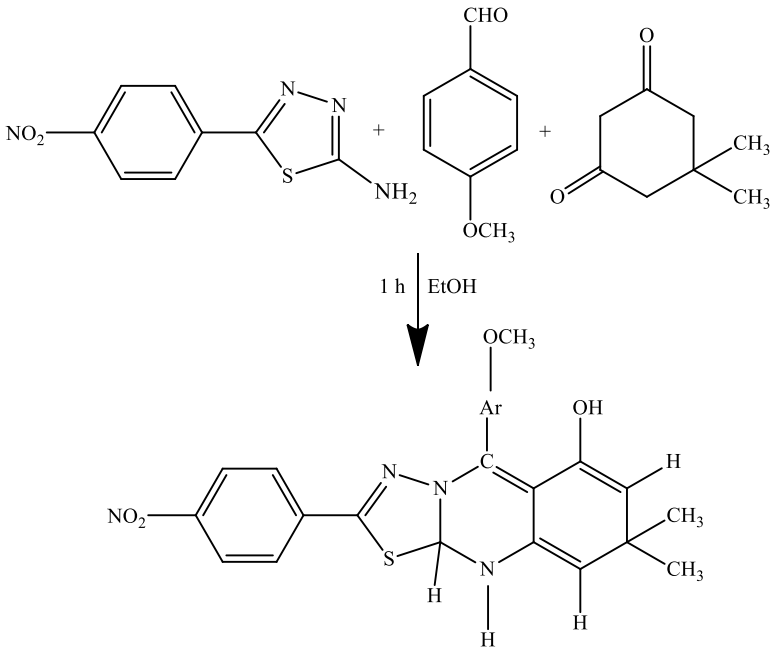

SHIMADZU
%T
40
35
30
25
20
15
10
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
SM-04
2961.80
1609.65
1511.28
1396.61
1230.60
1070.53
1008.80
850.64
575.77
Comment;
SM-04
No. of Scans; 45
Resolution; 2 [1/cm]
Date/Time; 8/9/2017 12:19:22 PM
User; dhaka
S1

Figure - 16


Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_4
Operated by: Md. Emdad Hossain, Scientist
11.407
8.209
8.066
8.032
7.849
7.827
7.465
7.434
3.406
2.508
1.138
1.127
1.122
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.12
1.00
1.00
1.15
3.17
1.06
7.37
BRUKER
Current Data Parameters
NAME BUET_SM_4
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180724
Time 10.50
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT DMSO
NS 16
DS 0
SWH 9012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 74.64
DW 62.400 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

3.5. Characterization of the compound 5-(4-methoxyxyphenyl)-8,8-dimethyl-2-(4-nitrophenyl)-10,10$_a$-dihydro-8H-[1,3,4] thiadiazole [2,3-b] quinazolin-6-ol . (5)

The desired product **5** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl]4-nitro benzene (0.01 mol) , dimedone (0.01 mol) and para methoxy benzaldehyde (0.01 mol) in ethanol under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The soild product was separated out by filtration . After filtration a yellow crude product was obtained . The crude product was then purified by recrystallisation from ethanol to yield 72% as yellow solid . The melting point was recorded as 190-195 $^{\circ}$C .



Compound 5

The IR spectra (**Fig .17**) of the compound **5** showed an absorption band at 3400-3410 cm^{-1} for OH . The peak at 3293 cm^{-1} was identified for N-H . The aromatic and aliphatic C-H stretching vibrations were assigned at 3159 cm^{-1} and 2961 cm^{-1} respectively . The C=N moiety was observed at 1607 cm^{-1}. The characteristics peaks at 1595 , 1510 , 1450 and 1452 cm^{-1} were distinguished for aliphatic and aromatic C=C . The peak at 842 cm^{-1} was identified for C-S-C bridge linkage .

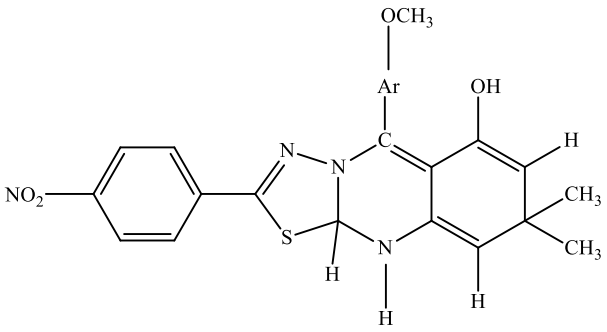
The ^{1}H NMR spectra (**Fig. 18-19**) of the compound **5** showed a sharp singlet for three protons of CH_3 . The sharp singlet at 1.117 was assigned for three protons of another methyl

group. The OCH_3 three protons was designated by the sharp singlet at 3.375 . The doublet with the coupling constant J=8.0 Hz at 6.76 was distinguished for two aromatic protons . The another doublet with the the coupling constant J=8.0 Hz at 6.91 was characterized for one olefinic proton . The broad singlet at 7.61 was distinctive for one proton of –S-CH . The doublet with the coupling constant J=8.0 Hz at 7.875 was ascribed for one hydroxyl proton .

The doublet with coupling constant J=8.0 Hz at 7.02 was identified for one olefinic proton . The doublet with the coupling constant J=8.0 Hz was distinctive for two aromatic protons at 7.24 . The multiplet at 8.243-8.332 was designated for four aromatic protons .

The ^{13}C NMR spectra (**Fig. 20)** of the compound **5** showed a signal at 162.183 for one carbon of C=N . The signal at 158.0 was indicative for one carbon of SCN . The signals at 136.459 , 135.184 , 132.360 , 132.024 and 131.217 were distinctive for six aromatic carbons . The signals at 130.665 , 129.315 , 129.202 , 125.588 , 123.507 , 123.494 were assigned for six aliphatic C=C . The signals at 115.840 , 114.425 , 114.351 , 113.800 and 113.012 were assigned for six aromatic carbons . The signals at 50.766 was identified for one carbon of NCS at 40.898 for one carbon of OCH_3 , at 32.195 for one carbon of CCH_3 and the signals at 30.969 and 27.349 were for two carbons of gem dimethyl group .

All the spectral evidences express harmony with the structure of the compound **5** as



Compound 5

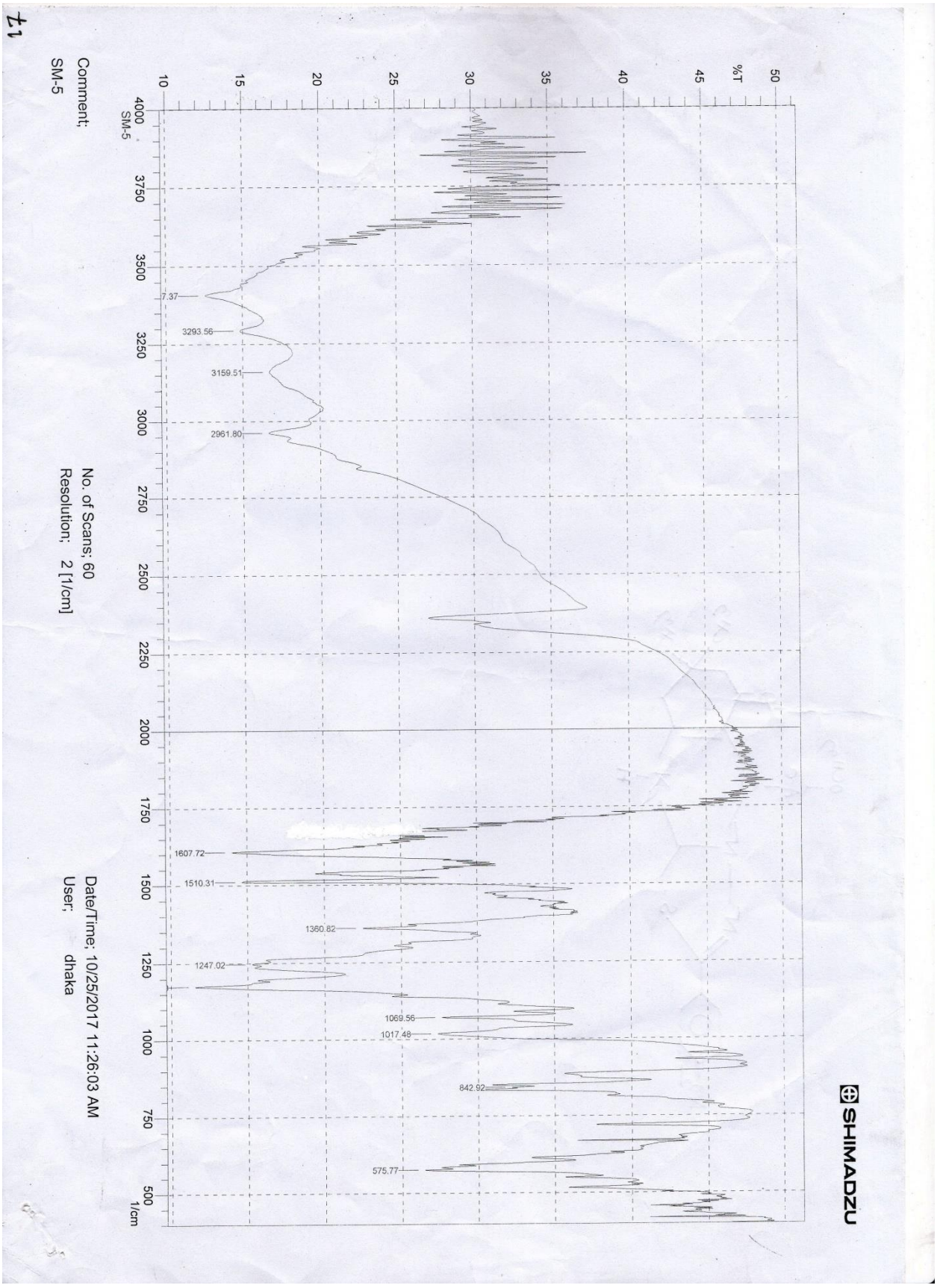

SHIMADZU
%T
1/cm
SM-5
7.37
3293.56
3159.51
2961.80
1607.72
1510.31
1360.82
1247.02
1069.56
1017.48
842.92
575.77
Comment;
SM-5
No. of Scans; 60
Resolution; 2 [1/cm]
Date/Time; 10/25/2017 11:26:03 AM
User; dhaka

Figure - 17

Figure - 18

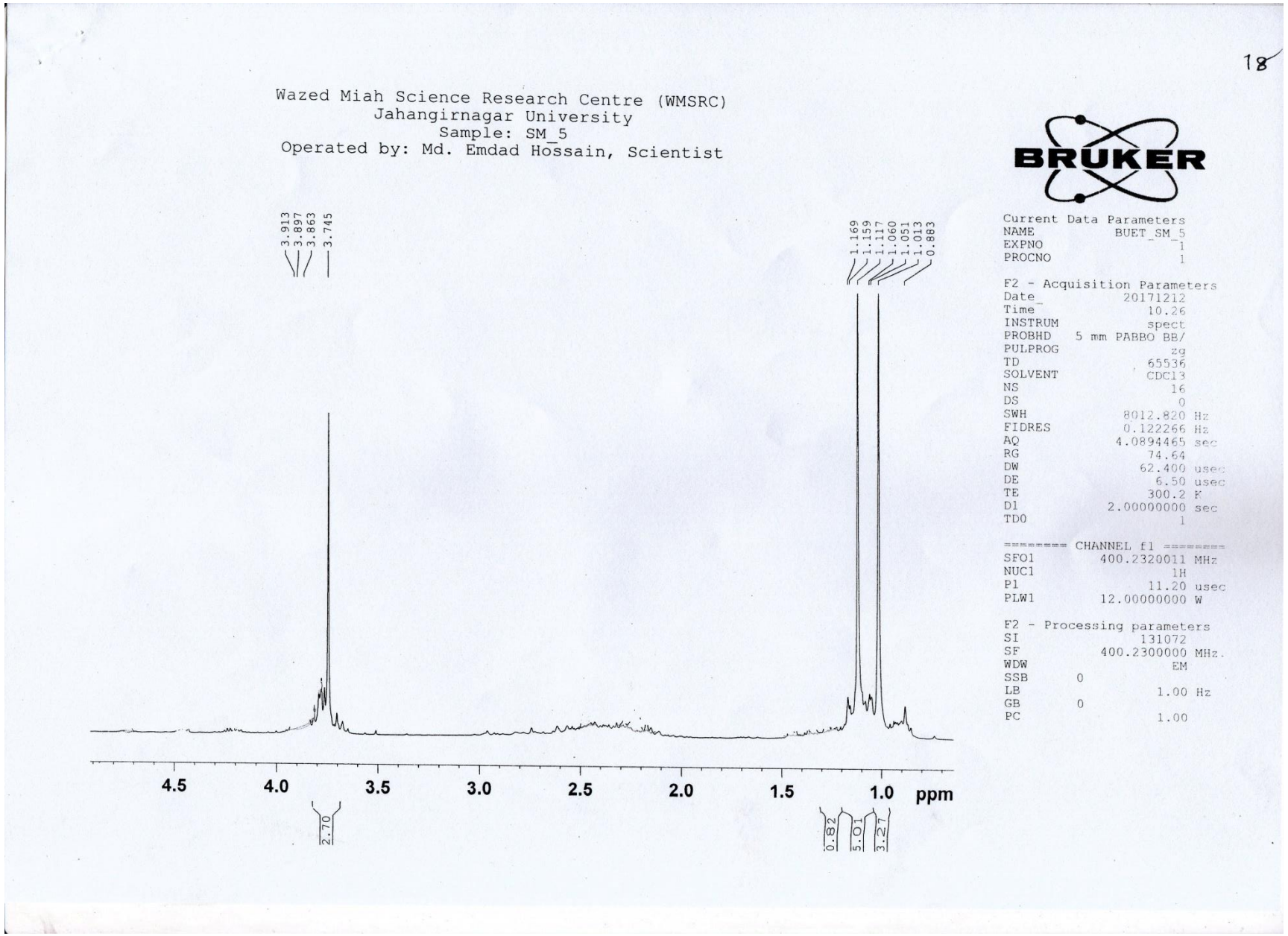

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_5
Operated by: Md. Emdad Hossain, Scientist
18
BRUKER
3.913
3.897
3.863
3.745
1.169
1.159
1.117
1.060
1.051
1.013
0.883
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.70
0.82
5.01
3.27
Current Data Parameters
NAME BUET_SM_5
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 10.26
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 74.64
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure - 19

