SYNTHESIS AND CHARACTERIZATION OF POTENTIALLY BIOLOGICALLY ACTIVE COMPOUNDS DERIVED FROM FIBRIC ACIDS

A thesis submitted to the University of the Punjab
For the Award of Degree of
Doctor of Philosophy
in
CHEMISTRY

BY
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INSTITUTE OF CHEMISTRY
UNIVERSITY OF THE PUNJAB
LAHORE PAKISTAN
2017

In The Name Of Almighty Allah

The Most Compassionate

The Most Merciful

Read! In the name of Lord, Who created.

He created man from clot of congealed blood.

Read and your Lord is the most honorable,

He Who taught by the pen,

Taught man that he did not know.

(Al-Alaq)

SAYING

OF

HAZRAT MUHAMMAD (S.A.W.W.)

ACQUIRE KNOWLEDGE. IT ENABLETH ITS POSSESSOR TO DISTINGUISH RIGHT FROM WRONG: IT LIGHTENTH THE WAY TO HEAVEN. IT IS OUR FRIEND IN THE DESERT. OUR SOCIETY SOLITUDE, OUR COMPANION WHEN FRIENDLESS: IT GUIDETH US TO HAPPINESS: IT SUSTAINETH US IN MISERY: IT IS ORNAMENT AMONGST FRIENDS AND ARMOUR AGAINST ENEMIES.

DEDICATION

Dedicated to

My Beloved Parents, Husband,

Prof. Dr. Riffat Parveen (Late)

&

Respectable Supervisors

"Prof. Dr. Munawar Ali Munawar"

"Dr. Asim Raza Basra"

"Dr. Muhammad Zia-ur-Rahman"

Declaration

I, Majda Batool d/o Syed Imdad Hussain Shah, solemnly declare that the thesis entitled "***Synthesis and Characterization of potentially biologically active compounds derived from fibric acids***" has been submitted by me for the fulfillment of the requirement of the degree of Doctor of Philosophy in Chemistry at Institute of Chemistry, University of the Punjab, Lahore, under the supervision of Prof. Dr. Munawar Ali Munawar, Dr. Muhammad Zia-ur-Rehman and Dr. Asim Raza Basra.

I also declare that the work is original unless otherwise referred or acknowledged and has never been submitted elsewhere for any other degree at any other institute.

Majda Batool

Institute of Chemistry,

University of the Punjab,

Lahore

Approval Certificate

It is hereby certified that thesis entitled "***Synthesis and Characterization of potentially biologically active compounds derived from fibric acids***" is based on the results of experiments carried out by **Ms. Majda Batool** and that it has not been previously presented for a higher degree elsewhere. She has done this research work under my supervision. She has fulfilled all requirements and is qualified to submit the accompanying thesis for the award of the degree of Doctor **of Philosophy in Chemistry**.

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If all the trees become paper and oceans ink, Allah's greatness and kindness cannot be explained. All praises to Almighty Allah Who is the Supreme authority and the Creator of the Universe Who guides us in the oceans of darkness enables us to overcome the difficulties in the crucial situation and all respects and regard to the Holy Prophet Hazrat Muhammad (SAW) for enlightening our conscience with the essence of faith in God, converging all his Kindness and Mercy upon us.

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(Majda Batool)

LIST OF ABBREVIATIONS

2D	Two dimensional
3D	Three dimensional
A	Absorbance
ACE	Atomic contact energy
AcOEt	Ethyl acetate
Arg	Arganine
b.w	Body weight
$CDCl_3$	Deutrated Chloroform
CD	Cardiovascular disease
CHD	Coronary heart disease
CT	Clotting time
d	Doublet
d	Deutrated
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
DNA	Deoxyribonucleic acid
D_2O	Deutrated water
D	Dipole moment
eV	Electron volts
E	Electrophile

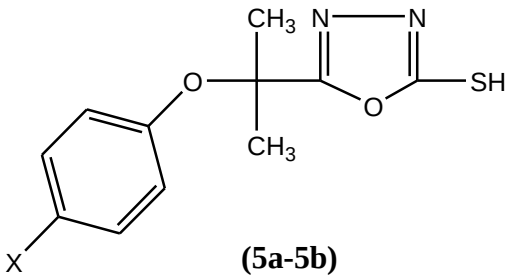
e.g.	For example
ESI	Electrospray Ionization
EIMS	Electron ionization spectroscopy
EP	Electrostatic potential
Et	Ethyl
FMOs	Frontier molecular orbitals
FT-IR	Fourier-transform infrared spectroscopy
FXa	Factor Xa
g	Gram
GC-MS	Gas chromatography–mass spectrometry
H or Hr	Hour
HIV	Human-immunodeficiency virus
Hz	Hertz
ICT	Intermolecular charge transfer
i.e.	That is to say
IR	Infrared
J	Coupling constant
lit.	Literature
Lig	Ligand
MEP	Molecular electrostatic potential
m	Multiplet
m	*meta*
M	Molarity

M^+	Molecular ion
Max.	Maximum
Me	Methyl
MHz	Mega Hertz
HUMO	Highest occupied molecular orbital
LUMO	Lowest occupied molecular orbital
min.	Minute
mL	Millilitre
mmol	Millimole
mol	Mole
m.p.	Melting Point
MS	Mass Spectroscopy
n	Normal
N	Normality
nm	Nanometer
Nu	Nucleophile
o	*ortho*
OAc	Acetate
OMe	Methoxy
p	*para*
Ph	Phenyl
pp.	Page No.
rt	Room temperature

s	Singlet
SAR	Structure-activity relationship
sec.	Second (Time)
sem.	Standard error of mean
t	Triplet
TBAB	Tetra-*n*-butylammonium bromide
t-BuO	Tertiary Butoxide
TLC	Thin layer chromatography
UV	Ultraviolet
vic.	Vicinal
viz.	Namely, that is to say, to wit, or as follows
δ	Chemical shift
ν	Frequency
Δ	Heat
μ	Micro
μl	microlitre
λ	Wavelength

ABSTRACT

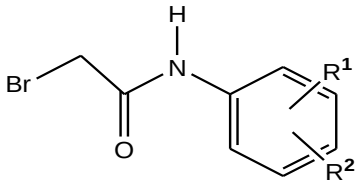
The present study deals with the synthesis of fibric acids derivatives. The thesis has been divided into three parts (**1**) Synthesis of fibric acids derivatives (**2**) Biological screening (**3**) *In silicio* studies. In the first part of thesis two fibric acids (**2a & 2b**) were synthesized from two phenols (**1a & 1b**) followed by their conversion into corresponding esters (**3a & 3b**) and carbohydrazides (**4a & 4b**). Cyclization of these carbohydrazides was carried out to synthesize 1,3,4-oxadiazoles (**5a & 5b**). In next step *N*-substituted-2-bromoacetamides (**7a-7y**) were prepared by using various anilines (**6a-6y**). Two main series of compounds **8-30** and **31-50** were synthesized successfully by reacting 5-(2-aryloxypropan-2-yl)-1.3.4-oxadiazol-2-thiols (**5a & 5b**) with *N*-substituted-2-bromoacetamides (**7a-7y**). Characterization of the compounds was carried out through spectroscopic analysis.



(5a-5b)

5a X=Cl
5b X=Br

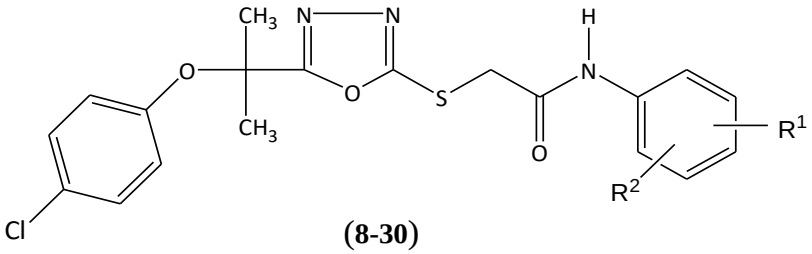
(Scheme 1)



(7a-7y)

7a	Cyclohexylamine		**7j**	$R^1 = 3CH_3$	$R^2=5CH_3$	**7s**	$R^1 = H$	$R^2=2Br$
7b	$R^1 = H$	$R^2=H$	**7k**	$R^1 = H$	$R^2=4C_2H_5$	**7t**	$R^1 = H$	$R^2=3Br$
7c	$R^1 = H$	$R^2=2CH_3$	**7l**	$R^1 =2C_2H_5$	$R^2=6CH_3$	**7u**	$R^1 = H$	$R^2=4Br$
7d	$R^1 = H$	$R^2=3CH_3$	**7m**	$R^1 = H$	$R^2=2OCH_3$	**7v**	$R^1 = H$	$R^2=2Cl$
7e	$R^1 = H$	$R^2=4CH_3$	**7n**	$R^1 = H$	$R^2=3OCH_3$	**7w**	$R^1 = H$	$R^2=4F$
7f	$R^1 = 2CH_3$	$R^2=3CH_3$	**70**	$R^1 = H$	$R^2=4OCH_3$	**7x**	$R^1 = H$	$R^2=4NO_2$
7g	$R^1 = 2CH_3$	$R^2=4CH_3$	**7p**	$R^1 = H$	$R^2=2OC_2H_5$	**7y**	$R^1 = H$	$R^2=2NH_2$
7h	$R^1 = 2CH_3$	$R^2=6CH_3$	**7q**	$R^1 = H$	$R^2=4OC_2H_5$			
7i	$R^1 = 3CH_3$	$R^2=4CH_3$	**7r**	$R^1 = 2OCH_3$	$R^2=5Cl$			

(Scheme 2)

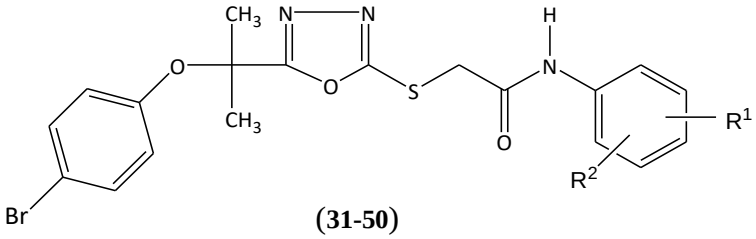


(8-30)

8	Cyclohexylamine		**16**	$R^1 = 3CH_3$	$R^2=4CH_3$	**24**	$R^1 = 2OCH_3$	$R^2=5Cl$
9	$R^1 = H$	$R^2=H$	**17**	$R^1 = 3CH_3$	$R^2=5CH_3$	**25**	$R^1 = H$	$R^2=2Br$
10	$R^1 = H$	$R^2=2CH_3$	**18**	$R^1 = H$	$R^2=4C_2H_5$	**26**	$R^1 = H$	$R^2=4Br$
11	$R^1 = H$	$R^2=3CH_3$	**19**	$R^1 =2C_2H_5$	$R^2=6CH_3$	**27**	$R^1 = H$	$R^2=2Cl$
12	$R^1 = H$	$R^2=4CH_3$	**20**	$R^1 = H$	$R^2=2OCH_3$	**28**	$R^1 = H$	$R^2=4F$

13	$R^1 = 2CH_3$	$R^2=3CH_3$	**21**	$R^1 = H$	$R^2=4OCH_3$	**29**	$R^1 = H$	$R^2=4NO_2$
14	$R^1 = 2CH_3$	$R^2=4CH_3$	**22**	$R^1 = H$	$R^2=2OC_2H_5$	**30**	$R^1 = H$	$R^2=2NH_2$
15	$R^1 = 2CH_3$	$R^2=6CH_3$	**23**	$R^1 = H$	$R^2=4OC_2H_5$			

(Scheme 3)



(**31**-**50**)

31	Cyclohexylamine		**38**	$R^1 = 2CH_3$	$R^2=6CH_3$	**45**	$R^1 = H$	$R^2=2OC_2H_5$
32	$R^1 = H$	$R^2=H$	**39**	$R^1 = 3CH_3$	$R^2=4CH_3$	**46**	$R^1 = H$	$R^2=4OC_2H_5$
33	$R^1 = H$	$R^2=2CH_3$	**40**	$R^1 = 3CH_3$	$R^2=5CH_3$	**47**	$R^1 = 2OCH_3$	$R^2=5Cl$
34	$R^1 = H$	$R^2=3CH_3$	**41**	$R^1 = H$	$R^2=4C_2H_5$	**48**	$R^1 = H$	$R^2=2Br$
35	$R^1 = H$	$R^2=4CH_3$	**42**	$R^1 =2C_2H_5$	$R^2=6CH_3$	**49**	$R^1 = H$	$R^2=3Br$
36	$R^1 = 2CH_3$	$R^2=3CH_3$	**43**	$R^1 = H$	$R^2=3OCH_3$	**50**	$R^1 = H$	$R^2=4Br$
37	$R^1 = 2CH_3$	$R^2=4CH_3$	**44**	$R^1 = H$	$R^2=4OCH_3$			

(Scheme 4)

After the successful completion of synthetic portion and their characterization fibric acids derivatives were evaluated for their biological activities. For this purpose, protocols of anti-thrombotic (*in vitro* and *in vivo*) and anti-inflammatory activity (*in vitro* and *in vivo*) were followed. The anti-thrombotic activity (*in vitro* and *in vivo*) was performed to evaluate the FXa inhibition potential of newly synthesized compounds. *In vitro,* compounds **17, 27** and **36** showed higher % age of clot lysis than standard drug streptokinase; however the

remaining compounds showed moderate to good activities. *In vivo,* for compounds **9, 12, 13, 16, 17, 24, 27, 32, 36, 39, 41,** and **48** enhanced clotting times (even better than standard drug heparin) were observed.

Anti-inflammatory activity was performed to evaluate the COX-2 enzyme inhibition potential of fibric acids derivatives. *In vitro*, these compounds showed moderate to good activity while *in vivo* compounds **8, 9, 11, 12, 16, 17, 24, 34** and **48** showed results even better than standard drug diclofenic sodium. Compounds **14, 15, 19, 21, 31, 38** and **42** results were comparable to that of standard drug while remaining compounds exhibited moderate activity. In the last part of research work *in silico* studies were performed for selected compounds. For anti-thrombotic activity compounds **9-17** were docked against FXa protein. Except the compound **5a,** all others showed higher docking score than the control ligand. In case of anti-inflammatory activity molecular docking of compounds **5a, 5b** and **8-50** was carried out against COX-2 protein. All the compounds except **5a, 5b, 13** and **25** showed higher docking score than standard. Density functional theory (DFT) computed molecular properties of compounds **9-17** were also calculated by computational methodology. Results of biological activities showed good commitment with *in silico study* results. In future these compounds might be evaluated at molecular level.

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CHAPTER 1
INTRODUCTION

The synthesis of new drug candidates is related to drug discovery program which is a multifarious and valuable job being conducted by scientists and pharmacological companies. Initially, the drug discovery included two modes, that is, through chance or identification of active part of conventional medicines. Second phase includes classical pharmacology nominating synthetic compounds or extracts of natural plants with required curative results. The modern pharmacology includes a multi-stepped drug discovery process. This process involves the analysis of bioavailability, stability, selectivity, efficacy and computational analysis. Therefore, there is a considerably too low rate of discovery of new therapeutic agents. Thus there is a constant need of new drug candidates fulfilling all the criteria.

Organic synthesis has been known to involve the synthesis of new drug candidates by using running methodologies or by using new more efficient methods. A number of derivatives of fibrate, 1,3,4-oxadiazole and acetamide have been known for their biological potential. The bioactive potential of these moieities prompted us to synthesize some new derivatives of these mentioned moieties. The current research work describes the synthesis of some new potent molecules bearing some bioactive moieties. The included bioactive moieties are fibrates, 1,3,4-oxadiazole and acetamides. All the synthesized molecules were subjected to the evaluation of their bioactivity potential including thrombolytic and anti-inflammatory activities (*in vivo* and *in vitro*).

1.1 Fibrates

The fibrates belong to amphipathic carboxylic acids and esters and are lipid lowering drugs being used since 1963 [1]. The use of this class as drug has diminished with the passage of time. This decrement in use may be regarded to less affectivity, less safety and also the introduction of statin. Among different fibrates, clofibrate was initially extensively utilized in 1970s but it showed normal effect on coronary heart disease reduction, increased gallstones and mortality frequencies. Gemfibrozil came in 1980s with all benefits but it did not affect the mortality rate. Fenofibrate appeared in 1990s. Valuable results were obtained for reducing cardiovascular events through "Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial". At present, still fibrate therapy is under practice [2]. The different members included in this class are given in Figure-1.1 [1, 2].

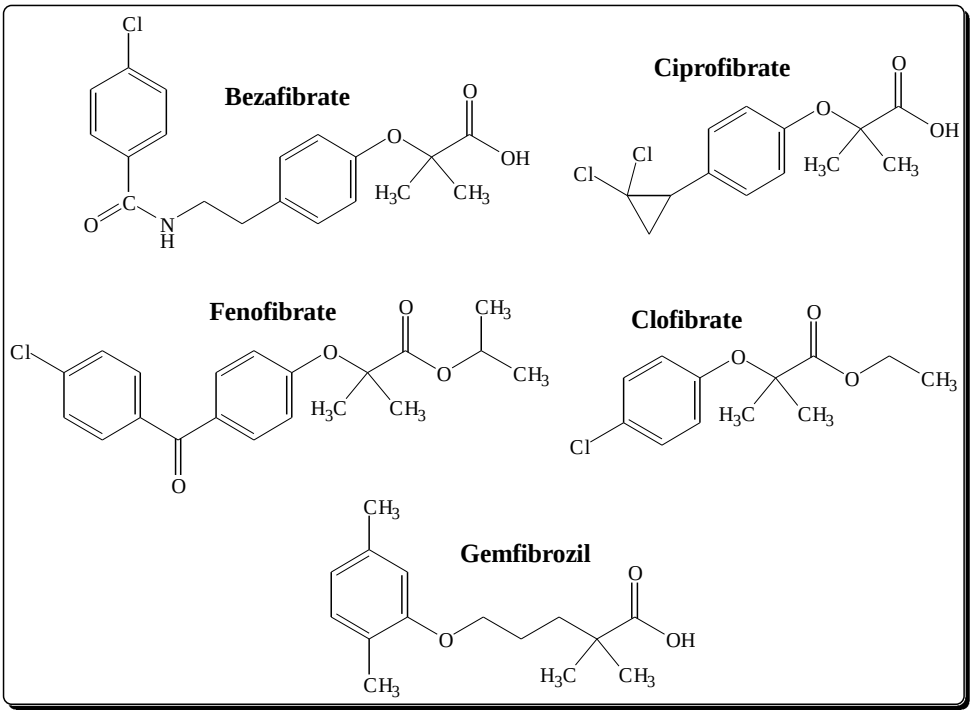


Figure-1.1 Bioactive fibrates

1.1.1 Pharmacology of Fibrate

The patients having abnormal levels of cholesterol owing to abnormality in triglyceride level are directed to fibrate therapy. This abnormality enhances the danger of heart diseases. Fibrates are commonly known as hypolipidemic agents because of their use against hypercholesterolemia. In addition to it, these are also utilized for the treatment of other metabolic disorders. The combination of fibrates and statins is generally used against different forms of hypercholesterolemia. Fibrates are also known to reduce the heart attacks without improving all-cause mortality [3-5].

Fibrates reduce insulin resistance due to its ability to reduce triglyceride levels and to enhance high density lipids. Fibrates have less ability to reduce low density lipids. The patients intending to decrease high density lipids are directed to check their high density lipids levels after a few months of fibrate therapy because there is too much reduction has been noted in some cases [6].

The fibrate therapy has some serious side effects. Fibrates are known to cause pain in muscles, disorder of stomach and enhancement of gallstones risk. The enhancement of gallstones risk is related to fibrate ability of incrementing cholesterol contents in bile. The fibrates in combination with statin are known to cause renal failure and the enhancement of rhabdomyolysis risk. The toxicity of drug includes intense harm to kidney [7].

The action of fibrates is known to activate peroxisome proliferator-activated receptors (PPAR). These receptors regulate the metabolism of fats and carbohydrates and also the differentiation of adipose tissue. Thus the lipid metabolism is facilitated due to transcription of genes by these PPARs. When respective ligands activate PPARs, they heterodimerize with

the receptor for RXR and 9-cis-retinoic acid. After heterodimerization, the binding of PPRs to specific REs in the regulatory regions of target genes known as PPREs takes place. These regulatory regions are composed of two degenerate hexanucleotide repeats (arrows) that are arranged in tandem as direct repeats separated by one nucleotide [1]. The Figure-1.2 explains this mechanism of action of fibrates.

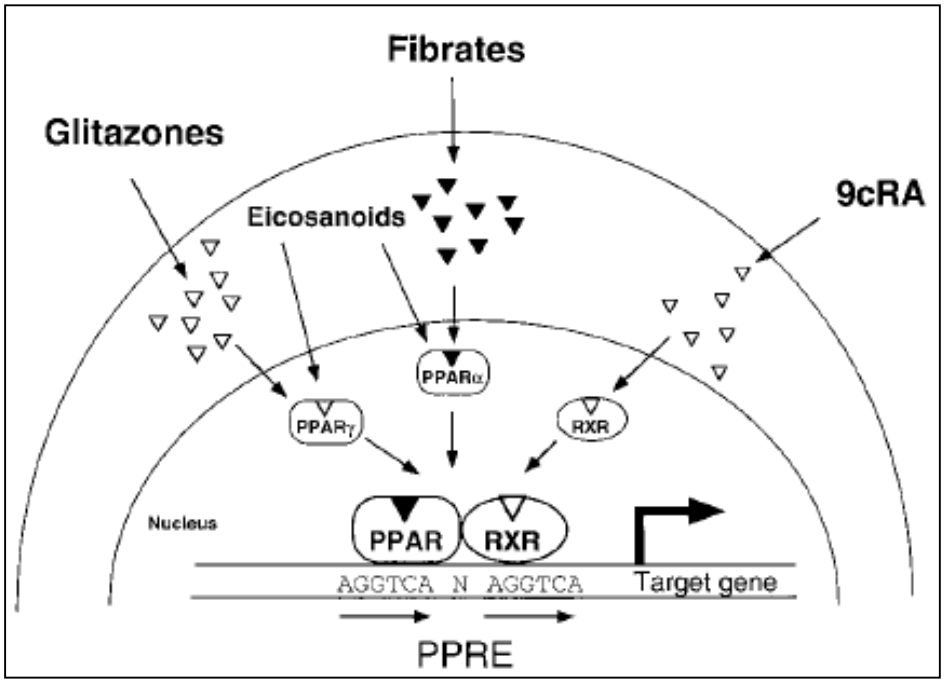


Figure-1.2 Signaling pathway of PPAR showing its synthetic and natural activators [1].

1.2 Oxadiazoles

The saturated heterocyclic compounds are alike to acyclic compounds. The unsaturated heterocyclic compounds have been given prime importance owing to their considerable chemical and biological properties . The heterocyclic moiety considered for the synthesis of presented compounds is oxadiazole. Oxadiazole is a heterocyclic aromatic compound with molecular formula of $C_2H_2N_2O$. In the name of oxadiazole, ‘oxa’ stands for

'oxygen', 'di' for 'two', 'az' for 'nitrogen' and 'ole' for 'five membered ring' [8]. Four possible isomers are shown in Figure-1.3.

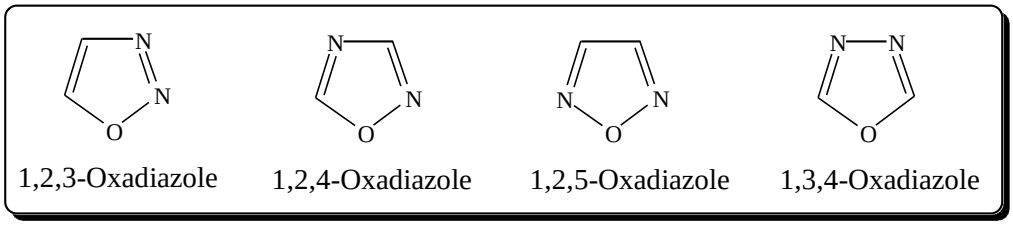


Figure-1.3 Isomers of oxadiazole

1.2.1 1,3,4-Oxadiazole

1,3,4-Oxadiazole is one of the important heterocycle with attracting chemistry and biological properties. The aromatic furan ring has exchanged two of its carbons by nitrogen atoms. The more electronegative nature of nitrogen atoms has made it weak base and also less liable for electrophillic substitution on carbons having least electron density. The nucleophillic substitution reactions have also been observed for the ring when there are halogens on the ring. The other reactions shown by 1,3,4-oxadiazole are photochemical and thermal ones [9].

Although all the isomers of oxadiazole are biologically important yet 1,3,4-oxadiazole ring has demonstrated exceptional pharmacokinetic behavior in its derivatives. A number of derivatives have been derived from 1,3,4-oxadiazole and investigated for a list of biological activities [10-70]. A large list of references has been provided to elaborate the bioactivity aimed synthetic work on 1,3,4-oxadiazole derivatives. The most prominent activities shown by derivatives of 1,3,4-oxadiazole are fungicidal [40], insecticidal [41], antibacterial [42], antitumor [44], antitubercular [45], anticonvulsant [46, 47], herbicidal

[71], analgesic [72], antiviral and anti-inflammatory [73-75] activities. The drugs bearing 1,3,4-oxadiazole moiety are Zibotentan (anticancer) and Raltegravir (antiretroviral) [31], given in Figure-1.4.

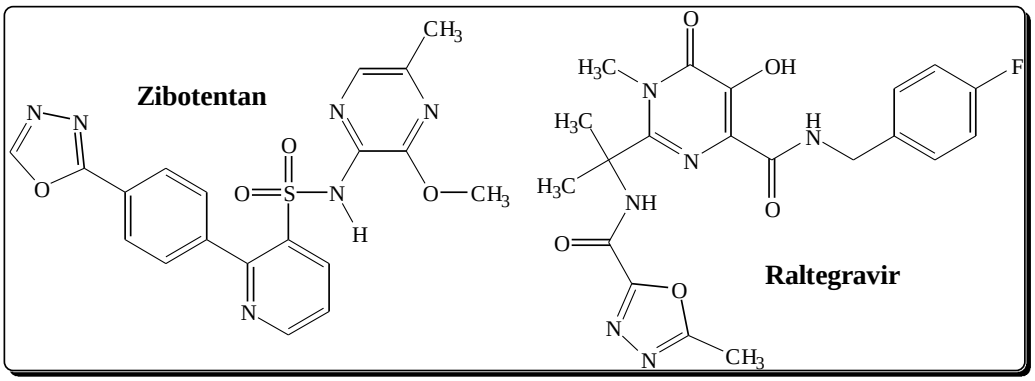


Figure-1.4 Drugs bearing 1,3,4-oxadiazole

1.3 Acetamide compounds

The acetamides are the derivatives bearing acetamoyl moiety. Acetamoyl moiety represents substituted derivatives of acetylamine, that is, carbonyl group attached to a nitrogen atom on one side and a carbon atom on other side. Acetyl halide produces this linkage on reaction with different alkyl/aralkyl/aryl amines. Figure-1.5 demonstrates the basic structure of acetamides. Here R, R^1, R^2, R^3 and R^4 can be alkyl/aralkyl/aryl groups.

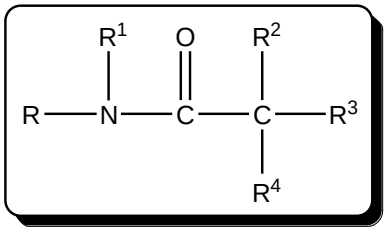


Figure-1.5 Acetamoyl moiety

A large number of biological activities are also demonstrated by acetamide derivatives. Furthermore, this functionality has been employed to synthesize molecules with multiple functionalities and having astonished bioactivities [76-89].

1.4 Thrombolytic activity

The clotting of blood plasma is the key point in repairing the blood vessel having a cut or other such type of injury [90, 91]. This is a valuable application of coagulum of blood but it is also formed at some unnecessary point and also at unnecessary time. This second point is too dangerous because it can cause stroke, heart attack, ischemia, embolism etc [92-94]. The term ‘embolism’ describes the coagulum of blood in a vessel and this coagulum ceases the movement of blood towards next body part. For instance, the obstruction of blood in lungs causes mid-section torment, hemoptysis and illogical breathing trouble and this is known as aspiratory embolism [95, 96]. The term ‘ischemia’ describes the blockage of oxygen or blood to tissue. For instance, the blockage of blood to cardiac muscle causes cardiac ischemia which has also severe results including cardiac arrhythmia, myocardial infarction, angina, syncope, shortness of breath or even death [97-99]. The term ‘ischemic stroke’ describes the obstruction of blood flow to brain [100]. This stroke can also be the result of embolic stroke, thromblic stroke or cerebral stroke as an aftereffect. Embolic stroke relates to the blood obstruction in any part of body leading to blockage of corridor in mind. Thromblic stroke relates to blood obstruction to cerebrum. Cerebral stroke relates to coagulum of blood in brain's narrow arteries and heart [101].

The blood clotting related cardiovascular disease is a severe one [102]. A number of thrombolytic agents have been employed to remove clotted blood including streptokinase,

Urokinase, tissue plasminogen activator etc. The side effects of these agents include anaphylactic reaction, hyper risk of haemorrhage and low specificity [103-106].

1.5 Anti-inflammatory activity

The term inflammation is related to different stresses observed as heat in injured tissues or cells, swelling, redness and pain. The membrane alteration, enhanced vascular permeability and vasodilation are the results of it. In other words, it is nonspecifically related to internal defense system of body [107]. Histamine, kinins and prostroglandins are emitted by injured cells. These emitted compounds are the cause of enhanced permeability of the capillaries and enhanced vasodilation. Both of these processes cause more blood flow towards injured tissues or cells. Inflammation has been subdivided into acute inflammation and chronic inflammation. After injury, the body initial response is acute inflammation. In this inflammation, plasma of the blood and granulocytes are moved towards ruptured tissues. Chronic inflammation is the next stage of acute inflammation. A number of procedures have been employed to evaluate the potential of different anti-inflammatory agents. Generally medicinal plants are widely utilized to cure disorders caused by inflammation.

Inflammation is mainly caused by prostaglandins produced by cyclooxygenase enzymes. These enzymes are of two isoforms including cyclooxygenases-1 and cyclooxygenases-2. The first one produces thromboxane, prostacyclin and prostaglandins which are the cause of stomach protection, blood clotting and pain [108]. The second one biosynthetically produces prostaglandin in central nervous system and inflammatory cells [109]. The inhibition of first one follows the reduction of inflammation. But the loss of protection of stomach has severe results including ulceration and bleeding. The inhibition of

second one involves less gastric irritation and decremented risk of peptic ulceration [110]. Rofecoxib and celecoxib have been used as inhibitors of cyclooxygenase-2 [111]. The rofecoxib and valdecoxib enhanced the rate of strokes and heart attacks due to long-term use and were banned in 2004-2005 [112]. The only drug as cyclooxygenase-2 inhibitor is celecoxib and so new drug candidates are required with least or no side effects. The structures of mentioned inhibitors are given in Figure-1.6.

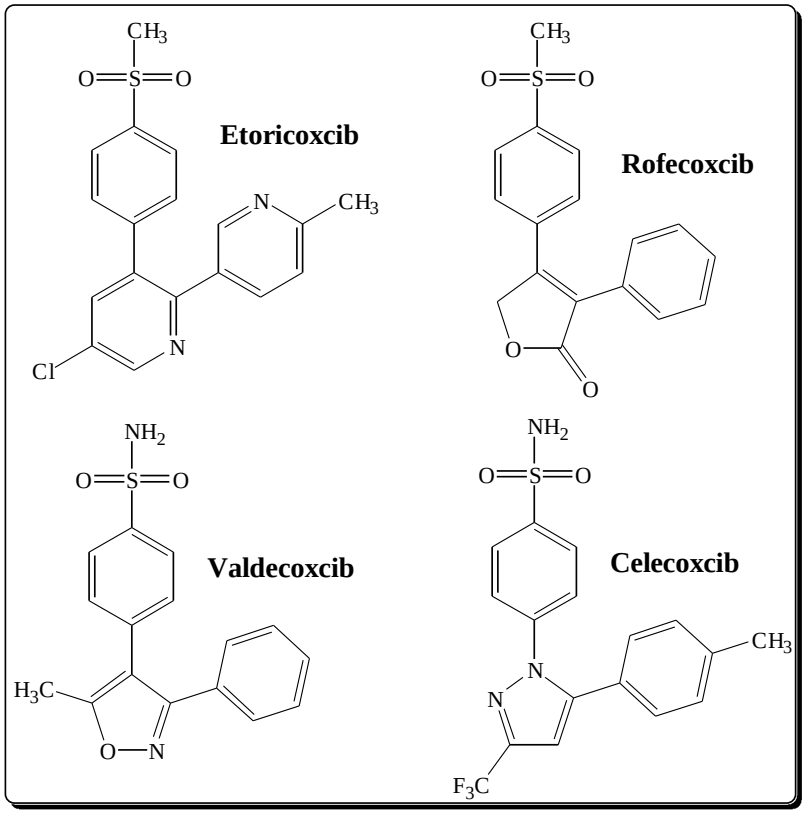


Figure-1.6 Structures of some anti-inflammatory agents

A list of inhibitors has been elucidated for cyclooxygenase-2 till now [113–118] including vicinal diaryl heterocycles [117-120]. Cyclooxygenase-2 was selectively inhibited

first time by celecoxib, a 1,5-substituted pyrazole derivative [121], but its less solubility in water decremented its oral bioavailability [122].

Many attempts have been made to produce a soluble form of celecoxib but still unsuccessful [123]. The cyclooxygenase-2 inhibitors have shown adverse cardiovascular events but no solid evidence [124-126]. The more inhibitors of this enzyme are continuously under study [113, 127-129].

Generally following things are considered for improving drug availability [130].

1. The basic structure of a routine drug is retained to avoid too much change in contributing parts of the molecule.
2. Polar groups are introduced to increase the solubility in aqueous medium and hence bioavailability in the body system.
3. The use of amide bonds which are easily hydrolyzed and also safe to a running body systems.

1.6 Aim of work

The search of new drug candidates for different diseases had remained necessary aspect of modern organic synthetic chemistry. New molecules erected on running methodologies have been extensively synthesized and evaluated for their bioactivity potential in different aspects.

The heterocyclic chemistry is reknowned one regarding bioactivity potential. Hence bioactive heterocycle, 1,3,4-oxadiazole has been considered for the synthesis of different compounds. The potential of this nucleus is proposed to be boosted up by the presence of

acetamide functionality in the synthesized molecules. Two fibric acids, 2-(4-chlorophenoxy)-2-methylpropanoic acid known as clofibric acid and 2-(4-bromophenoxy)-2-methylpropanoic acid, have been considered for the synthesis of different 1,3,4-oxadiazole bearing acetamide derivatives. The basic theme of this project was to introduce a few new drug candidates having valuable results for thrombolytic and anti-inflammatory activities. Both of these activities were performed *in vitro* and *in vivo* modes.

1.7 Plan of work

The synthesis of all compounds has been described in the presented research work through different schemes.

Scheme-1: Synthesis of 5-substitued-1,3,4-oxadiazol-2-thiols (**5a & 5b**) was carried out from para substituted phenols (**1a & 1b**), acetone, chloroform and NaOH in consecutive four steps.

Scheme-2: Synthesis of aromatic *N*-substituted 2-bromoacetamide **(7a-7y)** was carried out by reacting different substituted anilines **(6a-6y)** with 2-bromoacetyl bromide.

Scheme-3: Synthesis of N-substituted 5-{[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazole-2ylthio} acetamides **(8-30)** was carried out by reacting *N*-substituted 2-bromoacetamide **(7a-7m, 7o-7s & 7u-7y)** with **5a**.

Scheme-4: Synthesis of *N*-substituted 5-{[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazole-2ylthio} acetamides **(31-50)** was carried out by the same way as scheme-3 but this time the *N*-substituted 2-bromoacetamide **(7a-7l & 7n-7u)** were reacted with **5b**.

After the successful completion of synthetic portion and their characterization fibric acids derivatives were evaluated for their anti-thrombotic (*in vitro* and *in vivo*) and anti-inflammatory activity (*in vitro* and *in vivo*). Molecular docking study was performed to check the FXa and COX-2 inhibitory potential of the compounds. Density functional theory (DFT) computed molecular properties of compounds were also calculated.

CHAPTER 2
LITERATURE REVIEW

A selected literature review for fibrates, 1,3,4-oxadiazole and acetamides is explicated here expressing their biological potential and synthetic schemes at some instants. Otherwise a list of references has been listed in introduction section to emphasize their importance.

2.1 Fibrates

Salama *et al.* have developed two methods for fenofibrate determination through measurement of its degradation product. One method involves algorithm bivariate calibration derivative method. The other method involves the use of High Performance Liquid Chromatography. The results of both methods were compared and were found in good agreement [131].

Haubenwallner *et al.* have tested gemfibrozil, fenofibrate, clofibrate and bezafibrate to check out their role in the reduction of plasma apoC-III levels and hepatic apoC-III mRNA. The *in vivo* study was conducted on rats. Plasma triglyceride levels were strongly reduced by gemfibrozil, moderately by fenofibrate & bezafibratein and not affected by clofibrate. Thus the similar pattern was observed by apoC-III mRNA and plasma protein levels. The plasma apoE and plasma apoC-II & apoC-III ratio was also found to be affected by plasma triglyceride levels. This lowering of plasma triglycerides was due to hepatic apoC-III reduction [132].

Sashidhara *et al.* have introduced fibrates bearing indole moiety and also provided results for their effect as antiobesity and hypolipidemic. The two compounds among the whole series presented notable antidyslipidemic activity performed through Triton model. The structures of these compounds are given in Figure-2.1. These compounds were confirmed as hypolipidemic and antiobesity agents by decrease in weight with no effect on feed, decrease in steatosis in comparison of fenofibrate, increase in I^{131}-low density lipoproteins catabolism and increase in level of lecithin cholesterol acyl-transferase enzyme [133].

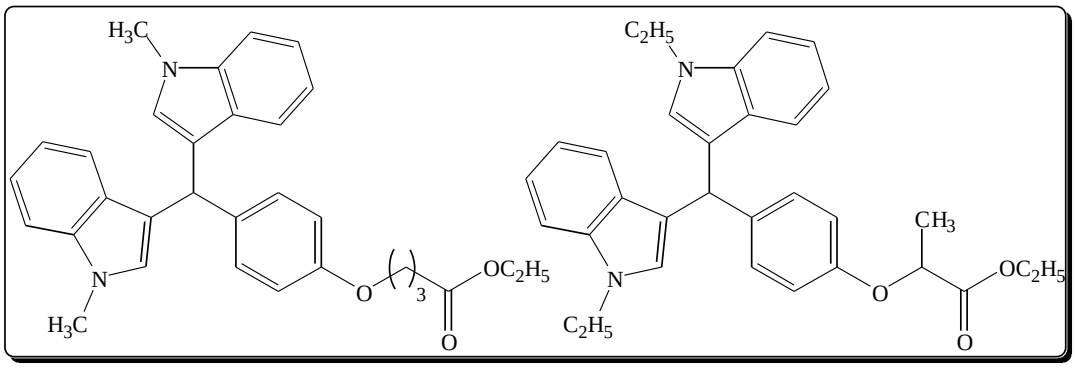


Figure-2.1 Structures of active hypolipidemic and antiobesity agents

Pinelli *et al.* have inaugurated some new ligands for peroxisome proliferator-activated receptors (PPARs) as alpha and gamma ones. Some chiral fibrates were introduced along with their optical isomers. Cell-based assays were used to testify these compounds. The stereochemistry greatly affected the results. The protease protection experiments and computational studies well supported the results. The peroxisome proliferator-activated receptors have a deep relation with homeostasis of glucose and lipid which is further related to diseases like diabetes, obesity and cardiovascular ones. Fibrates are known to treat hyperlipidemia and glitazones to treat insulin resistance [134].

Lalloyer and Staels have discussed the different peroxisome proliferator–activated receptors, their discovery and mechanism of action. Fibrates have an important role against dyslipidemia and type 2 diabetes [135].

Perrone *et al.* have synthesized analogues of clofibrate, that is, ethyl 2-(4-chlorophenoxy)-3-hydroxyalkanoates and ethyl 2-(4-chlorophenoxy)-3-oxoalkanoates, from 3-oxoalkanoates. The peroxisome proliferator–activated receptors activation was much prominent for clofibrate than its analogues [136].

Steiner has presented a review on the medicinal applications of fibrates and statins. These agents have been evaluated for the lipoprotein abnormalities, pleotropic and non-lipid effects regarding antiatherogenic activity [137].

Hong *et al.* have explained defective autophagy in batten disease (BD) lymphoblast cells, depolarization of mitochondrial membrane and apoptosis for gemfibrozil, bezafibrate and fenofibrate. The genetic disorder “juvenile neuronal ceroid lipofuscinosis” or “batten disease” is known to cause early death, cognitive decline, seizures and blindness. BD pathogenesis is deeply affected by enhanced apoptosis, disrupted autophagy, endoplasmic reticulum (ER) stress and mitochondrial oxidative stress. Fibrate treatment increased normal lymphoblast cells level and also depressed the process of mitochondrial membrane depolarization in BD lymphoblast cells [138].

Schelleman *et al.* have examined hypoglycaemia after induction of glipizide or glyburide in different persons and enzyme inhibition for cytochrome P450 (CYP) (*in vitro*) using glipizide, fenofibrate and statins. Among these only fenofibrate inhibited CYP2C19

potently. The combine use of glyburide with gemfibrozil or fenofibrate presented high ratio of hypoglycaemia [139].

2.2 1,3,4-Oxadiazole derivatives

Nagaraj *et al.* have inaugurated derivatives of 1,3,4-oxadiazole and listed their bioactivity results and supported their therapeutic applications. The derivatives inhibiting schistosomiasis growth were found to possess no danger for humans [9].

Khiati *et al.* have synthesized a list of derivatives bearing 1,3,4-triazole and 1,3,4-oxadiazole from L-tartaric acid. Furthermore, all the resulting molecules were subjected to screening against microbes and depicted substantial results [10].

Rashid *et al.* have synthesized anticancer agents bearing heterocyclic benzimidazole and 1,3,4-oxadiazole. These compounds were prepared from 2-aminoaniline [11].

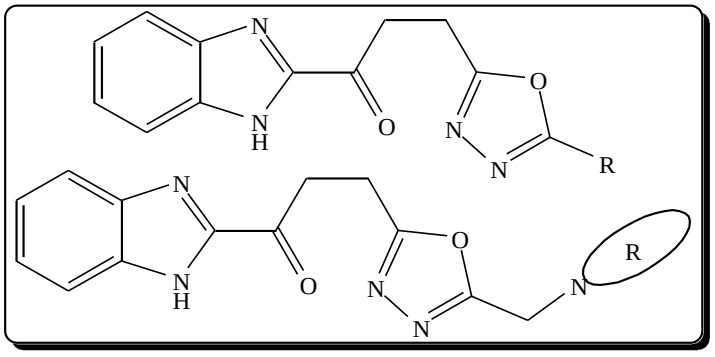


Figure-2.2 Heterocyclic benzimidazole and 1,3,4-oxadiazole derivatives

Rani *et al.* have synthesized different antibacterial agents using isonicotinohydrazide as starting compound. Isonicotinohydrazide was converted to different azomethine derivatives which were cyclized to 1,3,4-oxadiazole and oxoazetidine heterocyclic rings [12].

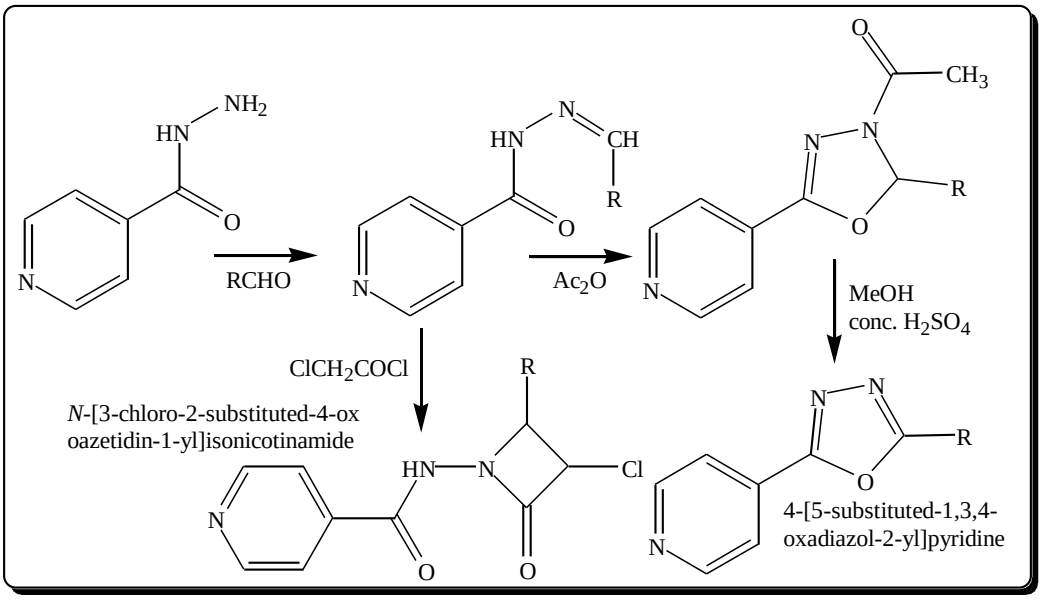


Figure-2.3 Synthesis of 1,3,4-oxadiazole and oxoazetidine derivatives from isonicotinohydrazide

Cui *et al*. have worked on antifungal activity of heterocyclic 1,3,4-oxadiazole derivatives. Different aromatic carbohydrazides were reacted with 5-arylfuran carboxylic acids to acquire the final antifungal agents [13].

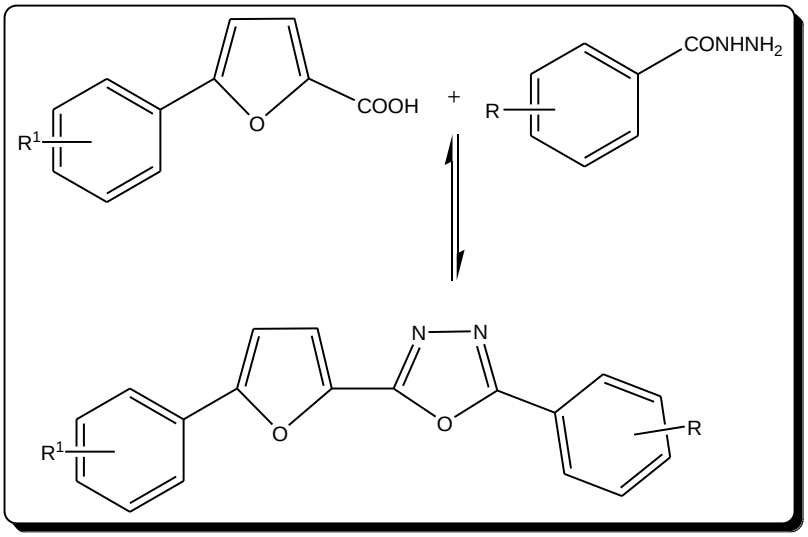


Figure-2.4 Synthesis of heterocyclic 1,3,4-oxadiazole and furan derivatives

Somani *et al.* have discussed different methods for the synthesis of 1,3,4-oxadiazole in a review [46]. Three selected and the mostly employed methods are given in Figure-2.5.

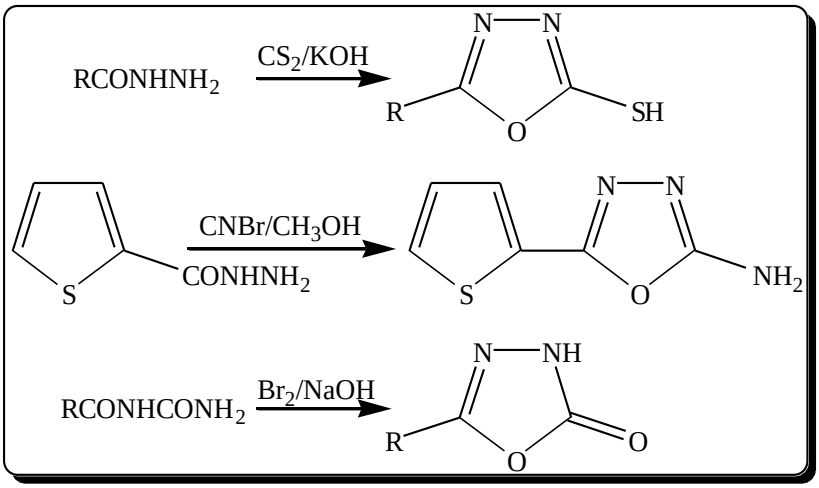


Figure-2.5 Cyclization to 1,3,4-oxadiazole by CS_2/KOH, CNBr/CH_3OH and Br_2/NaOH

Andrews and Ahmed have converted different thiosemicarbazides into five member heterocyclic compounds including 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,3,4-triazole [140].

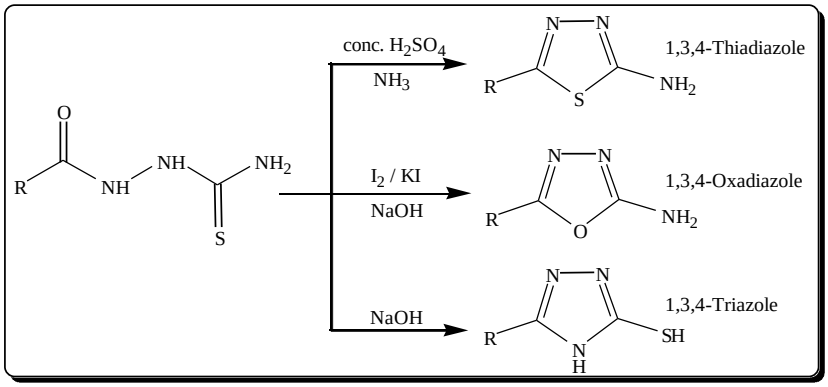


Figure-2.6 Conversion of thiosemicarbazide into five member heterocycles

Ghani *et al.* have introduced anti-tyrosinase agents in the form of 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole. The substitution on these rings resulted into enhancement in this enzyme inhibition activity. Furthermore, these heterocyclic cores were known to possess similarity to active site of the mentioned enzyme [141].

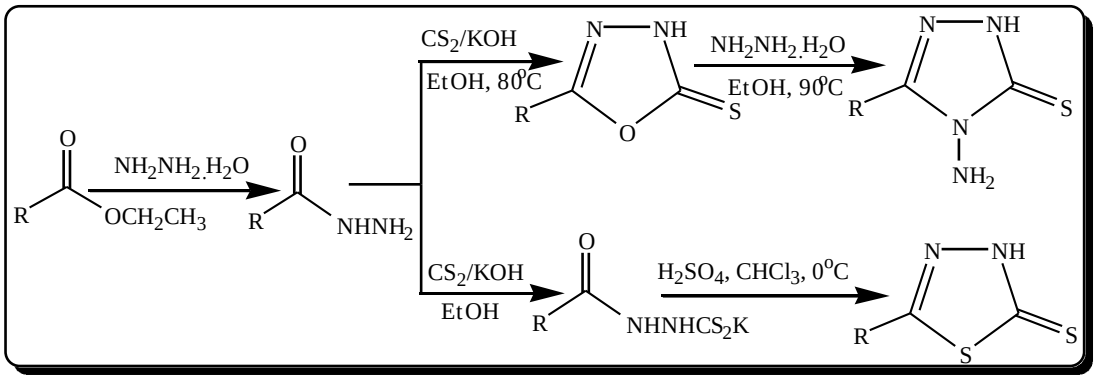


Figure-2.7 Anti-tyrosinase agents bearing 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole.

Gilani *et al*. have determined ulcerogenic, lipid peroxidation, anti-inflammatory, and analgesic activities for 1,2,4-triazole, 1,3,4-oxadiazole and 1,3,4-thiadiazoles compounds derived from isoniazid [142].

Bala *et al.* have studied physicochemical properties of substituted 1,3,4-oxadiazole derivatives and rendered them potent antibacterial agents. The different standard drugs were utilized as reference. Antibacterial activity was evaluated *in vitro* [143].

Abdelhafez *et al*. have studied monoamine oxidase (MAO) A and B inhibition for the thiazolidinones, thiadiazoles, triazoles and oxadiazoles derivatives bearing benzo-2-pyrone moiety. The *in vitro* inhibition analysis was reported in comparison of reference drugs and the series of compounds remained potent for the considered enzyme inhibition [144].

Rania *et al.* have introduced a series of antibacterial agents incorporating azomethine, isonicotinamide and 1,3,4-oxadiazole. The compounds were found to be potent inhibitors of *P. aeruginosa*, *E. coli*, *B. subtilus* and *S. aureus*. Ampicillinwas used as reference standard [145].

Aziz-ur-Rehman *et al.* have designed 5-benzyl-1,3,4-oxadiazole-2-thiol synthesis from phenylacetic acid through a series of steps. The list of compounds bearing the heterocyclic core was found to be potent inhibitors of antibacterial agents and their further use as drug was also supported through evaluation of cytotoxicity under the heading of hemolytic activity [146].

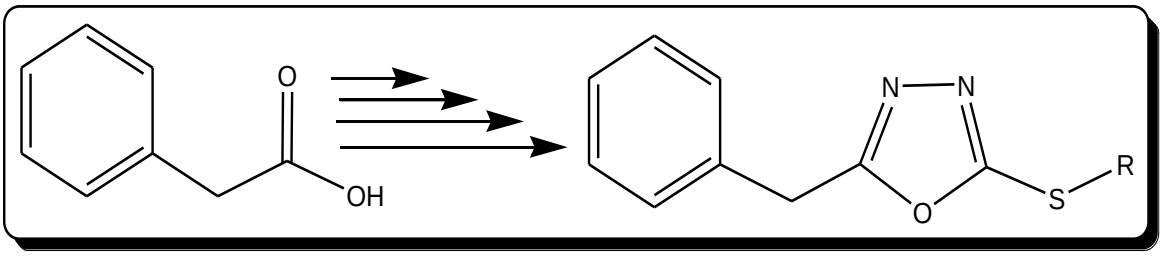


Figure-2.8 Synthesis of 1,3,4-oxadiazole derivatives from phenylacetic acid

Cao *et al.* have evaluated antifeedant potential for 20 molecules incorporating pyridazinone and oxadiazole moieties. Both of heterocyclic rings were supposed to boost up the bioactivity and the results well supported the aim of study [147].

Bhandari *et al*. have presented the scheme of synthesis for different derivatives of phenacyl 1,3,4-oxadiazoles bearing azomethine using diclofenac acid as starting compound. The histopathalogy, ulcerogenicity, analgesic and anti-inflammatory activities were listed with notable results [148].

Chen *et al.* have depicted antifungal potential of a list of compounds related to 1,3,4-thiadiazole and 1,3,4-oxadiazole. X-ray diffraction, elemental analysis and spectral analysis were the source of structural corroboration. The growth of mycelia was also inhibited by these compounds [149].

Kumar *et al.* have converted biphenyl-4-yloxy acetic acid into 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole, the five member heterocyclic cores. The compounds were found to be valuable anti-ulcerogenic, analgesic and anti-inflammatory agents [150].

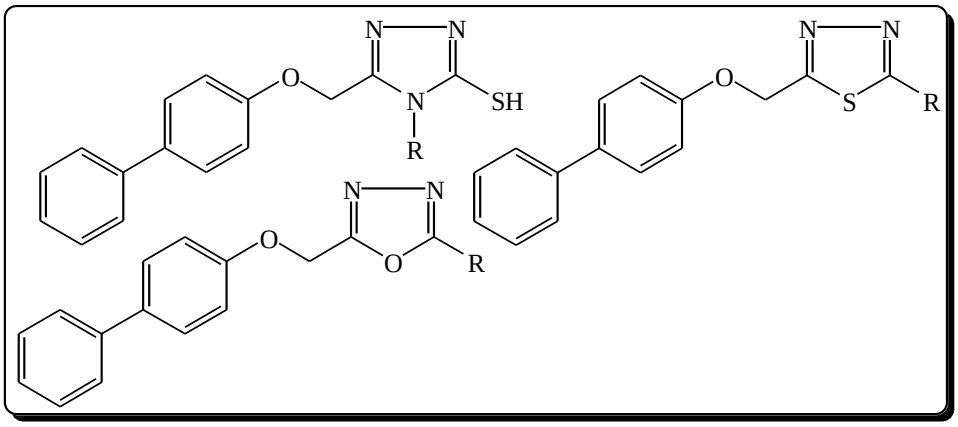


Figure-2.9 Five member heterocyclic cores from biphenyl-4-yloxy acetic acid

Ravi *et al.* have explained the antifungal potential of 1,3,4-oxadiazole derivatives with notable values. The two fungal strains taken into account for this activity were *F. moniliforme* and *A. alternata* [151].

Hasan *et al.* have introduced 2,5-substituted-1,3,4-oxadiazole and 3,4,5-substituted 1,2,4-triazole derivatives from carboxylic acids as precursors and have reported potent antifungal potency for them with reference of terbinafine [152].

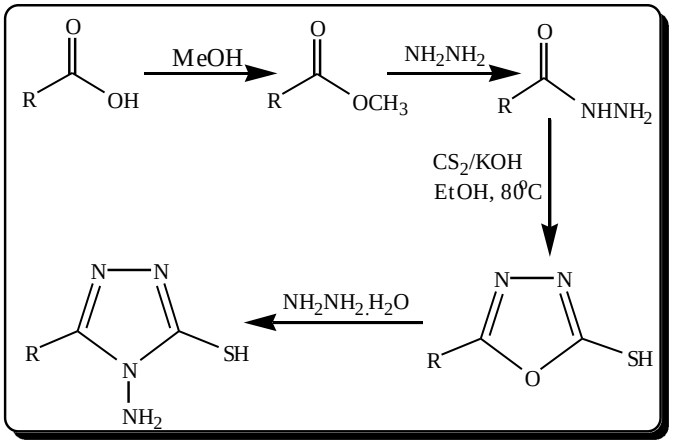


Figure-2.10 Carboxylic acids into 1,3,4-oxadiazoles and 1,2,4-triazoles

Ahmed *et al*. have evaluated antimicrobial activity including antibacterial and antifungal activities for the compounds bearing two oxadiazole cores in symmetry [153].

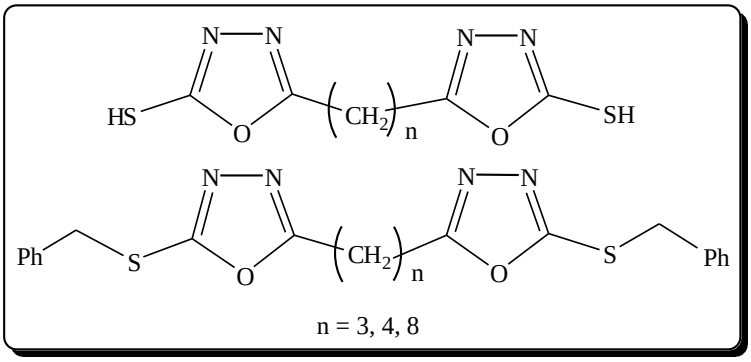


Figure-2.11 Bis-1,3,4-oxadiazoles as antimicrobial agents

Bhardwaj *et al.* have presented the synthesis of indole derivatives encompassing 1,3,4-oxadiazole. The structures of all the synthesized compounds are shown in Figure-2.12. Among these, three were effective antibacterial agents but also at a higher concentration with reference to standard. No one was found effective antifungal agent [154].

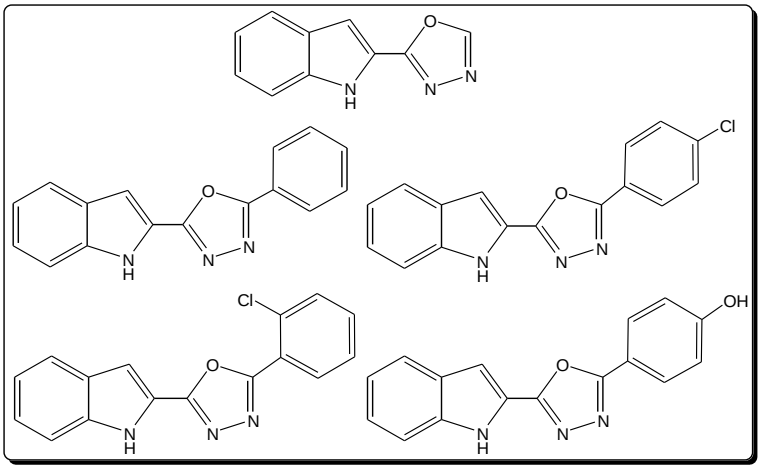


Figure-2.12 Synthesis of indole derivatives bearing 1,3,4-oxadiazole

Husain *et al.* have reported the synthesis of 1,3,4-oxadiazoles by the reaction of a carboxylic acid with a series of aromatic carbohydrazides in the presence of $POCl_3$ in good yields.. The synthesized compounds were subjected to antibacterial activity against *E. coli* and *S. aureus* [155].

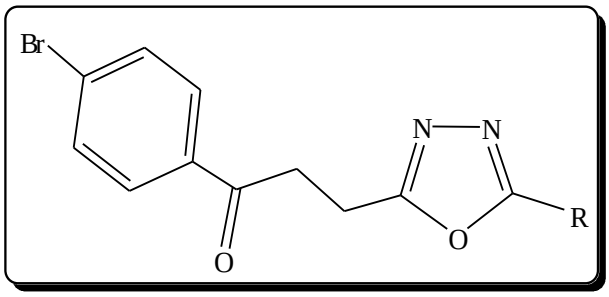


Figure-2.13 5-substituted-2-[2-(4-bromophenylcarbonyl)ethyl]-1,3,4-oxadiazole

Oliveira *et al.* have got published a review on various methods of 1,3,4-oxadiazole synthesis and the therapeutic potential of different synthesized compounds bearing 1,3,4-oxadiazole heterocyclic ring [156]. Two methods are given in Figure-2.14.

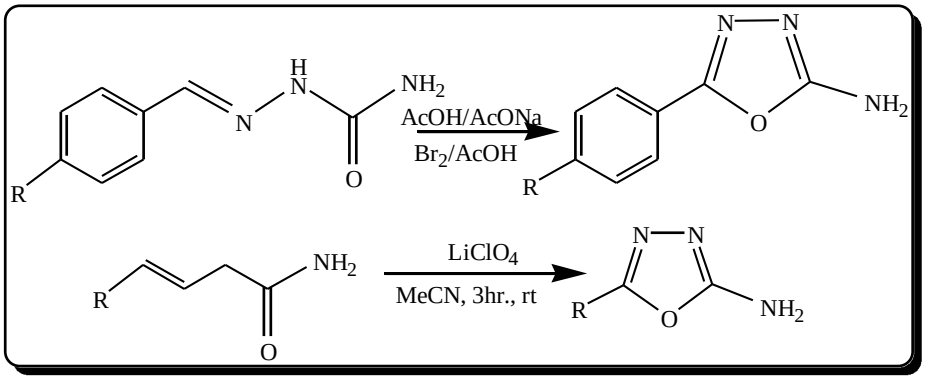


Figure-2.14 Two methods for 2-amino-1,3,4-oxadiazole derivatives

The structures of different bioactive molecules bearing 1,3,4-oxadiazole moiety are given in Figure-2.15.

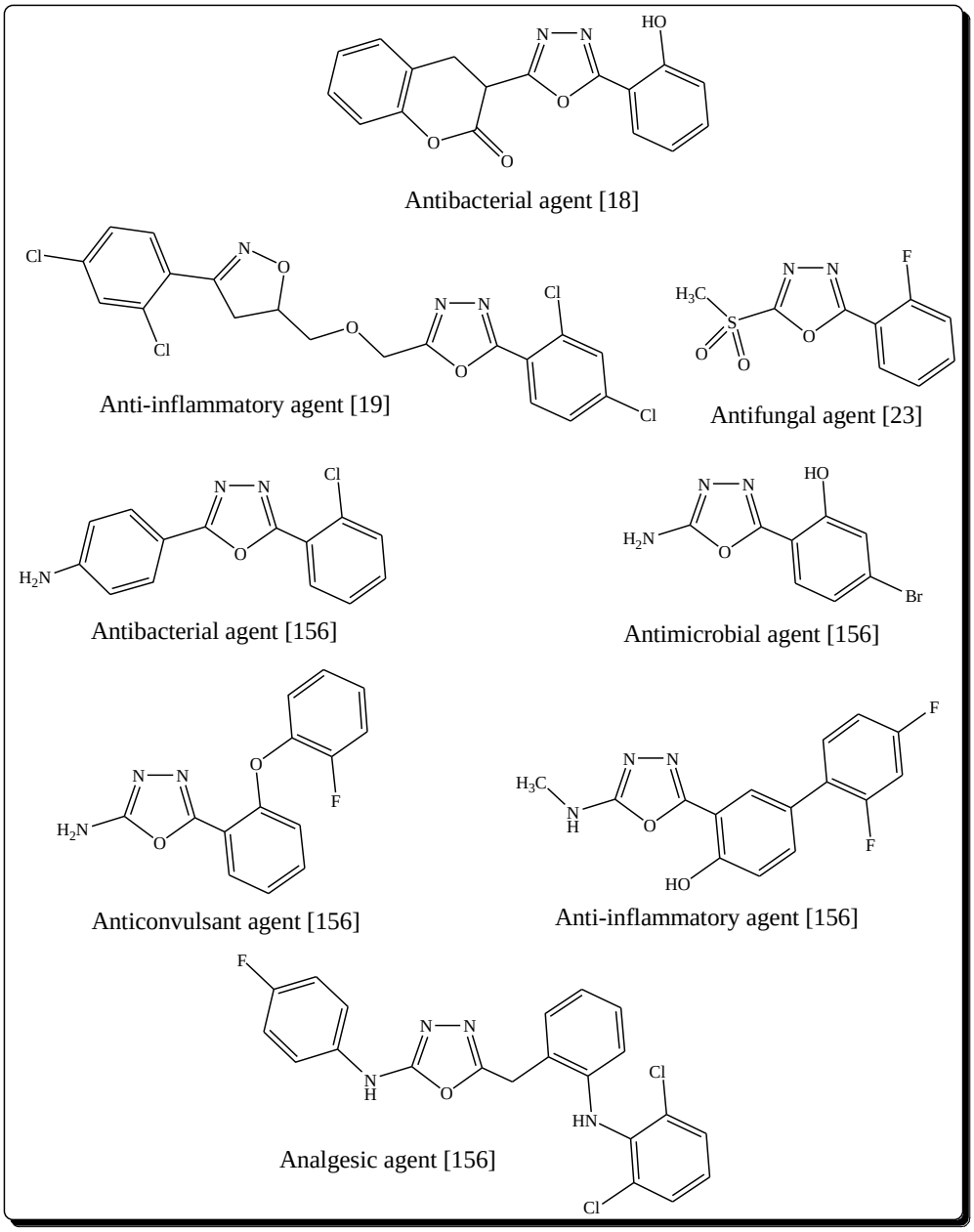


Figure-2.15 Different bioactive agents bearing 1,3,4-oxadiazole heterocyclic moiety

2.3 Acetamide derivatives

Khalid *et al.* have synthesized 1,3,4-oxadiazole derivatives by using different acetamides varying at nitrogen of acetamoyl moiety. Furthermore, sulfonamide and piperidine were also incorporated in the final structure of the molecules. The aim of study was to inaugurate new potent antibacterial agents and the attempt remained successful to a limited extent [76].

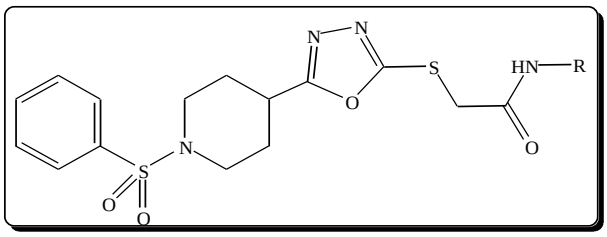


Figure-2.16 Acetamoyl bearing piperidine and 1,3,4-oxadiazole derivatives

Aziz-ur-Rehman *et al.* have demonstrated enzyme inhibition activity of compounds synthesized by encompassing 1,3,4-oxadiazole and acetamoyl functionalities. Here the fifth position of 1,3,4-oxadiazole was varied to acquire a list of derivatives. The results were found to be moderate ones against the inhibition of lipoxygenase, acetylcholinesterase and butyrylcholinesterase enzymes [77].

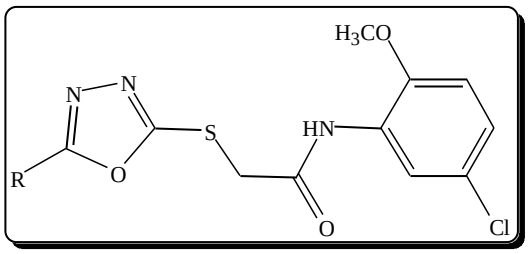


Figure-2.17 Acetamoyl bearing 1,3,4-oxadiazole derivatives

Chambers *et al.* have introduced antagonists of $P2X_7$ receptor in the form of acetamides bearing pyrazole moiety with varying group attached to nitrogen of acetamoyl moiety [157].

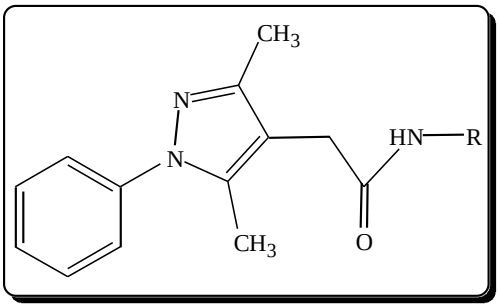


Figure-2.18 Pyrazole derivatives bearing acetamoyl moiety

Jagessar and Rampersaud have employed two different methods including pour plate method and Stokes Disc diffusion sensitivity method for antimicrobial potential of a series of amides. The antimicrobial potential included antifungal and antibacterial activities [79].

Larocca *et al.* have presented the synthesis of *N*-substituted bis-amides from 1,4-dicarboxylbenzene and 1,3-dicarboxylbenzene. The pharmacological evaluation resulted into no considerable results but yet the series remained less toxic [158].

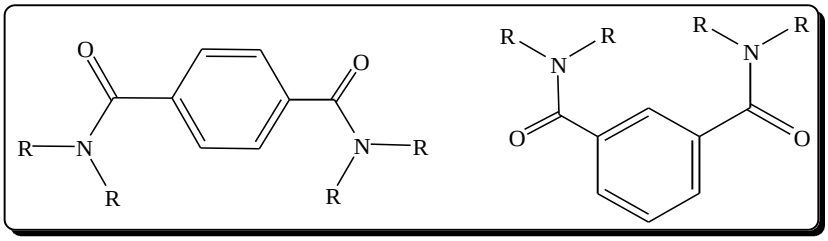


Figure-2.19 *N*-substituted bis-amides from 1,4-dicarboxylbenzene and 1,3-dicarboxylbenzene

Avalos-Alanis *et al*. have synthesized antimycobacterial agents and non-hepatotoxic ones as 2,4-disubstituted oxazolines and α,β-unsaturated amides [159].

Pachuta-Stec *et al*. have evaluated anticancer activity of different amides synthesized by the reaction of primary amines and 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid. In breast carcinoma cells, these compounds presented notable antiproliferative effect evaluated after *in vitro* analysis, they showed the least cytotoxicity [160].

Deng *et al*. have evaluated insecticidal activity of amide derivatives bearing pyrazole. Among the series of derivatives, only one was better against Mythimna Separata in comparison of tebufenozide, the reference. The molecular docking well confirmed the similarity in conformational analysis of active compound and the reference [161].

Tripathi *et al.* have designed a route to synthesize *N*-(4-substitutedphenyl)-2-[4-(substituted) benzylidene]hydrazine carbothioamides. The synthesized compounds were screening for neurotoxicity and anticonvulsant activity. The docking studies confirmed notable binding with epilepsy targets. In spite of this, the anticonvulsant activity mechanism requires to be uncovered [162].

Obniska *et al.* have synthesized 3-methyl-3-phenyl-2,5-dioxo-pyrrolidin-1-ylacetamides and hav listed the results of their neurological toxicity, anticonvulsant, analgesic and antiepileptic activities. Furthermore, the mutagenic and antimutagenic effects have also been provided [163].

The structures of different bioactive molecules bearing acetamide moiety are given in Figure-2.20.

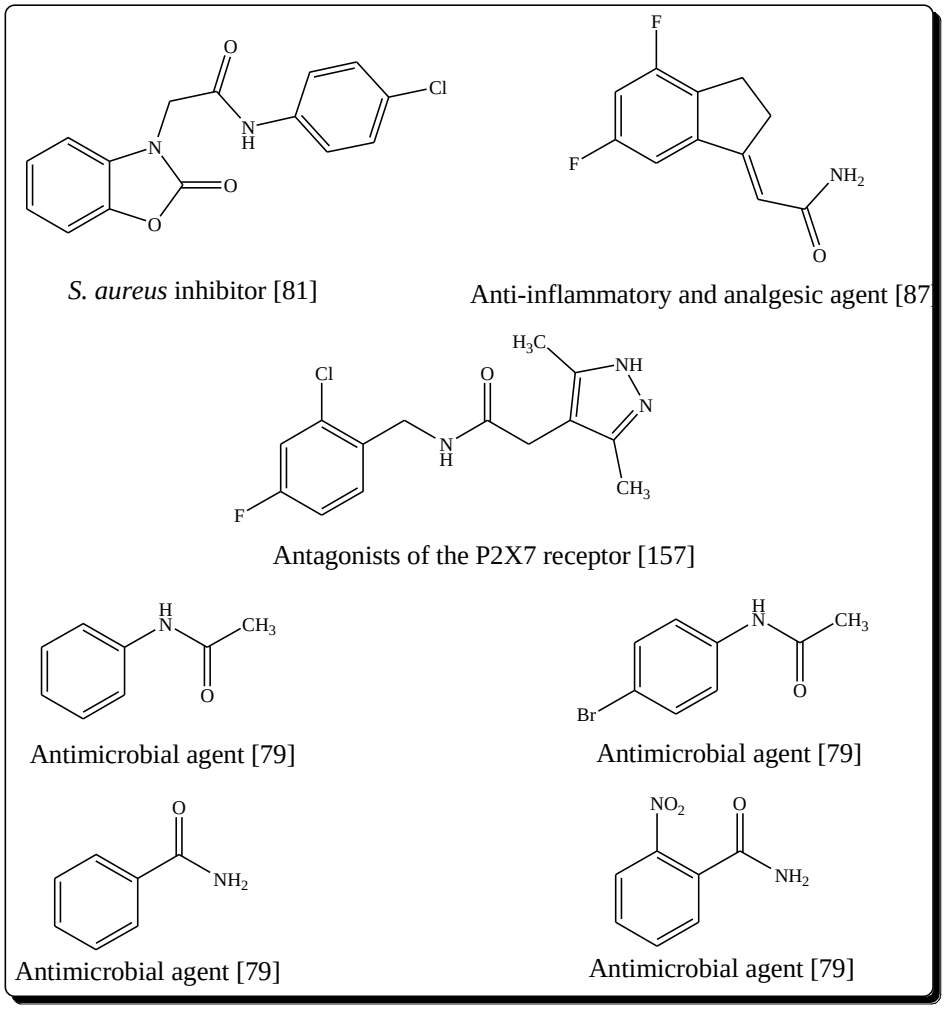


Figure-2.20 Different bioactive agents bearing amide moiety

CHAPTER 3
EXPERIMENTAL WORK

3.1 General

3.1.1 Reagents and Chemicals:

Chemicals and solvents were purchased from Sigma Aldrich and Alfa Aesar. They were pure enough that no further purification was required for these chemicals. Commercial available ethanol was dried by using "calcium oxide" and then distilled to get absolute ethanol. Thin layer chromatography (TLC) was carried out by using "Merck silica gel $60F_{254}$ plates".

3.1.2 Instruments:

By using open capillary tube method melting points were verified on Griffin and George melting point apparatus. Melting points were uncorrected. By using KBr discs, IR peaks were recorded on a Jasco-320-A spectrophotometer. ^{1}H-NMR signals were noted on AVANCE AV-300 MHz, AVANCE AV-400 MHz or AVANCE AV-500 MHz, while ^{13}C-NMR spectra were taken on a Bruker AVANCE 125 MHz spectrometer. The chemical shift values are mentioned in ppm unit. EIMS signals were recorded by utilizing "JEOL MS 600H-1".

3.1.3 Computational study:

Synthesized compounds and control ligands were docked with FXa (1NFY) and COX-2 (3LN1) by "*PatchDock* (http://bioinfo3d.cs.tau.ac.il/ PatchDock/)". *PatchDock* offers multiple solutions and the "solution 1" was selected as it surrounded the most crucial

residues as binding pocket for docking analyses assigned in crystal structure of target site. The docked structures were examined by using Discovery Studio 4.5 Visualizer and Chimera 1.9.

Selective compounds were subjected to computational calculations by using Gaussian 09 software [164] with Becke's three parameter hybrid exchange functionals [165] and Leee-Yange-Parr correlation functionals (B3LYP) [166,167]. The geometry of all the structures were optimized using B3LYP/6-31G** basis set. The Gauss view software package was used to visualize the computed structures including HOMO, LUMO and Molecular electrostatic potential (MEP) representations.

3.2 Synthetic work

3.2.1 General procedures, physical & spectral data:

In this section the general procedures are described for the synthesis of different organic compounds. Physical & spectral data of compounds is also furnished.

3.2.2 General procedure for the synthesis of Fibric acids (2a & 2b):

The acids **2a & 2b** were synthesized by refluxing a mixture of 4-chloro/bromo phenol **1a & 1b** (39 mmol), analytical grade acetone (645 mmol) and chloroform (53 mmol) using sodium hydroxide (187 mmol) as a base for four hours. On completion of reaction the excess of acetone was distilled off. The remaining viscous liquid was diluted with distilled water (50 mL), homogenized and cooled using an ice-bath. The mixture was then filtered and acidified with 50% HCl to congo red. Product separated as an oily layer which was solidified and

dried. Recrystallization was carried out by 30 % aquous ethanol. The products were achieved in remarkable yields [168].

3.1.3 General procedure for the synthesis of ethyl esters (3a & 3b):

The synthesized fibric acids **(2a & 2b,** 20 mmol **)** were converted into corresponding ethyl esters **(3a & 3b,** 20 mmol**)** by refluxing with absolute ethanol (30 mL) in the presence of conc. H_2SO_4 (0.05 mL) for 6 hours. Reaction completion was confirmed by TLC (silica; ethyl acetate and hexanes, 1:4). Reaction mixture was then poured in distilled water (50 mL). Chloroform (50 mL × 3) was used to extract the product. The combined chloroform layer was washed with saturated solution of Na_2CO_3 followed by water and dried over $MgSO_4$ .Viscous oily ester was collected by evaporating the chloroform.