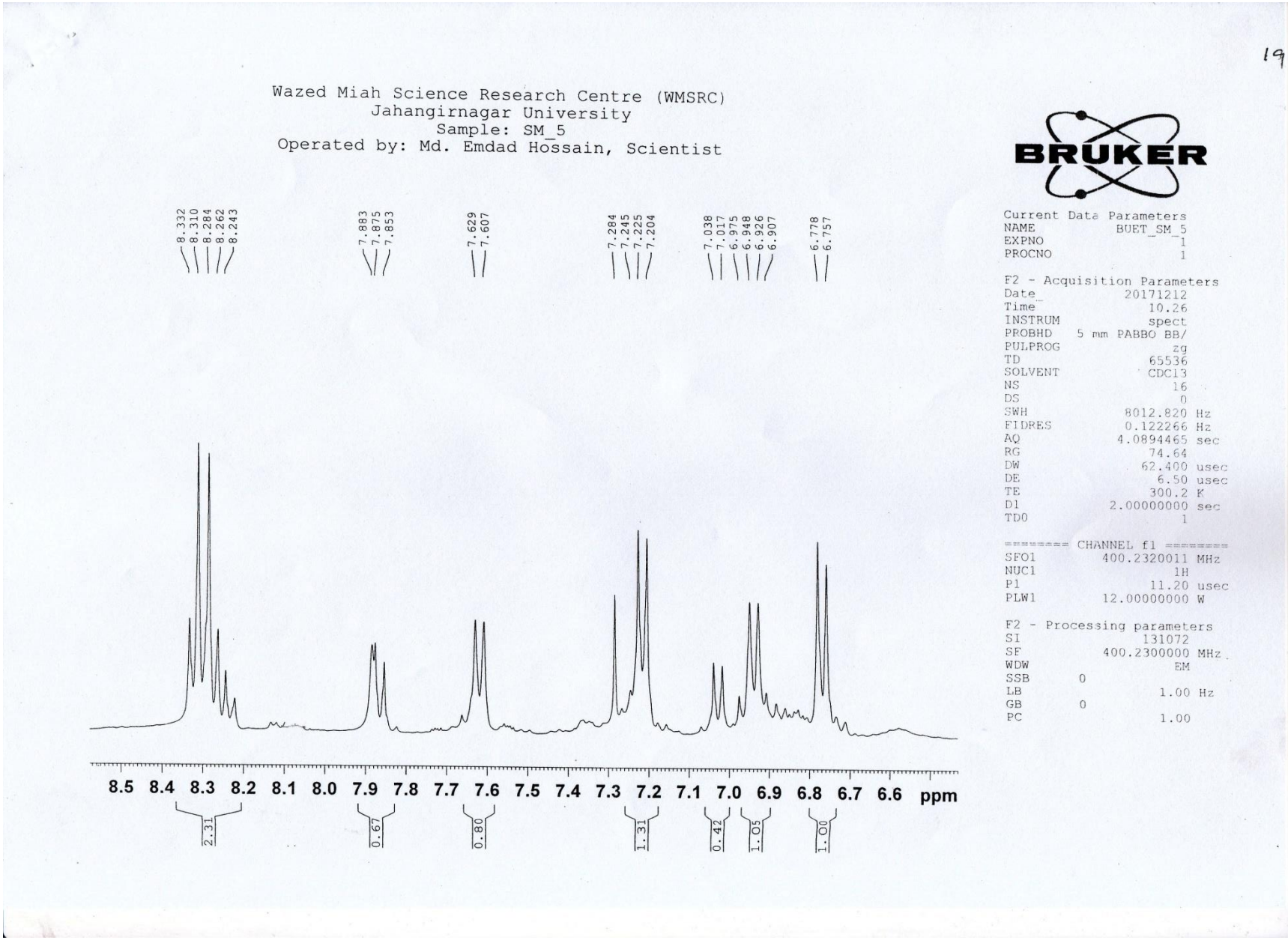
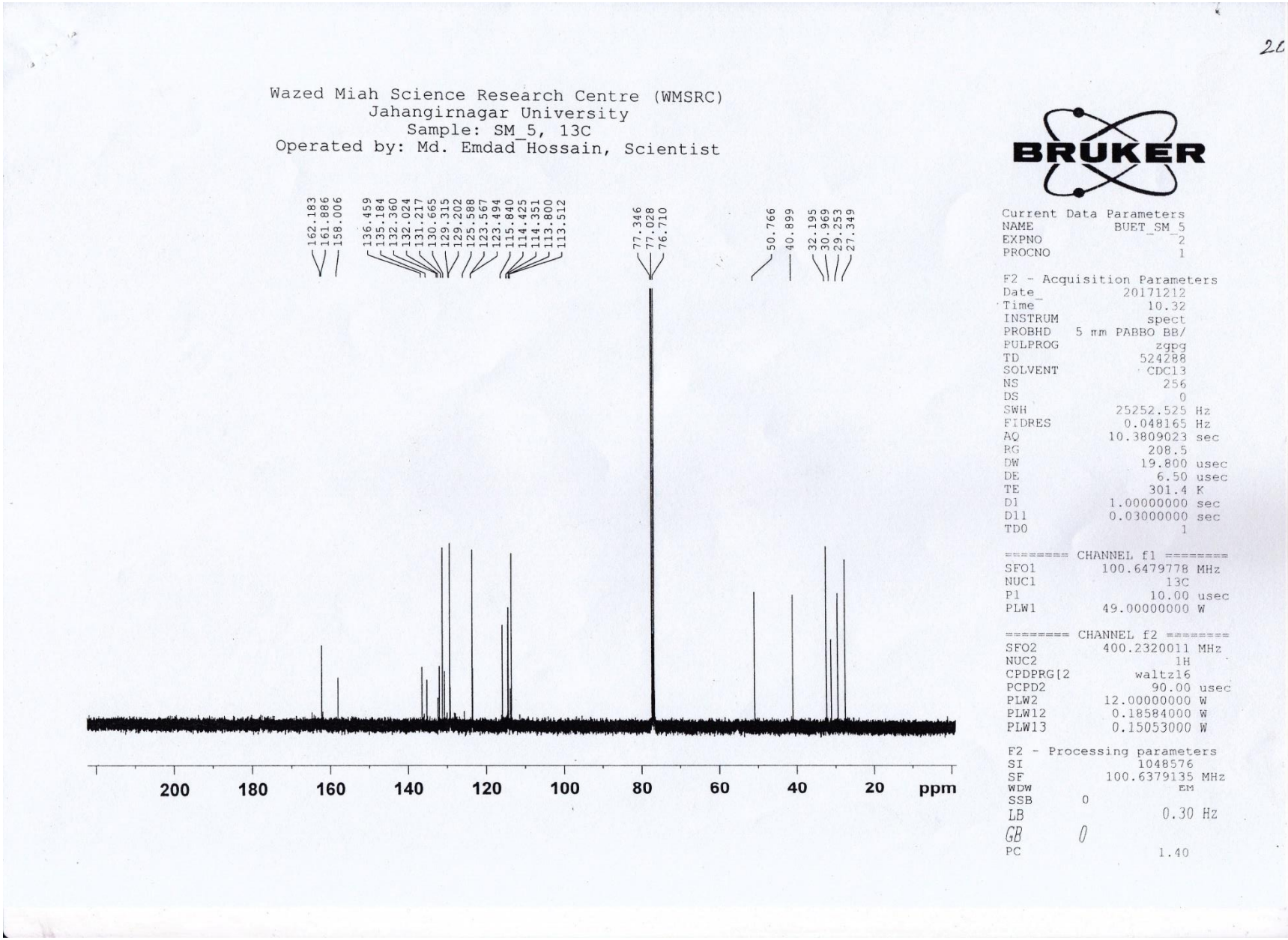
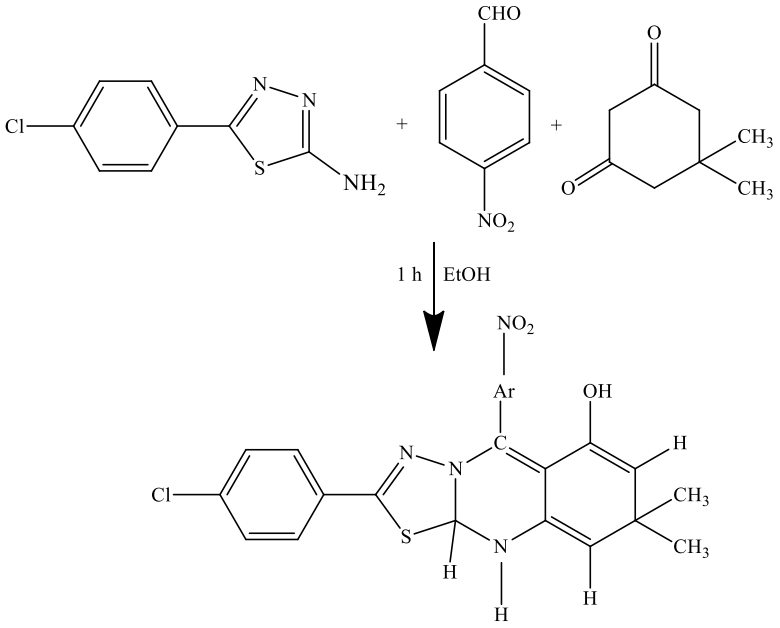

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_5
Operated by: Md. Emdad Hossain, Scientist
8.332
8.310
8.284
8.262
8.243
7.883
7.875
7.853
7.629
7.607
7.284
7.245
7.225
7.204
7.038
7.017
6.975
6.948
6.926
6.907
6.778
6.757
8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 ppm
2.31
0.67
0.80
1.31
0.42
1.05
1.00
BRUKER
Current Data Parameters
NAME BUET_SM_5
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 10.26
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 74.64
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure - 20


Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_5, 13C
Operated by: Md. Emdad Hossain, Scientist
162.183
161.886
158.006
136.459
135.184
132.360
132.024
131.217
130.665
129.315
129.202
125.588
123.567
123.494
115.840
114.425
114.351
113.800
113.512
77.346
77.028
76.710
50.766
40.899
32.195
30.969
29.253
27.349
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME BUET_SM_5
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 10.32
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg
TD 524288
SOLVENT CDCl3
NS 256
DS 0
SWH 25252.525 Hz
FIDRES 0.048165 Hz
AQ 10.3809023 sec
RG 208.5
DW 19.800 usec
DE 6.50 usec
TE 301.4 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6479778 MHz
NUC1 13C
P1 10.00 usec
PLW1 49.00000000 W
======== CHANNEL f2 ========
SFO2 400.2320011 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.18584000 W
PLW13 0.15053000 W
F2 - Processing parameters
SI 1048576
SF 100.6379135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

3.6 Characterizatio of the compound 5-(4-nitrophenyl)-8,8-dimethyl-2-(4-chlorophenyl)-10 ,10$_a$-dihydro-8H-[1,3,4] thiadiazole [2,3-b] quinazolin-6-ol . (6)



Compound 6

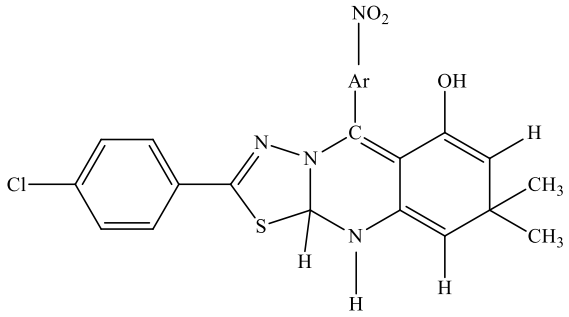
The desired product **6** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl]4-chloro benzene (0.01 mol) , dimedone (0.01 mol) and para nitro benzaldehyde (0.01 mol) in ethanol under reflux condition . The progress of the reaction was monitored by TLC . Reaction mixture was then kept on ice bath . The soild product was separated out by filtration . After filtration an orange crude product was obtained . The crude product was then purified by recrystallisation from ethanol to yield 73% as orange solid . The melting point was recorded as 210-212 $^{\circ}$C .

The IR spectra **(Fig. 21**) of the compound of the compound **6** showed a band at 3500-3510 cm^{-1} for O-H . The peak at 3386 cm^{-1} was assigned for N-H . The aromatic and aliphatic C-H stretching were designated at 3096 cm^{-1} and 2996 cm^{-1} respectively . The peak at 1600 cm^{-1} was identified for C=N . The characteristic absorptions at 1590 , 1540 , 1452 cm^{-1} were designated for C=C . The bridge linkages of C-S-C was observed at 820 cm^{-1} .

The ^{1}H NMR spectra **(Fig. 22)** of the compound **6** showed singlet at 1.266 for three protons of CH_3 and another singlet at 1.283 was assigned for gem CH_3 . The signal at 6.75 was detectable for one proton of S-CH . The olefinic two protons were designated at 690 and at 7.02 . The aromatic two protons were attributed at 7.24 , two protons at 7.62 , two protons at

7.87 and two protons at 8.06 . The one enolic proton and one N-H proton were designated at 8.2 at 9.96 respectively .

All the spectral evidences support in favour of the structure of the compound **6** as