3.2.4 General procedure for the synthesis of hydrazides (4a & 4b):

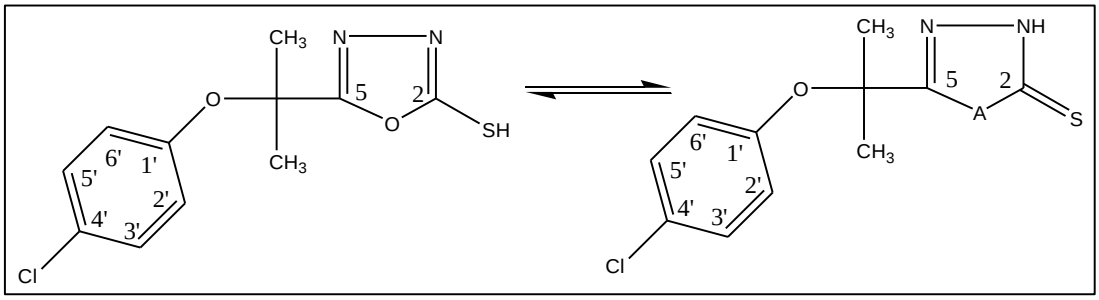
Esters **4a & 4b** (10 mmol) were dissolved in absolute ethanol (15 mL) and treated with hydrazine hydrate (80%, 3.0 mL). The reaction contents were refluxed for 4-5 hrs. Thin layer chromatography (silica; ethyl acetate and hexanes, 1:4) was used to check the completion of reaction. Excess of hydrazine hydrate was distilled off. Then the residue was treated with distilled water (100 mL) and precipitates were filtered, washed with water and recrystallized from 30% aqueous ethanol.

3.2.5 General procedure for the synthesis of 5-(2-aryloxypropane-2-yl)-1,3,4-Oxadiazol-2-thiols (5a & 5b):

To a solution of acid hydrazides (**4a & 4b** 20 mmol) in absolute ethanol (15 mL) was added carbon disulphide (1 mL, 20 mmol) followed by ethanolic potassium hydroxide (0.6 g, 10 mmol). The reaction contents were heated at refluxed for 5 hours with continuous stirring. By using TLC reaction coordinates were monitored after every hour. On completion of reaction, excess of ethanol was removed under reduced pressure. The remaining mixture was diluted using distilled water (200 mL). Then acidification with 4N HCl to pH 2-3 precipitated the product. Precipitates were then filtered washed with water and recrystallized using 30% aqueous ethanol [169].

3.2.5.1 5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazole-2-thiol (5a):

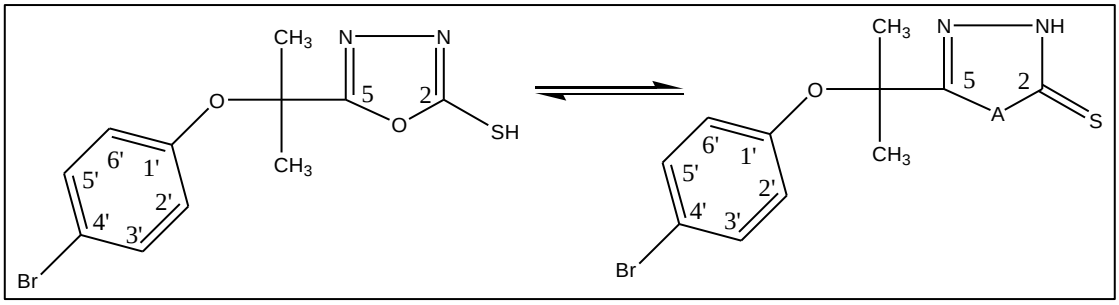
The following product was synthesized by reacting 2-(4-chlorophenoxy)-2-methylpropanehydrazide (4.58 g, 20 mmol) with carbon disulphide (1 mL, 20 mmol) and potassium hydroxide (0.6 g, 10 mmol).



Appearance:	Light yellow powder
Yield:	2.44 g (90 %)
Melting Point:	130-132 ^{o}C
FT-IR: υ (cm^{-1}):	2934 (C-H str.), 1637 (C=N str.), 1389 (C=C aromatic ring str.), 642 (C-S str.)
^{1}H NMR:	(DMSO), 500MHz): δ_H: 14.69 (s. 1H, NH), 7.36 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 6.84 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 1.71 (s, 3H, C***(CH$_3$)$_2$***).
^{13}C NMR:	(DMSO, 500MHz): δ_C: 178.55 (C-2), 164.36 (C-5), 153.15 (C-Í), 129.91 (C-3′ & C-5′), 128.72 (C-4′), 124.58 (C-2′ & C-6′), 75.88 (***C***(CH$_3$)$_2$), 25.12 (C***(CH$_3$)$_2$***).

3.2.5.2 5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol (5b):

The title compound was synthesized by reacting 2-(4-bromrophenoxy)-2-methylpropanehydrazide (5.54 g, 20 mmol) with carbon disulphide (1 mL, 20 mmol) and potassium hydroxide (0.6 g, 10 mmol).



Appearance:	Light yellow powder
Yield:	3.03 g (89 %)
Melting Point:	138-140 ^{o}C
FT-IR: υ (cm^{-1}):	2991 (C-H str.), 1609 (C=N str.), 1479 (C=C aromatic ring str.), 651 (C-S str.)
^{1}H NMR:	(DMSO, 500MHz): δ_H: 7.49 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 6.78 (d, *J* = 8 Hz, 2H, H-2′& H-6′), 1.67 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	(DMSO, 500MHz): δ_C : 183.31 (C-2), 169.11 (C-5), 158.38 (C-Í), 137.60 (C-3′& C-5′), 129.29 (C-2′& C-6′), 121.50 (C-4′), 80.58 (***C***$(CH_3)_2$), 29.89 (C***(CH₃)₂***).

3.2.6. General procedure for the synthesis of *N*-substituted-2-bromoacetamide (7a-7y):

Substituted anilines **(6a-6y,** 0.1 mmol**)** were taken in an iodine flask (100 mL) and sodium carbonate solution (10%, 10mL) was added to maintain pH 9. 2-Bromoacetyl bromide (0.1 mmol) was added to the above mixture and was shaken vigorously till precipitation occurred. Precipitates were then filtered, rinsed with distilled H_2O, dried and recrystallized from 30% aqueous ethanol. Purity of product was confirmed by TLC (silica; ethyl acetate and hexanes, 1:4) [170].

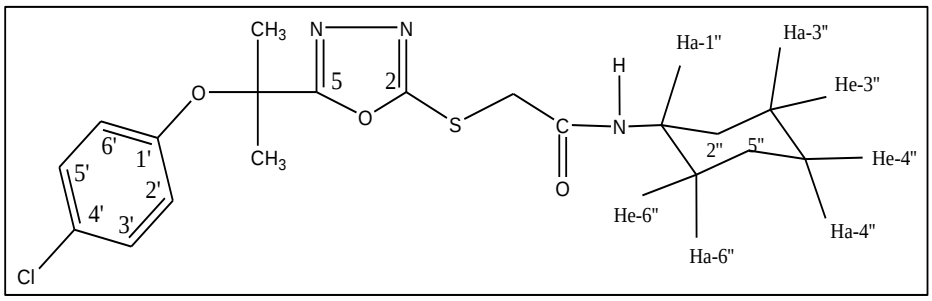
3.2.7 Synthesis of *N*-substituted 5-{[2-(4-chloro/bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides (8-50)

3.2.7.1 General procedure:

5-[2-(4-Chloro/bromophenoxy)propan-2-yl]-1,3,4-oxadiazole-2-thiol **(5a & 5b**,1 mmol**)** and lithium hydride (0.004 g, 2 mmol) were dissolved in DMF (15 mL) and submitted to ultrasound bath irradiations for 15 minutes at room temperature. Then *N*-substituted-2-bromoacetamide **(7a-7y,** 1 mmol) was added and the reaction mixture was further irradiated for 45-90 minutes at room temperature. The reaction was monitored by TLC (Ethylacetate : Hexanes, 1:4). After completion, the reaction mixture was poured on crushed ice. The precipitates obtained were filtered, washed with distilled water and dried to afford *N*-substituted 5-{[2-(4-chloro/bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides in remarkable yield. The product was recrystallized from 30% ethanol.

3.2.7.2 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-cyclohexylacetamide (8):

The title compound was achieved by reacting 0.219 g (1 mmol) of 2-bromo-*N*-cyclohexylacetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.20 hours.



Appearance: White powder

Yield: 0.364 g (89 %)

Melting Point: 94-96 ^{o}C

FT-IR: υ (cm^{-1}): 3178 (N-H str.), 2966 (C-H str.), 1653 (C=O amide str.), 1532 (C=C aromatic ring str.).

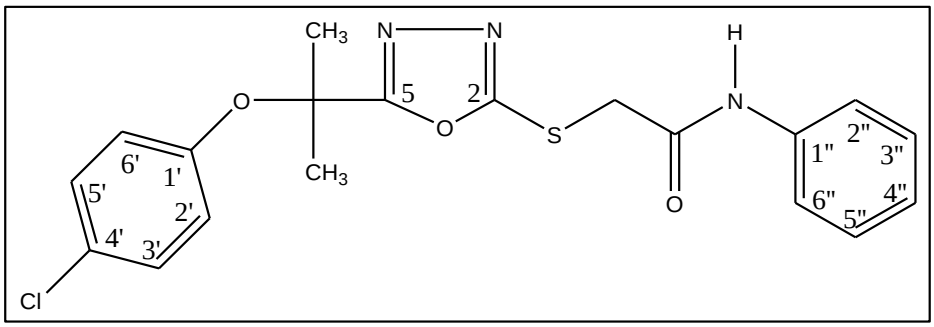
^{1}H NMR: (DMSO, 500MHz): δ_H: 8.19 (d, *J* = 7.5 Hz, 1H, NH), 7.31 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 6.76 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.06 (s, 2H, S-***CH₂***-CO), 3.55-3.50 (m,2H, Ha-1″), 1.71 (s, 8H, C***(CH₃)₂*** , He-2″& He-6″), 1.67-1.65 (m, 2H, He-3″& He-5″), 1.55-1.52 (m, 1H, He-4″), 1.29.1.21 (m, 2H, Ha-2″& Ha-6″), 1.18-1.11 (m, 3H, Ha-3″, Ha-4″& Ha-5″)

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.73 (C=O), 165.13 (C-2), 165.00 (C-5), 153.33 (C-Í), 129.77 (C-3′& C-5′), 128.54 (C-4′), 124.17 (C-2′& C-6′), 75.96 (***C***$(CH_3)_2$), 48.63 (C-1″), 36.44 (S-***CH₂***-CO), 32.67 (C-2″ & C-6″), 25.72 (C***(CH₃)₂***), 25.60 (C-4″), 24.85 (C-4″ &C-5″).

EIMS: m/z 410 [M^+, 2.7 %], 411 [M^++2, 0.6 %], 282 (100), 200 (97), 183 (47), 172 (51), 157 (12), 140 (11), 128 (24), 123 (71), 90 (16), 83 (29), 55 (33), 41 (17).

3.2.7.3 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-phenylacetamide (9):

The above stated compound was achieved by reacting 0.213 g (1 mmol) of 2-bromo-*N*-phenylacetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.



Appearance: White Shining fluffy amorphous flakes

Yield: 0.302 g (75 %)

Melting Point: 84-86 ^{o}C

FT-IR: υ (cm^{-1}): 3138 (N-H str.), 3000 (C-H str.), 1671 (C=O amide str.), 1552 (C=C aromatic ring str.).

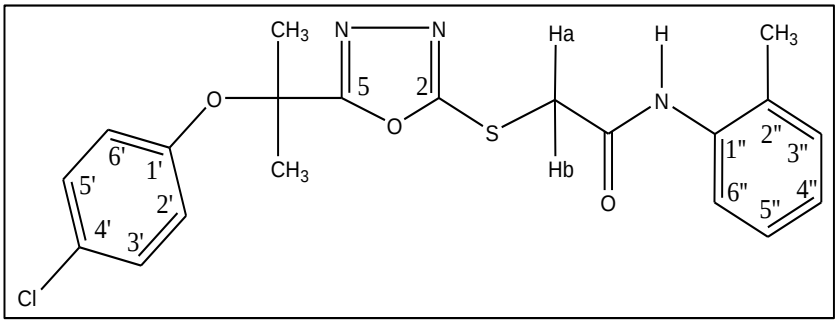
^{1}H NMR: (DMSO, 500MHz): δ_H: 10.42 (s, 1H, NH), 7.57 (d, *J* = 8 Hz, 2H, H-3′& H-5′), 7.33 (t, *J* = 7.8 Hz, 2H, H-2″& H-6″), 7.28 (d, *J* = 8.5 Hz, 2H, H- 3″&H-5″), 7.08 (t, *J* = 7.3 Hz, 1H, H-4″), 6.75 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 4.33 (s, 2H, S-***CH$_2$***-CO), 1.71 (s, 6H, C***(CH$_3$)$_2$***)

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.85 (C=O), 165.17 (C-2), 164.90 (C-5),153.29 (C-Í), 139.10 (C-1″), 129.93 (C-4′), 129.76 (C-3′& C-5′),129.32 (C-3″ & C-5″), 128.56 (C-4″), 124.18 (C-2″&C-6″), 119.62 (C-2′& C-6′), 75.99 (***C***$(CH_3)_2$), 37.32 (S-***CH$_2$***-CO), 25.70 (C***(CH$_3$)$_2$***).

EIMS: m/z 403 [M^+, 2 %], 405 [M^++2, 0.8 %], 276 (100), 248 (5), 202 (13), 183 (20), 166 (30), 128 (26), 123 (64), 106 (22), 93 (13), 77 (11), 65 (13), 55 (8), 41 (9).

3.2.7.4 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2-methylphenyl) acetamide (10):

The title compound was obtained by reacting 0.227 g (1 mmol) of 2-bromo-*N*-(2-methylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.20 hours.



Appearance: Light yellow powder

Yield: 0.362 g (87 %)

Melting Point: 140-142 ^{o}C

FT-IR: υ (cm^{-1}): 3339 (N-H str.), 2981 (C-H str.), 1667 (C=O amide str.), 1484 (C=C aromatic ring str.).

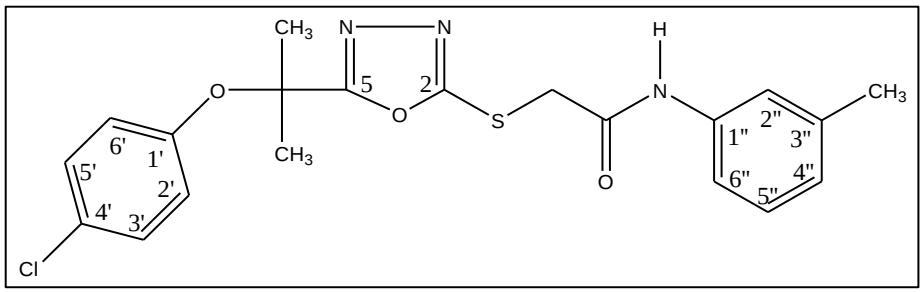
^{1}H NMR: (DMSO, 500MHz): δ_H: 10.48 (s, 1H, NH), 7.38-7.32 (m, 5H, H-3′, H-5′, H-4″, H-5″ & H-6″), 7.22 (d, *J* = 8 Hz, 1H, H-3″), 6.94 (d, *J* = 9 Hz, 2H, H- 2′ & H-6′), 4.26 (d, *J* = 17.5 Hz, 1H, Ha), 4.19 (d, *J* = 17.5 Hz, 1H, Hb), 2.18 (s, 3H, Ar-CH_3), 1.47 (s, 3H, C***H₃***), 1.48 (s, 3H, C***H₃***),

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.80 (C=O), 169.58 (C-2), 164.64 (C-5), 154.10 (C-1′),136.48 (C-1″), 134.57 (C-2″), 131.26 (C-5″), 129.71 (C-3″), 129.46 (C-3′ & C-5′), 129.15 (C- 4′), 127.31 (C-4″), 126.40 (C-6″), 121.91 (C-2′ & C-6′), 80.83 (***C***$(CH_3)_2$), 33.08 (S-***CH₂***-CO), 25.47 (C***H₃***), 25.44 (C***H₃***), 17.56 (Ar-CH_3).

EIMS: m/z 417 [M^+, 22 %], 419 [M^++2, 9 %], 290 (100), 272 (9), 262 (59), 248 (7), 216 (30), 190 (12), 177 (7), 169 (57), 149 (8), 128 (17), 111(11), 91 (17), 83 (9), 69 (17), 56 (5), 41 (13).

3.2.7.5 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(3-methylphenyl) acetamide (11):

The following product was synthesized by reacting 0.227 g (1 mmol) of 2-bromo-*N*-(3-methylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance: Lemon yellow powder

Yield: 0.325 g (78 %)

Melting Point: 71-73 ^{o}C

FT-IR: υ (cm^{-1}): 3155 (N-H str.), 2989 (C-H str.), 1655 (C=O amide str.), 1468 (C=C aromatic ring str.)

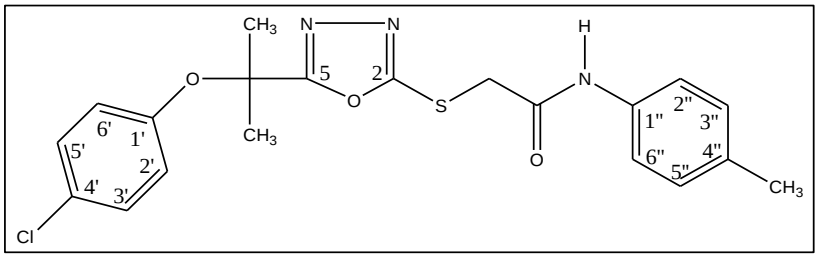
^{1}H NMR: ($CDCl_3$, 500 MHz): δ_H: 8.93 (s, 1H, NH),7.35 (s, 1H, H-2″),7.27 (d, *J* = 8.5 Hz, 1H, H-6″), 7.19 (t, *J* = 7.8 Hz, 1H, H-5″),7.11-7.10 (m, 2H, H-3′ & H-5′), 6.93 (d, *J* = 7.5 Hz, 1H, H-4″), 6.65-6.63 (m, 2H, H-2′ & H-6′), 3.97 (s. 2H, S-***CH$_2$***-CO **),** 2.32 (s, 3H, CH_3), 1.77 (s, 6H, C***(CH$_3$)$_2$***)

^{13}C NMR: (DMSO, 400 MHz):δ_C : 169.88 (C=O), 166.17 (C-2), 165.02 (C-5), 152.84 (C-1′), 139.04 (C-1″), 137.43 (C-3″), 129.41 (C-3′ & C-5′), 128.87 (C-5″), 125.61 (C-4′), 122.98 (C-2′, C-6′ & C-6″), 120.46 (C-4″), 116.99 (C - 2″), 75.55 (***C***$(CH_3)_2$), 36.23 (S-***CH$_2$***-CO), 25.86 (C***(CH$_3$)$_2$***), 21.44 (Ar-*CH$_3$*).

EIMS: m/z 417 [M^+, 12 %], 419 [M^++2, 4 %], 290 (100), 272 (4), 262 (18), 248 (3), 216 (25), 183 (35), 169 (24), 148 (12), 138 (35), 138 (25), 123 (71), 107 (16), 91 (17), 69 (10), 41 (7).

3.2.7.6 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(4-methylphenyl) acetamide (12):

The stated compound was achieved by reacting 0.227 g (1 mmol) of 2-bromo-*N*-(4-methylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.



Appearance: Light yellow powder

Yield: 0.350 g (84 %)

Melting Point: 68-70 ^{o}C

FT-IR: υ (cm^{-1}): 3313 (N-H str.), 2979 (C-H str.), 1676 (C=O amide str.), 1483 (C=C aromatic ring str.).

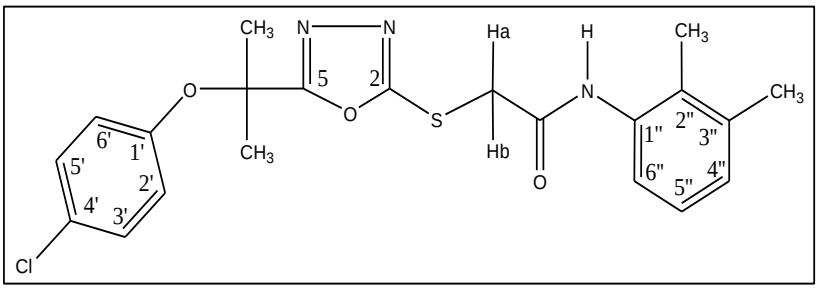
^{1}H NMR: (DMSO, 500MHz): δ_H: 10.33 (s, 1H, NH), 7.46 (d, *J* = 8 Hz, 2H, H-3′& H-5′), 7.27 (d, *J* = 9 Hz, 2H, H-2″ & H-6″), 7.12 (d, *J* = 8 Hz, 2H, H-3″& H-5″), 6.75 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.31 (s, 2H, S-***CH*$_2$**-CO), 2.25 (s, 3H, CH_3), 1.71 (s, 6H, C***(CH*$_3$*)*$_2$**).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.84 (C=O), 164.91 (C-2), 164.90 (C-5), 153.29 (C-1′), 136.60 (C-1″), 133.13 (C-4″), 129.75 (C-3′ & C-5′), 129.68 (C-3″ & C-5″), 128.57 (C- 4′), 124.18 (C-2″ & C-6″), 119.64 (C-2′ & C-6′), 75.98 (***C***$(CH_3)_2$), 37.31 (S-***CH*$_2$**-CO), 25.70 (C***(CH*$_3$*)*$_2$**), 20.91 (CH_3).

EIMS: m/z 417 [M^+, 5 %], 419 [M^++2, 2 %], 290 (100), 262 (5), 216 (7), 183 (24), 148 (10), 138 (22), 123 (55), 91 (8), 55 (5), 41 (5).

3.2.7.7 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-N-(2,3-dimethylphenyl) acetamide (13):

The above stated product was achieved by using 0.241 g (1 mmol) of 2-bromo-*N*-(2,3-dimethylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance: White powder

Yield: 0.371 g (86 %)

Melting Point: 186-188 ºC

FT-IR: υ (cm^{-1}): 3300 (N-H str.), 2952 (C-H str.), 1645 (C=O amide str.), 1478 (C=C aromatic ring str.).

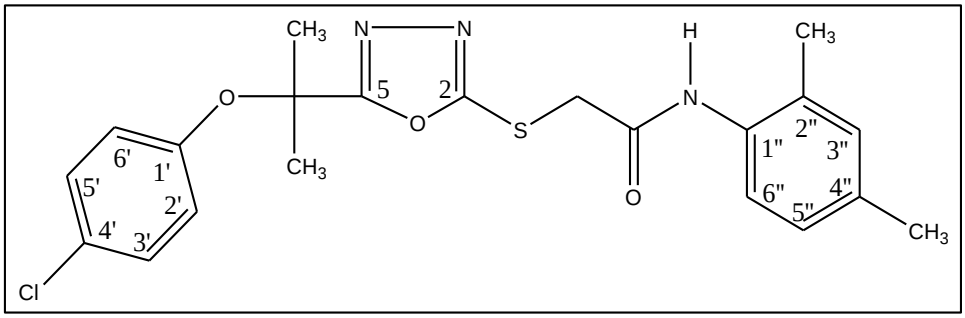
^{1}H NMR: (DMSO, 500MHz): δ_H: 10.45 (s, 1H, NH), 7.34 (d, *J* = 9 Hz, 2H, H-3′ & H-5′), 7.27 (d, *J* = 7.5 Hz, 1H, H-5″), 7.21 (t, *J* = 7.6 Hz, 1H, H-4″), 7.04 (d, *J* = 8 Hz, 1H, H-6″), 6.94 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.26 (d, *J* = 17.5 Hz, 1H, *Ha*), 4.18 (d, *J* = 7 Hz, 1H, *Hb*), 2.31 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.46, 1.47 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.87 (C=O), 169.49 (C-2), 164.72 (C-5), 154.07 (C-1′), 138.23 (C-1″), 134.94 (C-3″), 134.58 (C-2″), 130.93 (C-4′), 129.45 (C-3′& C-5′), 126.68 (C-5″), 126.60 (C-4″), 126.38 (C-6″), 121.90 (C-2′& C-6′), 80.82 (***C***$(CH_3)_2$), 33.03 (S-***CH₂***-CO), 25.45 (C***(CH₃)₂***), 20.36 (Ar-CH_3), 14.22 (Ar-CH_3)

EIMS: m/z 431 [M^+, 38 %], 433 [M^++2, 14 %], 304 (100), 286 (12), 276 (88), 261 (8), 230 (15), 219 (13), 204 (32), 191 (11), 169 (72), 152 (8), 145 (17), 128 (15), 105 (12), 77 (7), 69 (16), 56 (6), 41 (14).

3.2.7.8 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2,4-dimethylphenyl) acetamide (14):

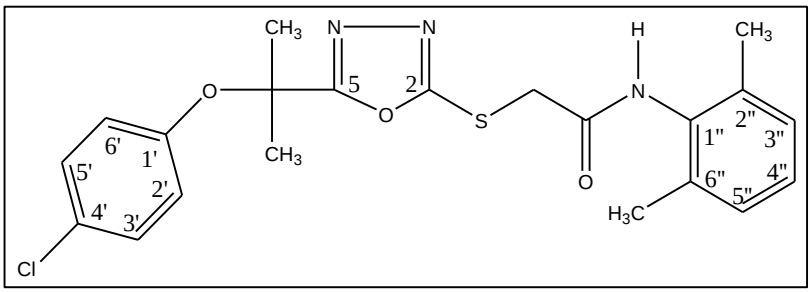
The title compound was achieved by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(2,4-dimethylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.20 hours.



Appearance:	Golden yellow powder
Yield:	0.349 g (81 %)
Melting Point:	78-80 ^{o}C
FT-IR: υ (cm^{-1}):	3358 (N-H str.), 2980 (C-H str.), 1680 (C=O amide str.), 1534 (C=C aromatic ring str.).
^{1}H NMR:	($CDCl_3$, 500MHz): δ_H: 8.59 (s, 1H, NH), 7.69 (d, *J* = 8 Hz, 1H, H-6″), 7.11-7.09 (m, 2H, H-3′ & H-5′), 6.98-6.97 (m, 2H, H-3″& H-5″), 6.65-6.63 (m, 2H, H-2′ & H-6′), 4.01 (s, 2H, S-***CH₂***-CO), 2.27 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 1.77 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	($CDCl_3$, 500MHz): δ_C : 169.93 (C=O), 166.13 (C-2), 165.32 (C-5), 152.87 (C-1′),135.19 (C-1″), 132.85 (C-4″), 131.24 (C-5″), 129.39 (C-3′ & C-5′), 129.17 (C-3″), 127.23(C-4′), 122.83 (C-2′ , C-6′ & C-2″), 122.66 (C-6″), 75.51 (***C***$(CH_3)_2$), 35.97 (S-***CH₂***-CO), 25.88 (C***(CH₃)₂***), 20.85 (CH_3), 17.85 (CH_3).
EIMS:	m/z 431 [M^+, 17 %], 433 [M^++2, 7 %], 304 (100), 286 (7), 276 (13), 262 (2), 230 (24), 204 (4), 194 (32), 183 (41), 162 (21), 152 (37), 128 (32), 123 (81), 83 (11), 55 (7), 41 (10).

3.2.7.9 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2,6-dimethylphenyl) acetamide (15):

The above stated product was achieved by using 0.241 g (1 mmol) of 2-bromo-*N*-(2,6-dimethylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.



Appearance: White powder

Yield: 0.383 g (89 %)

Melting Point: 98-100 ^{o}C

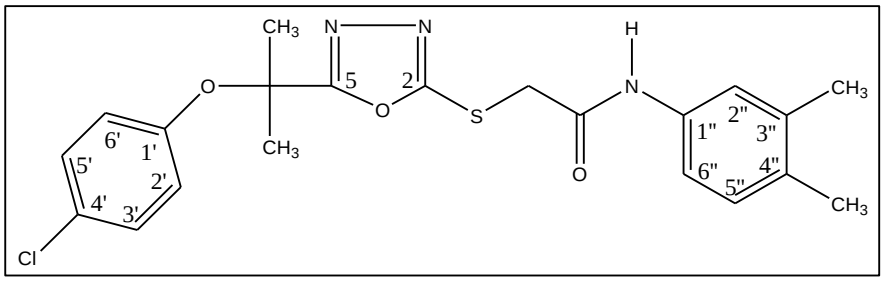
FT-IR: υ (cm^{-1}): 3330 (N-H str.), 2958 (C-H str.), 1661 (C=O amide str.), 1482 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.71 (s, 1H, NH), 7.26 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 7.09-7.06 (m, 3H, H-3″, H-4″ & H- 5″), 6.76 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.34 (s, 2H, S-***CH$_2$***-CO), 2.13 (s, 6H, Ar-2CH_3), 1.73 (s, 6H, C***(CH$_3$)$_2$***)

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.9 (C=O), 164.98 (C-2), 164.94 (C-5), 153.31 (C-1′), 135.60 (C-2″& C-6″), 135.01 (C-1″), 129.76 (C-3′ & C-5′), 128.54 (C-4′), 128.18 (C-3″ & C-5″), 127.14 (C-4″), 124.15 (C-2′ & C- 6′), 75.98 (***C***$(CH_3)_2$), 36.25 (S-***CH$_2$***-CO), 25.75 (C***(CH$_3$)$_2$*),** 18.47 (Ar-2CH_3).

3.2.7.10 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(3,4-dimethylphenyl) acetamide (16):

The desired product was obtained by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(3,4-dimethylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.10 hours.

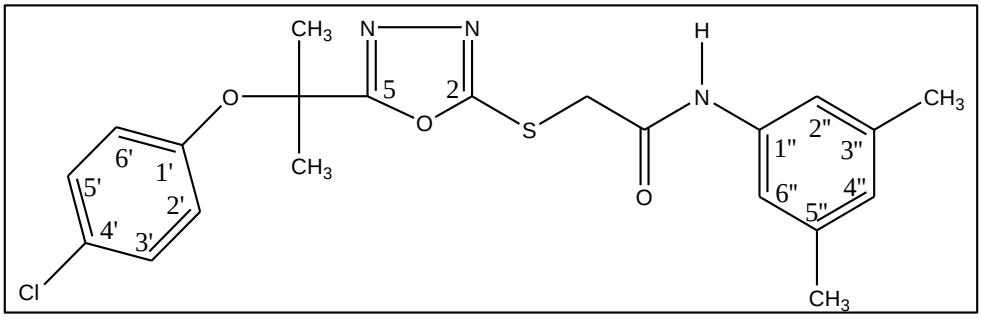


Appearance:	White powder
Yield:	0.392 g (91 %)
Melting Point:	80-82 ^{o}C

FT-IR: υ (cm^{-1}):	3357 (N-H str.), 2904 (C-H str.), 1640 (C=O amide str.), 1480 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 300MHz): δ_H: 10.22 (s, 1H, NH), 7.33 (s, 1H, H-2″),7.26-7.22 (m, 3H, H-3′ & H-5′ & H-6 ″), 7.04 (d, *J* = 8Hz, 1H, H-5″), 6.75-6.71 (m, 2H, H-2′ & H-6′), 4.27 (s, 2H, S-***CH₂***-CO), 2.16 (d, *J* = 7.5 Hz, 6H, Ar-2CH_3), 1.69 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	(DMSO, 300MHz): δ_C : 168.37 (C=O), 164.38 (C-2), 164.35 (C-5), 152.79 (C-1′), 136.42 (C-1″), 136.32 (C-3″), 131.47 (C-4″), 129.63 (C-5″), 129.24 (C-3′ & C-5′), 128.08 (C-4′), 123.74 (C-2′ & C-6′), 120.39 (C-2″), 116.72 (C-6″), 75.51 (***C***$(CH_3)_2$), 36.79 (S-***CH₂***-CO), 25.22(C***(CH₃)₂***), 19.75 (Ar-CH_3), 18.75 (Ar-CH_3)
EIMS:	m/z 431 [M^+, 11 %], 433 [M^++2, 5 %], 304 (100), 276 (9), 230 (12), 194 (23), 183 (42), 169 (14), 162 (20), 152 (37), 128 (22), 123 (84), 109 (10), 91 (9), 77 (10), 55 (6), 41 (9).

3.2.7.11 2-{5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(3,5-dimethylphenyl) acetamide (17):

The stated product was synthesized by using 0.241 g (1 mmol) of 2-bromo-*N*-(3,5-dimethylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance: Light yellow powder

Yield: 0.366 g (85 %)

Melting Point: 122-124 ºC

FT-IR: υ (cm^{-1}): 3299 (N-H str.), 2995 (C-H str.), 1618 (C=O amide str.), 1580 (C=C aromatic ring str.).

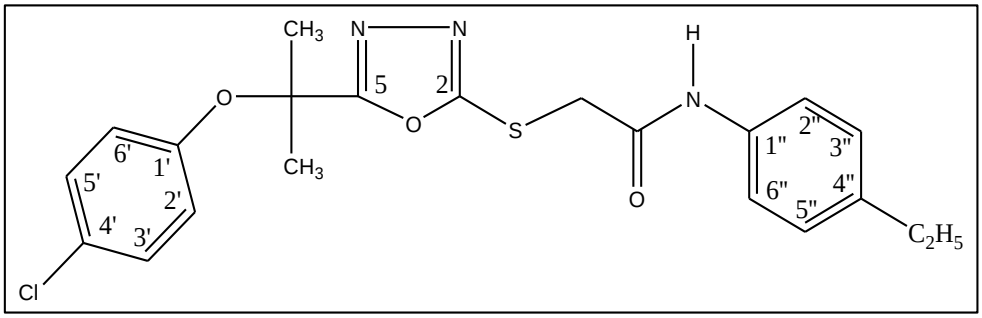
^{1}H NMR: (DMSO, 500MHz): δ_H: 10.27 (s, 1H, NH), 7.27 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.20 (s, 2H, H-2″ & H-6″), 6.75 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 6.72 (s, 1H, H-4″), 4.29 (s, 2H, S-***CH₂***-CO), 2.23 (s, 6H, Ar-2CH_3),1.70 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.3 (C=O), 165.03 (C-2), 164.90 (C-5), 153.27 (C-1′), 138.96 (C-1″), 138.29 (C-3″ & C-5″), 129.73 (C-3′ & C-5′), 128.59 (C-4′), 125.69 (C-4″), 124.27 (C-2′ & C-6′), 117.39 (C-2″ & C-6″), 76.00 (***C***$(CH_3)_2$), 37.31 (S-***CH₂***-CO),25.68 (C***(CH₃)₂***), 21.53 (Ar-2CH_3).

EIMS: m/z 431 [M^+, 11 %], 433 [M^++2, 5 %], 304 (100), 276 (31), 261 (4), 230 (21), 219 (10), 194 (26), 183 (46), 169 (33), 152 (44), 147 (20), 134 (37), 123 (95), 105 (22), 91(15), 77 (18),55 (8), 41 (16).

3.2.7.12 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-ethylphenyl)acetamide (18):

The above mentioned compound was prepared by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(4-ethylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.25 hours.



Appearance:	White powder
Yield:	0..220 g (51 %)
Melting Point:	88-90 ^{o}C

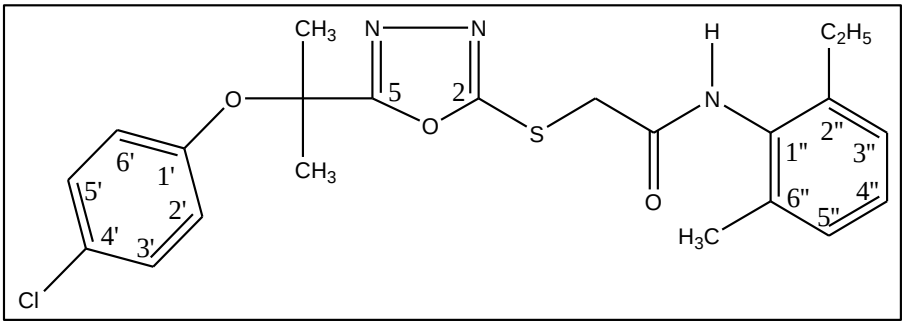
FT-IR: υ (cm^{-1}): 3350 (N-H str.), 2991 (C-H str.), 1650 (C=O amide str.), 1474 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.34 (s, 1H, NH), 7.48 (d, *J* = 8 Hz, 2H, H-3′& H-5′), 7.26 (d, *J* = 9 Hz, 2H, H-2″ & H-6″), 7.15 (d, *J* = 8 Hz, 2H, H-3″& H-5″), 6.75 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.31 (s, 2H, S-***CH₂***-CO), 2.53 (***CH₂***CH_3 merged in DMSO), 1.71 (s, 6H, C***(CH₃)₂***), 1.15 (t, *J* = 7.5 Hz, 3H, CH_2***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C: 168.82 (C=O), 164.90 (C-2), 153.27 (C-5), 139.58 (C-4″), 136.78 (C-1′), 129.74 (C-3′, C-4′ & C-5′), 128.55 (C-1″), 128.48 (C-3″ & C-5″), 124.18 (C-2′ & C-6′), 119.70 (C-2″ & C-6″), 75.98 (***C***$(CH_3)_2$), 37.28 (S-***CH₂***-CO), 28.06 (***CH₂***CH_3), 25.69 (C***(CH₃)₂***), 16.12 (CH_2***CH₃***).

3.2.7.13 2-(5-(2-(4-chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-ethyl-6-methylphenyl)acetamide (19):

The title compound was synthesized by reacting 0.255 g (1 mmol) 2-bromo-*N*-(2-ethyl-6-methylphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.



Appearance:	White crystals
Yield:	0.356 g (80 %)
Melting Point:	116-118 ^{o}C

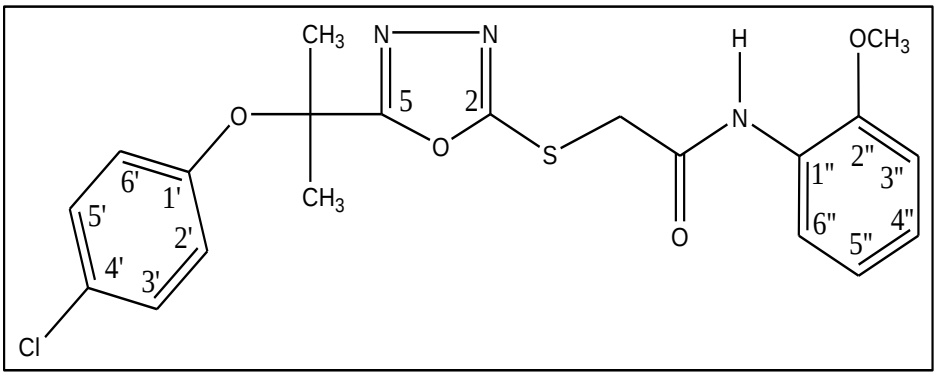
FT-IR: υ (cm^{-1}): 3232 (N-H str.), 2988 (C-H str.), 1654 (C=O amide str.), 1466 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.70 (s, 1H, NH), 7.27 (d, *J* = 6.5 Hz, 2H, H-3′& H-5′), 7.14-7.09 (m, 3H, H-3″, H-4″& H-5″), 6.77 (d, *J* = 6.5 Hz, 2H, H-2′& H-6′), 4.34 (s, 2H, S-***CH₂***-CO), 2.51 (2H, ***CH₂***-CH_3 merged in DMSO), 2.12 (s, 3H, CH_3), 1.73 (s, 6H, C***(CH₃)₂***), 1.06 (s, 3H, CH_2-***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.89 (C=O), 165.39 (C-2), 164.93 (C-5),153.32 (C-1′), 141.52 (C-1″), 136.04 (C-6″), 134.39 (C-3″), 129.75 (C-3′& C-5′), 128.52 (C-2″), 128.17 (C-4′), 127.51 (C-5″), 126.51 (C-4″), 124.15 (C-2′& C-6′), 75.98 (***C***$(CH_3)_2$), 36.23 (S-***CH₂***-CO), 25.76 (C***(CH₃)₂***), 24.68 (***CH₂***-CH_3), 18.49 (CH_3), 15.09 (CH_2-***CH₃***).

3.2.7.14 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-methoxyphenyl) acetamide (20):

Synthesis of above compound was carried out by reacting 0.244 g (1 mmol) of 2-bromo-*N*-(2-methoxyphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.25 hours.



Appearance:	White solid
Yield:	0..208 g (48 %)
Melting Point:	172-174 ºC

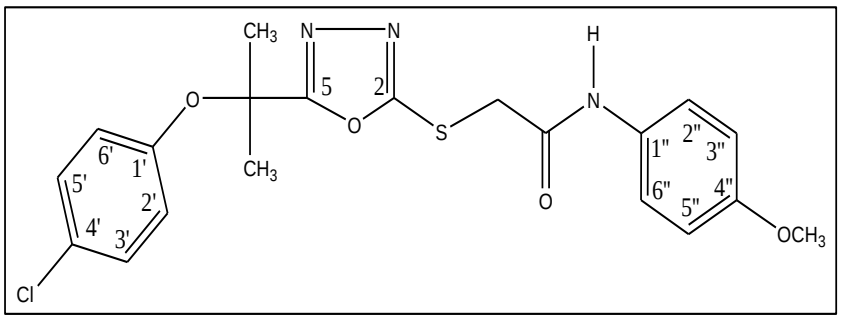
FT-IR: υ (cm^{-1}): 3318 (N-H str.), 2939 (C-H str.), 1616 (C=O amide str.), 1495 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.42 (s, 1H, NH), 7.46 (t, *J* = 7.8 Hz, 1H, H-6″), 7.33 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 7.24-7.19 (m, 2H, H-3″& H-5″), 7.07 (t, *J* = 7.5 Hz, 1H, H-4″), 6.93 (d, *J* = 8.5 Hz, 2H, H-2′& H-6′), 4.18 (s, 2H, S-***CH₂***-CO), 3.77 (s, 3H, CH_3), 1.46 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.47 (C=O), 169.48 (C-2), 155.22 (C-5), 154.20 (C-1′), 131.15 (C-2″), 130.42 (C-4′), 129.41 (C-3′ & C-5′), 126.23 (C-1″), 123.76 (C-4″), 121.76 (C-5″ & C-6″), 121.16 (C-2′ & C-6′), 113.22 (C-3″), 80.78 (***C***$(CH_3)_2$), 56.38 (OCH_3), 32.82 (S-***CH₂***-CO), 25.51, 25.45 (C***(CH₃)₂***).

3.2.7.15 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-methoxyphenyl) acetamide (21):

This title compound was synthesized by reacting 0.244 g (1 mmol) of 2-bromo-*N*-(4-methoxyphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance:	white solid
Yield:	0.334 g (77 %)
Melting Point:	83-85 ^{o}C

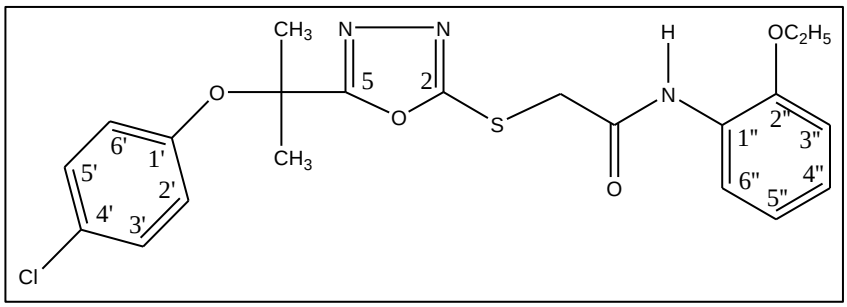
FT-IR: υ (cm^{-1}): 3229 (N-H str.), 2940 (C-H str.), 1650 (C=O amide str.), 1488 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.27 (s, 1H, NH), 7.47 (d, *J* = 9 Hz, 2H, H-2″& H-6″), 7.28 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 6.90 (d ,*J* = 9 Hz, 2H, H-2′& H-6′), 6.75 (d, *J* = 9 Hz, 2H, H- 3″ & H-5″), 4.28 (s, 2H, S-***CH$_2$***-CO), 3.73 (s, 3H, O***CH$_3$***), 1.71 (s, 6H, C***(CH$_3$)$_2$***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.84 (C=O), 164.91 (C-2), 164.63 (C-5), 155.99(C-4″),153.29 (C-1′), 132.22 (C-1″),129.76 (C-3′ & C-5′), 128.55 (C-4′), 124.19 (C-2″ & C-6″), 121.19 (C-2′ & C-6′), 114.42 (C-3″, C-5″) 75.99 (***C***$(CH_3)_2$), 55.64 (O***CH$_3$***), 37.20 (S-***CH$_2$***-CO), 25.70 (C***(CH$_3$)$_2$***).

3.2.7.16 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-ethoxyphenyl) acetamide (22):

The above compound was synthesized by reacting 0.258 g (1 mmol) of 2-bromo-*N*-(2-ethoxyphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance: white solid

Yield: 0.237 g (53 %)

Melting Point: 135-137 ^{o}C

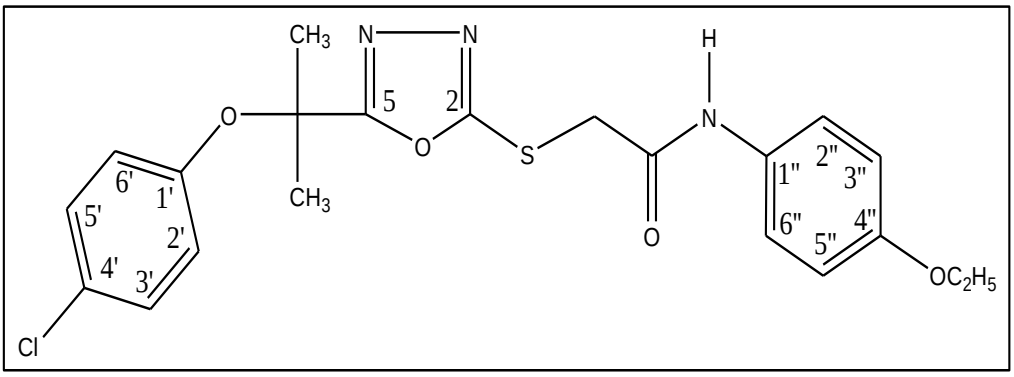
FT-IR: υ (cm^{-1}): 3320 (N-H str.), 2977 (C-H str.), 1614 (C=O amide str.), 1506 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.52 (s, 1H, NH), 7.98 (d, *J* = 7.5 Hz, 1H, H-6″), 7.24 (d, 2H, *J* = 8.5 Hz, H-3′& H-5′), 7.09-7.03 (m, 2H, H-3″ & H-5″), 6.90 (t, *J* = 7 Hz, 1H, H-4″), 6.75 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.41 (s, 2H, O***CH₂***CH_3), 4.11-4.07 (m, 2H, S-***CH₂***-CO), 1.72 (s, 6H, C***(CH₃)₂***), 1.36 (t, *J* = 7 Hz, 3H, OCH_2***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.89 (C=O), 165.41 (C-2), 164.89 (C-5), 153.27 (C-1′), 148.99 ((C-2″), 129.72 (C-3′ & C-5′), 128.57 (C-4′), 127.52 (C-1″), 125.19 (C-4″), 124.16 (C-2′ & C-6′), 121.88 (C- 5″), 120.69 (C-6″), 112.72 (C-3″), 75.98 (***C***$(CH_3)_2$), 64.46 (O***CH₂***CH_3), 37.18 (S-***CH₂***-CO), 25.69 (C***(CH₃)₂***)

3.2.7.17 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-ethoxyphenyl) acetamide (23):

The above compound was synthesized by using 0.258 g (1 mmol) of 2-bromo-*N*-(4-ethoxyphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance:	white solid
Yield:	0.219 g (49 %)
Melting Point:	103-106 ºC

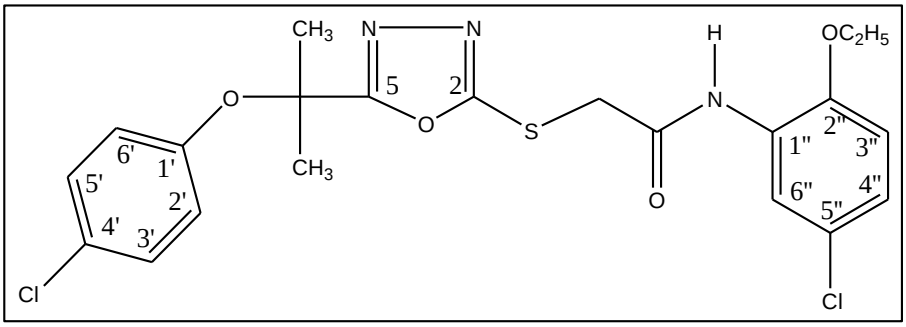
FT-IR: υ (cm^{-1}): 3297 (N-H str.), 2996 (C-H str.), 1664 (C=O amide str.), 1509 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.26 (s, 1H, NH), 7.46 (d, *J* = 9 Hz, 2H, H-2″& H-6″), 7.27 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 6.88 (d, *J* = 8.5 Hz, 2H, H- 3″, H-5″), 6.75 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 4.28 (s, 2H, O***CH₂***CH_3), 4.00-3.96 (m, 2H, S-***CH₂***-CO), 1.71 (s, 6H, C***(CH₃)₂***), 1.31 (t, *J* = 7 Hz, 3H, OCH_2***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.84 (C=O), 164.91 (C-2), 164.61 (C-5), 155.24 (C- 4″), 153.92 (C-1′), 132.11 (C-1″), 129.76 (C-3′ & C-5′), 128.55 (C-4′), 124.19 (C-2″& C-6″), 121.17 (C-2′ & C-6′), 114.93 (C-3″ & C- 5″), 75.99 (***C***$(CH_3)_2$), 63.56 (O***CH₂***CH_3), 37.20 (S-***CH₂***-CO), 25.70 (C***(CH₃)₂***), 15.14 (OCH_2***CH₃***),

3.2.7.18 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(5-chloro-2-methoxyphenyl)acetamide (24):

The title compound was obtained by reacting 0.288 g (1 mmol) of 2-bromo-*N*-(5-choloro-2-methoxyphenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance: white solid

Yield: 0.411 g (88 %)

Melting Point: 125-127 ^{o}C

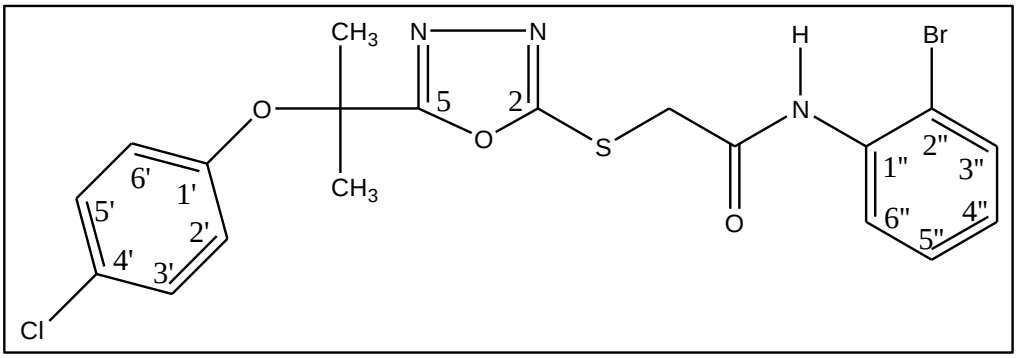
FT-IR: υ (cm^{-1}): 3290 (N-H str.), 2993 (C-H str.), 1641 (C=O amide str.), 1502 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.86 (s, 1H, NH), 8.12 (s, 1H, H-6″), 7.27 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.15-7.07 (m, 2H, H-3″ & H-4″), 6.74 (d, *J* = 9 Hz , 2H, H-2′ & H-6′), 4.41 (s, 2H, S-***CH₂***-CO), 3.85 (s, 3H, O***CH₃***), 1.71 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.88 (C=O), 166.11 (C-2), 164.80(C-5), 153.25 (C-1′), 148.40 ((C-2″), 129.71 (C-3′ & C-5′), 128.65 (C-4′), 128.61 (C-5″),124.35 (C-1″), 125.27 (C- 4″), 124.22 (C-2′ & C-6′), 120.82 (C-3″), 112.07 (C-6″), 75.99 (***C***$(CH_3)_2$), 56.58 (O***CH₃***), 37.03 (S-***CH₂***-CO), 25.67 (C***(CH₃)₂***).

3.2.7.19 2-(5-(2-(4-hlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-bromophenyl)acetamide (25):

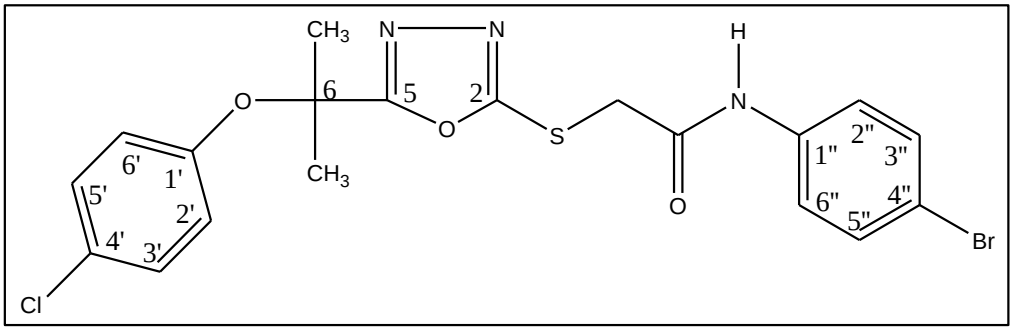
The title product was obtained by reacting 0.292 g (1 mmol) of 2-bromo-*N*-(2-bromophenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance:	Light yellow powder
Yield:	0.438 g (91 %)
Melting Point:	168-170 ^{o}C
FT-IR: υ (cm^{-1}):	3321 (N-H str.), 2979 (C-H str.), 1688 (C=O amide str.), 1481 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 500MHz): δ_H: 10.48 (s, 1H, NH), 7.83-7.81(m, 1H, H-6″), 7.58-7.54 (m, 1H, H-3″), 7.48-7.46 (m, 2H, H-3′, H-5′), 7.35-7.32 (m, 2H, H-4″ & H-5″), 6.95-6.92 (m, 2H, H-2′ & H-6′), 4.28-4.21 (m, 2H, S-***CH₂***-CO), 1.47 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	(DMSO, 500MHz): δ_C : 171.10 (C=O), 169.35 (C-2), 163.17 (C-5), 154.09 (C-1′), 134.63 (C-1″), 133.63 (C-3″), 131.74 (C-5″), 131.56 (C-4″), 129.43 (C-3′, C-4′ & C-5′), 126.33 (C-6″), 122.68 (C-2″), 121.82 (C-2′ & C-6′), 80.77 (***C***$(CH_3)_2$), 33.18 (S-***CH₂***-CO), 25.48 (C***CH₃***), 25.38 (C***CH₃***).

3.2.7.20 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-bromophenyl)acetamide (26):

The above mentioned compound was prepared by reacting 0.292 g (1 mmol) of 2-bromo-*N*-(4-bromophenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.25 hours.



Appearance: White solid

Yield: 0.241 g (50 %)

Melting Point: 118-120 ^{o}C

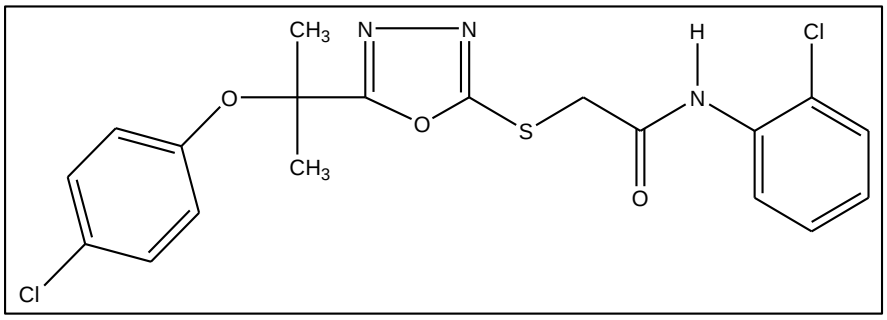
FT-IR: υ (cm^{-1}): 3369 (N-H str.), 2992 (C-H str.), 1668 (C=O amide str.), 1552 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.55 (s, 1H, NH), 7.56-7.50 (m, 4H, H-2″, H-6″, H-3″& H-5″), 7.27 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 6.74 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′),4.32 (s, 2H, S-***CH₂***-CO), 1.71(s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.86 (C=O), 165.39 (C-2), 164.81 (C-5), 153.26 (C-1′), 138.44 (C-1″), 132.15 (C-3″ & C-5″),129.75 (C-3′ & C-5′), 128.54 (C-4′), 124.13 (C-2″& C-6″), 121.54 (C-2′ & C-6′), 115.78 (C-4″), 75.97 (***C***$(CH_3)_2$), 37.26 (S-***CH₂***-CO), 25.69 (C***(CH₃)₂***).

3.2.7.21 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-chlorophenyl)acetamide (27):

The above mentioned compound was prepared by reacting 0.247 g (1 mmol) of 2-bromo-*N*-(2-chlorophenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance:	Light yellow solid
Yield:	0.356 g (74 %)
Melting Point:	134-136 ^{o}C

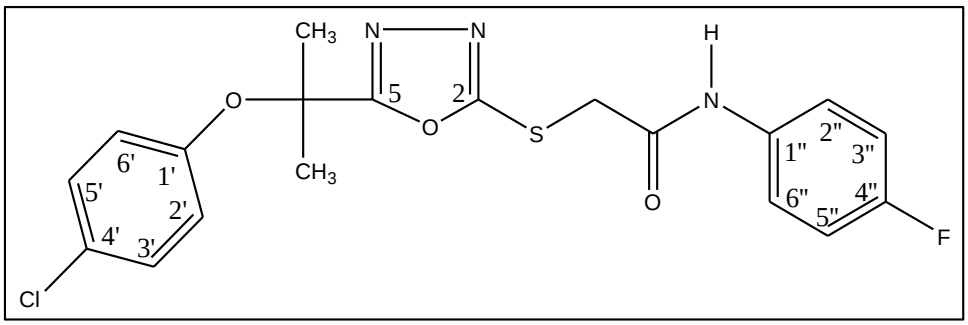
FT-IR: υ (cm^{-1}): 3364 (N-H str.), 2994 (C-H str.), 1697 (C=O amide str.), 1489 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.49 (s, 1H, NH), 7.68-7.67 (m, 1H, H-6″), 7.54-7.47 (m, 3H, H-3″, H-4″& H-5″), 7.34 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 6.94 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 4.30-4.21 (m, 2H, S-***CH₂***-CO), 1.47 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.22 (C=O), 169.40 (C-2), 163.27 (C-5), 154.10 (C-1′), 132.93 (C-1″), 132.19 (C-4′),131.59 (C-3″), 130.51 (C-5″), 129.44 (C-3′ & C-5′), 128.82 (C-2″), 126.35 (C-4″), 121.90 (C-6″), 121.84 (C-2′ & C-6′), 80.78 (***C***$(CH_3)_2$), 33.13(S-***CH₂***-CO), 25.48 (C***(CH₃)₂***).

3.2.7.22 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-flourophenyl)acetamide (28):

The title compound was synthesized by reacting 0.231 g (1 mmol) of 2-bromo-*N*-(4-flourophenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance: Light yellow solid

Yield: 0.206 g (49 %)

Melting Point: 70-72 ^{o}C

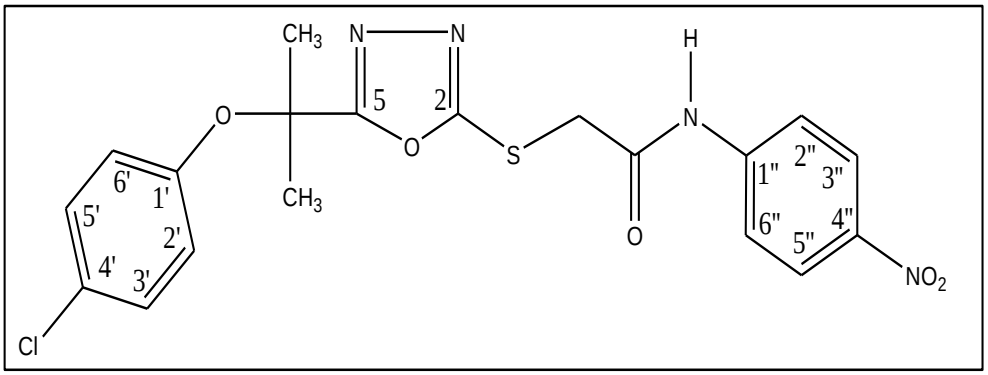
FT-IR: υ (cm^{-1}): 3385 (N-H str.), 2997 (C-H str.), 1667 (C=O amide str.), 1573 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.48 (s, 1H, NH), 7.60-7.57 (m, 2H, H-2″& H-6″), 7.27 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 7.17 (t, *J* = 8.5 Hz, 2H, H-3″& H-5″), 6.74 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 4.31 (s, 2H, S-***CH$_2$***-CO), 1.71 (s, 6H, C***(CH$_3$)$_2$***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.84 (C=O), 165.12 (C-2), 164.84 (C-5), 153.27 (C-4″), 135.48 (C-1′), 135.46 (C-1″), 129.75 (C-3′ & C-5′), 128.54 (C-4′),124.14 (C-2′ & C-6′), 121.45 (C-2″), 121.38 (C-6″), 116.00 (C-3″), 115.82 (C-5″), 75.97 (***C***$(CH_3)_2$), 37.18 (S-***CH$_2$***-CO), 25.69 (C***(CH$_3$)$_2$***).

3.2.7.23 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-N-(4-nitrophenyl)acetamide (29):

The above compound was synthesized by reacting 0.258 g (1 mmol) of 2-bromo-*N*-(4-nitrophenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance: Yellow powder

Yield: 0.233 g (52 %)

Melting Point: 128-130 ^{o}C

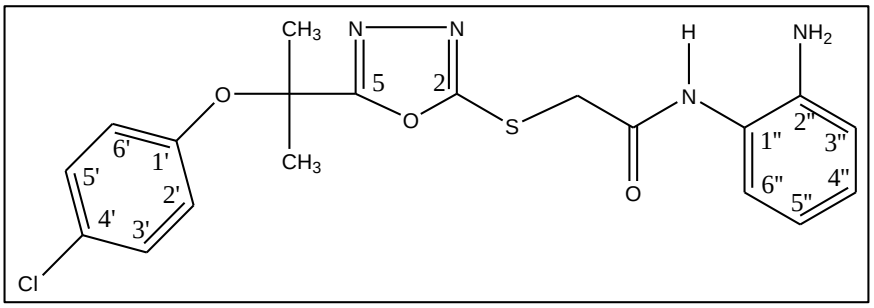
FT-IR: υ (cm^{-1}): 3335 (N-H str.), 2986 (C-H str.), 1693 (C=O amide str.), 1400 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 11.02 (s, 1H, NH), 8.24 (d, *J* = 9 Hz, 2H, H-3″& H-5″), 7.82 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 7.27 (d, *J* = 9 Hz, 2H, H-2″& H-6″), 6.74 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 4.39 (s, 2H, S-***CH*$_2$**-CO), 1.70 (s, 6H, C***(CH*$_3$*)*$_2$**).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.94 (C=O), 166.32 (C-2), 164.73 (C-5), 153.28 (C-1′), 145.14 (C-4″), 143.00 (C- 1″), 129.75 (C-3′ & C-5′), 128.52 (C-4′), 125.55 (C-3″ & C-5″), 124.07 (C-2′ & C-6′),119.42 (C-2″ & C-6″), 75.97 (***C***$(CH_3)_2$), 37.36 (S-***CH*$_2$**-CO), 25.70 (C***(CH*$_3$*)*$_2$**).

3.2.7.24 2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-aminophenyl)acetamide (30):

The following product was obtained by reacting 0.228 g (1 mmol) of 2-bromo-*N*-(2-aminophenyl)acetamide with 0.271 g (1 mmol) 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance: Light yellow solid

Yield: 0.188 g (45 %)

Melting Point: 131-133 ^{o}C

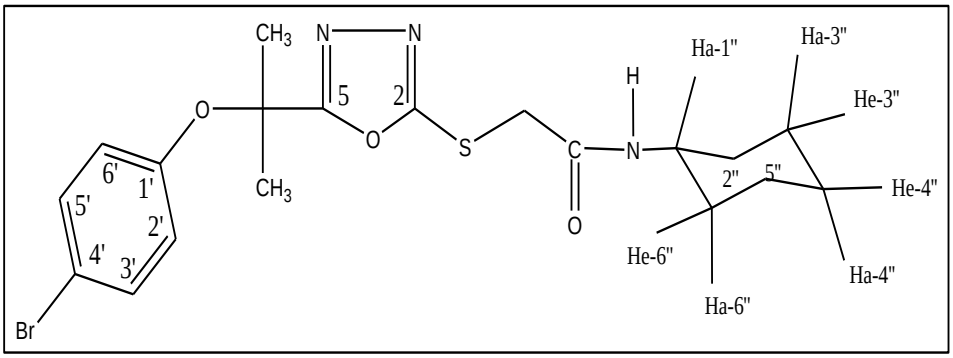
FT-IR: υ (cm^{-1}): 3401 (N-H str.), 2990 (C-H str.), 1658 (C=O amide str.), 1533 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.76 (s, 1H, NH), 7.55 (s, 1H, H-6″), 7.27 (d, *J* = 8 Hz, 3H, H-3′, H-5′& H-4″), 7.19 (s, 1H, H-3″), 6.77 (d, *J* = 8 Hz, 2H, H-2′, H-6′ & H-5″), 4.37 (s, 2H, S-***CH₂***-CO), 1.72 (s, 8H, C***(CH₃)₂*** & NH_2).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.892 (C=O), 165.77 (C-2), 164.98 (C-5), 153.31 (C-1′), 130.63 (C-6″), 129.77 (C-1″, C-3′ & C-5′), 128.55(C-2″ & C-5″), 125.91 (C-4′), 125.36 (C-4″), 124.11 (C-3″, C-2′ & C-6′), 75.98 (***C***$(CH_3)_2$), 37.20 (S-***CH₂***-CO), 25.73 (C***(CH₃)₂***).

3.2.7.25 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-cyclohexylacetamide (31):

The title compound was achieved by reacting 0.219 g (1 mmol) of 2-bromo-*N*-cyclohexylacetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.10 hours.



Appearance: Light yellow solid

Yield: 0.412 g (91 %)

Melting Point: 92-94 ^{o}C

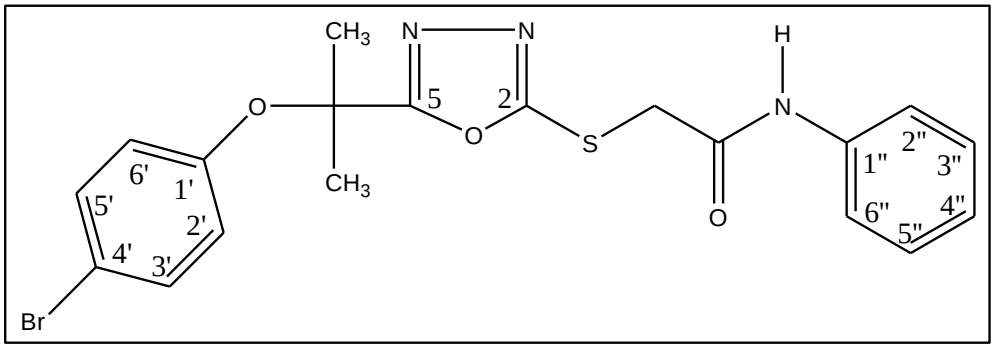
FT-IR: υ (cm^{-1}): 3381 (N-H str.), 2930 (C-H aromatic str.), 1644 (C=O amide str.), 1475 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 8.20 (d, *J* = 7.5 Hz, 1H, NH), 7.43 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 6.70 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.05 (s, 2H, S-***CH₂***-CO), 3.55-3.49 (m,2H, Ha-1″), 1.72 (s, 8H, C***(CH₃)₂*** , He-2″& He-6″), 1.67-1.65 (m, 2H, He-3″& He-5″), 1.55-1.53 (m, 1H, He-4″), 1.29.1.21 (m, 2H, Ha-2″& Ha-6″), 1.18-1.12 (m, 3H, Ha-3″, Ha-4″& Ha-5″)

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.70 (C=O), 165.11 (C-2), 164.98 (C-5), 153.79 (C-Í), 132.70 (C-3′& C-5′), 124.54 (C-2′& C-6′), 116.56 (C-4′), 75.90 (***C***$(CH_3)_2$), 48.63 (C-1″), 36.44 (S-***CH₂***-CO), 32.67 (C-2″ & C-6″), 25.73 (C***(CH₃)₂***), 25.60 (C-4″), 24.86 (C-3″ & C-5″).

3.2.7.26 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-phenylacetamide (32):

The above stated compound was synthesized by reacting 0.213 g (1 mmol) of 2-Bromo *N*-phenylacetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1hour.



Appearance:	White fluffy amorphous flakes
Yield:	0.384 g (86 %)
Melting Point:	88-90 ^{o}C

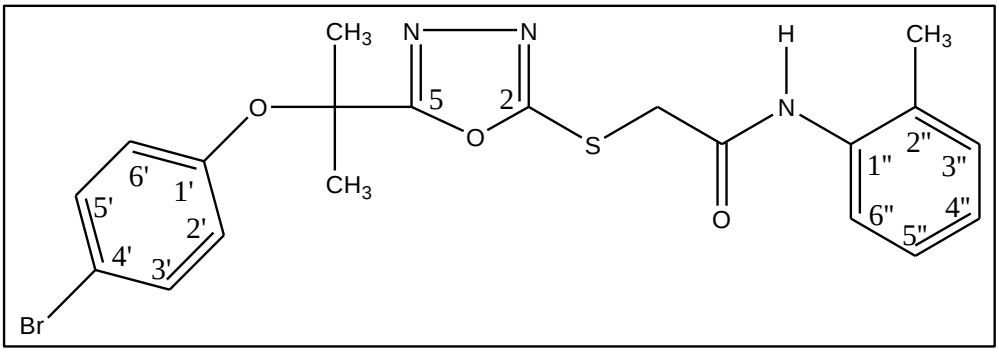
FT-IR: υ (cm^{-1}): 3365 (N-H str.), 2936 (C-H str.), 1601 (C=O amide str.), 1552 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.41 (s, 1H, NH), 7.57 (d, *J* = 8 Hz, 2H, H-2″& H-6″), 7.40 (d, *J* = 9 Hz, 2H, H- 3″&H-5″), 7.33 (t, *J* = 8 Hz, 2H, H-3′& H-5′), 7.08 (t, *J* = 7.5 Hz, 1H, H-4″), 6.69 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 4.32 (s, 2H, S-***CH₂***-CO), 1.71 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.82 (C=O), 165.15 (C-2), 164.88 (C-5), 153.75 (C-Í), 139.08 (C-1″), 132.70 (C-3′& C-5′), 129.32 (C-3″ & C-5″), 124.56 (C-2″ & C-6″), 124.09 (C-4″), 119.60 (C-2′& C-6′), 116.58 (C-4′), 75.94 (***C***$(CH_3)_2$), 37.31 (S-***CH₂***-CO), 25.71 (C***(CH₃)₂***).

3.2.7.27 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2-methylphenyl) acetamide (33):

The following product was achieved by using 0.227 g (1 mmol) of 2-Bromo-*N*-(2-methylphenyl)acetamide and 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.20 hours.



Appearance:	Light yellow powder
Yield:	0.373 g (81 %)
Melting Point:	84-86 ^{o}C

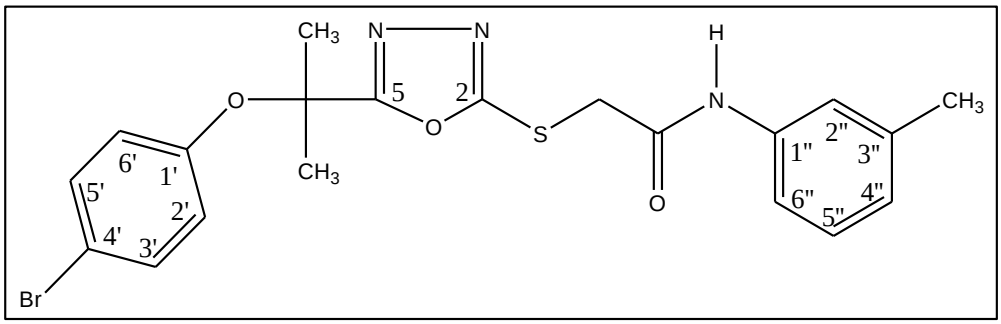
FT-IR: υ (cm^{-1}): 3301 (N-H str.), 2975 (C-H str.), 1651 (C=O amide str.), 1487 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.74 (s, 1H, NH), 7.39 (d, *J* = 8 Hz, 3H, H-3′, H-5′, H-6″), 7.22 (d, *J* = 7 Hz, 1H, H-3″), 7.16 (t, *J* = 7 Hz, 1H, H-5″), 7.10 (t, *J* = 7 Hz, 1H, H-4″), 6.70 (d, *J* = 8.5 Hz, 2H, H- 2′ & H-6′), 4.35 (s, 2H, S-***CH₂***-CO), 2.20 (s, 3H, Ar- CH_3), 1.47 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 173.60 (C=O), 170.13 (C-2), 169.68 (C-5), 158.53 (C-1′),140.99 (C-1″), 137.45 (C-3′ & C-5′), 136.83 (C-2″), 135.60 (C-5″), 131.22 (C-3″), 130.72 (C-4″), 129.97 (C-6″), 129.27 (C-2′ & C-6′), 121.32 (C- 4′), 80.68 (***C***$(CH_3)_2$), 41.57 (S-***CH₂***-CO), 30.49 (C***(CH₃)₂***), 22.97 (Ar-CH_3).

3.2.7.28 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(3-methylphenyl) acetamide (34):

The following product was obtained by using 0.227 g (1 mmol) of 2-Bromo-*N*-(3-methylphenyl)acetamide and 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 50 minutes.



Appearance: Light yellow powder

Yield: 0.401 g (87 %)

Melting Point: 64-66 ^{o}C

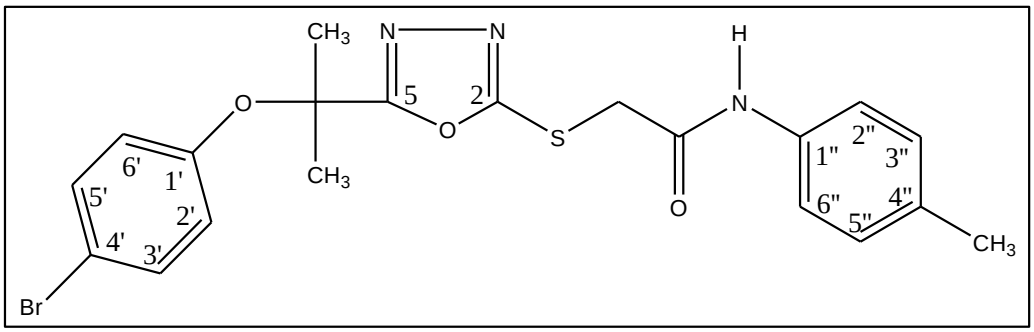
FT-IR: υ (cm^{-1}): 3327 (N-H str.), 2983 (C-H str.), 1604 (C=O amide str.), 1516 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500 MHz): δ_H: 10.44 (s, 1H, NH), 7.47 (d, *J* = 9 Hz, 2H, H-2″ & H-5″), 7.42 (t, *J* = 7.5 Hz, 1H, H-6″), 7.28 (d, *J* = 7.5 Hz, 1H, H-4″), 7.14 (d, *J* = 11.5 Hz, 2H, H-3′ & H-5′), 6.90 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 4.17 (s. 2H, S-***CH*$_2$**-CO**),** 2.37 (s, 3H, Ar-CH_3), 1.49 (s, 6H, C***(CH*$_3$*)*$_2$).

^{13}C NMR: (DMSO, 500 MHz):δ_C : 176.68 (C=O), 174.20 (C-2), 169.74 (C-5), 159.31 (C-1′), 143.83 (C-1″), 140.01 (C-3″), 137.11 (C-3′ & C-5′), 134.57 (C-5″), 134.16 (C-4″), 133.74 (C-2″), 130.48 (C-6″), 127.05 (C-2′, C-6′), 118.99 (C-4′), 85.54 (***C***$(CH_3)_2$), 37.89 (S-***CH*$_2$**-CO), 30.19 (C***(CH*$_3$*)*$_2$), 26.01 (Ar-CH_3).

3.2.7.29 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(4-methylphenyl) acetamide (35):

The above product was synthesized by reacting 0.227 g (1 mmol) of 2-Bromo-*N*-(4-methylphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.

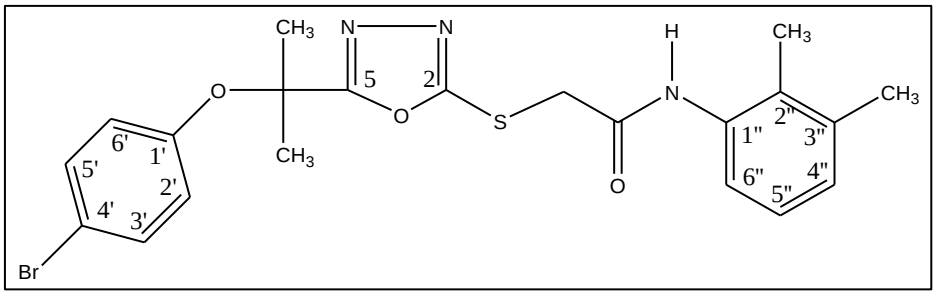


Appearance:	White powder
Yield:	0.230 g (50 %)
Melting Point:	60-62 ^{o}C

FT-IR: υ (cm^{-1}):	3401 (N-H str.), 2992 (C-H str.), 1621 (C=O amide str.), 1512 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 500MHz): δ_H: 10.31 (s, 1H, NH), 7.48 (d, *J* = 8 Hz, 2H, H-2″ & H-6″), 7.90 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 7.12 (d, *J* = 8.5 Hz, 2H, H-3″& H-5″), 6.69 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 4.29 (s, 2H, S-***CH$_2$***-CO), 2.25 (s, 3H, Ar-CH_3), 1.70 (s, 6H, C***(CH$_3$)$_2$***).
^{13}C NMR:	(DMSO, 500MHz): δ_C : 173.56 (C=O), 169.64 (C-2), 158.50 (C-5), 141.33 (C-1′), 137.88 (C-1″), 137.44 (C-3′ & C-5′), 134.43 (C-3″ & C-5″), 129.32 (C-2″, C-4″ & C-6″), 124.38 (C-2′ & C-6′), 121.34 (C-4′), 80.69 (***C***$(CH_3)_2$), 42.04 (S-***CH$_2$***-CO), 30.46 (C***(CH$_3$)$_2$***), 25.68 (Ar-CH_3).
EIMS:	m/z 461 [M^+, 3 %], 463 [M^++2, 2 %], 290(100), 262(6), 216(10), 174(15), 138(14), 123(36), 91(9), 65(7), 41(9).