Compound 6

Figure - 21

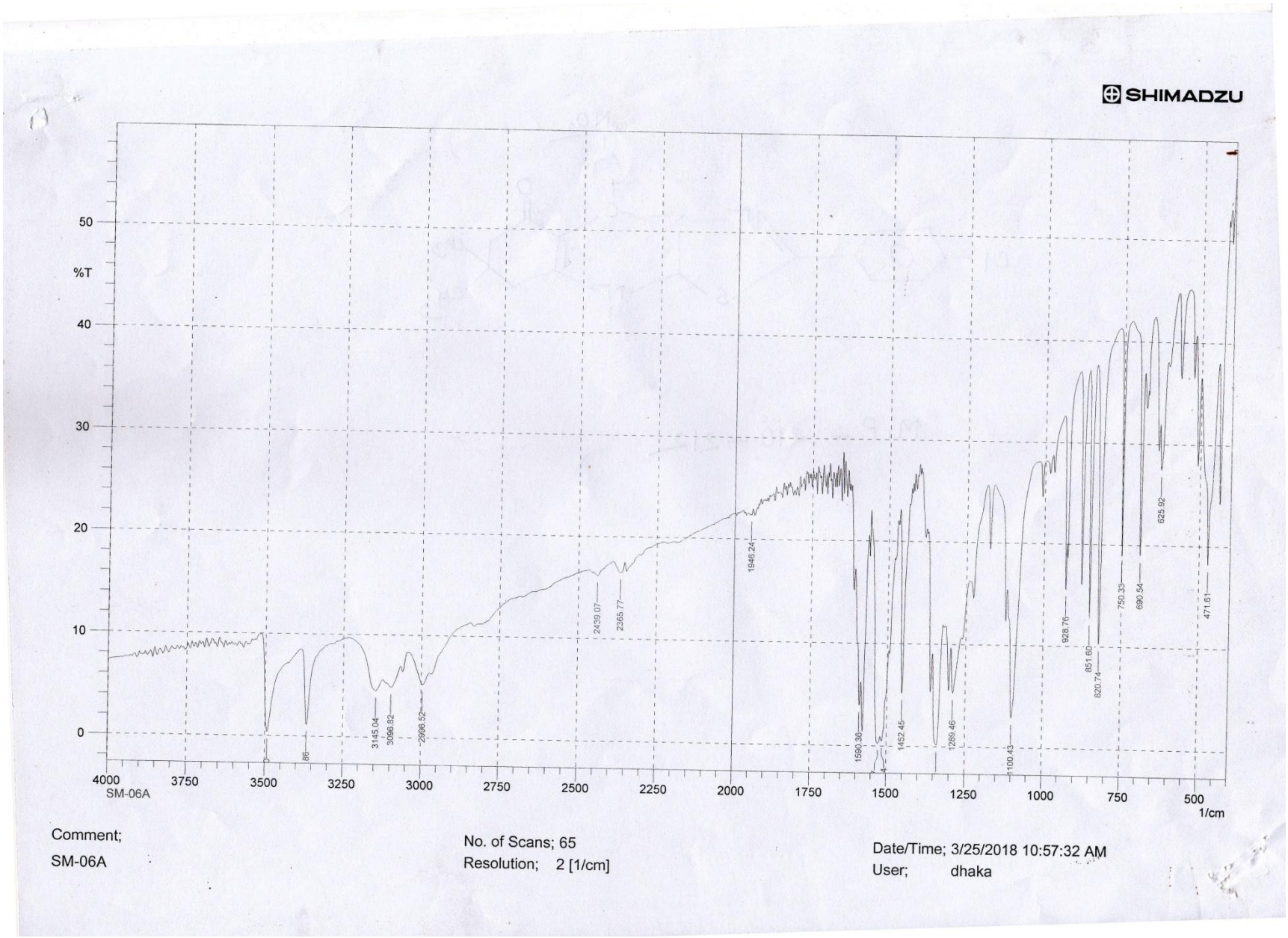
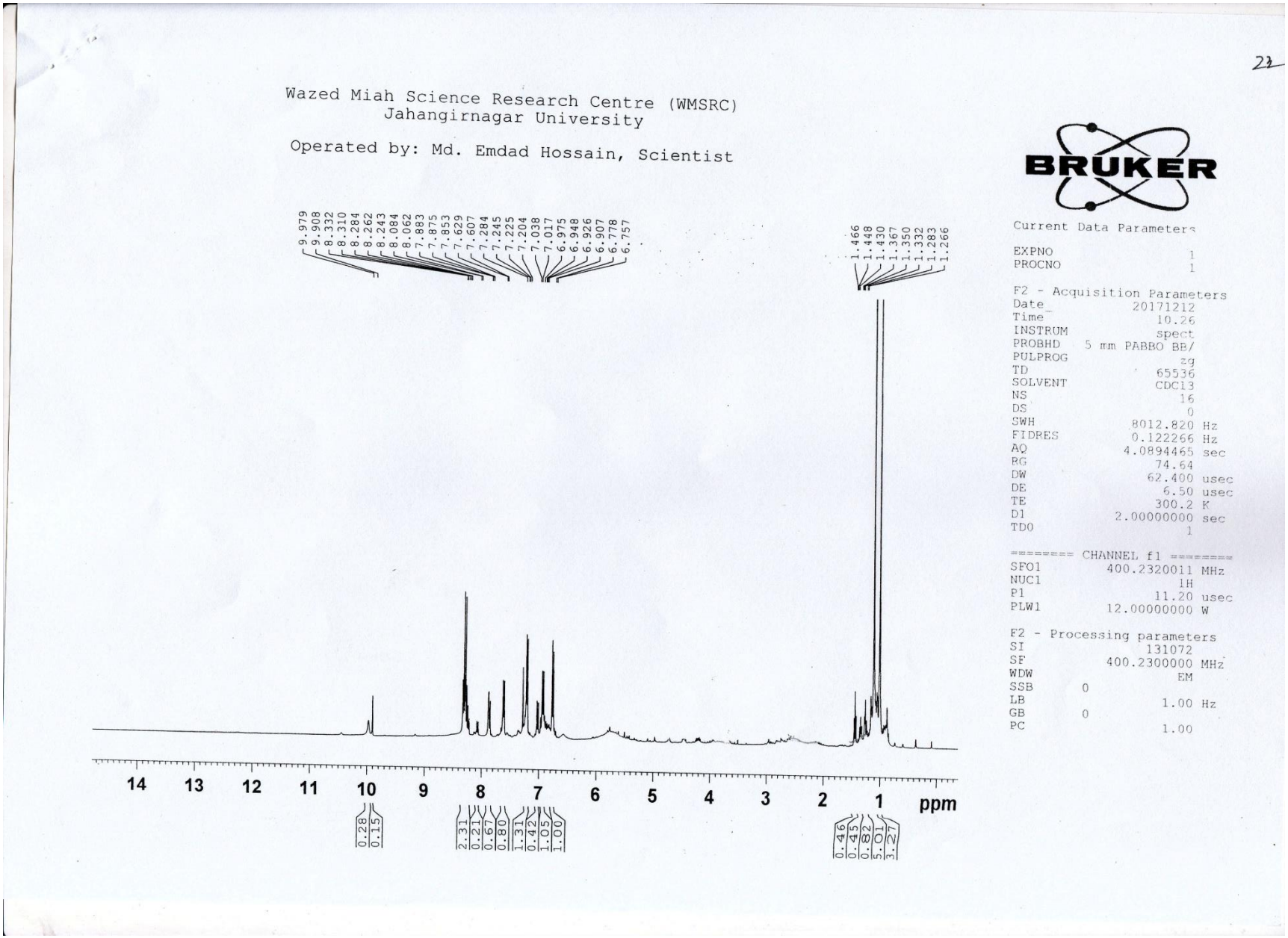
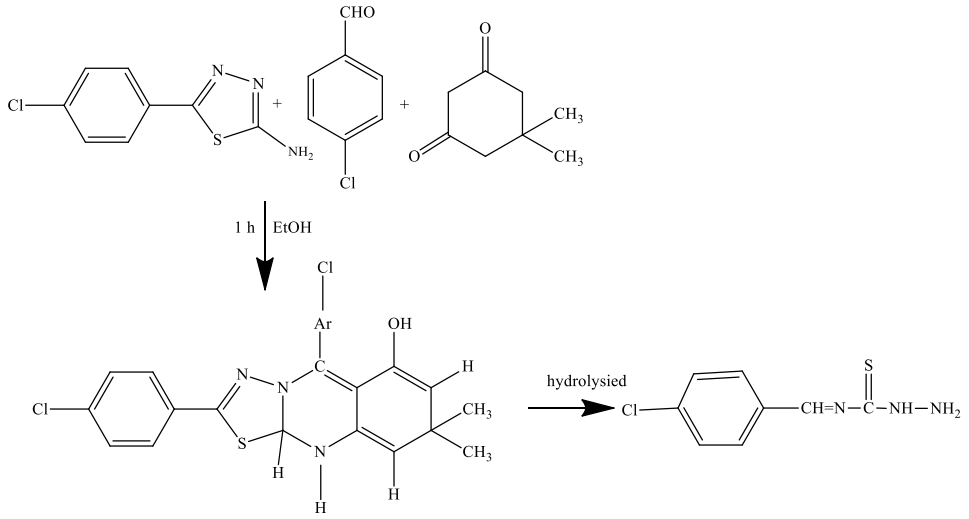

SHIMADZU
%T
50
40
30
20
10
0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
SM-06A
3145.04
3096.82
2996.52
2439.07
2365.77
1946.24
1590.30
1452.45
1289.46
1100.43
928.76
851.60
820.74
750.33
690.54
625.92
471.61
Comment;
SM-06A
No. of Scans; 65
Resolution; 2 [1/cm]
Date/Time; 3/25/2018 10:57:32 AM
User; dhaka

Figure - 22


Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Operated by: Md. Emdad Hossain, Scientist
22
9.979
9.908
8.332
8.310
8.284
8.262
8.243
8.084
8.062
7.883
7.875
7.853
7.629
7.607
7.284
7.245
7.225
7.204
7.038
7.017
6.975
6.948
6.926
6.907
6.778
6.757
1.466
1.448
1.430
1.367
1.350
1.332
1.283
1.266
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.28 0.15
2.31 0.21 0.67 0.80 1.31 0.42 1.05 1.00
0.46 0.45 0.82 5.01 3.27
BRUKER
Current Data Parameters
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20171212
Time 10.26
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 74.64
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

3.7. Characterization of the compound 5-(4-chlorophenyl)-8,8-dimethyl-2-(4-chlorophenyl)-10,10$_a$-dihydro-8H-[1,3,4] thiadiazole [2,3-b] quinazolin-6-ol . (7)



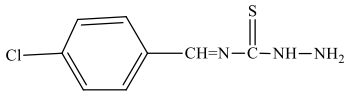
Compound 7 **Compound 7a**

The desired product **7** was attempted to synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl]4-chloro benzene (0.01 mol), dimedone (0.01 mol) and para nitro benzaldehyde (0.01 mol) in ethanol under reflux condition. The progress of the reaction was monitored by TLC. Reaction mixture was then kept on ice bath. The soild product was separated out by filtration. After filtration a white crude product was obtained. The crude product was then purified by recrystallisation from ethanol to yield 60% as white solid. The melting point was recorded as 150-152 $^{\circ}$C.

The IR spectrum (**Fig .23)** of the compound **7a** showed a band at 3445 cm^{-1} for N-H , the peak at 3300 cm^{-1} was assigned for NH_2. The aromatic C-H stretching was identified at 3122 cm^{-1}. The C=N moiety was designed at 1600 cm^{-1}. The characteristic peaks at 1550, 1502, 1455 were distinguished for C=C. The peak at 1283 cm^{-1} was distinctive for C=S.

The ^{1}H NMR spectra **(Fig. 24-25)** of the compound **7a** showed a doublet with the coupling constant J=8.0 Hz at 7.45 for two aromatic protons. The another doublet with the coupling constant J=8.0 Hz at 7.83 was designated for two aromatic protons. The singlet at 8.032 was distinctive for one olifinic proton. The broad singlet for two protons of NH_2 was attributed at 8.066 and 8.229. The downfielded singlet at 11.477 was assigned for one proton of N-H.

All the spectral evidences support the structure of the compound as **7a** but not 7. Probably initially formed **7** was hydrolysed to **7a**.



Compund 7a

Figure - 23

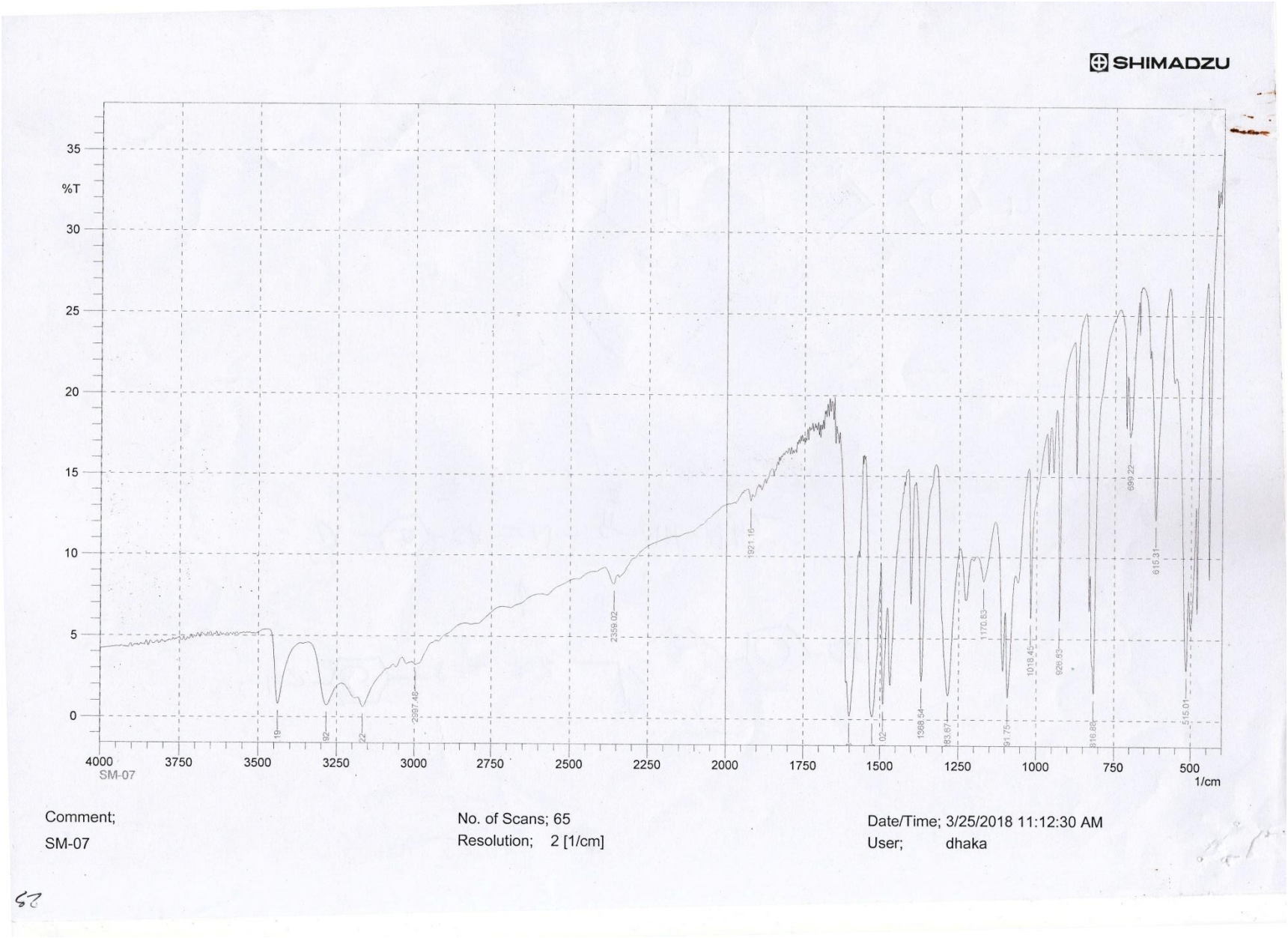

SHIMADZU
%T
35
30
25
20
15
10
5
0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
SM-07
2359.02
1921.16
1368.54
1170.83
1018.45
926.53
699.22
615.31
515.01
Comment;
SM-07
No. of Scans; 65
Resolution; 2 [1/cm]
Date/Time; 3/25/2018 11:12:30 AM
User; dhaka