3.2.7.30 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-N-(2,3-dimethylphenyl) acetamide (36):

The following product was achieved by reacting 0.241 g (1 mmol) of 2-bromo-N-(2,3-dimethylphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance: Pale yellow powder

Yield: 0.401 g (85 %)

Melting Point: 154-156 ^{o}C

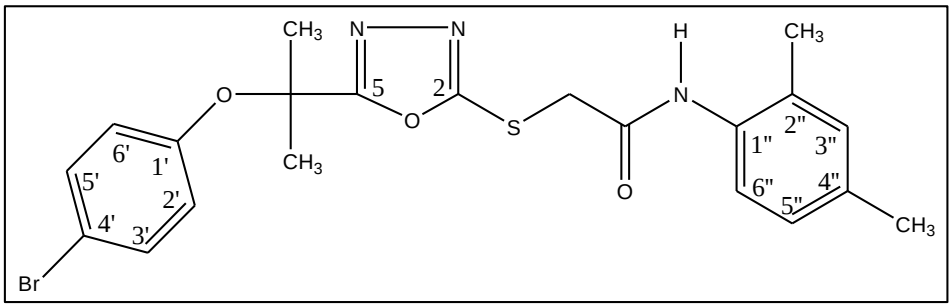
FT-IR: υ (cm^{-1}): 3327 (N-H str.), 2925 (C-H str.), 1601 (C=O amide str.), 1512 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.45 (s, 1H, NH), 7.34 (d, *J* = 9 Hz, 2H, H-3′ & H-5′), 7.27 (d, *J* = 7.5 Hz, 1H, H-5″), 7.21 (t, *J* = 7.5 Hz, 1H, H-4″), 7.04 (d, *J* = 8 Hz, 1H, H-6″), 6.94 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.26 (d, *J* = 7.5 Hz, 1H, *Ha*), 4.18 (d, *J* = 7 Hz, 1H, *Hb*), 2.31 (s, 3H, Ar-CH_3), 2.03 (s, 3H, Ar-CH_3), 1.46 (3H, C***CH₃***), 1.45 (3H, C***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.87 (C=O), 169.49 (C-2), 164.72 (C-5), 154.07 (C-1′), 138.23 (C-1″), 134.94 (C-3″), 134.58 (C-2″), 130.93 (C-4′), 129.45 (C-3′& C-5′), 126.68 (C-5″), 126.60 (C- 4″), 126.38 (C-6″), 121.90 (C-2′& C-6′), 85.51 (***C***$(CH_3)_2$), 33.03 (S-***CH₂***-CO), 25.45 (C***(CH₃)₂***), 20.36 (Ar-CH_3), 14.22 (Ar-CH_3).

3.2.7.31 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2,4-dimethylphenyl) acetamide (37):

The above stated compound was obtained by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(2,4-dimethylphenyl)acetamide and with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.20 hours.

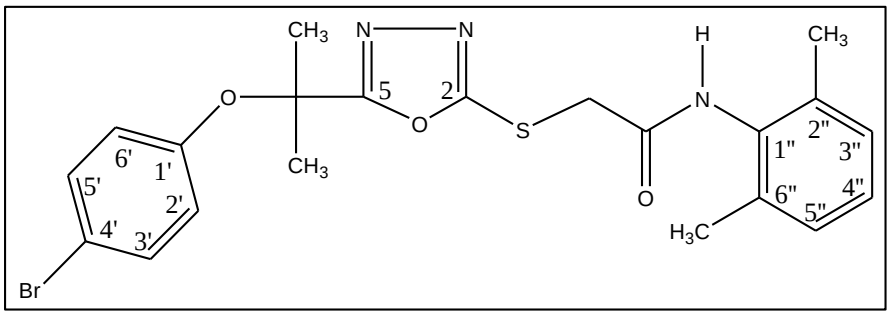


Appearance:	Golden yellow powder
Yield:	0.380 g (80 %)
Melting Point:	71-73 ^{o}C

FT-IR: υ (cm^{-1}):	3396 (N-H str.), 2971 (C-H str.), 1609 (C=O amide str.), 1522 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 500MHz): δ_H: 10.45 (s, 1H, NH), 7.45 (d, *J* = 8 Hz, 2H, H-3′ & H-5′), 7.170 (s, 1H, H-6″), 7.12-7.05 (m, 2H, H-3″& H-5″), 6.87 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 4.24-4.14 (m, 2H, S-***CH₂***-CO), 2.32 (s, 3H, Ar-CH₃), 2.12 (s, 3H, Ar-CH₃), 1.46 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	(DMSO, 500MHz): δ_C: 176.57 (C=O), 174.25 (C-2), 169.43 (C-5), 159.32 (C-1′), 143.93 (C-1″), 140.79 (C-4″), 137.11 (C-3′ & C-5′), 136.70 (C-5″), 136.51 (C-3″),133.58 (C-2″), 132.62 (C-4′), 127.02 (C-2′ , C-6′) 118.95 (C-6″), 85.51 (***C***$(CH_3)_2$), 37.75 (S-***CH₂***-CO), 30.22 (C***CH₃***), 30.18 (C***CH₃***), 25.94 (Ar-CH₃), 22.24 (Ar-CH₃).

3.2.7.32 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2-6-dimethylphenyl)acetamide (38):

The above stated product was obtained by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(2,6-dimethylphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.

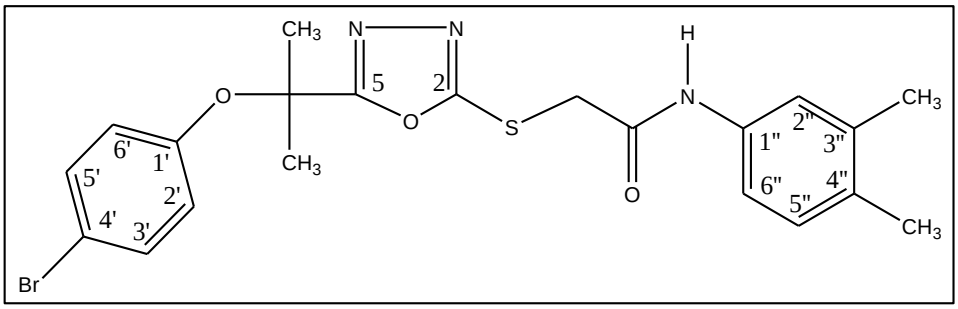


Appearance:	Light yellow powder
Yield:	0.437 g (92 %)
Melting Point:	104-106 ^{o}C

FT-IR: υ (cm^{-1}):	3310 (N-H str.), 2952 (C-H aromatic str.), 1645 (C=O amide str.), 1480 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 500MHz): δ_H: 9.75 (s, 1H, NH), 7.42 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.12 (s, 3H, H-3″, H-4″& H-5″), 6.74 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.37 (s, 2H, S-***CH₂***-CO), 2.17 (s, 6H, Ar-2CH_3), 1.76 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	(DMSO, 500MHz): δ_C: 173.62 (C=O), 169.71 (C-2), 169.68 (C-5), 158.53 (C-1′), 140.33 (C-2″ & C-6″), 139.75 (C-1″), 137.45 (C-3′ & C-5′), 132.93 (C-3″ & C-5″), 131.89 (C-4″), 129.27 (C-2′, C-6′), 121.30 (C-4′), 80.64 (***C***$(CH_3)_2$), 41.00 (S-***CH₂***-CO), 30.51 (C***(CH₃)₂***), 23.23 (Ar-CH_3), 23.23 (Ar-CH_3).

3.2.7.33 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(3,4-dimethylphenyl) acetamide (39):

The desired product was obtained by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(3,4-dimethylphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.

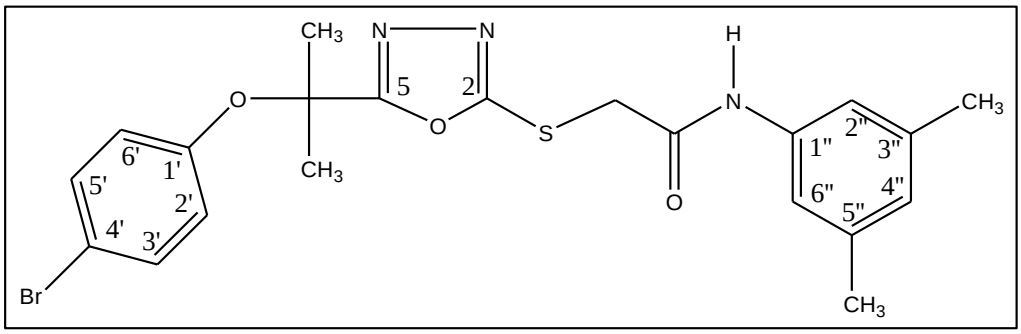


Appearance:	Light yellow powder
Yield:	0.442 g (93 %)
Melting Point:	79-81 ^{o}C

FT-IR: υ (cm^{-1}):	3393 (N-H str.), 2981 (C-H str.), 1629 (C=O amide str.), 1562 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 300MHz): δ_H: 10.24 (s, 1H, NH), 7.37 (t, *J* = 8.5 Hz, 3H, H-3′ & H-5′ & H-2 ″), 7.26 (d, *J* = 8 Hz, 1H, H-6″), 7.06 (d, *J* = 8 Hz, 1H, H-5″), 6.68 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.28 (s, 2H, S-***CH₂***-CO), 2.17 (d, *J* = 8 Hz, 6H, Ar-2CH_3), 1.70 (s, 6H, C***(CH₃)₂***).
^{13}C NMR:	(DMSO, 300MHz): δ_C : 173.55 (C=O), 169.64 (C-2), 169.57 (C-5), 158.49 (C-1′), 141.66 (C-1″), 141.57 (C-3″), 137.44 (C-3′ & C-5′), 136.69 (C-4″), 134.88 (C-5″), 129.37 (C-2′ & C-6′), 125.57 (C-2″), 121.92 (C-6″),121.36 (C-4′), 80.69 (***C***$(CH_3)_2$), 42.03 (S-***CH₂***-CO), 30.45 (C***(CH₃)₂***), 24.85 (Ar-CH_3), 24.02 (Ar-CH_3).
EIMS:	m/z 477 [M^+, 12 %], 479 [M^+ + 2, 1 %],304(100), 276(39), 261(4), 230(15), 215(20), 183(29), 152(31), 134(24), 123(50), 105(12), 69(13), 41(8).

3.2.7.34 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(3,5-dimethylphenyl) acetamide (40):

The following compound was synthesized by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(3,5-dimethylphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.



Appearance: White powder

Yield: 0.219 g (46 %)

Melting Point: 68-70 ^{o}C

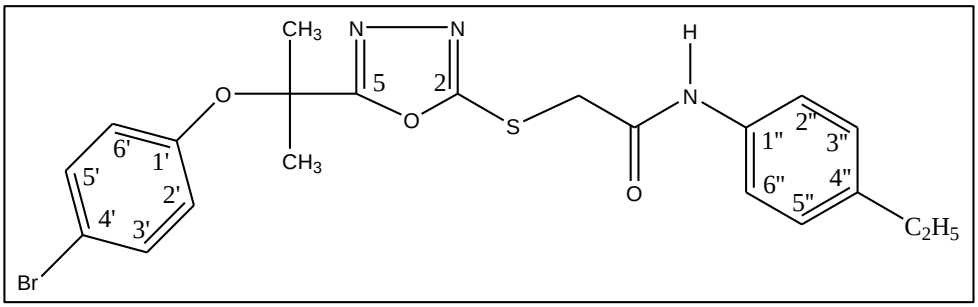
FT-IR: υ (cm^{-1}): 3398 (N-H str.), 2917 (C-H str.), 1614 (C=O amide str.), 1560 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.25 (s, 1H, NH), 7.39 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.20 (s, 2H, H-2″ & H-6″), 6.75 (t, *J* = 9.5 Hz, 3H, H-4″, H-2′ & H-6′), 4.29 (s, 2H, S-***CH₂***-CO), 2.23 (s, 6H, Ar-2CH_3),1.70 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 173.56 (C=O), 169.76 (C-2), 169.64 (C-5), 158.49 (C-1′), 143.70 (C-1″), 143.04 (C-3″ & C-5″), 137.43 (C-3′ & C-5′),130.44 (C-4″), 129.40 (C-2′ & C-6′), 122.13 (C-2″ & C-6″), 121.38 (C-4′), 80.70 (***C***$(CH_3)_2$), 42.07 (S-***CH₂***-CO), 30.44 (C***(CH₃)₂***), 26.30 (Ar-CH_3), 26.30 (Ar-CH_3).

3.2.7.35 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(4-ethylphenyl)acetamide (41):

The above stated compound was achieved by reacting 0.241 g (1 mmol) of 2-bromo-*N*-(4-ethylphenyl)acetamide and with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.120 hours.



Appearance: White powder

Yield: 0.428 g (90 %)

Melting Point: 85-87 ^{o}C

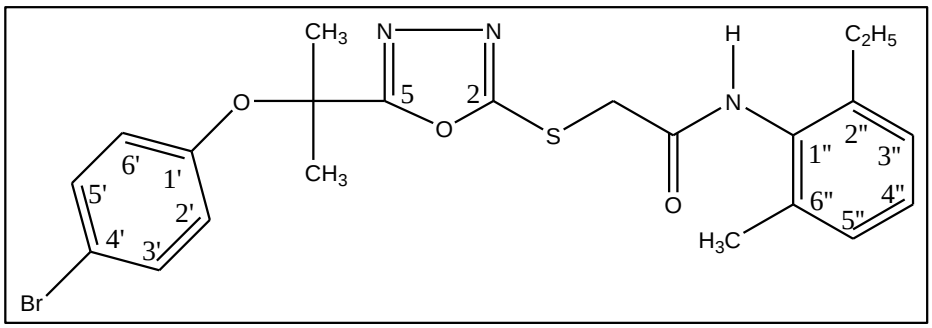
FT-IR: υ (cm^{-1}): 3357 (N-H str.), 2996 (C-H aromatic str.), 1654 (C=O amide str.), 1524 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.44 (s, 1H, NH), 7.46 (d, *J* = 9 Hz, 2H, H-2″ & H-6″), 7.35 (d, *J* = 8 Hz, 2H, H-3′& H-5′), 7.12 (d, *J* = 8 Hz, 2H, H-3″& H-5″), 6.88 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.15 (s, 2H, S-***CH₂***-CO), 2.69-2.64 (m, 2H, ***CH₂***CH_3), 1.47 (s, 6H, C***(CH₃)₂***), 1.22 (t, *J* = 7.5 Hz, 3H, CH_2***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.97 (C=O), 169.48 (C-2), 164.99 (C-5), 154.57 (C-4″), 144.85 (C-1′), 132.87 (C-1″), 132.36 (C-3′ & C-5′), 128.88 (C-3″ & C-5″), 128.41 (C-2′ & C-6′), 122.26 (C-2″ & C-6″), 114.22 (C-4′), 80.77 (***C***$(CH_3)_2$), 33.09 (S-***CH₂***-CO), 28.33 (***CH₂***CH_3), 25.44 (C***(CH₃)₂***), 15.99 (CH_2***CH₃***).

3.2.7.36 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(2-ethyl-6-methylphenyl)acetamide (42):

The following compound was achieved by reacting 0.255 g (1 mmol) of 2-bromo-*N*-(2-ethyl-6-methylphenyl)acetamide and with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.10 hours.



Appearance: Light yellow powder

Yield: 0.450 g (92 %)

Melting Point: 98-100 ^{o}C

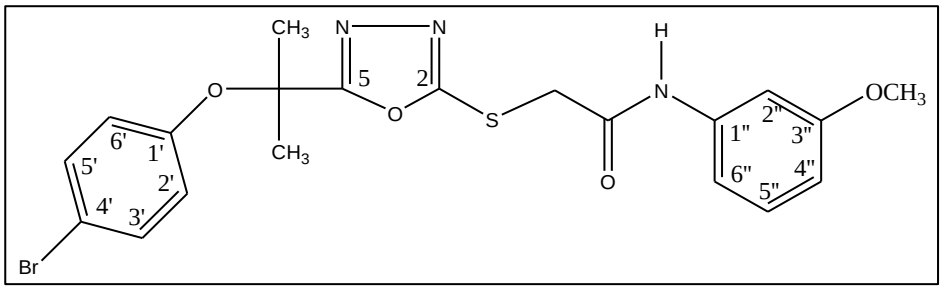
FT-IR: υ (cm^{-1}): 3343 (N-H str.), 2978 (C-H str.), 1657 (C=O amide str.), 1528 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.71 (s, 1H, NH), 7.39 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.14 (t, *J* = 7.5 Hz, 1H, H-4″), 7.08 (d, *J* = 8 Hz, 2H, H-3″& H-5″), 6.71 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 4.34 (s, 2H, S-***CH₂***-CO), 2.51 (CH₃***CH₂*** merged in DMSO), 2.12 (s, 3H, Ar-CH_3), 1.73 (s, 6H, C***(CH₃)₂***), 1.06 (t, *J* = 7.5 Hz, 3H, CH_2-***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.86 (C=O), 165.39 (C-2), 164.92 (C-5), 153.79 (C-1′),141.51 (C-1″), 136.03 (C-6″), 134.38 (C-5″), 132.69 (C-3′ & C-5′),128.17 (C-2″), 127.51(C-4′), 126.50 (C-3″), 124.52 (C-2′ & C-6′),116.55 (C-4″), 75.92 (***C***$(CH_3)_2$), 36.23 (S-***CH₂***-CO), 25.76 (C***(CH₃)₂***),24.68 (CH₃***CH₂***), 18.49 (Ar-CH_3), 15.09 (CH_2-***CH₃***).

3.2.7.37 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(3-methoxyphenyl) acetamide (43):

The following product was obtained by reacting 0.243 g (1 mmol) of 2-bromo-*N*-(3-methoxyphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.10 hours.



Appearance: Lemon yellow powder

Yield: 0.362 g (76 %)

Melting Point: 92-94 ^{o}C

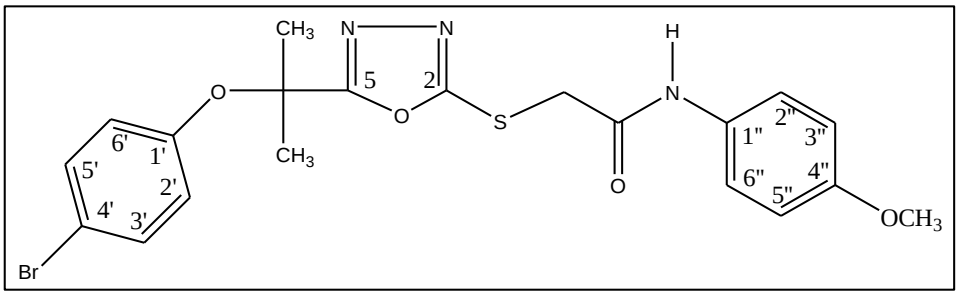
FT-IR: υ (cm^{-1}): 3485 (N-H str.), 2930 (C-H str.), 1623 (C=O amide str.), 1568 (C=C aromatic ring str.)

^{1}H NMR: (DMSO, 500 MHz): δ_H: 10.41 (s, 1H, NH), 7.40 (d, *J* = 9 Hz, 2H, H-3′ & H-5′), 7.28 (s, 1H, H-2″), 7.31 (t, *J* = 8 Hz, 1H, H-5″), 7.19 (d, *J* = 8 Hz, 1H, H-6″), 6.70-6.66 (m, 3H, H-4″, H-2′ & H-6′), 4.31 (s. 2H, S-***CH₂***-CO**),** 3.73 (s, 3H, O***CH₃***), 1.71 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 400 MHz):δ_C : 168.82 (C=O), 165.22 (C-2), 164.87 (C-5), 160.01 (C-3″), 153.74 (C-1″), 140.24 (C-1′), 132.69 (C-3′ & C-5′), 130.14 (C-5″),124.61 (C-2′ & C-6′), 116.62 (C-4′), 111.86 (C-6″), 109.56 (C-4″), 105.43 (C-2″), 75.94 (***C***$(CH_3)_2$), 55.48 (O***CH₃***) 37.34 (S-***CH₂***-CO), 25.69 (C***(CH₃)₂***).

3.2.7.38 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-methoxyphenyl) acetamide (44):

The above stated compound was achieved by reacting 0.243 g (1 mmol) of 2-bromo-*N*-(4-methoxyphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.

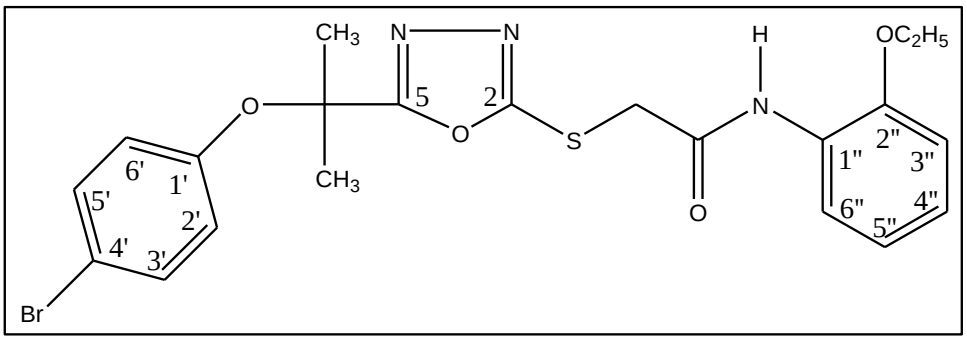


Appearance:	White powder
Yield:	0.200 g (42 %)
Melting Point:	71-73 ^{o}C

FT-IR: υ (cm^{-1}):	3357 (N-H str.), 2981 (C-H str.), 1678 (C=O amide str.), 1509 (C=C aromatic ring str.).
^{1}H NMR:	(DMSO, 500MHz): δ_H: 10.42 (s, 1H, NH), 7.46 (d, *J* = 9 Hz, 2H, H-2″& H-6″), 7.22 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 7.05 (d ,*J* = 9 Hz, 2H, H-2′& H-6′), 6.88 (d, *J* = 9 Hz, 2H, H-3″, H-5″), 4.14 (s, 2H, S-***CH$_2$***-CO), 3.80 (s, 3H, O***CH$_3$***), 1.47 (s, 6H, C***(CH$_3$)$_2$***).
^{13}C NMR:	(DMSO, 500MHz): δ_C : 172.05 (C=O), 169.47 (C-2), 165.12 (C-5), 159.61 (C-4″),154.57 (C- 1′), 132.36 (C-3′ & C-5′), 129.73 (C-2″ & C-6″), 127.78(C-1″), 122.26 (C-2′ & C-6′), 114.79 (C-3″, C-5″), 114.22 (C-4′), 80.78 (***C***$(CH_3)_2$), 55.89 (OCH_3), 33.01 (S-***CH$_2$***-CO), 25.44 (C***(CH$_3$)$_2$***).

3.2.7.39 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-ethoxyphenyl) acetamide (45):

The above compound was synthesized by reacting 0.258 g (1 mmol) of 2-bromo-*N*-(2-ethoxyphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.10 hours.



Appearance: White powder

Yield: 0.231 g (47 %)

Melting Point: 95-97 ^{o}C

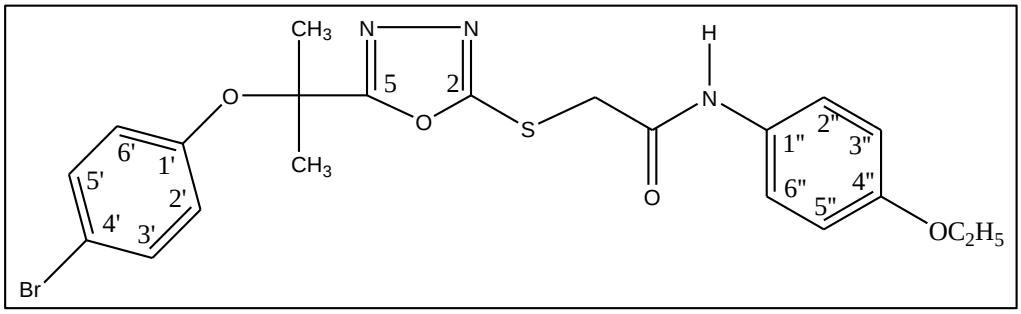
FT-IR: υ (cm^{-1}): 3327 (N-H str.), 2985 (C-H str.), 1603 (C=O amide str.), 1506 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.41 (s, 1H, NH), 7.47-7.41 (m, 3H, H-3′, H-5′ & H-6″), 7.23-7.18 (m, 2H, H-3″ & H-5″), 7.04 (t, *J* = 8 Hz, 1H, H-4″), 6.88 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.18 (s, 2H, O***CH₂***CH_3), 4.18-4.03 (m, 2H, S-***CH₂***-CO), 1.47 (s, 6H, C***(CH₃)₂***), 1.25 (t, *J* = 7 Hz, 3H, OCH_2***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 171.44 (C=O), 169.36 (C-2), 163.85 (C-5), 154.60 (C-1′), 154.46 (C-2″), 132.33 (C-3′ & C-5′), 131.01 (C-4′), 130.34 (C-1″), 124.17 (C- 4″), 122.19 (C-2′ & C-6′), 121.04 (C- 5″), 114.33 (C-6″), 114.14 (C-3″), 80.73 (***C***$(CH_3)_2$), 64.55 (O***CH₂***CH_3), 32.81 (S-***CH₂***-CO), 25.41 (C***(CH₃)₂***), 14.96 (OCH_2***CH₃***).

3.2.7.40 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-ethoxyphenyl) acetamide (46):

The above stated product was synthesized by reacting 0.258 g (1 mmol) of 2-bromo-*N*-(4-ethoxyphenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.25 hrs.



Appearance:	Light yellow solid
Yield:	0.241 g (49 %)
Melting Point:	89-91 ^{o}C

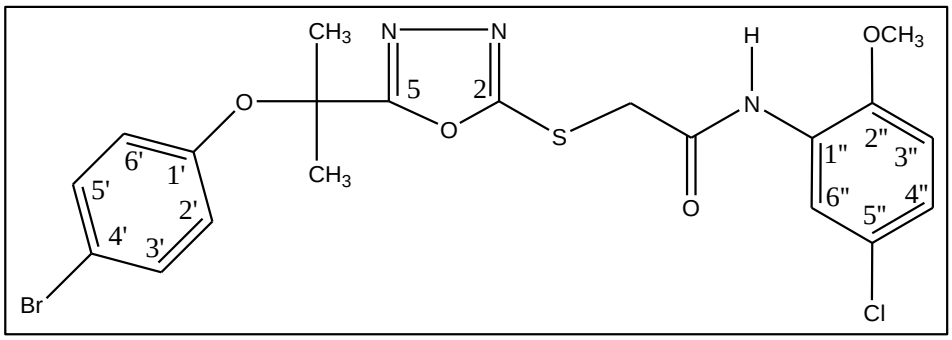
FT-IR: υ (cm^{-1}): 3384 (N-H str.), 2988 (C-H str.), 1660 (C=O amide str.), 1509 (C=C aromatic ring str.).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.42 (s, 1H, NH), 7.46 (d, *J* = 9 Hz, 2H, H-2″& H-6″), 7.21 (d, *J* = 8.5 Hz, 2H, H-3′& H-5′), 7.03 (d, *J* = 9 Hz, 2H, H-2′& H-6′), 6.88 (d, *J* = 9 Hz, 2H, H- 3″, H-5″), 4.13 (s, 2H, O***CH₂***CH_3), 4.10-4.05 (m, 2H, S-***CH₂***-CO), 1.47 (s, 6H, C***(CH₃)₂***), 1.35 (t, *J* = 7 Hz, 3H, OCH_2***CH₃***).

^{13}C NMR: (DMSO, 500MHz): δ_C: 172.05 (C=O), 169.46 (C-2), 165.16 (C-5), 158.88 (C- 4″), 154.57 (C-1′), 132.35 (C-3′ & C-5′), 129.72 (C-2″& C-6″), 127.63 (C-1″), 122.27 (C-2′ & C-6′), 115.19 (C-3″ & C-5″),114.22 (C-4′), 80.78 (***C***$(CH_3)_2$), 63.84 (O***CH₂***CH_3), 33.00 (S-***CH₂***-CO), 25.44 (C***(CH₃)₂***), 15.07 (OCH_2***CH₃***).

3.2.7.41 2-{5-[2-(4-Bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}-*N*-(5-chloro-2-methoxyphenyl) acetamide (47):

The above mentioned product was obtained by reacting 0.277 g (1 mmol) of 2-bromo-*N*-(4-chloro-2-methoxylphenyl)acetamide and with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1 hour.



Appearance: Golden yellow powder

Yield: 0.210 g (43 %)

Melting Point: 118-120 ^{o}C

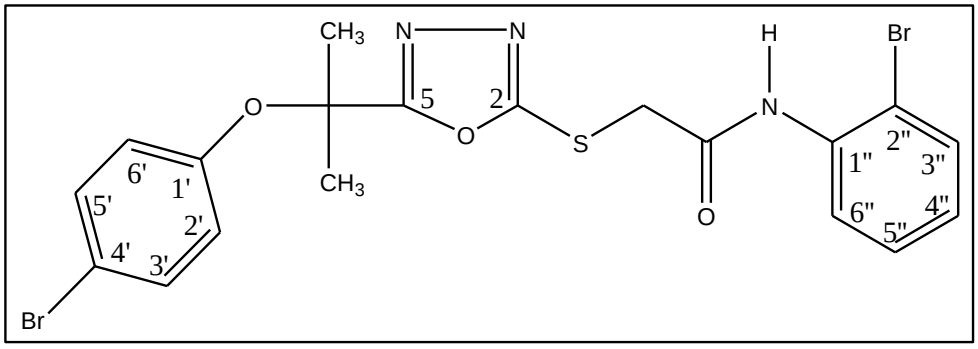
FT-IR: υ (cm^{-1}): 3310 (N-H str.), 2975 (C-H str.), 1665 (C=O amide str.), 1531 (C=C aromatic ring str.), 722 (C-Cl str).

^{1}H NMR: (DMSO, 500MHz): δ_H: 9.85 (s, 1H, NH), 8.12 (s, 1H, H-6″), 7.39 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.15-7.08 (m, 2H, H-3″ & H-4″), 6.69 (d, *J* = 9 Hz , 2H, H-2′ & H-6′), 4.41 (s, 2H, S-***CH₂***-CO), 3.86 (s, 3H, O***CH₃***), 1.71 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C: 168.88 (C=O), 166.11 (C-2), 164.80 (C-5), 153.74 (C-1′), 148.40 (C-2″), 132.66 (C-3′ & C-5′), 128.65 (C-5″), 124.61 (C-2′, C-6′), 124.35 (C-1″), 124.29 (C-4″), 120.83 (C-3″), 116.65 (C-4′), 113.08 (C-6″), 75.96 (***C***$(CH_3)_2$), 56.60(OCH_3), 37.03 (S-***CH₂***-CO), 25.68 (C***(CH₃)₂***).

3.2.7.42 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(2-bromophenyl)acetamide (48):

The following product was prepared by reacting 0.292 g (1 mmol) of 2-bromo-*N*-(2-bromophenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.15 hours.

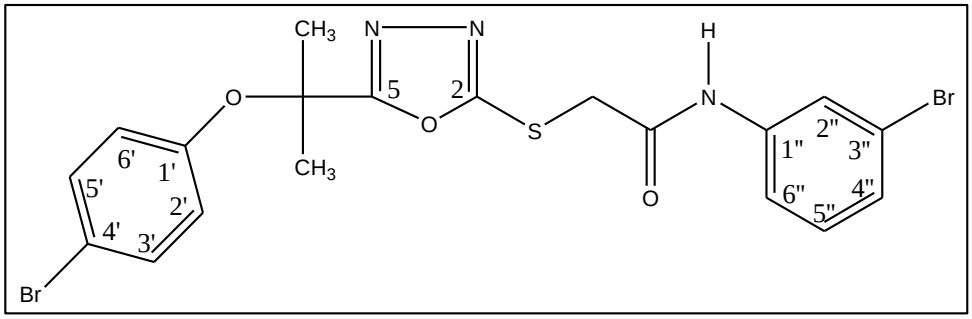


Appearance:	Light yellow powder
Yield:	0.215 g (41 %)
Melting Point:	164-166 ºC

FT-IR: υ (cm^{-1}):	3339 (N-H str.), 2981 (C-H str.), 1667 (C=O amide str.), 1484 (C=C aromatic ring str.)580 (C-Br str.).
^{1}H NMR:	(DMSO, 500MHz): δ_H: 10.49 (s, 1H, NH), 7.81 (d, *J* = 8.5 Hz, 1H, H-6″), 7.56 (t, *J* = 8 Hz, 1H, H-3″), 7.47-7.44 (m, 4H, H-3′, H-5′, H-4″ & H-5″), 6.88 (d, *J* = 9 Hz, 2H, H- 2′ & H-6′), 4.28-4.20 (m, 2H, S-***CH₂***-CO), 1.47 (s, 3H, C***CH₃***), 1.46 (s, 3H, C***CH₃***).
^{13}C NMR:	(DMSO, 500MHz): δ_C : 171.10 (C=O), 169.31 (C-2), 163.20 (C-5), 154.56 (C-1′),134.63 (C-1″), 133.63 (C-3″), 132.34 (C-3′ & C-5′), 131.74 (C-5″), 131.56 (C-4″), 129.40 (C-6″), 122.68 (C-4′), 122.24 (C-2′ & C-6′), 114.17 (C-2″), 80.72 (***C***$(CH_3)_2$), 33.19 (S-***CH₂***-CO), 25.48 (C***CH₃***), 25.37 (C***CH₃***).

3.2.7.43 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(3-bromophenyl)acetamide (49):

The stated product was synthesized by reacting 0.292 g (1 mmol) of 2-bromo-*N*-(3-bromophenyl)acetamide with 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.10 hours.

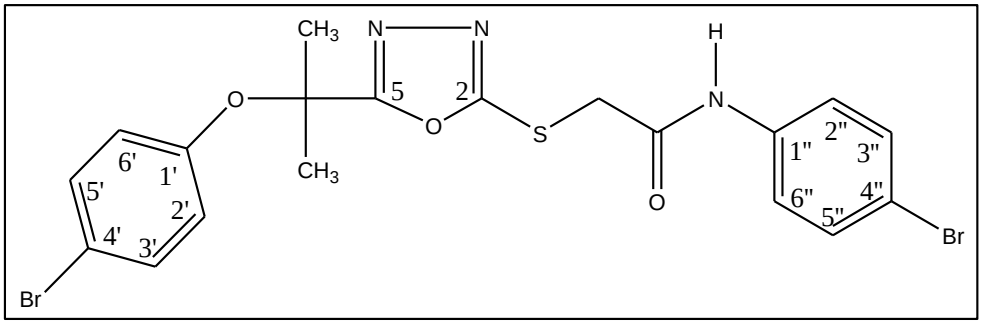


Appearance:	Light yellow powder
Yield:	0.445 g (85 %)
Melting Point:	105-107 ^{o}C

FT-IR: υ (cm^{-1}):	3939 (N-H str.), 2991 (C-H str.), 1643 (C=O amide str.), 1487 (C=C aromatic ring str.), 577 (C-Br str.)
^{1}H NMR:	(DMSO, 500 MHz): δ_H: 10.60 (s, 1H, NH), 7.94 (s, 1H, H- H-2″), 7.64 (d, *J* = 7 Hz, 1H, H-6″), 7.40 (d, *J* = 9 Hz, 2H, H-3′ & H-5′), 7.32-7.27 (m, 2H, H-4″ & H-5″), 6.69 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.32 (s. 2H, S-***CH*$_2$**-CO**),** 1.71 (s, 6H, C***(CH*$_3$*)*$_2$).
^{13}C NMR:	(DMSO, 500 MHz):δ_C : 168.85 (C=O), 165.63 (C-2), 164.79 (C-5), 153.73 (C-1′), 140.61 (C-1″), 132.67 (C-3′ & C-5′), 131.35 (C-5″), 126.81 (C-4″), 124.58 (C-2′ & C-6′), 122.10 (C-2″), 121.95 (C-3″), 118.40 (C-6″), 116.63 (C-4′), 75.94 (***C***$(CH_3)_2$), 37.22 (S-***CH*$_2$**-CO), 25.69 (C***(CH*$_3$*)*$_2$).

3.2.7.44 2-(5-(2-(4-Bromophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-(4-bromophenyl)acetamide (50):

The above mentioned compound was prepared by using 0.292 g (1 mmol) of 2-bromo-*N*-(4-bromophenyl)acetamide and 0.314 g (1 mmol) 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol for 1.30 hours.



Appearance:	Light yellow powder
Yield:	0.440 g (81 %)
Melting Point:	94-96 ^{o}C

FT-IR: υ (cm^{-1}): 3364 (N-H str.), 2995 (C-H str.), 1621 (C=O amide str.), 1481 (C=C aromatic ring str.), 574 (C-Br).

^{1}H NMR: (DMSO, 500MHz): δ_H: 10.55 (s, 1H, NH), 7.56-7.50 (m, 4H, H-2″, H-6″, H-3″& H-5″), 7.40 (d, *J* = 9 Hz, 2H, H-3′& H-5′), 6.68 (d, *J* = 9 Hz, 2H, H-2′ & H-6′), 4.32 (s, 2H, S-***CH₂***-CO), 1.70 (s, 6H, C***(CH₃)₂***).

^{13}C NMR: (DMSO, 500MHz): δ_C : 168.85 (C=O), 165.39 (C-2), 164.81 (C-5), 153.75 (C-1′), 138.43 (C-1″), 132.69 (C-3′ & C-5′), 132.16 (C-3″ & C-5″), 124.51 (C-2″ & C-6″), 121.50 (C-2′ & C-6′), 116.57 (C-4′), 115.79 (C-4″), 75.93 (***C***$(CH_3)_2$), 37.26 (S-***CH₂***-CO), 25.70 (C***(CH₃)₂***).

3.3 Biological Screening:

3.3.1 *In Vitro* Thrombolytic Effect:

The selective synthesized compounds were evaluated for in *vitro* clot lysis potential.

3.3.1.1 Sample solution preparation

A 100 mg each of each synthetic compound was mixed in 10 mL of distilled water. This mixture was shaken vigorously on a vortex mixer and stirred overnight. The resulting solution was then filtered by using 0.22 µm syringe filter. A 100 µl from this aqueous preparation was then added to the pre-weighed eppendorf tube containing the clots to check thrombolytic potential of tested compounds.

3.3.1.2 *In vitro* thrombolytic activity

Experiments for clot lysis were performed according to reported protocol [171]. Briefly, venous blood was taken from the healthy persons without a history of anticoagulant therapy or oral contraceptive. 0.5 ml was used in pre-weighed sterile eppendorf tubes and incubated at 37 °C for 45 minutes. When the clot was formed then serum was removed carefully without disturbing the clot. Then each tube containing clot was weighed again to determine the clot weight. 100 µl of tested compounds filtrate was added separately. Streptokinase (SK) 15, 00,000 I.U (Square Pharmaceuticals Ltd.) used as positive control (100 µl) while sterile distilled water (100 µl) was used as negative control. All the tubes were then incubated at 37 °C for one hour and 30 minutes and observed for clot lysis. After incubation, the released fluid from clot was removed carefully and tubes were weighed again to observe the difference in weight due to clot disruption. Difference obtained in weight

taken before and after clot lysis was expressed as percentage of clot lysis [172]. Blood samples were taken from 12 persons and experiment was repeated three times.

Following formula was used to determine the % age of clot lysis.

Clot lysis % age = [Initial clot weight-Final clot weight/Initial weight of clot]×100

3.3.2 In *Vivo* Thrombolytic activity:

3.3.2.1 Experimental animals

Sprauge Dawley (SD) rats (100-120 g) were used to determine the in vivo anti thrombotic and anti-inflammatory activities of tested compounds and kept under control temperature (25 ± 5 ºC) and humidity (50 ± 10 %) in animal house, with free access of pathogen and autoclave tap water for 24 hours. Experiments were approved by Institutional Ethical Committee, University of the Punjab, Lahore and international ethical guideline was also followed for the care of laboratory animals to provide them healthy environment.

3.3.2.2 *In vivo* Clotting Time (CT) determination

Blood CT determination was used to evaluate the anti-coagulant activity. Previously established method with slight modifications was used to estimate the CT [106, 173]. Seventy two rats were divided into twelve groups of 6 rats each. The first group was given 0.5% carboxy methyl cellulose (CMC) orally and served as negative control. The second groups were designated as positive control, received 500 IU/ kg unfractionated heparin orally. The group 3-12 was given the tested compounds suspended in 0.5% CMC and given to the rats orally at a dose of 25 mg/kg body weight. A drop of blood was drawn from the tail of each rat on clean dry glass slide. One end of a capillary tube was dipped into blood drop

without pressure. Three quarter length of capillary tube was filled with blood and CT was measure at the regular interval of 30 seconds.