Figure - 24

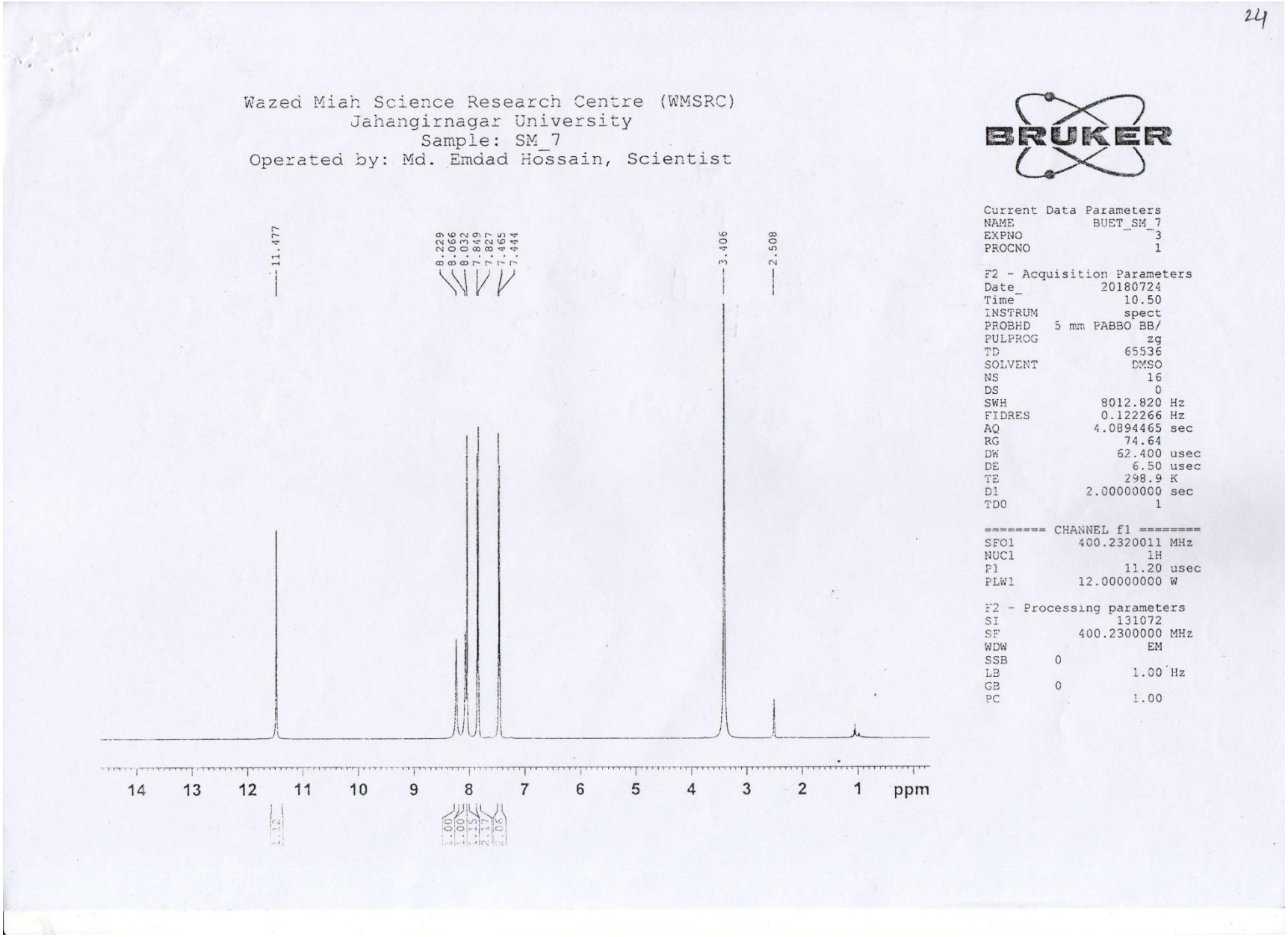
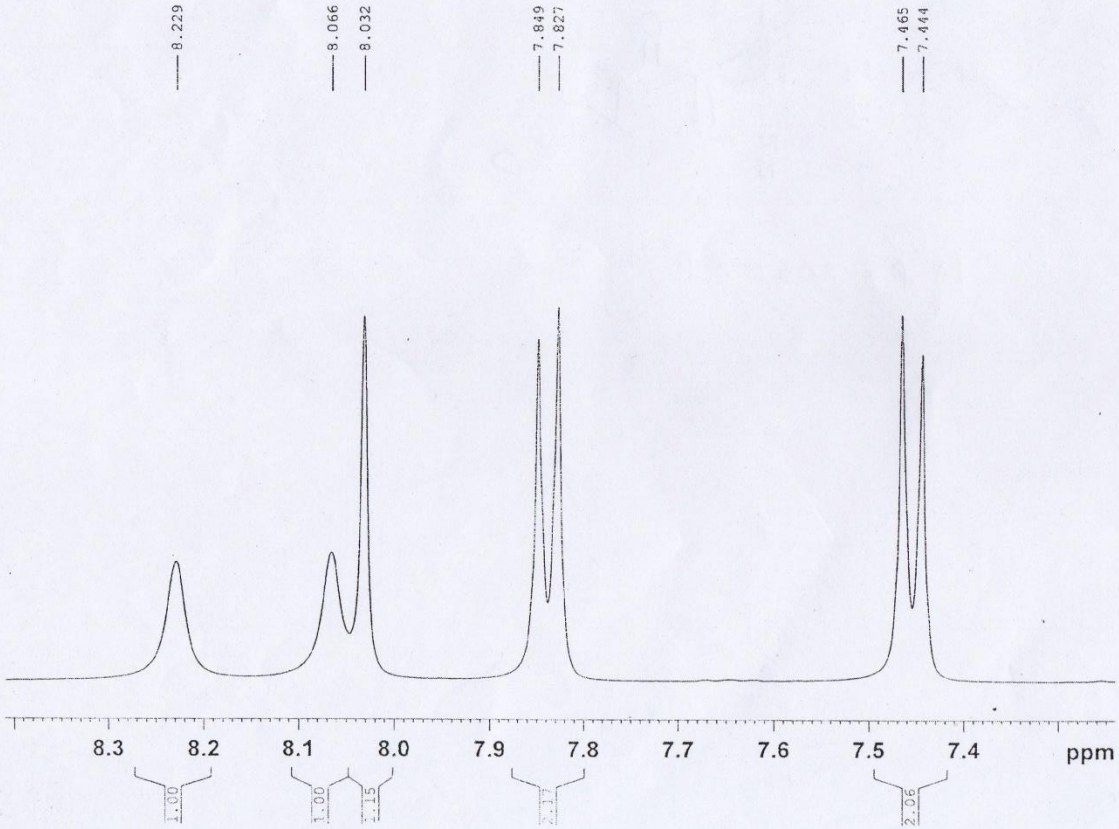

24
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_7
Operated by: Md. Emdad Hossain, Scientist
11.477
8.229
8.066
8.032
7.849
7.827
7.465
7.444
3.406
2.508
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.12
1.00
1.00
1.15
2.17
2.06
Current Data Parameters
NAME BUET_SM_7
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180724
Time 10.50
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg
TD 65536
SOLVENT DMSO
NS 16
DS 0
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 74.64
DW 62.400 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2320011 MHz
NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W
F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

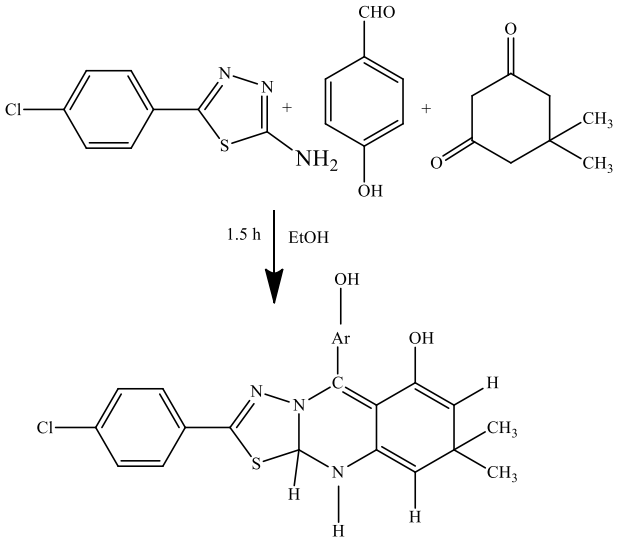
Figure - 25

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: SM_7
Operated by: Md. Emdad Hossain, Scientist




```
Current Data Parameters
NAME                 BUET_SM_7
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20180724
Time                     10.50
INSTRUM                  spect
PROBHD     5 mm PABBO BB/
PULPROG                    zg
TD                      65536
SOLVENT                  DMSO
NS                         16
DS                          0
SWH                   8012.820 Hz
FIDRES                0.122266 Hz
AQ                    4.0894465 sec
RG                        74.64
DW                       62.400 usec
DE                        6.50 usec
TE                       298.9 K
D1                    2.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1                400.2320011 MHz
NUC1                        1H
P1                       11.20 usec
PLW1               12.00000000 W

F2 - Processing parameters
SI                       131072
SF                  400.2300000 MHz
WDW                        EM
SSB          0
LB                        1.00 Hz
GB           0
PC                        1.00
```

3.8 Synthesis of 5-(4-hydroxyphenyl)– 8,8-dimethyl-2-(4-chlorophenyl)-10, 10a-dihydro-8H-[1,3,4]thiadiazolo[2,3-b]quinazolin-6-ol . (8)



Compound 8

The desired product **8** was synthesized by the three component one-pot reaction process from a mixture of [5-amino-1,3,4-thiadiazol-2-yl]4-chloro benzene (0.01 mol), dimedone (0.01 mol) and para hydroxy benzaldehyde (0.01 mol) in ethanol under reflux condition. The progress of the reaction was monitored by TLC. Reaction mixture was then kept on ice bath. The soild product was separated out by filtration. After filtration a white crude product was obtained. The crude product was not possible to purify.

The IR spectra **(Fig-26)** of the crude **8** showed an wide absorption band at 3400-3450 cm^{-1} for N-H and O-H groups. The band at 3275-3315 cm^{-1} was assigned for NH_2. The peak at 3190 cm^{-1} was designated for aromatic C-H stretching. The C=N moiety was observed at 1611 cm^{-1}. The characterizatized peaks at 1610, 1563 and 1515 cm^{-1} were observed for C=C. It was not possible to characterize the structure of the compound as **8.**

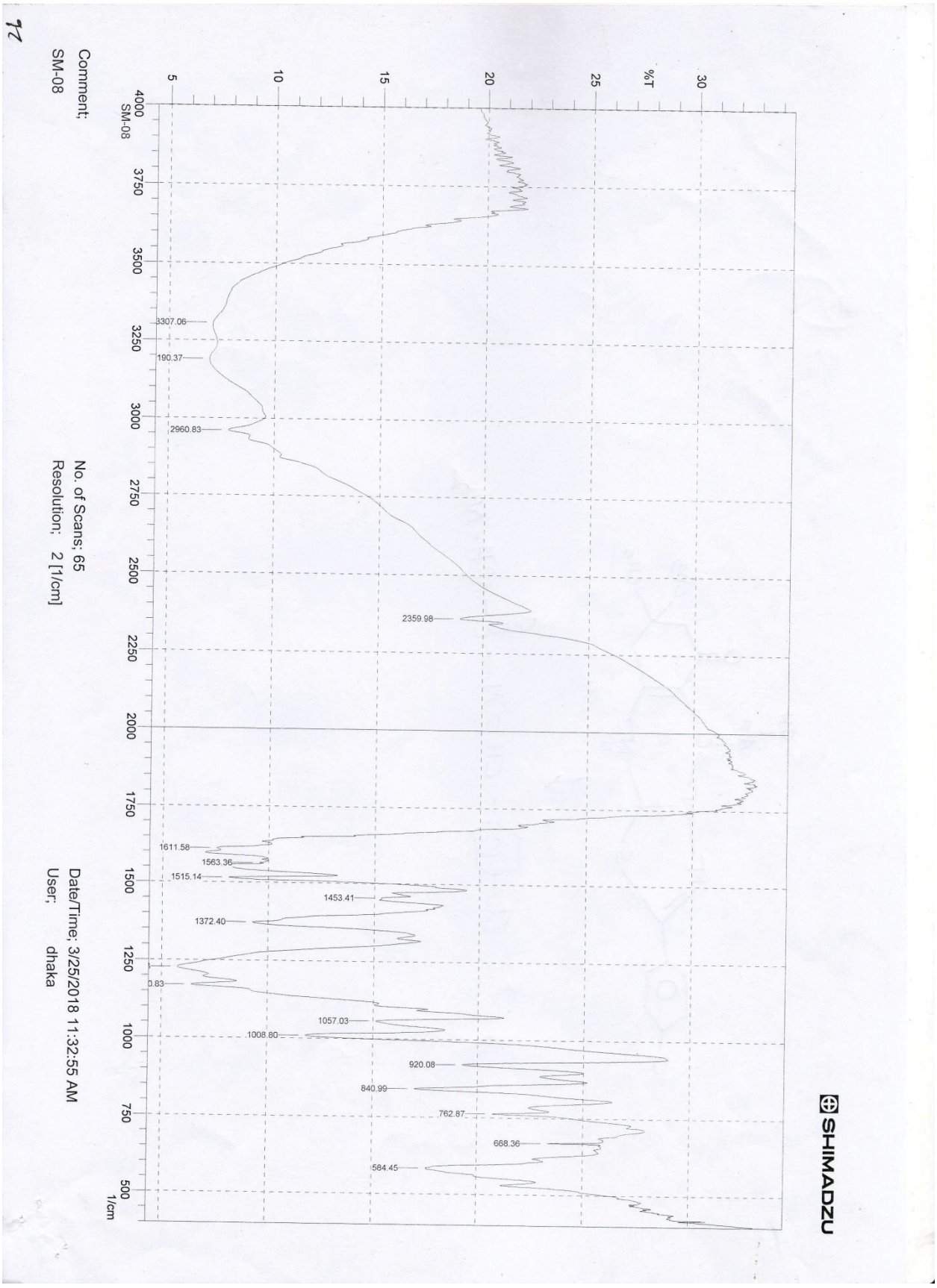

SHIMADZU
%T
1/cm
SM-08
Comment;
SM-08
No. of Scans; 65
Resolution; 2 [1/cm]
Date/Time; 3/25/2018 11:32:55 AM
User; dhaka
3307.06
190.37
2960.83
2359.98
1611.58
1563.36
1515.14
1453.41
1372.40
1057.03
1008.80
920.08
840.99
762.87
668.36
584.45

Figure - 26

ANTIMICROBIAL

Chapter 4

4.1 Introduction

The evolution and spread of antibiotic resistance, as well as the evolution of new strains of diseases causing agents , is of great concern to the global health community . Our ability to effectively treat disease is dependent on the development of new pharmaceuticals , and one potential source of novel drugs is traditional medicine . This study explores the antibacterial properties of fungal extracts of medicinal plants . Bacteria are responsible for many infectious diseases . The increasing clinical importance of drug resistant bacteria pathogens has lent additional urgency to antibacterial research . The antibacterial screening which is the first stage of antibacterial research is performed to ascertain the susceptibility of various bacteria to any agent . This test measures the ability of each antibacterial agent to inhibit the *in vitro* bacterial growth. This ability may be estimated by any of the following three methods .

- Disc diffusion method
- Serial dilution method
- Bio-autographic method

In serial dilution method the original culture suspension is diluted more one time , in tubes or in appropriate medium . Because of the reduction in the number of bacteria due to dilution isolation is obtained . When greatly diluted the specimen contains only few organisms of only one species . The cultured obtained is conserved by the spread plate or streak plate method . The disc diffusion technique [170] is a widely accepted *in vitro* investigation for preliminary screening of agents which may possess any antibacterial activity . It is essentially a quantitative or qualitative test indicating the sensitivity or resistance of the microorganisms to the test materials . However , no distinction between bacteriostatic or bactericidal activity can be made by this method [171] .

Fungi are responsible for many infectious diseases. Infectious diseases are caused by living organisms called pathogens . World health problems caused by drug resistant fungi are increasing . Invasive fungal infections have not only increased in frequency but also new fungal species have been reported to cause infection , especially in immune compromized patients . Concurrent with the increase in fungal infections , a large variety of antifungal drugs are available with different which give results that correspond to the clinical outcome of spectrum of activity . Our ability to effectively treat disease is dependent on the development of new pharmaceuticals , and one potential source of novel drugs is traditional medicine .

The increasing clinical importance of drug resistant fungal pathogens has lent additional urgency to antifungal research . The antifungal screening which is the first stage of antifungal research is performed to ascertain the susceptibility of various fungi to any agent . This test measures the ability of each antifungal agent to inhibit the *in vitro* fungal growth . This ability may be estimated by any of the following three methods such as disc diffusion method, serial dilution method and bio-autographic method .

4.2 Principle of disc diffusion method

Solutions of known concentration (µg/ml) of the test samples are made by dissolving measured amount of the samples in definite volume of solvents . Dried and sterilized filter paper discs (6 mm diameter) are then impregnated with known amounts of the test substances using micropipette . Discs containing the test material are placed on nutrient agar medium uniformly seeded with the test microorganisms . Standard antibiotic discs and blank discs (impregnated with solvents) are used as positive and negative control . These plates are then kept at low temperature (4 ^{0}C) for 24 hours to allow maximum diffusion . During this time dried discs absorb water from the surrounding media and then the test materials are dissolved and diffused out of the media . The diffusion occurs according to the physical law that controls the diffusion of molecules through agar gel [172] . As a result , there is a gradual change of test materials concentration in the media surrounding the discs . The plates are then incubated at 37 ^{0}C for 24 hours to allow maximum growth of the organisms . If the test materials have any antibacterial activity , it will inhibit the growth of the microorganisms giving a clear , distinct zone called “Zone of Inhibition”. The antibacterial activity of the test agent is determined by measuring the diameter of zone of inhibition expressed in millimeter . The experiment is carried out more than once and the mean of the readings is required [173] . In the present study synthesized compounds were tested for antibacterial activity by disc diffusion method .