3.3.3 *In vitro* Clotting Time (CT) determination

To 100 µl of each tested compound, standard drug heparin and distilled water as a control was added 0.5 ml blood from rat separately. The mixture was incubated at 37 °C for 5 seconds. After that one end of a capillary tube was dipped and three quarter length of capillary tube was filled with blood and CT was measured at the regular interval of 30 seconds. The procedure was repeated three times.

3.3.4 Anti-inflammatory activity

In *vitro* and *vivo* anti-inflammatory activity was performed according to protocol reported by Lincy et al. [174].

3.3.4.1 *In vitro* anti-inflammatory activity:

The reaction mixture was prepared by mixing 0.2 mL of fresh hen's egg albumin, 2.8 mL of phosphate buffer (pH=6.4) and 2 mL of each tested compounds (100 µg/mL) separately. Double distilled water (5 mL) was used as a control. The reaction mixtures were then incubated at (37 ± 2 ºC) for 15 minutes and further heated at 70 ºC for 5 minutes, After cooling the reaction mixtures, absorbance of each was measured at 660 nm. Vehicle was used as blank and diclofenic sodium was used as standard. The experiment was performed in triplet for each compound. Following formula was applied to calculate % age inhibition of protein denaturation potential of target compounds.

$$\% \text{ inhibition of protein denaturation} = (Vt/Vc - 1) \times 100$$

Vt = Absorbance of target compound

Vc = Absorbance of control

3.3.4.2 *In vivo* anti-inflammatory activity:

Acute inflammation in rats was induced by injecting 0.1 mL of 1 % carrageenan into hind paw of rats. Paw volume was measured at 0^{th}, I^{st}, 2^{nd}, 3^{rd} and 4^{th} hour.

For the said purpose, rats were divided in ten groups, each group contained 6 rats.

Group 1: Control given only 1% sodium CMC

Group 2: Received standard diclofenic sodium and 0.1mL of carrageenan

Group 3-10: Received target compounds (50 mg/Kg per body weight.) and 0.1mL of carrageenan

3.4 Molecular Docking:

In-silico analysis of the newly designed 1,3,4-oxadiazoles derivatives **5a** and **8-17** against F-Xa protein and compounds **5a, 5b** and **8-50** against COX-2 protien was carried out. The crystal structure of F-Xa protein and COX-2 protien was retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB ID 1NFY) and (PDB ID 3LN1). The experimental (*in vivo*) studies were carried out against Factor Xa and COX-2 from Sprague Dawley rats and docking study against human F-Xa (PDB ID: 1NFY) and COX-2 (PDB ID 3LN1) at 2.1 Å resolution.

3.4.1 Preparation of target F-Xa, COX-2 and compounds for docking

The coordinate files were subjected to Discovery Studio 4.5 Visualizer for pre-docking receptor preparation by removing water molecules and adding hydrogen atoms. Ligands **5a, RPR200095, 9-17** were docked with F-Xa (1NFY) and **5a, 5b**, **8-29** and **31-50** were docked with COX-2 (3LN1) by *Patch Dock* (http://bioinfo3d.cs.tau.ac.il/PatchDock/) to find the docking transformations that produce good molecular shape complementarily based on shape complementarily principles [175]. The input files include the receptor protein and ligand in PDB format. *Patch Dock* offers multiple solutions and the "solution 1" was selected as it surrounded the most crucial residues as binding pocket for docking analyses assigned in crystal structure of F-Xa target site (1NFY) [176]. The docked structures were examined by using Discovery Studio 4.5 Visualizer and Chimera 1.9.

3.4.2 Docking analysis

The binding affinities of the docked ligands were evaluated as scores and Atomic Contact Energy (ACE) of the docked complexes. The hydrogen bonding and hydrophobic interactions of each ligand was assessed within binding pocket of receptor protein. The conformation of the ligands which illustrated the highest biological activities is showed in Table 4.16 and Figures 4.4-4.7 for thrombolytic potential, Tables 4.17 & 4.18 and Figures 4.8-4.14 for anti-inflammatory potential with their favorable contacts in the binding pockets. To get qualitative evaluation and to recognize molecular basis of the calculated biological activities, the docked complexes of ligands **5a, 5b, RPR200095** and **8-50** were investigated.

3.5 Computational Methodology:

In this study, all the computational calculations (including representation of the "Highest Occupied Molecular Orbital" HOMO and "Lowest Unoccupied Molecular Orbital" LUMO in the checkpoint files) were performed by Gaussian 09 software [164] with Becke's three parameter hybrid exchange functional [165] and Leee-Yange-Parr correlation functionals (B3LYP) [166, 167]. The geometry of all the structures were optimized using B3LYP/6-31G** basis set. To ensure that the optimized geometry actually corresponds to the equilibrium (minimum energy) structure, the harmonic vibrational frequency analysis was also performed at same basic set level to detect any imaginary frequency. The Gauss view software package was used to visualize the computed structures including HOMO, LUMO and Molecular electrostatic potential (MEP) representations.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Plan of work:

The present work deals with the synthesis of fibric acids derived oxadiazoles and their hybrids with acetamides because of their broad and intrinsic applications in almost every field of life. The peer review of literature has revealed that these heterocyclic compounds play a vital role in pharmacology as an effective agents for clotlysis and the treatment of inflammation.

The whole synthetic work is generally divided into three main categories:

1. Synthesis of oxadiazoles **(5a & 5b)**
2. Synthesis of *N*-aryl-2-bromoacetamides **(7a-7y)**
3. Synthesis of novel hybrid acetamides of fibric acids derived oxadiazoles **(8-30)** and **(31-50)** by modified method.

Spectroscopic analysis was performed for the Characterization of all these synthesized compounds. After synthesis these desired products were passed through biological screening and *in silico* studies.

4.2 Present Work:

In the present work, two series of novel compounds *N*-substituted 5-{[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides **(8-30)** and *N*-substituted 5-{[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides **(31-50)** were synthesized by converting 2-(4-chloro/bromophenoxy)-2-methylpropanoic acid **(2a & 2b)**

consecutively into their corresponding ethyl esters **(3a & 3b)**, hydrazides **(4a & 4b)** and 5-(2-aryloxypropan-2-yl)-1,3,4-oxadiazol-2-thiols **(5a & 5b)**. Finally, the target compounds **(8-30)** and **(31-50)** were achieved by reacting the parent compounds 5-(2-aryloxypropan-2-yl)-1,3,4-oxadiazol-2-thiols (**5a & 5b)** with different 2-bromoacetamides **(7a-7y)** by using DMF as a solvent and NaH as a base under ultrasonic radiations.

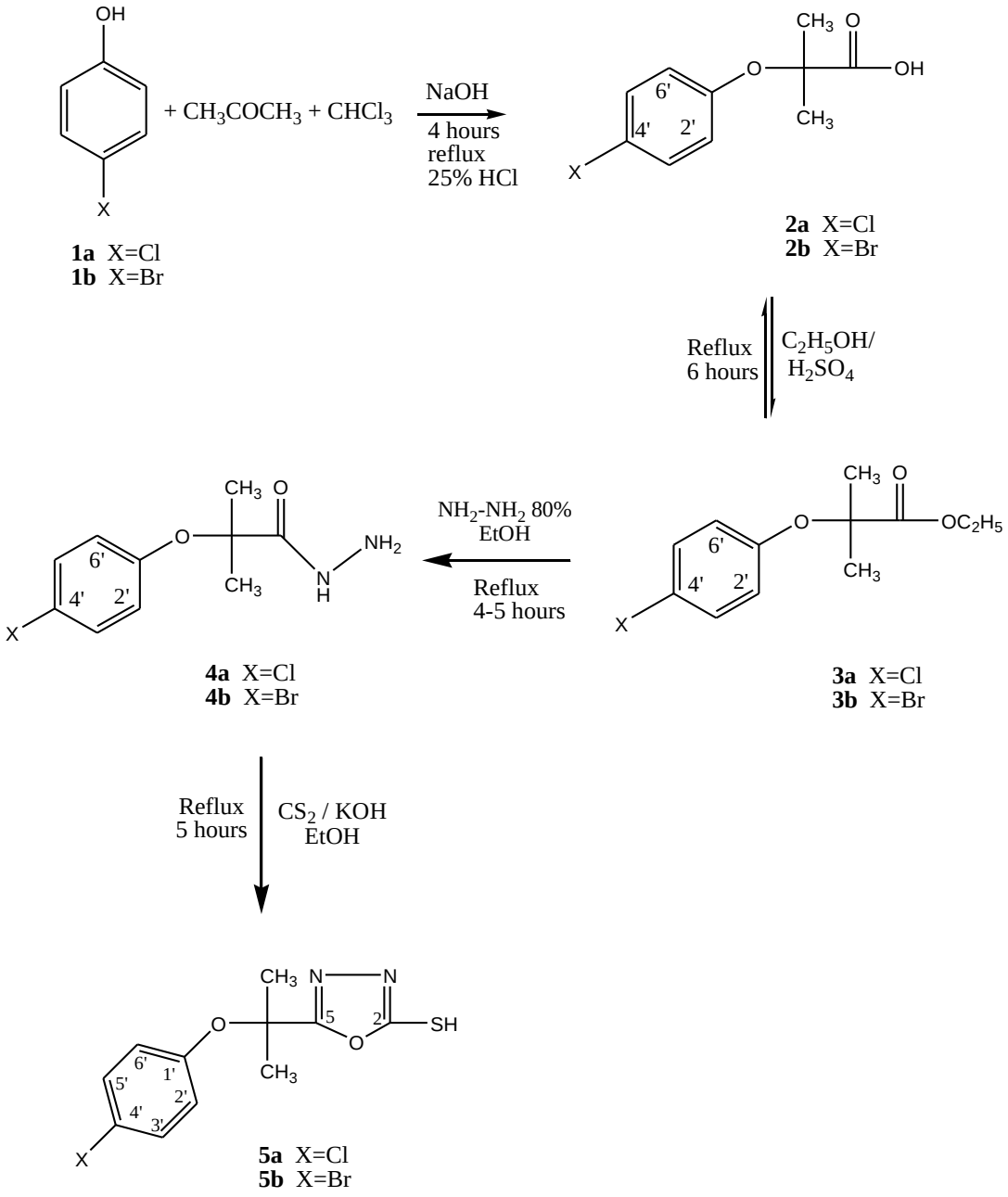
The synthesized compounds were screened for their *in vitro* and *in vivo* antithrombotic and anti-inflammatory activity, and also molecular docking related to both activities. SAR study was also carried out for selected compounds.

4.2.1 Synthesis of 5-(2-aryloxypropan-2-yl)-1,3,4-oxadiazol-2-thiols (5a & 5b):

The 5-(2-aryloxypropan-2-yl)-1,3,4-Oxadiazol-2-thiols **(5a & 5b)** were prepared according to the protocol sketched in scheme-1. Fibric acids **(2a & 2b)** were prepared by multicomponent reactions of 4-chloro/bromophenols **(1a & 1b),** acetone and chloroform using sodium hydroxide as base. The reaction mixture was continuous refluxed for 4 hours and acidified with 25 % HCl to obtain the products.

The fibric acids **(2a & 2b)** were converted to corresponding ethyl esters **(3a & 3b)** by refluxing with ethanol and in the presence of sulfuric acid. The esters **(3a & 3b)** were then converted to respective fibric acids hydrazides **(4a & 4b)** by treating with hydrazine hydrate at reflux in an alcoholic medium.

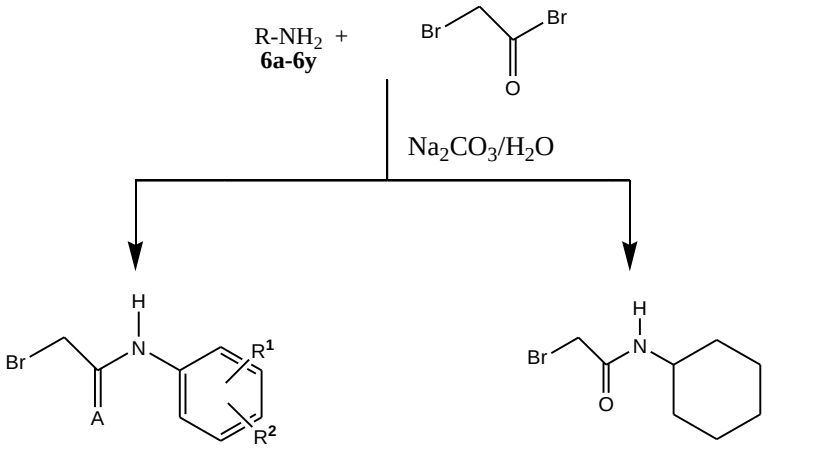
The hydrazides **(4a & 4b)** were then changed to 5-(2-aryloxypropan-2-yl)-1,3,4-oxadiazol-2-thiols **(5a & 5b)** by reacting with carbon disulfide in the presence of potassium hydroxide at reflux.



Scheme-1

4.2.2 Synthesis of *N*-substituted-2-bromoacetamide (7a-7y):

The *N*-substituted-2-bromoacetamides **(7a-7y)** were synthesized by stirring different substituted anilines **(6a-6y)** and 2-bromoacetyl bromide in a basic aqueous media at room temperature (Scheme-2).

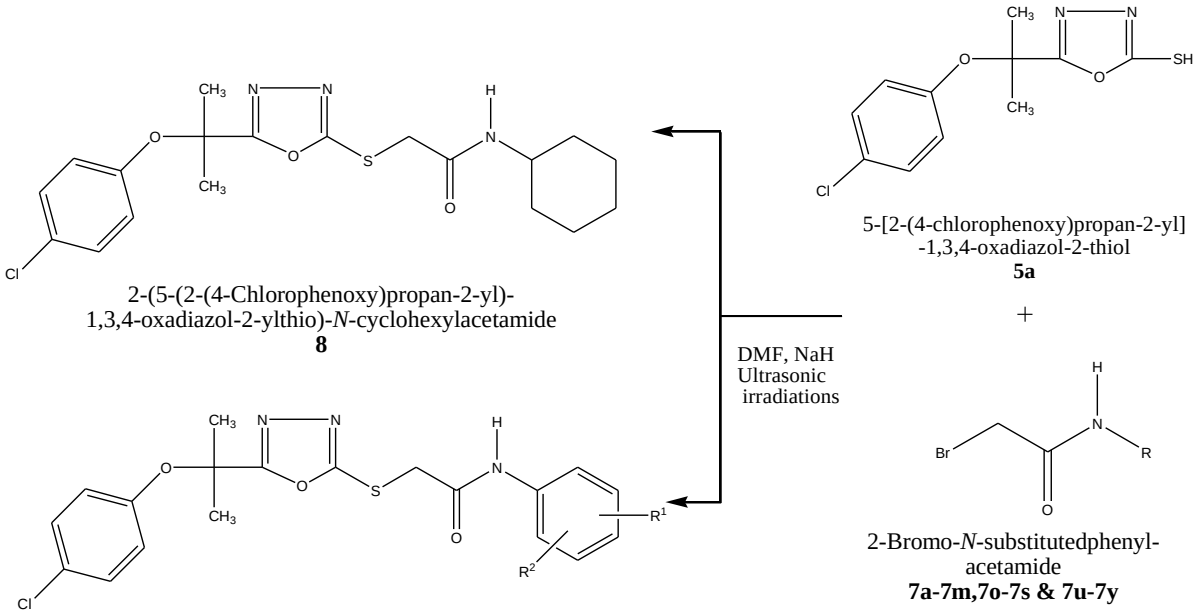


7a	Cyclohexylamine		**7j**	$R^1 = 3CH_3$	$R^2=5CH_3$	**7s**	R^1 = H	R^2=2Br
7b	R^1 = H	R^2=H	**7k**	R^1 = H	$R^2=4C_2H_5$	**7t**	R^1 = H	R^2=3Br
7c	R^1 = H	$R^2=2CH_3$	**7l**	$R^1=2C_2H_5$	$R^2=6CH_3$	**7u**	R^1 = H	R^2=4Br
7d	R^1 = H	$R^2=3CH_3$	**7m**	R^1 = H	$R^2=2OCH_3$	**7v**	R^1 = H	R^2=2Cl
7e	R^1 = H	$R^2=4CH_3$	**7n**	R^1 = H	$R^2=3OCH_3$	**7w**	R^1 = H	R^2=4F
7f	$R^1 = 2CH_3$	$R^2=3CH_3$	**70**	R^1 = H	$R^2=4OCH_3$	**7x**	R^1 = H	$R^2=4NO_2$
7g	$R^1 = 2CH_3$	$R^2=4CH_3$	**7p**	R^1 = H	$R^2=2OC_2H_5$	**7y**	R^1 = H	$R^2=2NH_2$
7h	$R^1 = 2CH_3$	$R^2=6CH_3$	**7q**	R^1 = H	$R^2=4OC_2H_5$			
7i	$R^1 = 3CH_3$	$R^2=4CH_3$	**7r**	$R^1 = 2OCH_3$	R^2=5Cl			

Scheme-2

4.2.3 Synthesis of *N*-substituted 5-{[2-(4-chlorophenoxy) propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides (8-30):

The series of *N*-substituted 5-{[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides **(8-30)** was prepared by the reacting equimolar quantity (0.271 g, 1 mmol) of 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol **5a** with various *N*-substituted-2-bromoacetamides (1 mmol) **(7a-7m, 7o-7s & 7u-7y)** in DMF using NaH as base under ultrasonic radiations.



2-(5-(2-(4-Chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-ylthio)-*N*-cyclohexylacetamide
8

5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol
5a

+

2-Bromo-*N*-substitutedphenyl-acetamide
7a-7m,7o-7s & 7u-7y

N-Substituted 5-{[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamide

9-30

8	Cyclohexylamine		**16**	$R^1 = 3CH_3$	$R^2=4CH_3$	**24**	$R^1 = 2OCH_3$	$R^2=5Cl$
9	R^1 = H	R^2=H	**17**	$R^1 = 3CH_3$	$R^2=5CH_3$	**25**	R^1 = H	$R^2=2Br$
10	R^1 = H	$R^2=2CH_3$	**18**	R^1 = H	$R^2=4C_2H_5$	**26**	R^1 = H	$R^2=4Br$
11	R^1 = H	$R^2=3CH_3$	**19**	$R^1 =2C_2H_5$	$R^2=6CH_3$	**27**	R^1 = H	$R^2=2Cl$

12	R^1 = H	R^2=4CH_3	**20**	R^1 = H	R^2=2OCH_3	**28**	R^1 = H	R^2=4F
13	R^1 = 2CH_3	R^2=3CH_3	**21**	R^1 = H	R^2=4OCH_3	**29**	R^1 = H	R^2=4NO_2
14	R^1 = 2CH_3	R^2=4CH_3	**22**	R^1 = H	R^2=2OC_2H_5	**30**	R^1 = H	R^2=2NH_2
15	R^1 = 2CH_3	R^2=6CH_3	**23**	R^1 = H	R^2=4OC_2H_5			

Scheme 3

4.2.4 Spectral studies of compounds (8-30):

The synthesized compounds were characterized by using spectroscopic techniques i-e FT-IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS.

The characteristic bands in FT-IR spectrum can be observed at 3138-3370 cm^{-1} for NH stretching and at 1616-1671 for C=O stretching in the amide moiety. C-H stretching and aromatic C=C stretching can be observed at 2900-3000 and 1450-1580 cm^{-1} (Table 4.1).

Table 4.1 General and FT-IR data of compounds (8-30)

Sr. No.	Code	Yiel %	m.p. ºC	FT-IR υ (cm^{-1})				
				NH	C-H	C=O	Aromatic ring C=C	Others
1	**8**	89	94-96	3178	2966	1653	1532	
2	**9**	75	84-86	3288	3000	1671	1552	-
3	**10**	87	140-142	3339	2981	1667	1484	-
4	**11**	78	71-73	3155	2989	1655	1488	-
5	**12**	84	68-70	3313	2979	1676	1483	-
6	**13**	86	186-188	3300	2952	1645	1478	-
7	**14**	81	78-80	3358	2980	1680	1534	-
8	**15**	89	98-100	3330	2958	1661	1482	-
9	**16**	91	80-82	3357	2904	1640	1480	-
10	**17**	85	122-124	3299	2995	1618	1580	-
11	**18**	88	88-90	3350	2991	1650	1474	-
12	**19**	80	116-118	3232	2988	1654	1466	-
13	**20**	65	172-174	3318	2939	1616	1495	-
14	**21**	77	83-85	3229	2940	1650	1488	-
15	**22**	87	135-137	3220	2977	1416	1506	-
16	**23**	81	103-106	3267	2987	1664	1508	-
17	**24**	88	125-127	3290	2993	1641	1502	732

18	**25**	91	168-170	3321	2979	1688	1481	543
19	**26**	72	118-120	3369	2992	1668	1552	540
20	**27**	74	134-136	3370	2960	1625	1482	727
21	**28**	69	70-72	3385	2997	1667	1573	-
22	**29**	68	126-128	3335	2986	1693	1400	1547
23	**30**	65	131-133	3401	2990	1658	1533	-

The ^{1}H-NMR spectra of compounds (**8-30**) indicate the characteristic signals in the respective region (Table 4.2 & 4.3). The NH proton of amide moiety can be observed at δ 8.19-11.02. The methylene protons (flanked by "S" and "C=O" moieties) can be seen in the region of δ 4.01-4.41. The signals due to two methyl groups attached to carbon (flanked by "O" and oxadiazole moieties) give their characteristic signals at about δ 1.46–1.77. The protons attached to p-chlorophenyl group can be observed as doublets each integrating to two protons at δ 6.63–6.95 corresponding to H-2′ & H-6′ and at δ 7.09-7.82 corresponding to H-3′& H-5′.

The signals for protons on *N*-aryl moiety can be observed in their respective region depending on the nature of aryl groups (Table 4.3).

Table 4.2 H^1-NMR data (aliphatic region) of compounds (8-30)

Sr.No.	Compound	Solvent	NH (s) (δ)	HS, OC, CH_2 (δ)	$C(CH_3)_2$ (δ)
1	**8**	DMSO 500 MHz	8.19, d, *J* = 7.5 Hz	4.06, s	1.67, s
2	**9**	DMSO, 500 MHz	10.42	4.33, s	1.71
3	**10**	DMSO, 500 MHz	10.48	4.26, 4.19 2d, *J* = 17.5 Hz, Ha & Hb	1.48, 1.46,
4	**11**	$CDCl_3$, 500 MHz	8.93	3.97, s	1.77
5	**12**	DMSO, 500 MHz	10.33	4.31, s	1.71
6	**13**	DMSO, 500 MHz	10.45	4.26, 4.18 2d, *J* = 17.5 Hz, Ha & Hb	1.46
7	**14**	$CDCl_3$, 500 MHz	8.59	4.01, s	1.77
8	**15**	DMSO, 500 MHz	9.71	4.34, s	1.73
9	**16**	DMSO, 300 MHz	10.22	4.27, s	1.69
10	**17**	DMSO, 500 MHz	10.27	4.29, s	1.70
11	**18**	DMSO, 500 MHz	10.34	4.31, s	1.71
12	**19**	DMSO, 500 MHz	9.70	4.34, s	1.06
13	**20**	DMSO, 500 MHz	10.42	4.18, s	1.46
14	**21**	DMSO, 500 MHz	10.27	4.28, s	1.71
15	**22**	DMSO, 500 MHz	9.52	4.41, s	1.72
16	**23**	DMSO, 500 MHz	10.26	4.28, s	1.71
17	**24**	DMSO, 500 MHz	9.86	4.41	1.71
18	**25**	DMSO, 500 MHz	10.48	4.28-4.21, m	1.47
19	**26**	DMSO, 500 MHz	10.55	4.23, s	1.71
20	**27**	DMSO, 500 MHz	10.49	4.30-4.21, m	1.47
21	**28**	DMSO, 500 MHz	10.48	4.31	1.71
22	**29**	DMSO, 500 MHz	11.02	4.39, s	1.70,
13	**30**	DMSO, 500 MHz	9.76	4.37, s	1.72

Table 4.3 H^1-NMR data (Aromatic region) of compounds (8-30)

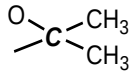
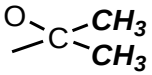
Sr.No.	Code	p-Cholorophenyl		N-Aryl				
		H-2′ & H-6′ (δ)	H-3′ & H-5′ (δ)	Aromatic (δ)			R^1 (δ)	R^2 (δ)
1	**8**	6.76, d, *J* = 9 Hz	7.31,d, *J* = 9 Hz	-	-	-	-	-
2	**9**	6.75, d, *J* = 9 Hz	7.57,d, *J* = 9 Hz	7.33, t, *J* = 7.8 Hz, 2″& 6″	7.28, d, *J* = 8.5Hz, 3″& 5″	7.08, t, *J* = 7.3 Hz, 4″	-	-
3	**10**	6.94, d , *J* = 8.5 Hz	7.38-7.32, m	7.38-7.32,m, 4″, 5″ , 6″	7.22, d, *J* = 8 Hz, 3″	-	-	2.18,s, 2- CH_3
4	**11**	6.65-6.63, m	7.11-7.10, m	7.35, s, 6″	7.27, d, *J* = 8.5 Hz, 5″	7.19, t , *J* = 7.8 Hz, 2″	-	2.32, s, 3-CH_3
5	**12**	6.75, d , *J* = 9 Hz	7.46, d, *J* = 8 Hz	7.27, d, *J* = 9 Hz, 2″& 6″	7.12, d, *J* = 8 Hz, 3″& 5″	-	-	2.25, s, 4-CH_3
6	**13**	6.94, d, *J* = 9 Hz	7.34, d, *J* = 9 Hz	7.27, d, *J* = 7.5 Hz, 5″	7.21, t, *J* = 7.6 Hz, 4″	7.04, d, *J* = 8 Hz, 6″	2.31, s, 2-CH_3	2.03, s, 3-CH_3
7	**14**	6.65-6.63, m	7.11-7.09, m	7.69, d, *J* = 8 Hz, 6″	6.98-6.97, m, 3″& 5″	-	2.27, s , 2-CH_3	2.16,s, 4- CH_3
8	**15**	6.76, d, *J* = 9 Hz	7.26, d, *J* = 9 Hz	7.09-7.06, m, 3″, 4″ ,5″	-	-	2.13, s, 2-CH_3	2.13, s, 6-CH_3
9	**16**	6.75-6.71, m	7.26-7.22, m	7.33, s, 2″	7.26-7.22, m, 6″	7.04, d, *J* = 8 Hz, 5″	2.16, s, 3- CH_3	2.16,s, 4-CH_3
9	**17**	6.75, d, *J* = 8.5 Hz	7.27,d, *J* = 8.5 Hz	7.20, s. 2″& 6″	7.72, s, 4″	-	2.23,s, 3- CH_3	2.23,s, 5-CH_3
10	**18**	6.75, d, *J* = 9 Hz	7.48, d, *J* = 8 Hz,	7.26, d, *J* = 9 Hz, 2″ & 6″	7.15, d, *J* = 8 Hz, 3″& 5″	-	-	2.53, 4-***CH_2***CH_3 merged in DMSO, 1.15, t, *J* = 7.5 Hz, 4-CH_2***CH_3***,
11	**19**	6.77, d, *J* = 6.5 Hz	7.27, d, *J* = 6.5 Hz	7.14-7.09, m, 3″, 4″ 5″	-	-	2.53 , ***2-CH_2***CH_3 merged in DMSO, 1.06, s, 2-CH_2***CH_3***	2.12,s, 6-CH_3

12	**20**	6.93,d, *J* = 8.5 Hz	7.33, d, *J* = 8.5 Hz	7.46, t, *J* = 7.8 Hz, 6″	7.24-7.19, m, 3″& 5″	7.07, t, *J* = 7.5 Hz, 4″	-	3.77, s, 2-O***CH₃***
13	**21**	6.90, d, *J* = 9 Hz	7.28, d, *J* = 9 Hz	7.47, d, *J* = 9 Hz, 2″& 6″	6.75, d, *J* = 9 Hz, 3″& 5″	-	-	3.73, s, 4-O***CH₃***
14	**22**	6.75 ,d, *J* = 9 Hz	7.24, d, *J* = 8.5 Hz	7.98, d, *J* = 7.5 Hz H-6″	7.09-7.03 ,m, 3″& 5″	6.90, t, *J* = 7 Hz, H-4″		4.41, s, 2- O***CH₂***CH_3, 1.36, t, *J* = 7 Hz, 2-OCH_2***CH₃***
15	**23**	6.75, d, *J* = 9 Hz	7.27, d, *J* = 8.5 Hz	7.46, d, *J* = 9 Hz, 2″& 6″	6.88, d, *J* = 8.5 Hz, 3″& 5″	-	-	4.00-3.96, m, 4-O***CH₂***CH_3 , 1.31, t, *J* = 7 Hz, 4-OCH_2***CH₃***
16	**24**	6.74, d, *J* = 9 Hz	7.27 , d, *J* = 8.5 Hz	8.12, s, 6″	7.15-7.07, m, 3″ & 4″	-	3.85, s, 2-O***CH₃***	-
17	**25**	6.95-6.92, m,	7.48-7.46, m	7.83-7.81, m, 6″	7.58-7.54, m, 3″	7.35-7.32 m,4″&5″	-	-
18	**26**	6.74 , d, *J* = 8.5 Hz	7.27 , d, *J* = 9 Hz	7.56-7.50, m, 2″, 6″, 3″& 5″	-	-	-	-
19	**27**	6.94, d, *J* = 9 Hz	7.34, d, *J* = 8.5 Hz	7.68-7.67, m, 6″	7.54-7.47, m, 3″, 4″ ,5″	-	-	-
20	**28**	6.74, d, *J* = 9 Hz	7.27, d, *J* = 8.5 Hz	7.60-7.57, m, 2″& 6″	7.17, t, *J* = 8.5Hz, 3″& 5″	-	-	-
21	**29**	6.74 ,d, *J* = 9 Hz	7.82, d, *J* = 9 Hz	8.24, d, *J* = 9 Hz, 3″& 5″	7.27, d, *J* = 9 Hz, 2″& 6″	-	-	-
22	**30**	6.77, d, *J* = 8 Hz	7.27, d, *J* = 8 Hz	7.55, s, 6″	7.27, d, *J* = 8 Hz, 4″	7.19, s, 3″, 6.77, d, *J*=8Hz, 5″	-	1.72, s, NH_2

^{13}C-NMR spectra of the compounds (**8-30**) also confirmed the formation of products. The characteristic signals are around δ168.30-171.87 corresponding to carbonyl moiety, at δ 33.03-37.36 corresponding to methylene carbon (-S-***CH₂***-CO). The signals for

C-2 and C-5 of oxadiazole moiety appeared at δ 164.38-169.58 and δ 153.27-165.32 respectively. Signals for α–carbon attached to oxadiazole ring seen at δ 75.51-80.87 and at δ 25.22-25.86 corresponding to two methyl groups attached to α–carbon atom. The signals for carbons of p-chlorophenyl group can be seen at 152.79-154.10 for C-1′, 119.62-124.27 for C-2′ & C-6′. 129.24-129.77 for C-3′ & C-5′ and 125.61-130.42 for C-4′. The signals for carbons of *N*-aryl moiety and their substituents can be observed in their respective positions (Table 4.4 &4.5).

Table 4.4 ^{13}C-NMR data (Non-aromatic region) of compounds (8-30)

Sr. No.	**Code**	**Solvent**	C=O (δ)	S-**CH$_2$**-CO (δ)	 (δ)	 (δ)	**Oxadiazole ring**	
							C-2 (δ)	**C-5** (δ)
1	**8**	DMSO, 500MHz	168.73	36.44	75.96	25.72	165.13	164.99
2	**9**	DMSO, 500MHz	168.85	37.32	75.99	25.70	165.17	164.90
3	**10**	DMSO, 500MHz	171.80	33.08	80.83	25.47, 25.44	169.58	164.64
4	**11**	DMSO, 400MHz	169.88	36.23	75.55	25.86	166.17	165.02
5	**12**	DMSO, 500MHz	168.84	37.31	75.98	25.70	164.91	164.90
6	**13**	DMSO, 500MHz	171.87	33.03	80.82	25.45	169.49	164.72
7	**14**	$CDCl_3$ 500MHz	169.93	35.97	75.51	25.88	166.13	165.32
8	**15**	DMSO, 500MHz	168.90	36.25	75.98	25.75	164.98	164.94
9	**16**	DMSO,	168.37	36.79	75.51	25.22	164.38	164.35

		300MHz						
10	**17**	DMSO, 500MHz	168.30	37.31	76.00	25.68	165.03	164.90
11	**18**	DMSO, 500MHz	168.82	37.28	75.98	25.69	164.90	153.27
12	**19**	DMSO, 500MHz	168.89	36.23	75.98	25.76	165.39	164.93
13	**20**	DMSO, 500MHz	171.47	32.82	80.78	25.51, 25.45	169.48	155.22
14	**21**	DMSO, 500MHz	168.84	37.20	75.99	25.70	164.91	164.63
15	**22**	DMSO, 500MHz	168.89	37.18	75.98	25.69	165.41	164.89
16	**23**	DMSO, 500MHz	168.84	37.20	75.99	25.70	164.91	164.61
17	**24**	DMSO, 500MHz	168.88	37.03	75.99	25.67	166.11	164.80
18	**25**	DMSO, 500MHz	171.10	33.18	80.77	25.48, 25.38	169.35	163.17
19	**26**	DMSO, 500MHz	168.86	37.26	75.97	25.69	165.39	164.81
20	**27**	DMSO, 500MHz	171.22	33.13	80.78	25.48	169.40	163.27
21	**28**	DMSO, 500MHz	168.84	37.18	75.97	25.69	165.12	164.84
22	**29**	DMSO, 500MHz	168.94	37.36	75.97	25.70	166.32	164.73
23	**30**	DMSO, 500MHz	168.892	37.20	75.98	25.73	165.77	164.98

Table 4.5 C^{13}-NMR data (aromatic region) of compounds (8-30)

Sr. No.	p-Chlorophenyl				N-Aryl							
	Í (δ)	2′ & 6′ (δ)	3′ & 5′ (δ)	4′ (δ)	Aromatic						R^1 (δ)	R^2 (δ)
					1″ (δ)	2″ (δ)	3″ (δ)	4″ (δ)	5″ (δ)	6″ (δ)		
9	153.29	119.62	129.76	129.93	139.10	124.18	129.32	128.56	129.32	124.18	-	-
10	154.10	121.91	129.46	129.15	136.48	134.57	129.71	127.31	131.26	126.40	-	17.56, 2-CH_3
11	152.84	122.98	129.41	125.61	139.04	116.99	137.43	120.46	128.87	122.98	-	21.44, 3-CH_3
12	153.29	119.64	129.75	128.57	136.60	124.18	129.68	133.13	129.68	124.18	-	20.91, 4-CH_3
13	154.07	121.90	129.45	130.93	138.23	134.58	134.94	130.93	126.68	126.38	14.22, 2-CH_3	20.36, 3-CH_3
14	152.87	122.83	129.39	127.23	135.19	122.83	129.17	132.85	131.24	122.66	17.85, 2-CH_3	20.85, 4-CH_3
15	153.31	124.15	129.76	128.54	135.01	135.60	128.18	127.14	128.18	135.60	18.47, 2-CH_3	18.47, 6-CH_3
16	152.79	123.74	129.24	128.08	136.42	120.29	136.32	131.47	129.63	116.72	19.75, 3-CH_3	18.75, 4-CH_3
17	153.27	124.27	129.73	128.59	138.96	117.39	138.29	125.69	138.29	117.39	21.53, 3-CH_3	21.53, 5-CH_3
18	136.78	124.18	129.74	129.74	128.55	119.70	128.48	139.58	128.48	119.70		28.06, 4-$\boldsymbol{CH_2}CH_3$,16.12, 4- $CH_2\boldsymbol{CH_3}$
19	153.32	124.15	129.75	128.17	141.52	128.52	134.39	126.51	127.51	136.04	24.66, 15.09, 2-C_2H_5	18.49, 6-CH_3
20	154.20	121.16	129.41	130.42	126.23	131.15	113.22	123.76	121.76	121.76	-	56.38, 2-OCH_3
21	153.29	121.19	129.76	128.55	132.22	124.19	114.42	155.99	114.42	124.19	-	55.64, 4-OCH_3
22	153.27	124.16	129.72	128.57	127.52	148.99	112.72	125.19	121.88	120.69		64.46, 14.98 2-OC_2H_5

23	153.92	121.17	129.76	128.55	132.11	124.19	114.93	155.24	114.93	124.19	-	63.56, 15.14. 4-OC_2H_5
24	153.25	124.22	129.71	128.65	124.35	148.40	120.82	125.27	128.61	112.07	-	56.58, 2-OCH_3
25	154.09	121.82	129.43	129.43	134.63	122.68	133.63	131.56	131.74	126.33	-	-
26	153.26	121.54	129.75	128.54	138.44	124.13	132.15	115.78	132.15	124.13	-	-
27	154.10	121.84	129.44	129.43	132.93	128.82	131.59	126.35	130.51	121.90	-	-
28	135.48	124.14	129.75	128.54	135.46	121.45	116.00	153.27	115.82	121.38	-	-
29	153.28	124.07	129.75	128.52	143.00	119.42	125.55	145.14	125.55	119.42	-	-
30	153.31	124.11	129.77	125.91	129.77	128.55	124.11	125.36	128.55	130.63	-	-

The EI-MS spectrum of compound **9** showed molecular ion peak as base peak at m/z 403 and M+ 2 peaks at m/z 405. Some other main peaks have been described in Figure-4.1.

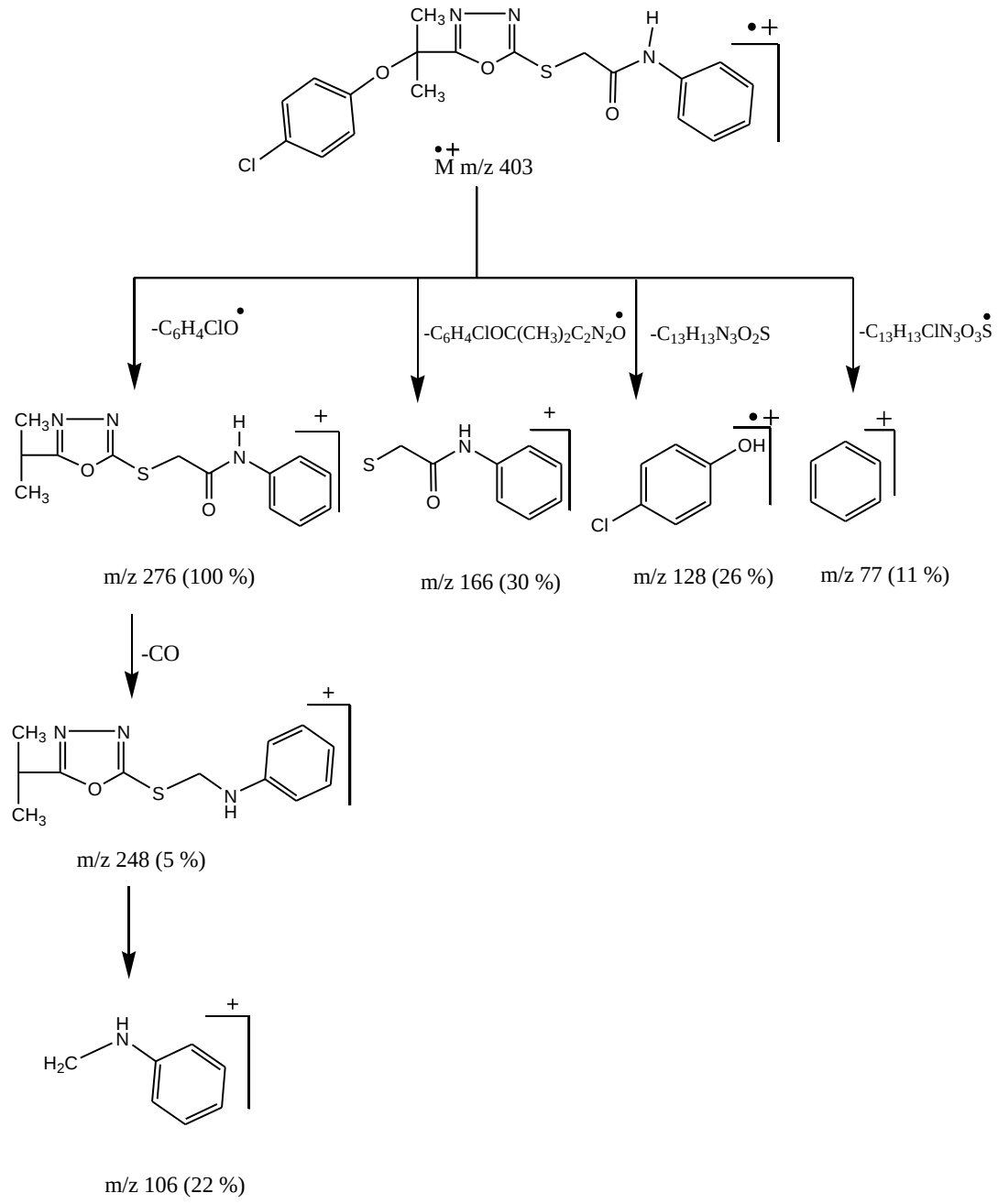


Figure-4.1 EIMS peaks of compound 9

The EI-MS spectrum of compound **13** showed molecular ion peak as base peak at m/z 431 and M+ 2 peaks at m/z 433. Some other main peaks have been described in Figure-4.2.

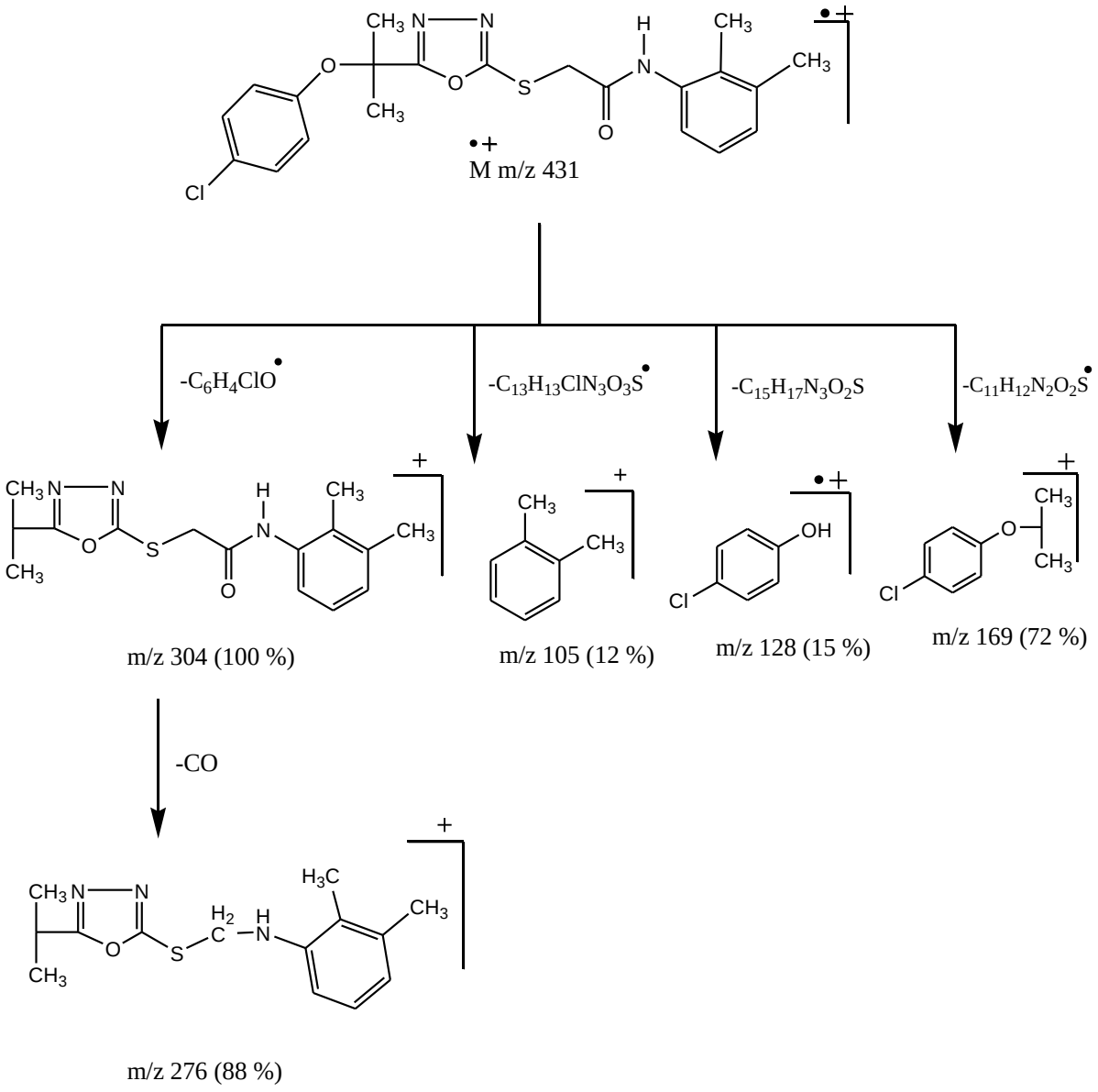
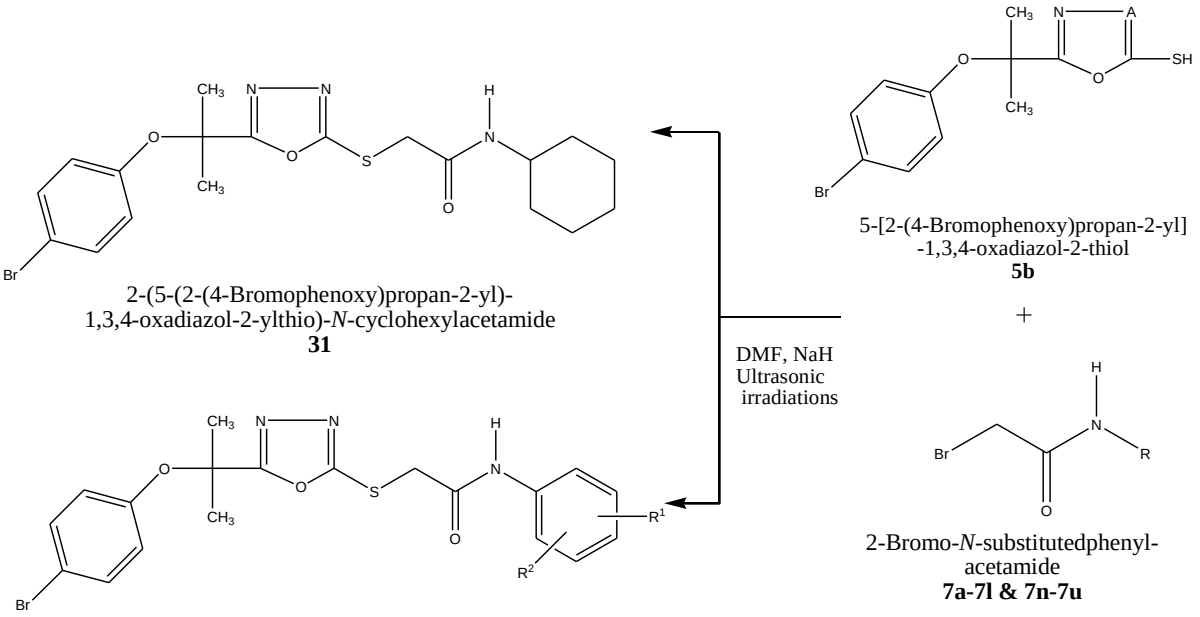


Figure 4.2 EIMS peaks of compound 13

4.2.5 Synthesis of *N*-substituted 5-{[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides (31-50)

The series of *N*-substituted 5-{[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio}acetamides **(31-50)** was synthesized by the reacting equimolar quantity of 5-[2-(4-bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol **5b** (0.314 g, 1 mmol) with various *N*-substituted-2-bromoacetamides (1 mmol) **(7a-7l & 7n-7u)** in DMF using NaH as base under ultrasonic radiations (scheme 4).



31	Cyclohexylamine		**38**	$R^1 = 2CH_3$	$R^2=6CH_3$	**45**	R^1 = H	$R^2=2OC_2H_5$
32	R^1 = H	R^2=H	**39**	$R^1 = 3CH_3$	$R^2=4CH_3$	**46**	R^1 = H	$R^2=4OC_2H_5$
33	R^1 = H	$R^2=2CH_3$	**40**	$R^1 = 3CH_3$	$R^2=5CH_3$	**47**	$R^1 = 2OCH_3$	R^2=5Cl
34	R^1 = H	$R^2=3CH_3$	**41**	R^1 = H	$R^2=4C_2H_5$	**48**	R^1 = H	R^2=2Br
35	R^1 = H	$R^2=4CH_3$	**42**	$R^1 =2C_2H_5$	$R^2=6CH_3$	**49**	R^1 = H	R^2=3Br

36 $R^1 = 2CH_3$ $R^2=3CH_3$ **43** $R^1 = H$ $R^2=3OCH_3$ **50** $R^1 = H$ $R^2=4Br$

37 $R^1 = 2CH_3$ $R^2=4CH_3$ **44** $R^1 = H$ $R^2=4OCH_3$

Scheme 4

4.2.6 Spectral studies of compounds (31-50):

The synthesized compounds **31-50** were characterized by using spectroscopic techniques i-e FT-IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS.

The characteristic bands in FT-IR spectrum can be observed at 3301-3939 cm^{-1} for NH stretching and at 1601-1678 for C=O stretching in the amide moiety. C-H stretching and aromatic C=C stretching can be observed at 2930-2995 and 1475-1568 cm^{-1} (Table 6).

Table 4.6 General and FT-IR data of compounds (31-50)

Sr. No.	Code	Yiel %	m.p. °C	FT-IR υ (cm^{-1})				
				NH	C-H	C=O	Aromatic ring	Others
1	**31**	91	92-94	3381	2930	1644	1475	-
2	**32**	86	88-90	3365	2936	1601	1552	
3	**33**	81	84-86	3301	2975	1651	1487	-
4	**34**	87	64-66	3327	2983	1604	1516	-
5	**35**	89	60-62	3401	2992	1621	1512	-
6	**36**	85	154-156	3327	2925	1601	1512	-
7	**37**	80	71-73	3396	2971	1609	1522	-
8	**38**	92	104-106	3310	2952	1645	1480	-
9	**39**	93	79-81	3393	2981	1629	1562	-
10	**40**	88	68-70	3398	2917	1614	1560	-
11	**41**	90	85-87	3357	2996	1654	1524	-
12	**42**	92	98-100	3343	2978	1657	1528	-
13	**43**	76	92-94	3485	2930	1623	1568	-

14	**44**	79	71-73	3357	2981	1678	1509	-
15	**45**	84	95-97	3327	2985	1603	1506	-
16	**46**	87	89-91	3384	2988	1660	1509	-
17	**47**	86	118-120	3310	2975	1665	1531	722
18	**48**	83	164-166	3339	2981	1667	1484	580
19	**49**	85	105-107	3939	2991	1643	1487	577
20	**50**	81	94-96	3364	2995	1621	1481	574

The ^{1}H-NMR spectra of compounds **31-50** indicate the characteristic signals in the respective region. The NH proton of amide moiety can be observed at δ 8.20-10.60. The methylene protons (flanked by "S" and "C=O" moieties) can be seen in the region of δ 4.03-4.41. The signals due to two methyl groups attached to carbon (flanked by "O" and oxadiazole moieties) give their characteristic signals at about δ 1.45–1.71. The protons attached to p-chlorophenyl group can be observed as doublets each integrating to two protons at δ 6.66–7.03 corresponding to H-2′ & H-6′ and at δ 6.70-7.90 corresponding to H-3′& H-5′.

The signals for protons on *N*-aryl moiety can be observed in their respective region depending on the nature of aryl groups (Table 4.7 & 4.8).

Table 4.7 H^1-NMR data (aliphatic region) of compounds (31-50)

Sr.No.	Compound	Solvent	NH (δ)	HS, OC–CH_2 (δ)	>C$(CH_3)_2$ (δ)
1	**31**	DMSO 500 MHz	8.20,d, *J* = 7.5 Hz	4.06, s	1.72, s
2	**32**	DMSO 500 MHz	10.41, s	4.32, s	1.71, s
3	**33**	DMSO 500 MHz	9.74, s	4.35, s	1.47, s
4	**34**	DMSO 500 MHz	10.44, s	4.17, s	1.49, s
5	**35**	DMSO 500 MHz	10.31, s	4.29, s	1.70, s
6	**36**	DMSO 500 MHz	10.45, s	4.26, d, *J* = 7.5 Hz, *Ha*, 4.18, d, *J* = 7 Hz, *Hb*,	1.46, s,C***CH₃***, 1.45, s, C***CH₃***
7	**37**	DMSO 500 MHz	10.44, s	4.24-4.14, m	1.46, s
8	**38**	DMSO 500 MHz	9.75, s	4.37, s	1.76, s
9	**39**	DMSO 500 MHz	10.24, s	4.28, s	1.70, s
10	**40**	DMSO 500 MHz	10.25, s	4.29, s	1.70, s
11	**41**	DMSO 500 MHz	10.44, s	4.15, s	1.47, s
12	**42**	DMSO 500 MHz	9.71, s	4.34, s	1.73, s
13	**43**	DMSO 500 MHz	10.41, s	4.31, s	1.71, s
14	**44**	DMSO 500 MHz	10.42, s	4.14, s	1.47, s

15	**45**	DMSO 500 MHz	10.41, s	4.18-4.03, m	1.47, s
16	**46**	DMSO 500 MHz	10.42, s	4.10-4.05, m	1.47, s
17	**47**	DMSO 500 MHz	9.85, s	4.41, s	1.71, s
18	**48**	DMSO 500 MHz	10.49,s	4.28-4.20, m	1.47, s, 1.46, s
19	**49**	DMSO 500 MHz	10.60, s	4.32, s	1.71, s
20	**50**	DMSO 500 MHz	10.55, s	4.32, s	1.70, s

Table 4.8 H^1-NMR data (aromatic region) of compounds (31-50)

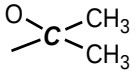
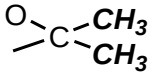
		p-Bromophenyl		**N-Aryl**				
Sr.No.	**Code**	**H-2′&H-6′ (δ)**	**H-3′&H-5′ (δ)**	**Aromatic (δ)**			**R^1 (δ)**	**R^2 (δ)**
1	**31**	6.70, d, *J* = 9 Hz	7.43, d, *J* = 9 Hz	-	-	-	-	-
2	**32**	6.69, d, *J* = 9 Hz	7.33, t, *J* = 8 Hz	7.57, d, *J* = 8 Hz, 2″& 6″	7.40, d, *J* = 9 Hz, 3″& 5″	7.08, t, *J* = 7.5Hz, 4″	-	-
3	**33**	6.70, d, *J* = 8.5 Hz	7.39, d, *J* = 8 Hz	7.39, d, *J* = 8 Hz, 6″	7.22, d, *J* = 7 Hz, 3″	7.16, t, *J* = 7 Hz, 5″, 7.10, t, *J* = 7 Hz, 4″	-	2.20, s, 2-CH_3
4	**34**	6.90, d, *J* = 8.5 Hz	6.70, d, *J* = 11.5 Hz	7.47, d, *J* = 9 Hz, 2″ & 5″	7.42, t, *J* = 7.5 Hz, 6″	7.28, d, *J* = 7.5Hz, 4″	-	2.37, s, 3-CH_3
5	**35**	6.69, d, *J* = 8.5 Hz	7.90, d, *J* = 8.5 Hz	7.48, d, *J* = 8 Hz, 2″ & 6″	7.12, d, *J* = 8.5 Hz, 3″ & 5″	-	-	2.25, s, 4-CH_3

6	**36**	6.94, d, *J* = 9 Hz	7.34, d, *J* = 9 Hz	7.27, d, *J* = 7.5 Hz, 5″	7.21, t, *J* = 7.5 Hz, 4″	7.04, d, *J* = 8 Hz, 6″	2.31, s, 2-CH_3	2.03, s, 3-CH_3
7	**37**	6.87, d, *J* = 8.5 Hz	7.45, d, *J* = 8 Hz	7.17, s, 6″	7.12-7.05, m, 3″& 5″	-	2.32, s, 2-CH_3	2.12, s, 4-CH_3
8	**38**	6.74, d, *J* = 9 Hz	7.42, d, *J* = 8.5 Hz	7.12, s, 3″, 4″ & 5″	-	-	2.17, s, 2-CH_3	2.17, s, 6-CH_3
9	**39**	6.88, d, *J* = 9 Hz	7.37, t, *J* = 8.5 Hz	7.37, t, *J* = 8.5 Hz, 2″	7.26, d, *J* = 8 Hz, 6″	7.06, d, *J* = 8.5 Hz, 5″	2.17, d, *J* = 8 Hz, 3-CH_3	2.17, d, *J* = 8 Hz, 4-CH_3
10	**40**	6.75, t, *J* = 9.5 Hz	7.39, d, *J* = 8.5 Hz	7.20, s, 2″& 6″	6.75, t, *J* = 9.5 Hz, 4″	-	2.33, s, 3-CH_3	2.33, s, 5-CH_3
11	**41**	6.88, d, *J* = 9 Hz	7.35, d, *J* = 8 Hz	7.46, d, *J* = 9 Hz, 2″ & 6″	7.12, d, *J* = 8 Hz, 3″ & 5″	-	-	2.69-2.64, m, 4-***CH₂***CH_3, 1.22,t, *J* = 7.5 Hz, CH_2***CH₃***
12	**42**	6.71, d, *J* = 8.5 Hz	7.39, d, *J* = 8.5 Hz	7.14, t, *J* = 7.5 Hz, 4″	7.08, d, *J* = 8 Hz, 3″ & 5″	-	2.51, 2-***CH₂***CH_3merged inDMSO,1.06, t, *J* = 7.5Hz, CH_2***CH₃***	2.12, s, 6-CH_3
13	**43**	6.70-6.66, M	7.40, d, *J* = 9 Hz	7.28, s, 2″	6.70-6.66, m, 4″	-	-	3.73, s, 3-O***CH₃***
14	**44**	7.05, d, *J* = 9 Hz	7.22, d, *J* = 9 Hz	7.46, d, *J* = 9 Hz, 2″ & 6″	6.88, d, *J* = 9 Hz, 3″ & 5″	-	-	3.80, s, 4-O***CH₃***
15	**45**	6.88, d, *J* = 9 Hz	7.47-7.41, m	7.47-7.41, m, 6″	7.23-7.18, m, 3″ & 5″	7.04, t, *J* = 7.5Hz, 4″	-	4.18, s, 2-O***CH₂***CH_3, 1.25, t, *J* = 7 Hz, OCH_2***CH₃***
16	**46**	7.03, d, *J* = 9 Hz	7.21, d, *J* = 8.5 Hz	7.46, d, *J* = 9 Hz, 2″ & 6″	6.88, d, *J* = 9 Hz, 3″ & 5″	-	-	4.13, s, 2-O***CH₂***CH_3, 1.35, t, *J* = 7 Hz, OCH_2***CH₃***

17	**47**	6.69, d, *J* = 9 Hz	7.39, d, *J* = 8.5 Hz	8.12, s, 6″	7.15-7.08, m, 3″ & 4″	-	3.86, s, 2-O***CH₃***	-
18	**48**	6.88, d, *J* = 9 Hz	7.47-7.44, m	7.81, d, *J* = 8.5 Hz, 6″	7.56, t, *J* = 8 Hz, 3″	7.47-7.44, m, 4″ & 5″	-	-
19	**49**	6.69, d, *J* = 9 Hz	7.40, d, *J* = 9 Hz	7.94, s, 2″	7.64, d, *J* = 7 Hz, 6″	7.32-7.27, m, 4″ & 5″	-	-
20	**50**	6.68, d, *J* = 9 Hz	7.40, d, *J* = 9 Hz	7.56-7.50, m, 2″, 6″, 3″ & 5″	-	-	-	-

^{13}C-NMR spectra of the compounds **31-50** also confirmed the formation of products. The characteristic signals are around δ168.82-176.68 corresponding to carbonyl moiety, at δ 33.01-42.07 corresponding to methylene carbon (-S-***CH₂***-CO). The signals for C-2 and C-5 of oxadiazole moiety appeared at δ 165.11-174.25 and δ 163.20-169.74 respectively. Signals for α–carbon attached to oxadiazole ring seen at δ 75.90-85.51 and at δ 25.41-30.51 corresponding to two methyl groups attached to α–carbon atom. The signals for carbons of p-chlorophenyl group can be seen at 140.24-159.31 for C-1′, 119.60-129.40 for C-2′ & C-6′. 129.45-137.45 for C-3′ & C-5′ and 114.22-132.62 for C-4′. The signals for carbons of *N*-aryl moiety and their substituents can be observed in their respective positions (Table 4.9 & 4.10).

Table 4.9 ^{13}C-NMR data (non-aromatic region) of compounds 31-50

Sr. No.	Code	Solvent	C=O (δ)	S-**CH$_2$**-CO (δ)	 (δ)	 (δ)	Oxadiazole ring	
							C-2 (δ)	C-5 (δ)
1	**31**	DMSO, 500MHz	168.70	36.44	75.90	25.73	165.11	164.98
2	**32**	DMSO, 500MHz	168.82	37.31	75.94	25.70	165.15	164.88
3	**33**	DMSO, 500MHz	173.60	41.57	80.68	30.49	170.13	169.68
4	**34**	DMSO, 500MHz	176.68	37.89	85.54	30.19	174.20	169.74
5	**35**	DMSO, 500MHz	173.56	42.04	80.69	30.46	169.64	158.50
6	**36**	DMSO, 500MHz	171.87	33.03	85.51	25.45	169.49	164.72
7	**37**	DMSO, 500MHz	176.57	37.75	85.51	30.22	174.25	169.43
8	**38**	DMSO, 500MHz	173.62	41.00	80.64	30.51	169.71	169.68
9	**39**	DMSO, 500MHz	173.55	42.03	80.69	30.45	169.64	169.57
10	**40**	DMSO, 500MHz	173.56	42.07	80.70	30.44	169.76	169.64
11	**41**	DMSO, 500MHz	171.97	33.09	80.77	25.44	169.48	164.99
12	**42**	DMSO, 500MHz	168.86	36.23	75.92	25.76	165.39	164.92
13	**43**	DMSO, 500MHz	168.82	37.34	75.94	25.69	165.22	164.87
14	**44**	DMSO, 500MHz	172.05	33.01	80.78	25.44	169.47	165.12
15	**45**	DMSO,	171.44	32.81	80.73	25.41	169.36	163.85

		500MHz						
16	**46**	DMSO, 500MHz	172.05	33.00	80.78	25.44	169.46	165.16
17	**47**	DMSO, 500MHz	168.88	37.03	75.96	25.68	166.11	164.80
18	**48**	DMSO, 500MHz	171.10	33.19	80.72	25.48	169.31	163.20
19	**49**	DMSO, 500MHz	168.85	37.22	75.94	25.69	165.63	164.79
20	**50**	DMSO, 500MHz	168.85	37.26	75.93	25.70	165.39	164.81

Table 4.10 ^{13}C-NMR data (Aromatic region) of compounds 31-50

Code	**p-Chlorophenyl**				**N-Aryl**							
					Aromatic							
	1′ (δ)	**2′ & 6′** (δ)	**3′ & 5′** (δ)	**4′** (δ)	**1″** (δ)	**2″** (δ)	**3″** (δ)	**4″** (δ)	**5″** (δ)	**6″** (δ)	**R^1** (δ)	**R^2** (δ)
31	153.79	124.54	132.70	116.56	48.63	32.67	24.86	25.60	24.86	32.67	-	-
32	153.75	119.60	132.70	116.58	139.08	124.56	129.32	124.09	129.32	124.56	-	-
33	158.53	129.27	137.45	121.32	140.99	136.83	131.22	130.72	135.60	129.97	-	22.97, 2-CH_3
34	159.31	127.05	137.11	118.99	143.83	133.74	140.01	134.16	134.57	130.48	-	26.01, 3-CH_3
35	141.33	124.38	137.44	121.34	137.88	129.32	134.43	129.32	134.43	129.32		25.68, 4-CH_3
36	154.07	121.90	129.45	130.93	138.23	134.58	134.94	126.60	126.68	126.38	14.22, 2-CH_3	20.36, 3-CH_3
37	159.32	127.02	137.11	132.62	143.93	133.58	136.51	140.79	136.70	118.95	22.24, 2-CH_3	25.94, 4-CH_3
38	158.53	129.27	137.45	121.30	139.75	140.33	132.93	131.89	132.93	140.33	23.23, 2-CH_3	23.23, 6-CH_3
39	158.49	129.37	137.44	121.36	141.66	125.57	141.57	136.69	134.88	121.92	24.02, 3-CH_3	24.08, 4-CH_3

40	158.49	129.40	137.43	121.38	143.70	122.13	143.04	130.44	143.04	122.13	26.30, 3-CH_3	26.30, 5-CH_3
41	144.85	128.41	132.36	114.22	132.87	122.26	128.88	154.57	128.88	122.26	-	28.33, 4-$\boldsymbol{CH_2}CH_3$, 15.99, $CH_2\boldsymbol{CH_3}$
42	153.79	124.52	132.69	127.51	141.51	128.17	126.50	116.55	134.38	136.03	18.49, 6-CH_3	24.68 , 2-($CH_3\boldsymbol{CH_2}$), 15.09 (CH_2-$\boldsymbol{CH_3}$
43	140.24	124.61	132.69	116.62	153.74	105.43	160.01	109.56	130.14	111.86	-	55.48, 3-O$\boldsymbol{CH_3}$
44	154.57	122.26	132.36	114.22	127.78	129.73	114.79	159.61	114.79	129.73	-	55.89, 4-O$\boldsymbol{CH_3}$
45	154.60	122.19	132.33	131.01	130.34	154.46	114.14	124.17	121.04	114.33	-	64.55, 2-O$\boldsymbol{CH_2}CH_3$, 14.96, 2-$OCH_2\boldsymbol{CH_3}$
46	154.57	122.27	132.35	114.22	127.63	129.72	115.19	158.88	115.19	129.72	-	63.84 - O$\boldsymbol{CH_2}CH_3$, 15.07, 4-$OCH_2\boldsymbol{CH_3}$
47	153.74	124.61	132.66	116.65	124.35	148.40	120.83	124.29	128.65	113.08	56.60,OCH_3	
48	154.56	122.24	132.34	122.68	134.63	114.17	133.63	131.56	131.74	129.40	-	-
49	153.73	124.58	132.67	116.63	140.61	122.10	121.95	126.81	131.35	118.40	-	-
50	153.75	121.50	132.69	116.57	138.43	124.51	132.16	115.79	132.16	124.51		

The EI-MS spectrum of compound **39** showed molecular ion peak as base peak at m/z 477 and M+ 2 peaks at m/z 479. Some other main peaks have been described in Figure-4.3

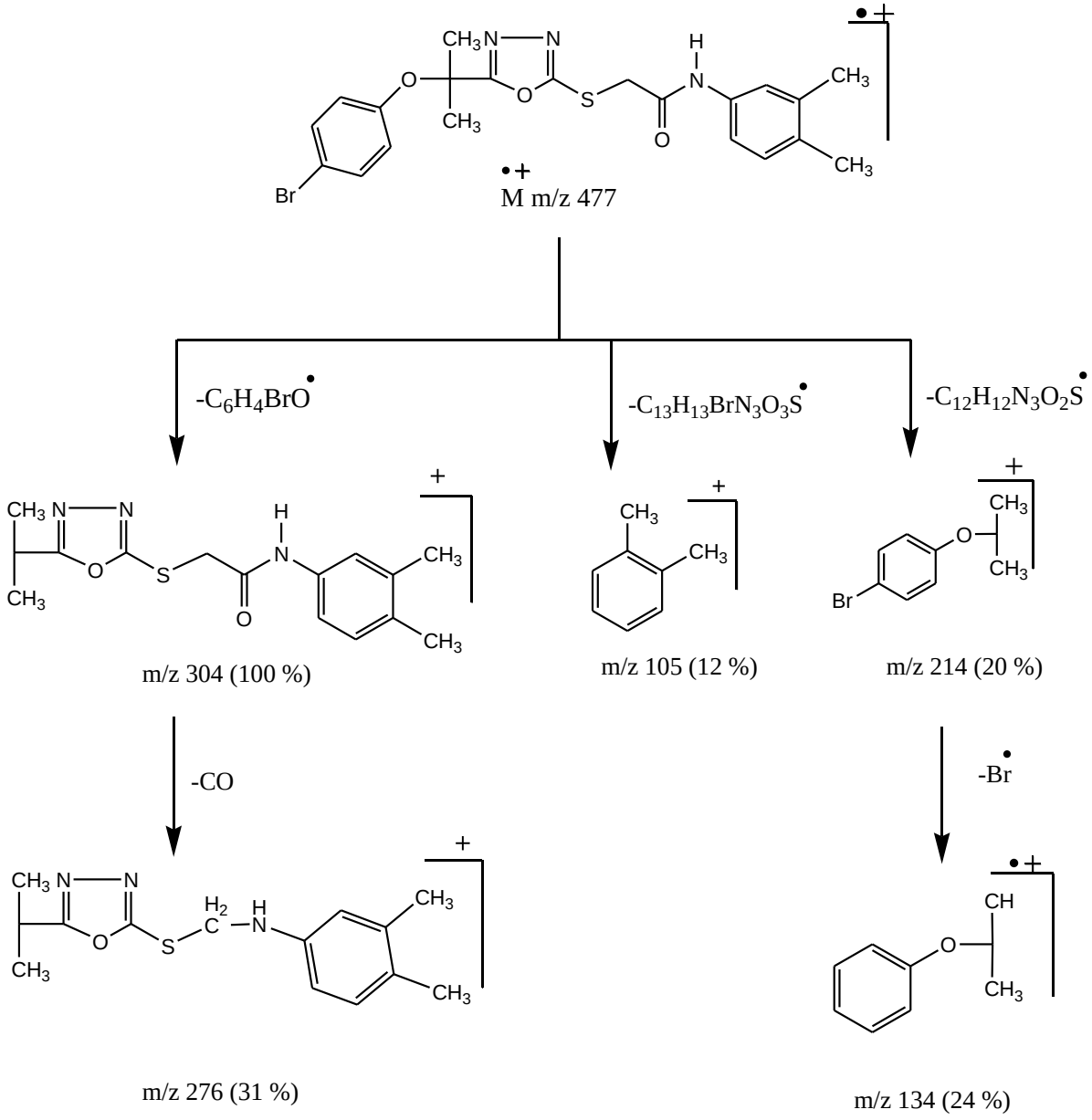


Figure 4.3 EIMS peaks of compound 39

4.3 Biological Screening:

The selected synthesized compounds were evaluated for anti-inflammatory and anti-thrombotic activity both *in vivo* and *in vitro*.

4.3.1 Anti-thrombotic activity (*in vitro & in vivo*):

Fibric acids derivatives were assessed in *vitro* for their thrombolytic potential by clot lysis study. The results of tested compounds were compared with standard drug streptokinase. The results of clot lysis revealed that compound **17, 27** and **36** showed excellent percentage of clot lysis even higher than standard drug. Compound **39** showed results comparable to standard drug. All remaining compounds exhibited normal to moderate activity (Table 4.11).

Table 4.11 Clot lysis effect of synthetic compounds on human blood (*in vitro*)

Sr. No.	Compounds	% Clotlysis	Sr. No.	Compounds	% Clotlysis
1	**5a**	20	**18**	**31**	28
2	**5b**	18	**19**	**32**	30
3	**8**	26	**20**	**33**	35
4	**9**	27	**21**	**34**	27
5	**10**	21	**22**	**36**	39
6	**11**	11	**23**	**37**	33
7	**12**	25	**24**	**39**	38
8	**13**	32	**25**	**38**	29
9	**14**	25	**26**	**41**	35
10	**15**	21	**27**	**42**	33
11	**16**	21	**28**	**43**	26
12	**17**	41	**29**	**48**	32
13	**19**	30	**30**	**50**	31
14	**21**	21	**31**	**Distilled water**	4
15	**24**	22			
16	**27**	39	**32**	**Streptokinase (SK)**	38
17	**30**	22			

The synthesized compounds were also evaluated for anti-thrombotic activity in rats. Clotting time (CT) of these compounds was checked in *vivo* and in *vitro.* Whole blood after removal from vascular system and on exposure to external environment was converted into solid clot. Within limits, time required for conversion of blood into solid clot is a measure of coagulation system. In *vivo* studies majority of the tested compounds showed prominent prolongation in clotting time. Compound **9** (342 sec.), **32** (246 sec.), **17** (214 sec.), **13** (167 sec.), **36** (158 sec.), **41** (149 sec.), **48** (137 sec.), **24** (134 sec), **12** (132 sec.), **16** (130 sec.) and **27** (128 sec.) showed CT values even greater than standard drug heparin (110 sec.). Compound **43** showed results comparable to standard drug. All remaining compounds showed moderate inhibitory potential.

Table 4.12 *In vivo* antithrombotic activity (CT) of compounds

Sr. No.	Code	1 hr (sec)	2 hr (sec)	3hr (sec)	4 hr (sec)	5 hr (sec)	6 hr (sec)	7 hr (sec)
1	**5a**	45	57	70	76	91	98	74
2	**5b**	43	58	66	75	80	85	87
3	**9**	188	201	254	279	310	341	342
4	**10**	58	71	83	90	101	105	108
5	**11**	42	50	58	75	90	93	95
6	**12**	70	98	123	142	154	161	132
7	**13**	118	150	170	200	205	194	167
8	**14**	54	65	75	90	99	95	84
9	**15**	116	133	141	110	91	92	92
10	**16**	80	100	105	110	113	123	130
11	**17**	122	150	189	219	220	202	214
12	**19**	61	70	81	89	96	108	112
13	**21**	68	74	86	91	100	104	106
14	**24**	77	89	101	109	119	124	134
15	**27**	81	90	103	112	117	123	128
16	**31**	52	67	78	83	90	93	85
17	**32**	136	151	175	192	118	133	246
18	**33**	49	58	71	85	93	96	101
19	**34**	41	48	57	72	86	99	97
20	**36**	111	123	148	164	170	176	158
21	**37**	50	63	69	83	90	94	86
22	**38**	105	122	134	121	108	101	95
23	**39**	83	98	107	115	121	122	127
24	**41**	76	97	113	123	138	146	149
25	**42**	55	69	81	90	99	104	106
26	**43**	57	74	88	101	109	116	111
27	**48**	74	105	117	139	146	149	137
28	**50**	71	96	105	119	123	130	120
29	**Standard**	70	84	97	101	105	109	110

In *vitro* clotting time studies none of the compounds showed higher clotting time than standard drug heparin. Majority of compounds showed moderate activity. Results are given below in Table 4.13

Table 4.13 *In vitro* CT of compounds

Sr. No.	Code	CT (sec)	Sr. No.	Code	CT (sec)
1	**5a**	37	**17**	**31**	74
2	**5b**	34	**18**	**32**	158
3	**8**	130	**19**	**33**	120
4	**9**	174	**20**	**34**	118
5	**10**	135	**21**	**36**	142
6	**11**	102	**22**	**37**	126
7	**12**	80	**23**	**38**	116
8	**13**	120	**24**	**39**	163
9	**14**	117	**25**	**40**	168
10	**15**	150	**26**	**41**	98
11	**16**	60	**27**	**42**	124
12	**17**	160	**28**	**43**	127
13	**19**	101	**29**	**48**	170
14	**21**	46	**30**	**50**	173
15	**24**	138	**31**	**Control**	47
16	**27**	132	**32**	**Heparin**	207

4.3.2 Anti-inflammatory Activity (in *vitro* and in *vivo*):

In *vitro* anti-inflammatory activity has been performed by following "percentage inhibition of protein denaturation" protocol. The increase in absorbance value of target compounds as compared to control is due to stabilization or inhibition of albumin denaturation effect of tested compounds and standard drug diclofenic sodium [177]**.**

In vitro none of the target compounds showed higher activity than standard drug diclofenic sodium. Compounds **28, 36, 37, 38, 39** and **50** exhibited good activity. Remaining compounds showed moderate activity while compounds **11, 16** and **41** exerted poor results.

Table 4.14 *In vitro* anti-inflammatory activity

Sr. No.	Code	Absorbance (nm)	% inhibition	Sr. No.	Code	Absorbance (nm)	% inhibition
1	**5a**	0.627	13	**20**	**28**	2.05	271
2	**5b**	0.834	18	**21**	**31**	1.48	164
3	**8**	1.79	223	**22**	**32**	1.25	118
4	**9**	1.85	234	**23**	**33**	1.69	204
5	**10**	1.51	173	**24**	**34**	1.86	236
6	**11**	0.98	76	**25**	**36**	1.97	267
7	**12**	1.77	219	**26**	**37**	2.17	280
8	**13**	1.76	218	**27**	**38**	2.10	278
9	**14**	1.56	182	**28**	**39**	2.20	287
10	**15**	1.17	111	**29**	**41**	1.15	108
11	**16**	1.09	97	**30**	**42**	1.72	194
12	**17**	1.83	230	**31**	**43**	1.74	215
13	**19**	1.88	241	**32**	**48**	1.87	238
14	**21**	1.89	242	**33**	**50**	2.14	284
15	**23**	1.76	219	**34**	**Control**	0.55	0
16	**24**	1.84	232				
17	**25**	1.55	180	**35**	**Diclofenic sodium**	2.26	308
18	**26**	1.93	249				
19	**27**	1.85	235				

In *vivo* anti-inflammatory activity the “carrageenan induced paw edema” protocol was applied and volumes of paw were noted within 4 hours interval of time. Carrageenan is a polysaccharide that facilitates the activation of inflammatory mediators. Inflammation causes vasodilation of blood vessels and capillaries. Thus dilation of capillaries occurs due to inflammation below the surface where carrageenan is applied. This causes an in increase of blood flow to that area resulting in redness or swelling.

Table 4.15 In *vivo* anti-inflammatory activity

Sr. No.	Code	0 hour (Ml)	1hour (Ml)	2hour (Ml)	3hour (Ml)	4hour (Ml)
1	**5a**	0.4	0.7	0.68	0.65	0.6
2	**5b**	0.4	0.72	0.64	0.62	0.58
3	**8**	0.4	0.7	0.64	0.54	0.45
4	**9**	0.3	0.7	0.63	0.59	0.4
5	**10**	0.3	0.7	0.69	0.66	0.64
6	**11**	0.4	0.5	0.48	0.44	0.4
7	**12**	0.4	0.69	0.62	0.51	0.45
8	**13**	0.4	0.6	0.58	0.53	0.5
9	**14**	0.3	0.7	0.62	0.55	0.5
10	**15**	0.3	0.6	0.57	0.54	0.5
11	**16**	0.3	0.5	0.49	0.46	0.41
12	**17**	0.3	0.6	0.52	0.42	0.40
13	**19**	0.3	0.6	0.56	0.55	0.5
14	**21**	0.3	0.6	0.58	0.56	0.5
15	**24**	0.4	0.65	0.58	0.47	0.45
16	**27**	0.4	0.68	0.7	0.7	0.7
17	**31**	0.3	0.59	0.55	0.52	0.51
18	**32**	0.4	0.7	0.67	0.61	0.56
19	**33**	0.4	0.7	0.67	0.65	0.63
20	**34**	0.4	0.68	0.63	0.59	0.55
21	**36**	0.4	0.7	0.66	0.64	0.63
23	**37**	0.3	0.6	0.57	0.55	0.53
24	**38**	0.3	0.6	0.54	0.5	0.48
25	**39**	0.4	0.68	0.66	0.65	0.64
26	**41**	0.3	0.6	0.58	0.56	0.56
27	**42**	0.3	0.6	0.56	0.53	0.5
28	**43**	0.4	0.7	0.68	0.61	0.55
29	**48**	0.4	0.65	0.61	0.58	0.55
30	**50**	0.4	0.75	0.71	0.7	0.69
31	**Control**	0.3	0.7	0.72	0.75	0.76
32	**Diclofenic sodium**	0.3	0.7	0.61	0.54	0.5

The findings of experiments indicated that target compounds **8, 9, 11, 12, 16, 17, 24, 34** and **48** showed potent COX-2 inhibitory potential in *vivo*. These compounds showed reduction in paw volume greater than standard drug. Compounds **14**, **15**, **19**, **21**, **31, 38** and **42** results were comparable to that of standard drug while all remaining compounds exhibited moderate activity.