4.3 Determination of antimicrobial activity by the zone of inhibition

The antibacterial potency of the test agents is measured by their activity to prevent the growth of the microorganisms surrounding the discs which gives clear zone of inhibition . After incubation , the antibacterial activities of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with a transparent scale .

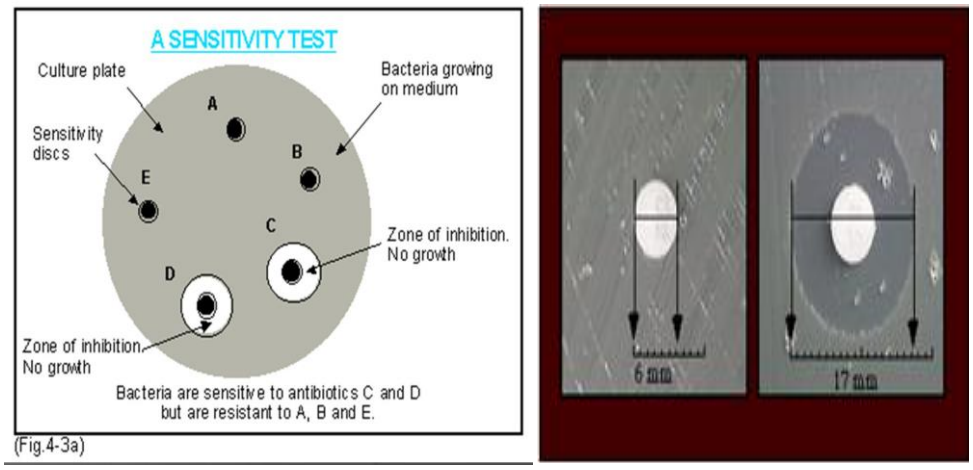


Figure 27 : Inhibition Zone measurement .

In the present study synthesized compounds were tested for antibacterial activity by disc diffusion method .

4.4 Antimicrobial Screening

4.4.1 Disc diffusion methods

The Kirby-Bauer and Stokes' methods are usually used for antibacterial susceptibility testing, with the Kirby-Bauer method being recommended by the NCCLS. The accuracy and reproducibility of this test are dependent on maintaining a standard set of procedures as described here.

4.4.2 Materials used

a) Test Organisms: Both gram positive and gram-negative organisms were taken for the test and they are listed in the Table.

Gram positive Bacteria	**Gram negative Bacteria**
Staphylococcus aureus	*Salmonella typhimurium*
	Escherichia coli
	Pseudomonas aeruginosa
	Bacillus subtilis
	Citrobacterfreundii

The fungal strains used for the experiment were collected as pure cultures and two organisms were taken for the test.

Aspergillusniger	*Tricodarmaharzianum*

a) Growth Media: The activity was conducted on the Nutrient Agar Media produced from TSA (Tryptone Soya Agar) .

Composition :

Pancreatic digest of casein	15.0 g/L
Enzymatic digest of soya bean	5.0 g/L
Sodium chloride	5.0 g/L
Agar	15.0 g/L

a) Apparatus Used:

- **Petri plate** : Plastic plate, which was previously sterilized.

- **Pipette :** Micropipette was used for adding the required concentration of sample to the plates.
- **Blank discs :** Susceptible blank discs were used, which was stored in 20^0C to 8^0C.
- **Glasswares :** 500 ml conical flask and test tubes were used.
- **Compounds Screened :** All the synthesized compounds.
- **Solvent Used :** Dimethyl sulfoxide.
- **Standard Used :** Ciprofloxacin for bacteria and Michanazole for fungi.

a) Test materials

P-1 , P- 2 , P-3

4.5 Procedure for Performing the Disc Diffusion Test

Inoculums Preparation

4.5.1 Growth Method

The growth method is performed as follows

At least three to five well-isolated colonies of the same morphological type were selected from an agar plate culture. The top of each colony was touched with a loop.

a) Growth was transferred into a tube containing 4 to 5 ml of a suitable broth medium, such as tryptic soy broth.

b) The broth culture was incubated at 37°C until it achieved or exceed the turbidity of the 0.5 McFarland standard (usually 2 to 6 hours) .

c) The turbidity of the actively growing broth culture was adjusted with sterile saline or broth to obtain a turbidity optically comparable to that of the 0.5 McFarland standard .

4.5.2 Inoculation of Test Plates

a) Media was prepared by adding 40.0 gm of Nutrient agar to 1L of distilled water . Then it was sterilized by autoclaving at 15 lb/inch and at 210^{o}C temperatures for two hours .

b) Media was cooled to the temperature of approximately 40^0C and microorganisms were inoculated to the media. 25ml was transferred to a petriplate. Two such plates were prepared for each organism. Plates were allowed to cool for 20 minutes .

c) Optimally , within 15 minutes after adjusting the turbidity of the inoculum suspension , a sterile cotton swab was dipped into the adjusted suspension . The swab should be rotated

several times and pressed firmly on the inside wall of the tube above the fluid level . This will remove excess inoculum from the swab .

d) The dried surface of a TSA plate is inoculated by streaking the swab over the entire sterile agar surface . This procedure was repeated by streaking two more times , rotating the plate approximately 60 °C each time to ensure an even distribution of inoculums . As a final step , the rim of the agar was swabbed .

e) The lid may be left the plate for 3 to 5 minutes , but no more than 15 minutes , to allow for any excess surface moisture to be absorbed before applying the drug impregnated disks .

4.5.3 Application of Discs to Inoculated Agar Plates

The predetermined battery of antibacterial discs was dispensed onto the surface of the inoculated agar plate . Each disc was pressed down to ensure complete .

a) contact with the agar surface. The discs were placed such a way so that they were no closer than 24 mm from center to center .

b) The plates are inverted and placed in an incubator set to 37 °C within 15 minutes after the discs were applied .

4.5.4 Application of Samples on the discs

a) Crude fungal extract was dissolved in DMSO and diluted to get concentration of 300 µg/disc .

b) Four blank discs were placed in the petri plates . Reference standard Tetracycline was impregnated on one of the discs , and only solvent as a blank was impregnated on one of the discs , and others experimental solutions were impregnated on others discs . Each disc was marked by a marker as a small symbol so that each of the discs could be easily identified . 25µl of solution was injected on each disc .

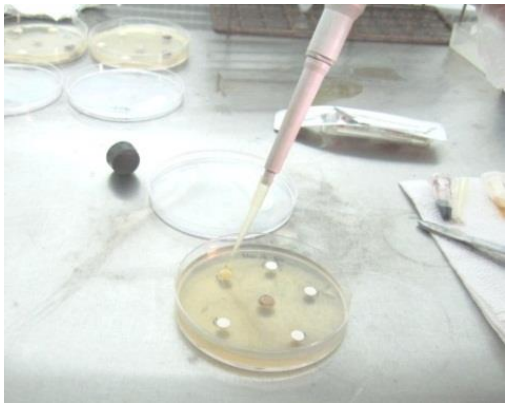


Figure 28 : Application of Samples on the discs.

4.5.5 Reading Plates and Interpreting Results

The above culture plates were incubated at 37°C for 24 hours. The zones of inhibition produced by compounds and Ciprofloxacin for bacteria and Michanazole for fungi were recorded in mm and compared.

4.6 Determination of antimicrobial activity by measuring the Zone of Inhibition

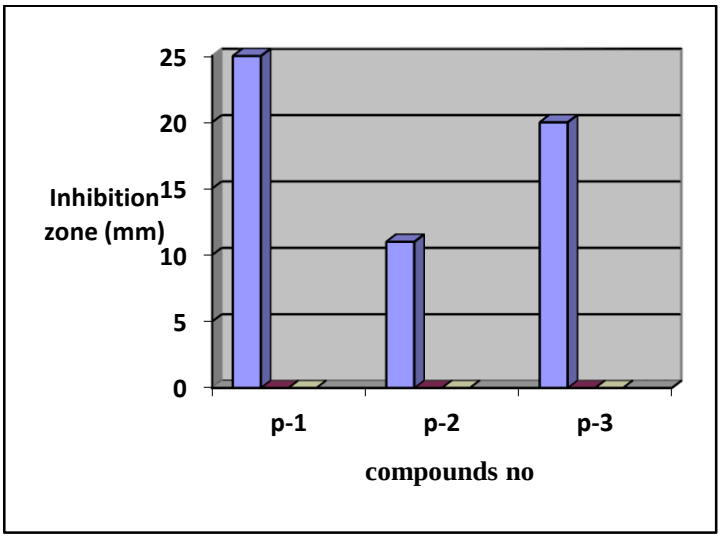
After incubation, the antimicrobial activities of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with transparent scale. Synthesized compounds were tested for antibacterial activity against eight bacteria and antifungal activity against two fungi. All compounds were tested at 300 µg/disc concentration.

Table 2: *In Vitro* Bactericidal Profiles of compounds in terms of Zone of Inhibition

Comp.	Bacterial species						Fungal Species	
Comp.	Gram positive	Gram negative					Fungal Species	
Comp.	*S.a*	*B.s*	*E.c*	*P.a*	*S.t*	*C.f*	*T.h*	*A.n*
P – 1	25	23	26	22	18	32	9	7
P – 2	11	15	10	9	13	15	6	13
P – 3	20	20	15	7	10	25	13	7

* 50 µL dose used & concentration was 300 µg $disc^{-1}$. The observed zone of inhibition is indicated by diameters (in mm) and (-) representsnn no activity. *S.a*., *Staphylococcus aureus* (cars-2), *B.s.*, *Bacillus subtilis*, (carsgp-3), *E.c.*, *Escherichia coli*, (carsgn-2), *P.a.*, *Pseudomonas aeruginosa* , (carsgn-3) , *S.t.*, *Salmonella typhimurium*, (JCM-1652) , *C.f.*, *Citrobacterfreundii*, (JCM-1657) , *T.h.*, *Tricodarmaharzianum*, (carsm-2) , *A.n.*, *Aspergillusniger*. (carsm-3) .*Michonazole (Mc)* used as Standard antifungal agent & *Ciprofloxacin (Cp)* as standard antibacterial agent .

Antibacterial activity against S.a



Antibacterial activity against *P.a*

Figure 29 : Antibacterial activity of synthesized compounds against *S.a*

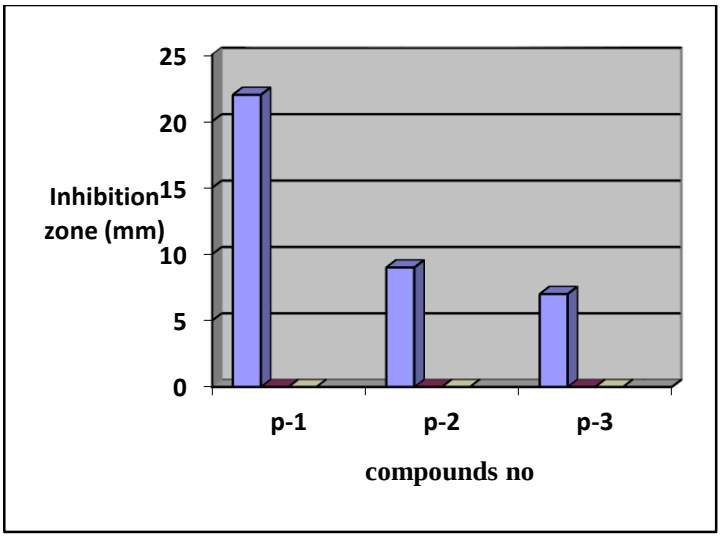


Figure 30 : Antibacterial activity of synthesized compounds against *P.a*

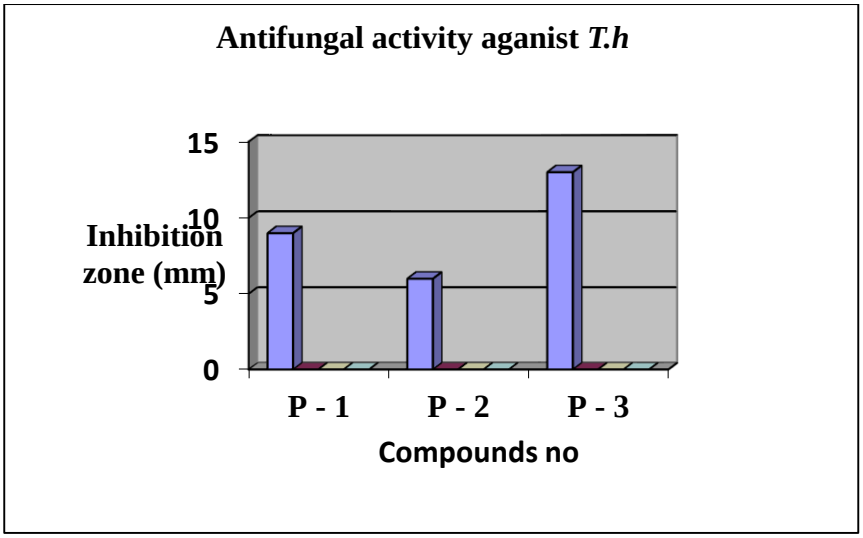
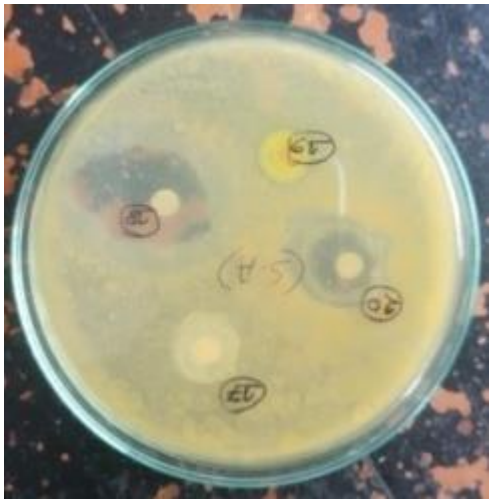
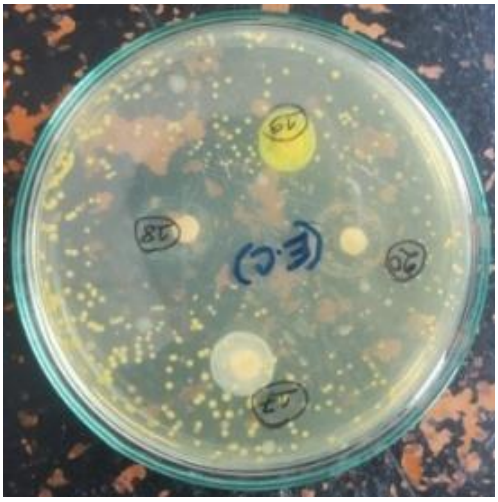


Figure 31 : Antibacterial activity of synthesized compounds against *T.h*



(a)

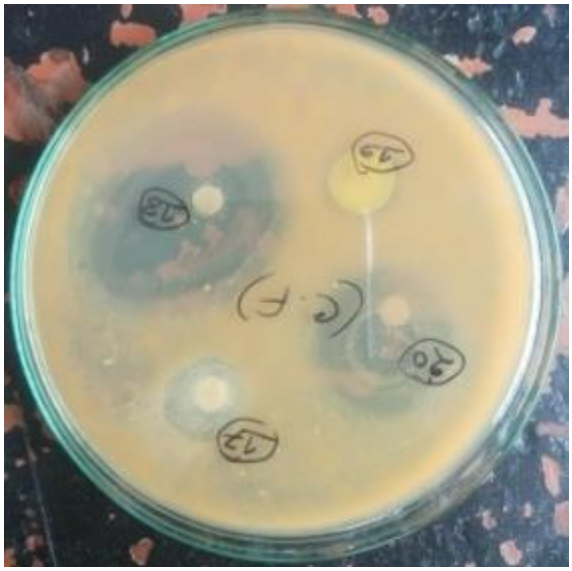


(b)

(c)

(d)

Figure 32 : Effect of activity of P_1 , P_2 , P_3 on *S.a* , *E.c* , *P.a* , *B.s* . [(a) , (b) , (c) , (d)]



(e)

(f)

(g)

Figure 33 : Effect of activity of P-1 , P-2 , P-3 on *C.f* , *S.t* , *T.h* . (e , f , g)

4.7 Comparatively study of the three compounds

The tested compounds showed activities at a dose of 300 µg $disc^{-1}$ comparable to Ciprofloxacin for bacteria and Michonazole for fungi (standard) at 300 µg $disc^{-1}$.

The P-2 compound showed bactericidal moderate activity against *S. aureus* , *B. subtilis* , *P. aeruginosa.*Noticeably,all the compounds showed the antibacterial activity against *B. subtilis. P. aeruginosa E. coli* , *S.* aureus, *C. freundii* . Among them P -1 showed very good activity against *B. subtilis, P. aeruginosa, E. coli* , *S.* aureus. P-3 compound showed very good activity against *C. freundii.*

P-1, P-2 and P-3 compounds showed the antifungal activity against both *T. harzianum* and *A. niger* .

Conclusion

We have synthesized a novel dihydro - thiadiazole quinozoline derivatives . The products were synthesized by multi – component one – pot process in which three reactants come together in a single reaction vessel gave a final product . Multi – component one – pot synthetic method is very easy to carry out and provide rapid access to libraries of organic compounds with diverse substitution patterns . Multi – component one – pot methods eliminate the isolation of intermedials , thereby reduces the reaction time and increases the yield than the normal multistep methods . Multi – component one – pot method is the simplest and most straight forward procedure involves three components one – pot cyclo conduction of aldehydes , thiadiazole and dimedone . The synthesized dihydro – thiadiazole quinozolino showed moderate to good antibacterial and antifungal activity .

Scheme List

Figure List

REFERENCES

Chapter-5

[1] Ugi, I., “Recent progress in the chemistry of multi-component reaction”. *Pure Appl; Chem:* vol. 73, pp. 187-191 **(2001).**
[2] Kumaravel, K., and Vasuki, G., “Multi-component reaction in water.” *Curr. org. Chem:* vol. 13, pp. 1820 **(2009).**

[3] Zhu, J., and Bienayne, H., “Multi-component Reactions.” *Wiley-VCH: weinheim,* pp. 1-21. **(2005).**

[4] Ishikawa, H., Suzuki, T., Hayashi, Y., "High-yielding synthesis of the anti-influenza neuramidase inhibitor (-)-oseltamivir by three "one-pot" operations". *Angewandte Chemie International Edition in English*. vol. 48 (7),pp. 1304–1307, **(2009).**

[5] Cameron, M., Hoerrner, R., S., McNamara, J., M., Figus, M., Thomas, S., "One-Pot Preparation of 7-Hydroxyquinoline". *Organic Process Research & Development*, vol. 10 (1), p. 149, **(2006).**

[6] A., Strecker, Ann, “Three-component reaction:(3CR)”. vol.27, p.27,**(1850).**

[7] A., Hantzsch, Ber," Hantzch dihydropyridine synthesis”, vol.14, p.1637,**(1881).**

[8] (i) R., Alajarin, J., J., Vaquero, J., L., G., Navio, J., A., Builla, Synlett ″A new approach to the synthesis of 2-aminoimidazo[1,2-a] pyridine derivatives through microwave-assisted N-alkylation of 2-halopyridines.*”* p.297,**(1992).** (ii) R., Alajarin, P., Jordan, J., J., Vaquero , J., A., Builla, Synthesis, *“*Microwave Technology-chemical Synthesis Applications.*”* p.389, **(1995).** (iii) B., M., Khadilkar, A., A., Chitnavis, Ind. J., Chem. “Synthèse de molécules d’intérêt biologique: Préparation des dérivés de la 3,4-dihydropyrimidinone et de la 1,4-dihydropyridine par des réactions à composants multiples.*”*vol. 34B,p.652, **(1995)**. (iv) B., M., Khadilkar, V., G., Gaikar, A., A., Chitnavis, Tetrahedron “Nifedipine” *Lett*, vol.36, p.8083, **(1995).**

[9] P.,Biginelli, Ber. “Multicomponent eco-friendly synthesis of 3,4-dihydropyrimidine-2-(1H)-ones using an organocatalyst lactic acid*”*. vol.24,pp.1317,2962,**(1891).**

[10] A., R., Trivedi, V., R., Bhuva, B., H., Dholariya, D., K., Dodiya, V., B., Kataria, V., H., Shah, Bioorg. *Med. Chem. Lett*, vol.20, p. 6100, **(2010).** V., Virsodia, R., R., S., Pissurlenkar, D., Manvar, C., Dholakia, P., Adlakha, A., Shah, E., Coutinho, *Eur. J. Med. Chem*, vol.43, p. 2103,**(2008).**

[11] M., Passerini, Gazz., Chim. *Ital*, vol.51, p.181. **(1921).**

[12] A.,Y., Shaw, F., Medda, C., Hulme "Facile and rapid route for the synthesis of novel norstatine analogs via PADAM cyclization methodology." *Tetrahedron Lett*. Vol.53, p.1313. **(2012)**.

[13]. M., I., Kabachnik, T., Y., Medved, Dokiady Akademii Nauk SSSR, E., K., Fields, J., Am., *Chem. Soc*, vol.83,p.689,**(1952).**

[14]. S., Shibuya, YAKUGAKU ZASSHI, vol.124, p.725,**(2004).** M., C., Allen, W., Fuhrer, B., Tuck, R.,Wade, J., M., Wood, J., *Med. Chem*, vol.32, p.1652,**(1989).** M., K., Manthey, D., T., C., Huang, W., A., Bubb, R., I., Christpherson, J., *Med. Chem*. vol.41,p.4550, **(1998).**

[15]. I., Ugi, Angew. **"**Innovative multicomponent reactions and their use in medicinal chemistry." *Chem. Int. Ed*,**(1962).**

[16] A., M., V., Leusen, *Org. Synth*., vol.57, p.102, **(1977).**

[17]. O., Possel, A., M., V., Leusen, "Heterocycles.'' vol.7, p.77, **(1977).** A., M., V., Leusen, O., H., Oldenziel, *Tetrahedron Lett*, vol. 23, p.2373,**(1972).**

[18]. C., Neochoritis, J., Stephanidou-Stephanatou, C., A., Tsoleridis, **"**Heterocyclizations via TosMIC-Based Multicomponent Reactions: A New Approach to One-Pot Facile Synthesis of Substituted Quinoxaline Derivatives."*Synlett*, p. 302. **(2009).**

[19]. H., Yoshida, H., Fukushima, J., Ohshita, A., Kunai, **"**Three-Component Coupling Using Arynes and Aminosilanes for ortho-Selective Double Functionalization of Aromatic Skeletons." *J. Am. Chem. Soc*, vol.128, p.11040,**(2006).**

[20]. Domling A., Ugi I., "Multi-component reactions with Isocyanides." *Angew Chem Int Ed*, vol.39, pp.3168-3210, **(2000).**

[21]. Domling A., "Multi-component reactions.'' *Org Chem Highlights*, vol. 5, **(2004).**

[22]. Hulme C., Gore V., "Multi-component reactions: Emerging chemistry in drug discovery from xylocain to crixivan." Curr Med Chem.;10(1):51-80,**(2003).**

[23]. Gao K., Wu J., "Synthesis of functionalized 1,2-dihydroisoquinolines via multi-component one-pot reaction of 2- alkynylbenzaldehyde, amine, zinc, and allylic bromide or

benzyl bromide." *J Org Chem*,72:8611-8613,**(2007).** (B) Muller FL, "Multi-component domino reaction from âketoamides: Highly efficient access to original polyfunctionalized 2,6- diazabicyclo [2.2.2]octane Cores." *J Am Chem Soc*. 27:171-176,**(2005).** (C) Simon C., Peyronel JF., Rodriguez A., "New multicomponent domino reaction of 1,3- dicarbonyl compounds: one-pot access to polycyclic N/O-, N/S- and N/N-aminals." *J Org Lett.*;3(14):2145-2148,**(2001).**

[24].(a) Majumdar KC., Ponra S., Ghosh T., "Green approach to highly functionalized thiopyrano derivatives via domino multicomponent reaction in water." *RSC Adv.2*,pp.1144-1152**,(2012).** (b) Kumaravel K., Vasuki G., "Four-component catalyst-free reaction in water: Combinatorial library synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4Hchromene-3- carbonitrile derivatives." *Green Chem.*vol.11,pp.1945-1947, **(2009).**

[25]. S.,E., Denmark, A.,Thorarensen. *Chem Rev.*vol.96, pp.137-165:Google Scholar,**(1996).**

[26]. T.,L., Loht, T.,J.,Marks. *Nat.Chem*, vol. 7.pp. 477-482; Google Scholar. **(2015).**

[27]. I., N., N., Namboothiri, A., Hassner, H., E., Gottlieb, *J. Org. Chem*, vol. 62, pp. 485–492, **(1997).** Google Scholar.

[28]. H., Behera, V., Ramkumara, N., Madhavan, *Org. Biomol. Chem*, vol.15, pp.4937–4940,**(2017).** Google Scholar.

[29]. M., Tang, D., Xing, H., Huang, W., Hu., *Chem. Commun.*,vol. 51, pp.10612–10615,**(2015).** Google Scholar.

[30]. M., P., S., Ishar, K., Kumar, *Tehtrahedron Lett.* vol. 40,pp.175–176,Google Scholar.**(1999).**

[31]. Diederich, P., J., Stang, R., R., Tykwinski in "Acetylene Chemistry: Chemistry, Biology and Material Science." *(Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim*, pp. 1–492, Google Scholar. **(2005).**

[32]. X., Jie, Y., Shang, P., Hu., W., Su., Angew, **"**Palladium-Catalyzed Oxidative Cross-Coupling between Heterocycles and Terminal Alkynes with Low Catalyst Loading." *Chem. Int. Ed*, vol.52, pp.3630–3633; Google Scholar,**(2013).**

[33]. T., de Haro, C., Nevado, *J. Am. Chem. Soc.* vol.132, pp. 1512–1513; Google Scholar. (**2010).**

[34]. K., M., Cergol, C., G., Newton, A., L., Lawrence, A., C., Willis, M., N., P., Row, M., S., Sherburn, *Angew. Chem. Int. Ed.*vol. 50, pp.10425–10428; *Angew. Chem.* vol.123,pp.10609–10612, **(2011).** Google Scholar.

[35].S., Kamijo, G., B., Dudley, *J. Am. Chem. Soc.* vol.128, pp.6499–6507, **(2006).** Google Scholar.

[36]. D., A., Alonso, C., Najera, M., C., Pacheco, *Adv. Synth. Catal.* Vol. 345, pp.1146–1158; Google Scholar. **(2003).**

[37]. S., Ahammed, D., Kundu, B., C., Ranu, *J. Org. Chem.* vol.79, pp.7391–7398,**(2014).** Google Scholar.

[38]. C.,Y., Chang, S.,Y., Chien, C.,S., Hsu, S., Gauza, S.,T., Wu., *Liquid Crystals*, vol.35, pp. 1–9, Google Scholar. **(2008).**

[39]. G., Bort, T., Gallavardin, D., Ogden, P., I., Dalko, *Angew. Chem. Int. Ed.*vol.52, pp.4526–4537, Google Scholar . *Angew. Chem*, vol.125, pp.4622–4634, **(2013).**

[40]. A.,C., Jones, J., A., May, R., Sarpong, B., M., Stoltz, *Angew. Chem. Int. Ed*,vol. 53, pp. 2556–2591; *Angew. Chem.* vol. 126,pp.2590–2628, **(2014).** Google Scholar.

[41]. D., A., Fulmer, W., C., Shearouse, S., T., Medonza, J., Mack, *Green Chem.*vol.11,pp. 1821–1825, **(2009).** Google Scholar.

[42]. M.,Bakherad,A., Keivanloo,S.,Samangooei, *Tetrahedron Lett.*vol.53,pp.5773–5776,**(2012).** Google Scholar.

[43]. A.,W., Franz, S., Stoycheva, M., Himmelhaus, T., J., J., Müller, *Beilstein J. Org. Chem.*vol. 6, p.72, **(2010).** Google Scholar .

[44]. S., Borman, *Chem. Eng. News* , vol.70, pp. 29–31,**(1992).** Google Scholar.

[45]. R., Chinchilla, C., Nájera, *Chem. Rev.*vol.107, pp.874–922, **(2007).** Google Scholar.

[46]. X., Zhang, A., Liu, W., Chen, *Org. Lett*, vol. 10, pp.3849–3852, **(2008).** Google Scholar.

[47]. D., S., Kim, J., Ham, *Org. Lett*, vol.12, pp.1092–1095, **(2010).** Google Scholar.

[48]. E., Negishi, M., Qian, F., Zeng, L., Anastasia, D., Babinski, *Org. Lett*.vol.5, pp.1597–1600, **(2003),** Google Scholar.

[49]. M., El., Sayed Moussa, K., Guillois, W., Shen, R., Reau, J., Crassous, C., Lescop, *Chem. Eur. J.* vol.20, pp. 14853–14867,**(2014).**Google Scholar.

[50] P., Pachfule, M., K., Panda, S., Kandambeth, S., M., Shivaprasad, D., D., Dıaz, R., Banerjee, *J. Mater. Chem. A*, vol.2, pp.7944–7952,**(2014).** Google Scholar.

[51]. Ł.,Albrecht, H., Jiang, K., A., Jørgensen, *Angew. Chem. Int. Ed*, vol.50, pp. 8492–8509,**(2011)** Google Scholar .*Angew. Chem*,vol. 123, pp.8642–8660,**(2011).** Google Scholar.

[52]. R., H., Crabtree, *Science*, vol.318, pp. 756–757**,(2007).** Google Scholar.

[53]. C., Schweez, P., Shushkov, S., Grime, S., Höger, *Angew. Chem. Int. Ed*,vol. 55, pp.3328–3333; *Angew. Chem*, vol. 128, pp.3389–3394; Wiley Online Library.**(2016).** Google Scholar.

[54]. K., Becker, G., Gaefke, J., Rolffs, S., Höger, J., M., Lupton, *Chem. Commun*.vol.46, pp. 4686–4688,**(2010).** Google Scholar.

[55]. G., N., Tew, M., U., Pralle, S., I., Stuff, *J. Am. Chem. Soc*,vol. 121, pp.9852–9866,**(1999).** Google Scholar.

[56]. D., P., Flaherty, T., Kiyota, Y., Dong, T., Ikezu, J., L., Vennerstrom, *J. Med. Chem*,vol.53, pp. 7992–7999,**(2010).** Google Scholar.

[57].N., Sharma, D., Mohanakrishnan, A., Shard, A., Sharma, A., K., Sinha, D., Sahal, *J. Med. Chem*,vol. 55, pp.297–311,**(2012).** Google Scholar.

[58]. R., Kumar, A., Shard, R., Bharti, Y., Thopate, A., K., Sinha, *Angew. Chem. Int. Ed*,vol. 51, pp. 2636–2639; *Angew. Chem*, vol.124, pp.2690–2693,**(2012).** Google Scholar.

[59]. A., Shard, N., Sharma, R., Bharti, S., Dadhwal, R., Kumar, A., K., Sinha, *Angew. Chem. Int. Ed*, vol.51,pp.12250–12253, *Angew. Chem*, vol.124, pp.12416–12419,**(2012).** Google Scholar.

[60]. A., D., Patil, N., V., Kumar, W., C., Kokke , M.,F., Bean, A.,J., Freyer, C., Bors, S.,Mai, A., Trunch, D.,J., Faulkner, B.,Carte, A.,L.,Preen, R.,P., Hertzberg, R.,K., Johnson & W.,J., Westley, *J. Org. Chem*,vol.60,p.1182**,(1995).**

[61]. K.,S., Atwal, G.,C., Rovnyak, S.,D., Kimball, D.,M., Floyd, J., Z., Gourgoutas, J., Sehwartz, K.,M. Smillie & M.,F., Malley, *J. Med. Chem*., vol.33,p.2629,**(1990).**

[62]. C.,O., Kappe, *Eur. J. Med. Chem*, vol.35,p.1043,**(2000).**

[63]. D.,Bozing, P.,Benko L.,Petocz, M.,Szecsey, P.,Toempe, G.,Gigler, I.,Gacsalyi & I., *Gyertyan, (EGIS Gyogyszergyar) Eur. Pat. Appl. EP) Chem. Absrt*,vol.233,p.409 (**1991)**.

[64]. T.,U., Mayer, S.,J., Haggarty, R.,W., King, S.,I., Schreiber & T.,J., Mitchison, *Science*, vol.286,p.971.**(1999).**

[65]. P., Biginelli, Gazz. *Chim. Ital.*, vol.23,p 360.**(1893).**

[66]. (a) M., M., Khodaei, A.,R., Khosropur, M., Beygzadeh, *Synth. Commun*,vol. 34,p.1551.**(2004).** (b) S., Tu., F.,Fang, S., Zhu, T., Li., X., Zhang.,Q.,Zhuang, *Synlett*, vol.93,p.537,**(2004).**(c) M.,Gohain, D., Prajapatti, J., S.,Sandhu, *Synlett* **(2004).** (d) D., S.,Boss, K., Kumar, L., Fatima, *Synlett*,p.279,**(2004).**(e) Z., T., Wang, L., W., Xu., C., G.,Xia & H., Q., *Wang Tetrahedron Lett*,vol.45,p.7951,**(2004).**

[67]. (a) P.,Salehi, M., Dabiri, M., Zolfigol , Bodagh Ford, *Tetradedron Lett*,vol.44,p.2889 **(2003)**.(b) G., S.,Kiran Kumar,K.,Bhaskar.Reddy, C.,H.,Srinivas,J., S., Yadav, G.,Sabitha, *Synlett* 67,**(2003).** (c) K., R., Reddy, C., V., Reddy, M.,Mahesh, P., V., Raju, V., N., Reddy *Terahedron Lett*, vol.44.p.8173,**(2003).**(d) S.,Tu., F.,Fang, C.,Mioo, H.,Jiang, Y., Feng, D.,Shi, X.,Wang, *Tetrahedron Lett*.,vol.44,p.6153 .**(2003).**

[68]. (a) A., S.,Paraskar, G., K.,Dewkar & A., Sudalai, *Tetrahedron Lett*, vol.44,p.3305,**(2003).** (b) S.,D.Boss, L., Fatima & H., B., Mereyala, *J. Org. Chem*. vol.68,p.587.**(2003).**

[69]. (a) C., V.,Reddy, M., Mahesh, P., V., K., Raju., T., R.,BaBu, V.,N.,Reddy, *Tetrahedron Lett*,vol.43,p.2657,**(2002).**(b)J.,Lu.,Y.,Bai,Synthesis,vol.23,p.466,**(2002).**(c)T.,S.,Zhang,S.,L., Zhang,S.,Y.,Zhang,J.,.J.,Guo, T., Li., J., Chem. Res. (S), p.37.**(2002).**

[70]. (a) J.,Lu., Y., Bai., Z.,Wang., B., Yang.& B., Ma., *Tetrahedron Lett*.vol.41,p.9075,**(2000).** (b) C., O., Kappe, J., *Org. Chem*,vol.62,p.7201,**(1997).**

[71]. Takai S., Fernandez-Salguero P., Kimura S., Gonzalez F.,J.,Yamada K., **(December 1994).** "Assignment of the human dihydropyrimidine dehydrogenase gene (DPYD) to chromosome region 1p22 by fluorescence in situ hybridization". *Genomics*.vol. 24(3),p.613.

[72]. Chung T., Na., J., Kim Y.,I., Chang D.,Y., Kim Y.,I., Kim H., Moon H.,E., Kang K.,W., Lee D.,S., Chung J.,K., Kim S.,S., Suh-Kim H., Paek S.,H., Youn H., **(2016).** "Dihydropyrimidine Dehydrogenase Is a Prognostic Marker for Mesenchymal Stem Cell-Mediated Cytosine Deaminase Gene and 5-Fluorocytosine Prodrug Therapy for the Treatment of Recurrent Gliomas". *Theranostics*. Vol. 6 (10), pp.1477–90.

[73]. Caudle K.,E., Thorn C.,F., Klein T.,E., Swen J.,J., McLeod H.,L., Diasio R.,B., Schwab M., "Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing". *Clinical Pharmacology and Therapeutics*. vol.94,p.640, **(December 2013).**

[74]. Remuzzi G., Scheppati A., Ruggenenti P., "Clinical Practice. Nephropathy in Patients with Type 2 Diabetes". *New England Journal of Medicine*, vol. 346 (15), pp.1145–51.**(2002).**

[75]. Khadilkar, B., Borkar, S., "Silica gel supported ferric nitrate: A convenient oxidizing reagent." *Synth. Commun* vol.28, pp. 207-212.**(1998).**

[76]. (a) Buhler, F.,R., Kiowski, W., "Calcium antagonists in hypertension" J., *Hypertens. Suppl*,vol.S310,**(1987).** (b) Zolfigol, M.,A., Salehi, P., Safaiee M., "An efficient and eco-friendly procedure for the synthesis of Hantzsch ethyl 1,4-dihydro-2,6-dimethylpyridine-

3,5-dicarboxylates under mild and green conditions." *Lett. Org. Chem*,vol.3, pp.153-156,**(2006).**

[77]. Vo., D., Matowe, W.,C., Ramesh, M., Iqbal, N., Wolowyk, M.,W., Howlett, S.,E., Knaus, E.,E., "Synthesis, calcium channel agonist-antagonist modulation activities, and voltage-clamp studies of iso-propyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridinylpyridine-5-carboxylate racemates and enantiomers." *J. Med. Chem*, vol.38,pp.2851-2859,**(1995).**

[78]. Krechl, J., Smrčková, S., "Biomimetic models of lactate dehydro-genase." *Tetrahedron Lett.*,vol.30, pp.5315-5318,**(1989).**

[79]. Rueping, M., Antonchick, A.,P., Theissmann, T., A., "Highly enantioselective brønsted acid catalyzed cascade reaction: organocatalytic transfer hydrogenation of quinolines and their application in the synthesis of alkaloids." *Angew. Chem. Int. Ed.Engl*, vol.45, pp. 3683-3686,**(2006).**

[80]. Hoffmann, S., Nicoletti, M., List, B., "Catalytic asymmetric reduc-tive amination of aldehydes via dynamic kinetic resolution." *J. Am.Chem*. Soc,vol. 128, pp.13074-13075,**(2006).**

[81]. (a) Yang, J.,W., Fonseca, M.,T.,H., List, B., "A metal-free transferhydrogenation: Organocatalytic conjugate reduction of α, β unsaturated aldehydes." *Angew. Chem. Int. Ed. Engl*, vol.43,pp.6660-6662,**(2006).** (b) Martin, N.,J.,A., List, B., "Highly enantioselective transfer hydrogenation of α,β-unsaturated ketones." *J. Am. Chem.Soc*,vol.128, pp. 13368-13369,**(2006).**

[82] (a) Rovnyak, G.,C., Kimball, S.,D., Beyer, B., Cucinotta, G., Di-marco, D.,J., Gougoutas, J., Hedberg, A., Malley, M., McCarthy,J.,P., Zhang, R., Moreland, S., "Calcium entry blockers and activa-tors: Conformational and structural determinants of dihydro-pyrimidine calcium channel Modulators." *J. Med. Chem*,vol.38,pp.119-129,**(1995).** (b) Kappe, C.,O., "Biologically active dihydropyrimidones of the Biginelli-type-a literature survey.'' *Eur. J. Med. Chem*,vol.35, pp.1043-1052.**(2000).**

[83]. Atwal, K.,S., Swanson, B.,N., Unger, S.,E., Floyd, D.,M., Moreland,S., Hedberg, A., O'Reilly, B.,C., "Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-

1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihyperten-sive agent." *J. Med. Chem*, vol.34, pp.806-811.**(1991).**

[84]. Kappe, C.,O., Fabian, W.,M.,F., Semones, M.,A., "Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators.A comparison of ab initio, semiempirical and X-ray crystallo-graphic studies." Tetrahedron, vol.53, pp.2803-2816,**(1997).**

[85]. (a) Kappe,C.,O., "Recent Advances in the Biginelli dihydropyrimidine synthesis." New tricks from an old dog. *Acc. Chem. Res*, vol.33, pp.879-888,**(2000).** (b) Kappe, C.,O., Shishkin, O.,V., Uray, G., Verdino, P., "X-Ray structure,conformational analysis, enantioseparation, and determination of absolute configuration of the mitotic kinesin Eg5 inhibitor monastrol." *Tetrahedron,* vol.56,pp.1859-1862,**(2000).**

[86]. Ranu, B.,C., Hajra, A., Jana, U., "Indium(III)chloride-catalyzed one-pot synthesis of dihydropyrimidinones by a three-component cou-pling of 1,3-dicarbonyl compounds, aldehydes, and urea: An improved procedure for the Biginelli reaction." *J. Org. Chem.*,vol.65, pp. 6270-6272,**(2000).**

[87]. Atwal, K.,S., Rovnyak,G.,C., Schwartz, J., Moreland, S., Hedberg, A., Gougoutas, J.,Z., Malley, M.,F., Floyd, D.,F., "Dihydropyrimidine calcium channel blockers: 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidine carboxylic acid esters as potent mimics of dihydropyridines." *J. Med. Chem*,vol. 33, pp.1510-1515,**(1990).**

[88]. Kappe, C.,O., "100 years of the Biginelli dihydropyrimidine synthesis." *Tetrahedron*,vol. 49, pp.6937-6963,**(1993).**

[89]. Biginelli, P., "Derivati aldeidureidici degli eteri acetil-ed os-sal-acetico." *Gazz. Chim. Ital*,vol. 23, pp.360-416,**(1893).**

[90]. Hu., Yang, Li., Cui-Yun, Wang, Xiao-Ming, Yang, Yong-Hua, Zhu, Hai-Liang, "1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry". *Chemical Reviews*, vol. 114 (10), pp.5572–5610,**(2014).**

[91]. Jain, Abhishek Kumar, Sharma, Simant, Vaidya, Ankur, Ravichandran, Veerasamy, Agrawal, Ram Kishore, "1,3,4-Thiadiazole and its Derivatives: A Review on Recent

Progress in Biological Activities". *Chemical Biology & Drug Design*, vol.81(5),pp.557–576,**(2013).**

[92]. Wim, Dehaen, Vasiliy A., Bakulev, Edward C., Taylor, Jonathan A., Ellman, "The Chemistry of Heterocyclic Compounds, The Chemistry of 1,2,3-Thiadiazoles." *John Wiley & Sons*. p. 5, **(27 April 2004).**

[93]. Hetzhein, A., Mockel, K., *Adv. Heterocycl. Chem*,vol.7, p.183.**(1996).**

[94]. Sandstrom, J., *Adv. Heterocycl. Chem*, vol.9, p.165.**(1968).**

[95]. Demirbas, A., Sahin, D., Demirbas, N., Karaoglu, S.,A., "Synthesis of some new 1,3,4-thiadiazol-2-ylmethyl-1,2,4-triazole derivatives and investigation of their antimicrobial activities." *Eur. J. Med. Chem,* vol.44, pp.2896–2903**.(2009)**

[96]. Kadi, A.A., El-Brollosy, N.R., Al-Deeb, O.A., Habib, E.E., Ibrahim, T.M., El-Emam, A.A., "Synthesis, antimicrobial, and antiinflammatory activities of novel 2-(1-adamantyl)-5-substituted1,3,4-oxadiazoles and 2-(1-adamantylamino)-5- substituted-1,3,4-thiadiazoles." Eur. J. Med. Chem. 42, 235–242. **(2007).**

[97]. Bekhit, A.A., Abdel-Aziem, T., "Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatoryantimicrobial agents." Bioorg. Med. Chem. 12, 1935–1945. **(2004).**

[98]. Mullican, M.D., Wilson, M.W., Connor, D.T., Kostlan, C.R., Schrier, D.J., Dyer, R.D., "Design of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, 1,3,4-oxadiazoles, and 1,2,4-triazoles as orally-active, nonulcerogenic, antiinflammatory agent." J. Med. Chem. 36, 1090–1099**. (1993).**

[99]. Song, Y., Connor, D.,T., Sercel, A.,D., Sorenson, R.,J., Doubleday, R., Unangst, P.,C., Roth, B.,D., Beylin, V.,G., Gilbertson, R.,B., Chan, K., Schrier, D.,J., Guglietta, A., Bornemeier, D.,A., Dyer, R.,D., "Synthesis, structure-activity relationships, and in vivo evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. 2. 1,3,4-and 1,2–4-thiadiazole series." *J. Med. Chem*. 42, pp.1161–1169. **(1999).**

[100]. Mathew, V., Keshavayya, J., Vaidya, V.,P., Giles, D., "Studies on synthesis and pharmacological activities of 3,6-disubstitued-1,2,4- triazole-[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues." *Eur. J. Med. Chem,* vol.42, pp.823–840**.(2007)**

[101]. Chapleo, C.,B., Myers, M., Myers, P.,L., Saville, J.,F., Smith, A.,C.,B., Stilling, M.,R., Tulloch, I.,F., Walter, D.,S., Welbourne, A.,P., "Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 1. Hydrazines." *J. Med. Chem,*vol.29, pp.2273–2280. **(1986).**

[102]. Chapleo, C.,B., Myers, P.,L., Smith, A.,C., Stilling, M.,R., Tulloch, I.,F., Walter, D.,S., "Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 4. Amidines." *J. Med. Chem,*vol. 31, pp.7–11. **(1988).**

[103]. Cressier, D., Prouillac, C., Hernandez, P., Amourette, C., Diserbo, M., Lion, C., Rima, G., 2 "Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles." *Biol. Med. Chem,* vol.17, pp. 5275–5284. **(2009).**

[104]. Matysiak, J., Nazulewicz, A., Pelczynska, M., Switalska, M., Jaroszewicz, I., Opolski, A., "Synthesis and antiprolipherative activity of some 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles." *Eur. J. Med. Chem*, vol.41, pp.475–482. **(2006).**

[105]. Chou, J.,Y., Lai, S.,Y., Pan, S.,L., Jow, G.,M., Chern, J.,W., Guh, J.,H., "Investigation of anticancer mechanism of thiadiazole-based compound in human non small cell lung cancer A549 cells." *Biochem. Pharmacol*, vol.66, pp.115–124. **(2003).**

[106]. Radi, M., Crespan, E., Botta, G., Falchi, F., Maga, G., Manetti, F., Corradi, V., Mancini, M., Santucci, M.,A., Schenone, S., Botta, M., "Discovery and SAR of 1,3,4-thiadiazole derivatives as potent Abl tyrosine kinase inhibitors and cytodifferentiating agents." *Biol. Org. Med. Chem, Lett,* vol.18, pp.1207–1211. **(2008).**

[107]. Swamy, S.,N., Basappa, Priya, B.,S., Prabhuswamy, B., Doreswamy, B.,H., Prasad, J.,S., Rangappa, K.,S., "Synthesis of pharmaceutically important condensed heterocyclic 4,6-disubstituted-1,2,4- triazolo-1,3,4-triadiazole derivatives as antimicrobials." *Eur. J. Med. Chem,* vol.41, pp.531–538. **(2006).**

[108]. Bauer, W., Kirby, W.,M.,M., Sherris, J.,C., Turck, M., 1966. "Antibiotics susceptibility testing by a standardized single disk method." *Am. J. Clin. Pathol*, vol.45, pp.493–496, **(1966).**

[109]. Jones, D.,H., Slack, R., Squires, S., and Wooldridge, K.,H., *J. Med. Chem*, vol.8, pp.676-80, **(1965).**

[110].Sidwell, R.,W., Robins, R.,K., and Hillyard, I.,W., *Pharmacol. Ther*, vol.6,pp.123-8, **(1978).**

[111]. Sughen, J.,K., and Yologe, T., *Pharm. Acta Helv*, vol.58, pp.64-8, **(1978).**

[112]. Kelarev, V.,I., Karakhanov, R.,A., Gassanvo, S.,Sh., Morozova, G.,V., and Kuatbekova, K.,P., J., *Org. Chem. USSR*, vol.29, pp.323-9,**(1993).**

[113]. Kane, J.,M., Dubley, M.,W., Sorenson, S.,M., and Miller, F.,P., J., *Med. Chem*, vol.31, pp. 1253-58,**(1988).**

[114]. Seaborg, G.,T., *Science*, vol.9, pp.223,**(1984).**

[115]. Sawhney, S.,N., Gupta, A., and Sharma, P.,K., Indian J., *Heterocycl. Chem*. vol.1, p.8,**(1991).**

[116]. Mullican, M.,D., Wilson, M.,W., Connor, D.,T., Kostlan, C.,R., and Schrier, D.,J., J., *Med. Chem*.vol.36, pp.1090-99,**(1993).**

[117]. Kramer, J.,B., Boschelli, D.,H., and Connor, D.,T., J., "Heterocycle Chem", vol.31, p.1439. **(1994).**

[118]. Lee, B.,H., Dutton, F.,E., Clothier, M.,F., Bowman, J.,W., Davis, J.,P., Johnson, S.,S., Thomas, E.,M., Zantello, M.,R., Zinser, E.,W., McGuire, J.,C., Thompson, D.,P., and Geary, T.,G., Bioorg, *Medic. Chem. Lett.* vol. 9, p.1727, **(1999).**

[119]. Teicher, B.,A., Liu, S.,D., Liu, J.,T., and Holden, S.,A., Herman, *Anticancer Res*, vol.13, p.149,**(1993).**

[120]. Chegwidden, W.,R., and Spencer, I.,M., "Inflammopharmaco" vol.3, p. 231, **(1995)**

[121]. Parkkila, S., Rajaniemi, H., Parkkila, A.,K., Kivela, J., Waheed, A., Pastorekova, S., Pastorek, J., and Sly, W.,S., Proc, *Natl Acad Sci USA*, vol.97, p.2220, **(2000).**

[122]. Supuran, C.,T., and Scozzafava, A., *Eur. J. Med. Chem*. vol. 35, p. 867, **(2000).**

[123]. Lalezari, I., Shafiee, A., *J. Org. Chem.* vol.36, p.2836, **(1971).**

[124]. Lalezari, I., Shafiee, A., Yalpani, M., *J. Org. Chem*,vol.38, p.338. **(1973).**

[125]. Hurd, C.,D., Mori, R.,I., J., Am., *Chem. Soc*,vol. 77, p.5359. **(1955).**

[126]. Katritzky, A., R., Ramsden, C.,A., Joule, J.,A., Zhdankin, V.,V., "Handbook of Heterocyclic Chemistry," *3rd ed.; Elsevier: Oxford, UK,* **(2010).**

[127]. Gupta, R.,R., Kumar, M., Gupta, V., "Five membered heterocycles with more than two heteroatoms. In Heterocyclic Chemistry II," *3rd ed.; Springer: New Delhi, India,* p.491, **(2005).**

[128]. Li., Q., Ren, J., Dong, F., Feng, Y., Gu, G., Guo, Z., "Synthesis and antifungal activity of thiadiazole-functionalized chitosan derivatives. Carbohydr," vol. 373, pp.103–107, **(2013).**

[129]. Zou, Y., Zhao, Q., Liao, J., Hu, H., Shichong, Y., Chai, X., Xu., M., Qiuye, W., "New triazole derivatives as antifungal agents: Synthesis via click reaction, in vitro evaluation and molecular docking studies. Bioorg." *Med. Chem*, vol. 22, pp.2959–2962. **(2012).**

[130]. Mathew, V., Keshavayya, J., Vaidya, V.,P., Giles, D., "Studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues." *Eur. J. Med. Chem.*vol. 42, pp. 823–840, **(2007).**

[131]. Rajak, H., Kharya, M., Mishra, P., "Synthesis of some novel oxadiazole and oxadiazoline analogues for their anti-inflammatory activity." *J. Pharm. Soc. Jpn*,vol. 127, pp. 1757–1764**.(2007).**

[132]. Karabasanagouda, T., Adhikari, A.,V., Shetty, N.,S., "Synthesis and antimicrobial activities of some novel 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-b]-

1,3,4-thiadiazines carrying thioalkyl and sulphonyl phenoxy moieties." *Eur. J. Med. Chem.* vol. 42, pp. 521–529. **(2007).**

[133]. Sadek, B., Fahelelbom, K.,M.,S., "Synthesis, characterization, and antimicrobial evaluation of oxadiazole congeners Molecules" vol.16, pp. 4339–4347. **(2011).**

[134]. Dong, W., Liu, Z., Liu, X., Li, Z., Zhao, W., "Synthesis and antiviral activity of new acrylamide derivatives containing 1,2,3-thiadiazole as inhibitors of hepatitis B virus replication." *Eur. J. Med. Chem,* vol. 45, pp. 1919–1926, **(2010).**

[135]. Li., Z., Zhan, P., Liu, X., "1,3,4-Oxadiazole: A privileged structure in antiviral agents." *Mini Rev. Med. Chem,* vol. 13, pp.1130–1142,**(2011).**

[136]. Kumar, D., Kumar, N.,M., Chang, K.,H., Shah, K., "Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles." *Eur. J. Med. Chem,* vol 45, pp.4664–4668,**(2010).**

[137]. Ahsan, M.,J., Rathod, V.,P.,S., Singh, M., Sharma, R., Jadav, S.,S., Yasmin, S., Salahuddin, S., Pradeep, K., "Synthesis, anticancer and molecular docking studies of 2-(4-chlorophenyl)-5-aryl1,3,4-oxadiazole analogues." *Med. Chem,* vol. 3, pp.294–297,**(2010).**

[138]. Bayrak, H., Demirbas, A., Karaoglu, S.,A., Demirbas, N., "Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities." *Eur. J. Med. Chem,* vol.44, pp. 1057–1066.**(2009).**

[139]. Güzeldemirci, N.,U., Küçükbasmaci, Ö., "Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo [2,1-b] thiazole." *Eur. J. Med. Chem.* vol.45, pp. 63–68**.(2010).**

[140]. Suresh Kumar, G.,V., Rajendraprasad, Y., Mallikarjuna, B.,P., Chandrashekar, S.,M., Kistayya, C., "Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents." *Eur. J. Med. Chem*. Vol. 45, pp. 2063–2074. **(2010).**

[141]. Rudrapal, M., De., B., "Chemistry and biological importance of heterocyclic Schiff's bases." *Int. Res. J. Pure Appl. Chem,*vol. 3, pp. 232–249.**(2010).**

[142]. Aouad, M.,R., Rezki, N., Kasmi, M., Aouad, L., Rezki, M.,A., "Synthesis, characterization and evaluation of antimicrobial activity of some novel 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazole nuclues. Heterocycles" vol. 85, pp.1141–1154,**(2012).**

[143]. Aouad, M.,R., Messali, M., Rezki, N., Ali, A.,A., Lesimple, A., "Synthesis and characterization of some novel 1,2,4-triazoles, 1,3,4-thiadiazoles and Schiff bases incorporating imidazole moiety as potential antimicrobial agents." *Acta Pharm*. vol. 65, pp.117–132,**(2015).**

[144]. G., Kolavi, V., Hegde, I., A., Khazi, P., Gadad, Bioorg. *Med. Chem*,vol.14,p. 3069,**(2006).**

[145]. F., Poorrajab, S., K., Ardestani, S., Emani, M., Behrouzi-Fardmoghadam, A., Shafiee, A., Foroumadi, *Eur. J. Med. Chem,* vol.44, p.1758,**(2009).**

[146]. H., Kaur, S., Kumar, P., Vishwakarma, M., Sharma, K., K., Saxena, A., Kumar, *Eur. J. Med. Chem,* vol.45, p. 2777,**(2010).**

[147]. V., Jatav, P., Mishra, S., Kashaw, J., P., Stables, *Eur. J. Med. Chem*,vol.43, p. 1945,**(2008).**

[148]. A., K., Gadad, S., S., Karki, V., G., Rajurkar, B., A., Bhongade, Arzneim.-Forsch, *Drug Res,* vol. 49, p.858,**(1999).**

[149]. A., Senff-Ribeiro, A., Echevarria, E., F., Silva, C., R., Franco, S., S., Veiga, M., B., Oliveira, Br., J., Cancer, vol. 91, p.297,**(2004).**

[150]. D., Kumar, N., Maruthi Kumar, K.,H.,Chang, K., Shah, Eur, *J. Med. Chem*, vol.45, p. 4664,**(2010).**

[151]. R., F., Asbury, A., Kramar, D., G., Haller, Am., J., Clin, Oncol, vol.10, p.380, **(1987)**

[152]. P., J., Elson, L., K., Kvols, S., E., Vogl, D., J., Glover, R., G., Hahn, D., L., Trump, P., P., Carbone, J., D., Earle, T., E., Davis, *Invest. New Drugs* vol.6, p.97**,(1988).**

[153]. G., Y., Locker, L., Kilton, J., D., Khandekar, T., E., Lad, R., H., Knop, K., Albain, R., Blough, S., French, A., B., Benson, *Invest. New Drugs* vol.12, p.299**,(1994).**

[154]. R.,F., Asbury, J., A., Blessing, D., M., Smith, L., F., Carson, Am., J., Clin, Oncol, vol. 18, p. 397,**(1995).**

[155]. K., Tsukamoto, M., Suno, K., Igarashi, Y., Kozai, Y., Sugino, *Cancer Res*, vol.35,p. 2631,**(1975).**

[156]. C., T., Supuran, A., Scozzafava, *Eur. J. Med. Chem*, vol. 35, p.867**,(2000).**

[157]. F., Vergne, P., Bernardelli, E., Lorthiois, N., Pham, E., Proust, C., Oliveira, A.,K., Mafroud, F., Royer, R., Wrigglesworth, J., K., Schellhaas, M., R., Barvian, F., Moreau, M., Idrissi, A., Tertre, B., Bertin, M., Coupe, P., Berna, P., Soulard, Bioorg, *Med. Chem. Lett.* vol. 14, p. 4607,**(2011).**

[158]. H., Rajak, A., Agarawal, P., Parmar, B., S., Thakur, R., Veerasamy, P., C., Sharma, M., D., Kharya, Bioorg. *Med. Chem. Lett.*, vol.21, p. 5735, **(2011).**

[159]. K.,Y., Jung, S.,K., Kim, Z.,G., Gao, A., S., Gross, N., Melman, K., A., Jacobson, Y.,Ch., Kim, Bioorg, *Med. Chem* vol.12, p. 613, **(2004).**

[160]. I., H., Krakoff, M., E., Balis, J., Clin, *Invest*, vol.38, p. 907, **(1959).**

[161]. M.,M., Ciotti, S., R., Humphreys, J., M., Venditti, N., O., Kaplan, A., Goldin, *Cancer Res*, vol. 20, p. 1195, **(1960).**

[162]. H., F., Oettgen, J., A., Reppert, V., Coley, J., H., Burchenal, *Cancer Res*, vol. 20, p.1597, **(1960).**

[163]. J., A., Nelson, L., M., Rose, L., L., Jr., Bennett, *Cancer Res*, vol. 36,p. 1375, **(1976).**

[164]. J., A., Nelson, L., M., Rose, L., L., Jr., Bennett, *Cancer Res*,vol. 37, p.182. **(1977).**

[165] Sevgi Karakus, Bedia Kocyigit-Kaymakcioglu, Hale Z., Toklu, Feyza Ariciogiu, and Sevium Rollas, "Synthesis and Anticonvulsant activity of New N-(Alkyl/Substituted aryl)-N'-[4-(5-cyclohexylamino)- 1,3,4- thiadiazole-2-yl)phenyl]thioureas", *Archiv der Pharmazie*, p.342(1),**(2009).**

[166] Arun Gupta, S.,N., Pandeya, Pradeep Mishra, Sushil K., Kashaw, Varsha Jatav, J., P., Stables, "Synthesis and anticonvulsant activity of some novel 3-aryl amino/amino-4-aryl-5-

imino-Delta(2)-1,2,4-thiadiazoline", *European Journal of Medicinal Chemistry*, vol43(4), pp749-754 **(2008).**

[167] Varsha Jatav, Pradeep Mishra, Sushil Kashaw, and J.,P., Stables, "Synthesis and CNS depressant activity of some novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones", *European Journal Medicinal Chemistry*, vol 43(1), pp135-141, **(2008).**

[168] Khosrow Zamania,, Khalil Faghihia, Malek S., Mehranjanib, "Synthesis of some new 2,5-disubstituted 1,3,4- thiadiazoles containing Isomeric pyridyl as potent antimicrobial agents", *Polish Journal of Pharmacology*, vol 55, pp1111–1117,**(2003).**

[169] Shar S., Al-Shihry, "Synthesis and spectral studies of Schiff bases of 2-amino-5-mercapto-1, 3, 4-thiadiazole", *Scientific Journal of King Faisal University (Basic and Applied Sciences)*, vol 6, p 2, **(2005).**

[170] S., Olafsdottira, Lise Bolt Jørgensenb and Jerzy W., Jaroszewski Phytochemistry,vol 60,pp 269-273 **(3 june 2002).**

[171] S., Grabley, R., Thiericke, pp. 3-33, (**1999)**. vol. 93, pp 2325-2327, (**1971).**

[172] S., Kusari, M., Lamschöft, S., Zühlke and M., Spiteller. J., *Nat. Prod*., vol 71(2), **(2008)** Spalding, B., J., *Bio-Technology*, vol 9, p 701,(**1991**).

[173] Kusari, M., Lamschöft, S., Zühlke and M., Spiteller. J., *Nat. Prod*, vol 71(2) **(2008)** Spalding, B., J., *Bio-Technology*, vol 9, p701, **(1991).** Frei, B., "Natural antioxidants in human health and disease". *San Diego: Academic Press.*(**1994).**