4.4 Molecular docking studies:

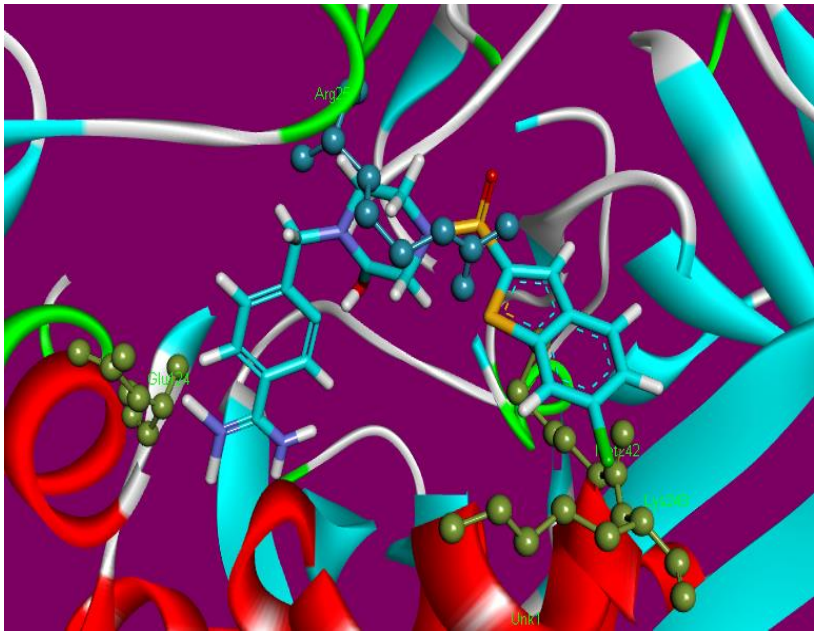
4.4.1 Anti-thrombotic activity (Factor Xa protien)

The serine protease F-Xa plays a crucial role in blood coagulation process by converting prothrombin to thrombin. This F-Xa is located at the conjunction point of extrinsic and intrinsic pathway. In coagulation process one molecule of F-Xa activates many molecules of prothrombin to thrombin by signal amplification [178, 176].Therefore the inhibition of F-Xa is considered to be an effective treatment for many thrombotic events with low risk of bleeding as compared to direct thrombin inhibition [179].

There are four binding pockets labeled as S1 to S4 within the active site. The most important are S1 and S4 binding pockets that are exploited by Factor Xa inhibitor. The S1 pocket is in the form of a narrow cleft and it usually favors positively charged moieties such as benzamidine, amine and guanidine [180]. The second main binding pocket is S4 and is

shaped by different amino acid residues [181, 182]. The energy score (S) was the main criterion to evaluate the binding affinity of ligand. The compound which showed highest binding affinity forms the most stable ligand-enzyme complex. The result of docking studies; energy score, involved factor Xa active site amino acid residues, interacting ligands moieties for each compound and reference inhibitor are given in Table 4.16 and Figures 4.4-4.7. Analysis of docking results showed that:

Standard **RPR200095** was also docked with F-Xa for comparison and has depicted score 5192 with an ACE value -197.81 kcal/mol (Figure 4.4). **RPR200095** has exhibited hydrophobic contact potential with pocket amino acids Lys^{243}, Arg^{25}, Met^{242}.



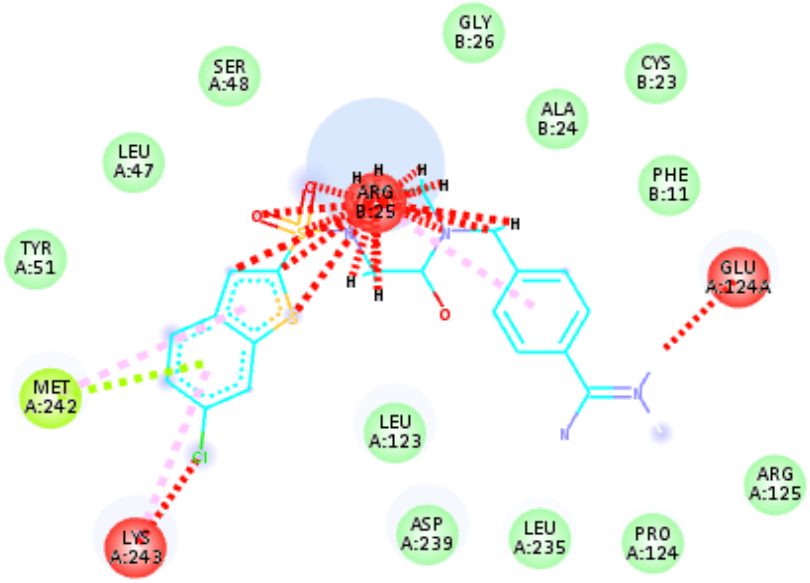


Figure-4.4 Binding site interaction of standard RPR200095

In the initial assessment of the docked complexes of F-Xa **(5a, RPR200095, 9-17)** revealed that five ligands **9, 12, 13, 16** and **17** showed significant interaction patterns even better than standard **RPR200095**. These were found to bind near the entrance of active site george. However, as compared to binding of standard RPR200095, ligands **9, 12, 13, 16** and **17** do not penetrate deep into the binding pocket like RPR200095 instead due to the bulkiness of these ligands they fit on the top of the binding pocket, possibly blocking the substrate entry or the product release from the active site, in that way showing anticoagulant activity.

Ligand **9** showed most potent interaction with F-Xa active site with a score of 6270 and an ACE of -352.28 kcal/mol. Visual inspections of these complexes predicts a binding conformation of ligand **9** showed significant interaction with F-Xa binding site compared to the other 10 ligands. The interacting residue of this complex is Arg^{25} (Figure 4.7). Ligand **9** has shown a potential hydrogen bond between *NH* adjacent to carbonyl and phenyl-groups and Arg^{25}. The length of the hydrogen bond was 2.94 Å indicating significant interaction. Similarly, ligand **9** exhibited hydrophobic contact potential with pocket amino acids Ala^{24}, $Pro^{43}$and also depicted pi-sulphur contact potential with Cys^{44}.

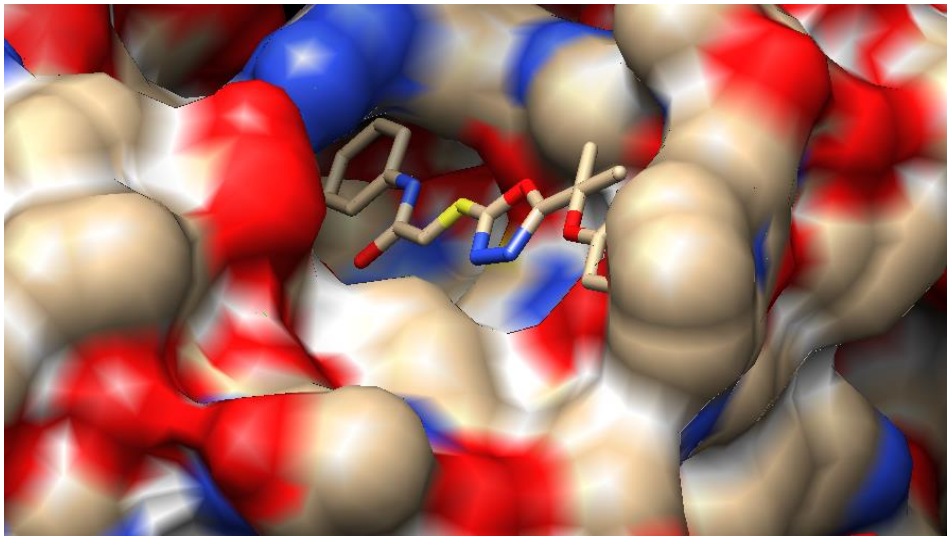


Figure 4.5 Hyde affinity analysis of most active inhibitor 9

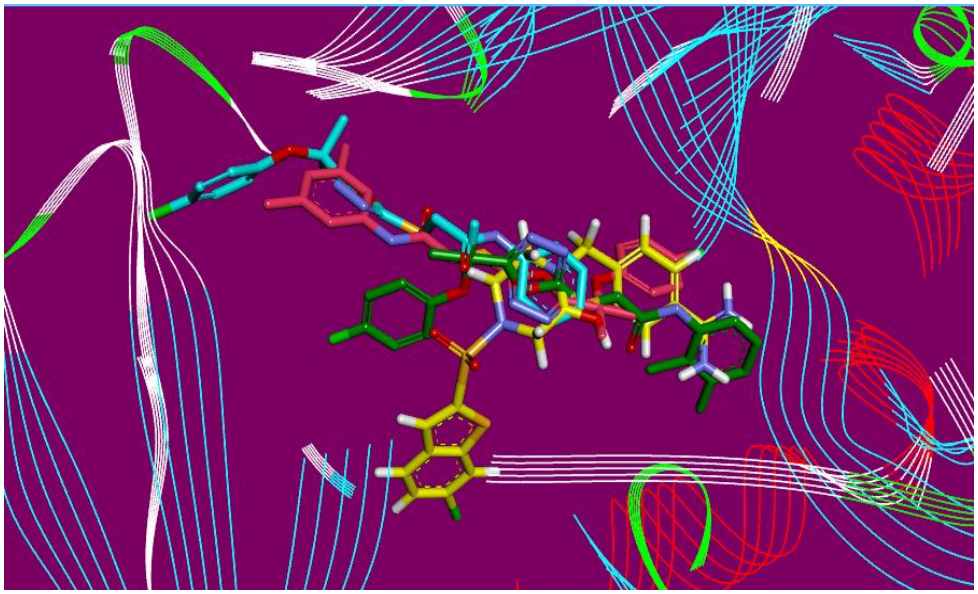


Figure 4.6 Overlap of bound conformations of RPR200095 (yellow) with compounds 9 (blue), 17 (pink) and 13 (green).

Interestingly, ligand **17** showed no hydrogen bond interaction with F-Xa receptor but instead found significant geometric fit of this ligand in the receptor and hence scoring in *Patch Dock* being based on shape complementarily principles it gave a score of 5612 and an ACE of -312.12 kcal/mol with Factor Xa (Figure 4.7). Ligand **17** exhibited pi-cation contact potential with Arg^{25} and 1,3,4-oxadiazole, and hydrophobic interaction found between Arg^{25} and 4-chlorophenyl- group. Ligand **13** showed interaction with F-Xa active site with a score of 5518 and an ACE of -189.68 kcal/mol. Ligand **13** showed three hydrogen bonds between Arg^{25} and oxygen of *1,3,4-oxadiazole* (2.98 Å), Leu^{123} and nitrogen of*1,3,4-oxadiazole* (3.03 Å), Pro^{124} and *NH* adjacent to *carbonyl* and *2,3-dimethylphenyl* groups (3.17 Å). Similarly, ligand **13** has exhibited hydrophobic contact potential with pocket amino acids Lys^{236}, Ala^{24}, Arg^{25}, Leu^{123} and Cys^{44} respectively. Ligand **13** has shown potential for pi-stack interaction with Leu^{235} and *2,3-dimethylphenyl* moiety (Figure 4.7).

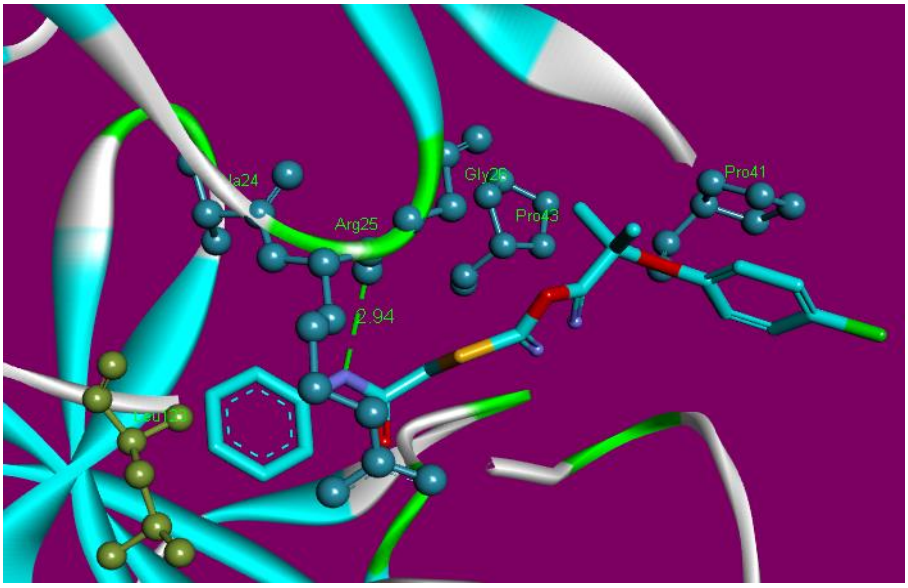
In case of ligands **12** and **16** depicted scores 5646 and 5612 with an ACE values –287.52 and -311.48 kcal/mol, respectively. This ligand **12** showed a potential to accept a hydrogen bond from the backbone amino groupArg^{25} and sulphur attached with *1,3,4-oxadiazole* (3.19 Å), Leu^{123} and nitrogen of 1,3,4-oxadiazole (3.25 Å) and also exhibited hydrophobic contact potential with pocket amino acids Cys^{44}, Pro^{120}, Arg^{25}, Leu^{235}, Lys^{236} and can play an important part to give this ligand good binding affinity than other ligands of this series. Ligand **16** has shown potential for van der Waals contact and such interactions involve the hydrophobic contact with Pro^{43}, Leu^{123} and Phe^{114}. This ligand depicted arene-cation contact with Arg^{25}, also exhibited pi-sulphur contact with Met^{242} and 1,3,4-oxadiazole and was unable to show polar interactions with the pocket amino acids.

Table 4.16 Docking results for the antithrombotic activity of compounds 9-17

Compd. No.	Score	*In-vivo* anticoagulant activity at 7th h (Sec)	ACE Kcal/mole	Amino acids showing hydrogen bond contacts	Distance (Å)	Amino acids showing van der Waals contacts lie within 4 Å	Amino acids showing hydrophobic contacts lie within 4 Å	Amino acids showing arene-cation contacts
5a	3562	74	-197.87	Glu^{49}	3.22	Ser^{48}, Leu^{47}, Met^{242}, Ala^{24}, Cys^{122}, Pro^{43}, Tyr^{42}	Pro^{120}, Phe^{114}, Cys^{44}, Arg^{25}, Leu^{123}	Arg^{25}
9	6270	342	-352.28	Arg^{25}	2.94	Tyr^{42}, Met^{242}, Phe^{114}, Cys^{122}, Leu^{47}, Ser^{48}, Pro^{120}, Gly^{26}, Gly^{40}, Thr^{39}	Ala^{24}, Pro^{43}	-
10	5312	108	-370.05	-	-	Leu^{47}, SER^{48}, Pro^{120}, Tyr^{42}, Phe^{114}, Pro^{41}, Gly^{40}, Pro^{124}, Glu^{124}	Cys^{44}, Pro^{43}, Gly^{26}, Pro^{124}, Met^{242}, Phe^{11}, Ala^{24}, Leu^{123}	Arg^{25}
11	5324	95	-253.57	Arg^{25}	2.83	Arg^{125}, Glu^{124}, Pro^{124}, Ala^{24}, Cys^{122}, Phe^{114}, Glu^{49}, Ser^{48}, Leu^{47}, Met^{242}, Asp^{239}	Leu^{123}, Arg^{25}, Pro^{120}, Leu^{235}, Lys^{236}	-
12	5646	132	-287.52	Arg^{25}, Leu^{123}	3.19, 3.25	-	Cys^{44}, Pro^{120}, Arg^{25}, Leu^{235}, Lys^{236}	-
13	5658	167	-189.68	Arg^{25}, Leu^{123}, Pro^{124}	2.98, 3.03, 3.17	Arg^{125}, Glu^{124}, Phe^{114}, Glu^{44}, Ser^{48}	Lys^{236}, Ala^{24}, Arg^{25}, Leu^{123}, Cys^{44}	-
14	5626	84	-340.54	Arg^{25}, Arg^{25}	2.99, 274	Ala^{24}, Gly^{26}, Phe^{114}, Gly^{40}, Pro^{43}, Tyr^{42}, Leu^{47}, Met^{242}, Glu^{124}	Phe^{11}, Leu^{123}, Leu^{235}, Cys^{44}, Pro^{41}, Pro^{120}	-
15	5442	92	-262.48	-	-	Asp^{239}, Pro^{124}, Glu^{124}, Trp^{127}, Cys^{122}	Ala^{24}, Phe^{11}, Cys^{44}, Arg^{25}, Lys^{236}, Arg^{125}, Leu^{235}	-
16	5612	130	-311.48	-	-	Thr^{39}, Gly^{40}, Pro^{41}, Gly^{26}, Pro^{120}, Cys^{44}, Leu^{47}, Asp^{239}, Ala^{24}, Phe^{11}, Glu^{124}	Pro^{43}, Leu^{123}, Phe^{114}	Arg^{25}
17	5662	214	-312.12	-	-	Pro^{41}, Tyr^{42}, Pro^{120}, Leu^{47}, Cys^{44}, Met^{242}, Ala^{24}, Asp^{239}, Gly^{26}, Pro^{43}, Thr^{39}, Gly^{40}	Arg^{25}	Arg^{25}
RPR200095	5192	110	-197.81	-	-	Leu^{47}, Ser^{48}, Cys^{23}, Tyr^{51}, Cys^{122}, Gly^{26}, Ala^{24}, Phe^{11}, Pro^{124}, Leu^{235}, Asp^{239}, Leu^{235}	Lys^{243}, Arg^{25}, Met^{242}	-

No. = Specific code assigned to ligand; ACE= Atomic contact energy calculated by *Patchdock* (kcal/mol); Distance = hydrogen bond length calculated from docked pose by using *Ligand interaction* tool of *Patch Dock.*

No. = Specific code assigned to ligand; ACE= Atomic contact energy calculated by *Patchdock* (kcal/mol); Distance = hydrogen bond length calculated from docked pose by using *Ligand interaction* tool of *Patch Dock.*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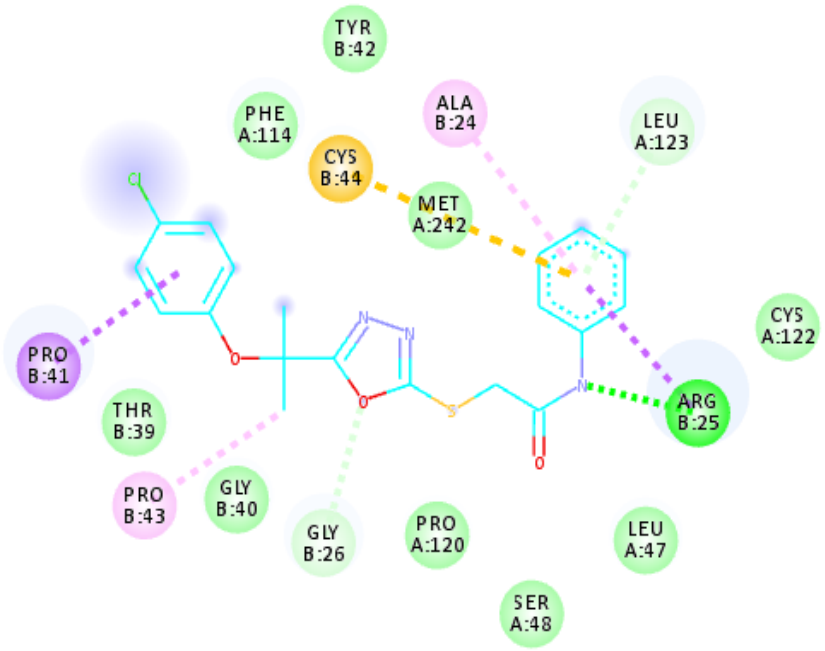
Pro41
Pro43
2.94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PHE A:114
ALA B:24
LEU A:123
CYS B:44
MET A:242
CYS A:122
PRO B:41
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PRO A:120
LEU A:47
SER A:48

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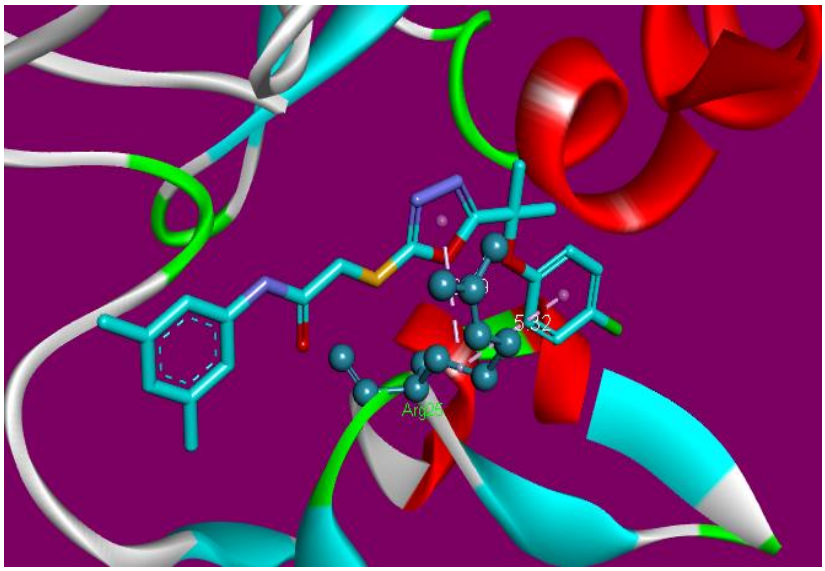

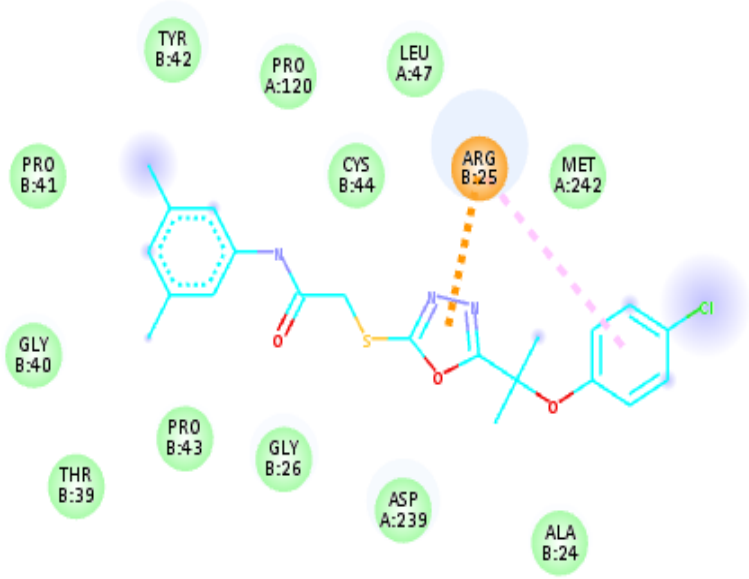
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PRO B:41
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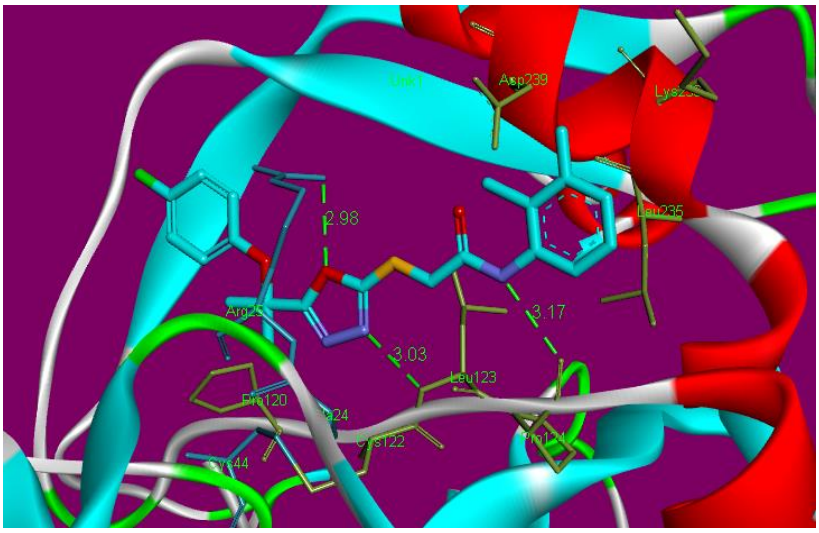
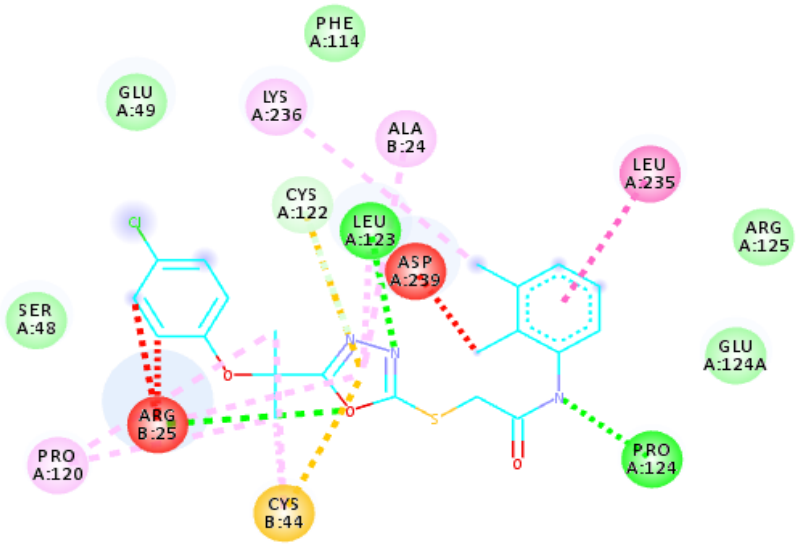
N
O
S
N
N
O
O
Cl

(17)





(13)

Figure 4.7 3D and 2D binding site interactions of the most probable docked ligands 9, 17 and 13 within F-Xa active site showing their binding interactions with *Patch Dock*, depicting unfavorable bump (red), carbon hydrogen bond (light green), pi-alkyl (light pink), pi-cation (brown) and amide pi-stack (pink) interactions.

In order to elaborate the structural elements liable for the observed inhibitory effect against the binding site F-Xa, the most active ligand **9** bound to protein was focused to binding affinity assessment using Hyde utility of Lead IT software. Hyde allows visual approximation of favorable and unfavorable contributions due to the structure/bound conformation of inhibitor with the neighboring amino acids. The favorably contributing structural elements (atoms and torsions) to the overall binding energy are visually color in green, similarly the structural elements that are not contributing favorably are colored in red, and neutral elements are in white (Figure 4.5). The aromatic phenyl moieties substituted 1,3,4-oxadiazole are contributing favorably to the binding energy. The only unfavorable structural element was the unsubstituted nitrogen atoms of 1,3,4-oxadiazole ring. This lead to the assumption that if these nitrogen atoms are substituted by some other atoms *i.e.*, carbon or other heteroatoms it may reason of even better binding affinity and thereby showing anticoagulant activity.

4.4.2 Anti-inflammatory activity (COX-2 protein):

To evaluate the anti-inflammatory potential compounds **5a, 5b** and **8-50** were docked against COX-2 enzyme protein by using the same softwares as used above for factor Xa. In the initial assessment of the docked complexes of COX-2 **(5a, 5b, Diclofenic sodium & 8-29)** revealed that all the compounds have higher docking score than standard drug diclofenic sodium except compounds **5a** and **13**. Compounds **8, 22** and **24** showed excellent value of global energy much higher than standard.

Table 4.17 Molecular docking results of compounds 5a, 8--29 against COX-2

Sr. No.	Compd. No.	Global Energy	ACE/ Kcal/mole	Amino acids showing hydrogen bond contacts	Distance (Å)	Amino acids showing van der Waals contacts lie within 4 Å
1	**5a**	4300	-232.83	-	-	Leu_{345}, Val_{102}, Phe_{504}, Leu_{338}, Leu_{370}, Ser_{516}
2	**8**	6150	-369.25	Gln_{447}, Gln_{447}, Arg_{29}, Glu_{451}	2.80,2.26, 2.85, 3.25	Gly_{27}, Ser_{457}, Asn_{19}, Pro_{140}, Val_{141}, Asn_{124}, Glu_{31}, Gly_{30}, Arg_{455}
3	**9**	5722	-320.10	Ala_{142}, Pro_{140}	2.62, 2.12	Asn_{28}, Arg_{29}, Gln_{27}, Leu_{138}, Asn_{24}, Gln_{447}, Val_{141}, Gly_{121}, Tyr_{122}, Asn_{19}, Glu_{31}, Gly_{30}, Gln_{451}, Arg_{455}
4	**10**	5938	-380.56	-	-	Asn_{28}, Gln_{27}, Cys_{26}, Gly_{30}, Asn_{19}, Tyr_{122}, Ser_{34}, Asn_{24}, Gln_{447}, Leu_{138}, Glu_{451}, Lys_{454}
5	**11**	5902	-157.95	Thr_{198}, Thr_{198}	2.97, 2.87	Ile_{260}, Val_{277}, Lys_{197}, Thr_{369}, His_{200}, Gln_{440}, Phe_{196}, Lys_{201}
6	**12**	5738	-316.77	Asn_{24}	2.83	Gly_{121}, ASn_{19}, Cys_{32}, Arg_{455}, Gly_{30}, Gln_{27}, Glu_{451}, Cys_{26}, Gln_{447}, Val_{141}, Cys_{22}
7	**13**	4466	-395.84	Gln_{447}	3.37	Glu_{451}, Asn_{24}, Asn_{19}, Tyr_{122}, Gly_{90}, Cys_{26}, Gln_{27}, Arg_{29}, Asn_{28}
8	**14**	5790	-336.43	Gly_{30}, Arg_{29}, Cys_{26}	3.34, 2.26, 3.18	-

9	**15**	5072	-354.34	Gln_{447}	3.37	Asn_{28}, Arg_{29}, Gln_{27}, Cys_{26}, Gly_{30}, Asn_{19}, Tyr_{122}, Asn_{24}, Glu_{451}
10	**16**	5820	-141.21	Thr_{198}, Arg_{208}	2.72, 2.76	Thr_{369}, Asn_{368}, Phe_{196}, Gln_{275}, Val_{277}, Lys_{197}, Lys_{201}, His_{200}
11	**17**	5840	-143.21	Thr_{198}, Arg_{208}	2.72, 2.76	Thr_{369}, Asn_{368}, Phe_{196}, Gln_{275}, Val_{277}, Lys_{197}, Lys_{201}, His_{200}, Arg_{226}
12	**18**	5752	-325.23	-	-	Asn_{19}, Asn_{28}, Arg_{455}, Gln_{27}, Cys_{26}, Asn_{24}, Gln_{447}, Gly_{121}, Tyr_{122}
13	**19**	5904	-360.79	-	-	Glu_{451}, Asn_{28}, Asn_{24}, Val_{141}, Ala_{142}, Pro_{140}, Cys_{22}, Gly_{121}, Tyr_{116}, Glu_{31}, Tyr_{108}
14	**20**	5838	-351.48	-	-	Tyr_{122}, Gly_{121}, Tyr_{116}, Glu_{451}, Ser_{457}, Asn_{28}, Gln_{27}, Arg_{455}, Gly_{30}, Asn_{24}, Cys_{26}, Gln_{447}, Glu_{31}
15	**21**	5800	-141.90	Thr_{198}, Thr_{198}	2.87, 2.41	Lys_{201}, Asp_{199}, His_{200}, Phe_{196}, Asn_{368}, Thr_{369}, Gln_{440}, Ser_{437}, Met_{444}, Lys_{197}, Gln_{275}, Val_{277}
16	**22**	6174	-378.06	-	-	Asn_{19}, Gln_{447}, Asn_{24}, Glu_{451}, Ser_{457}, Asn_{28}, Gln_{27}, Cys_{26}, Gly_{30}, Gln_{31}, Lys_{123}, Tyr_{122},

						$Gly_{121,}$ Cys_{32}
17	**23**	5954	-379.35	-	-	Lys_{454}, Glu_{451}, Gln_{447}, Asn_{19}, Ser_{34}, Pro_{140}, Asn_{24}, Gly_{30}, Cys_{26}, Gln_{27}
18	**24**	6138	-307.92	Lig	1.38	Asn_{24}, Glu_{451}, Cys_{26}, Cys_{32}, Gln_{447}, Asn_{19}, Gly_{121}, $Cys_{22,}$ Pro_{140}, Val_{141}, Glu_{31}, Arg_{29}, Gln_{27}
19	**25**	4874	-392.52	Cys_{32}, Asn_{28}	2.65, 1.69	Val_{141}, Cys_{22}, Cys_{145}, Pro_{140}, Ser_{23},Glu_{31}, Gly_{30}, Glu_{451}, Pro_{25}, Gln_{27}, Pro_{139}, Cys_{26}, Gln_{447}, Asn_{19}
20	**26**	5430	-270.11	Cys_{26}	3.26	Glu_{451}, Gln_{27}, Asn_{24}, Asn_{19}, Gln_{447}, $Leu1_{38}$, Arg_{455}, Asn_{38}
21	**27**	5702	-279.73	Arg_{106}	2.56	Lys_{68}, Thr_{70}, Pro_{71}, Ser_{339}
22	**28**	5210	-352.11	Gly_{30}, Asn_{19}, Lig	2.27, 1.13, 2.13	Asn_{28}, Ser_{457}, Val_{141}, Arg_{29}, Leu_{138}, Asn_{24}, Pro_{140}, Gly_{121}, Glu_{131}, Gln_{27}, Glu_{451}
23	**29**	5778	-340.76	Gln_{447}	2.77	Gly_{121}, Asn_{24}, Gly_{30}, Cys_{26}, Glu_{27}, Arg_{455}, Glu_{451}, Leu_{138}, Asn_{19}
24	**Diclofenic Sodium**	4612	-242.58	Ser_{516}	1.99	Ser_{339}, Leu_{345}, Val_{102}, Met_{99}, Leu_{517}, Trp_{373}, Phe_{504}

Standard diclofenic sodium was also docked with COX-2 for comparison and has depicted score 4612 with an ACE value -242.58 kcal/mol (Figure 4.8). Diclofenic sodium has shown hydrogen bonding with Ser_{516}. The length of hydrogen bond was 1.99 Å.

Ligand **8** showed potent interaction with COX-2 active site with a score of 6270 and an ACE of -352.28 kcal/mol. Visual inspections of these complexes predicts a binding conformation of ligand **8** showed significant interaction with COX-2 binding site compared to the other ligands. The interacting residues of this complex are Gln_{447}, Arg_{29} and Glu_{451} (Figure 4.10). Ligand **8** has shown a potential hydrogen bond between *NH* adjacent to carbonyl and phenyl-groups and Arg_{29}. The length of the hydrogen bond was 2.85 Å. Nitrogen of oxadiazole ring and oxygen of chlorophenoxy group showed hydrogen bonding with Gln_{447} having length of hydrogen bonds 2.26 Å and 2.85 Å. Similarly carbonyl oxygen of amide moiety showed hydrogen bonding with Glu_{451} with bond length 3.25 Å indicating significant interaction.

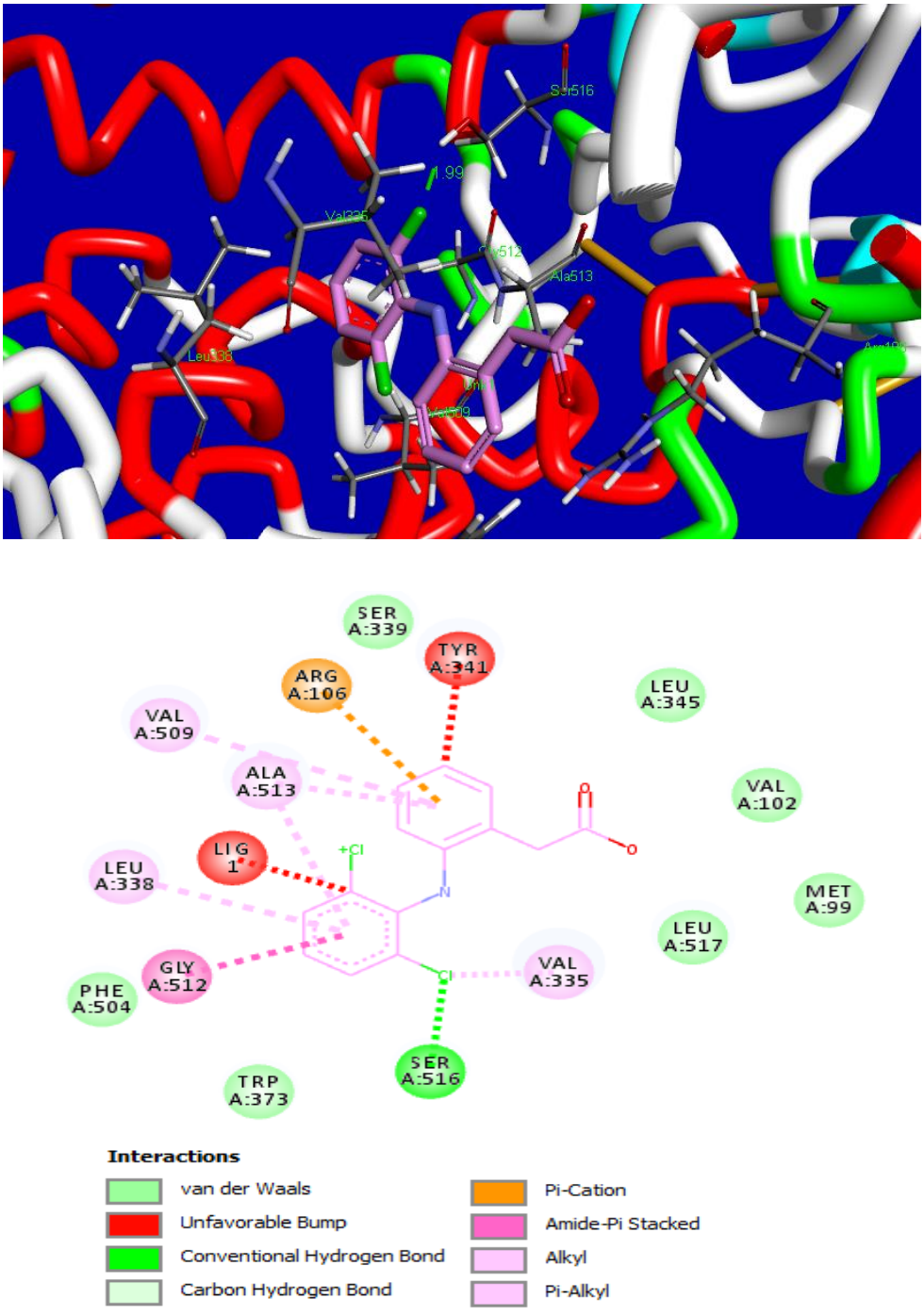


Figure 4.8 3D and 2D binding site interaction of standard diclofenic sodium

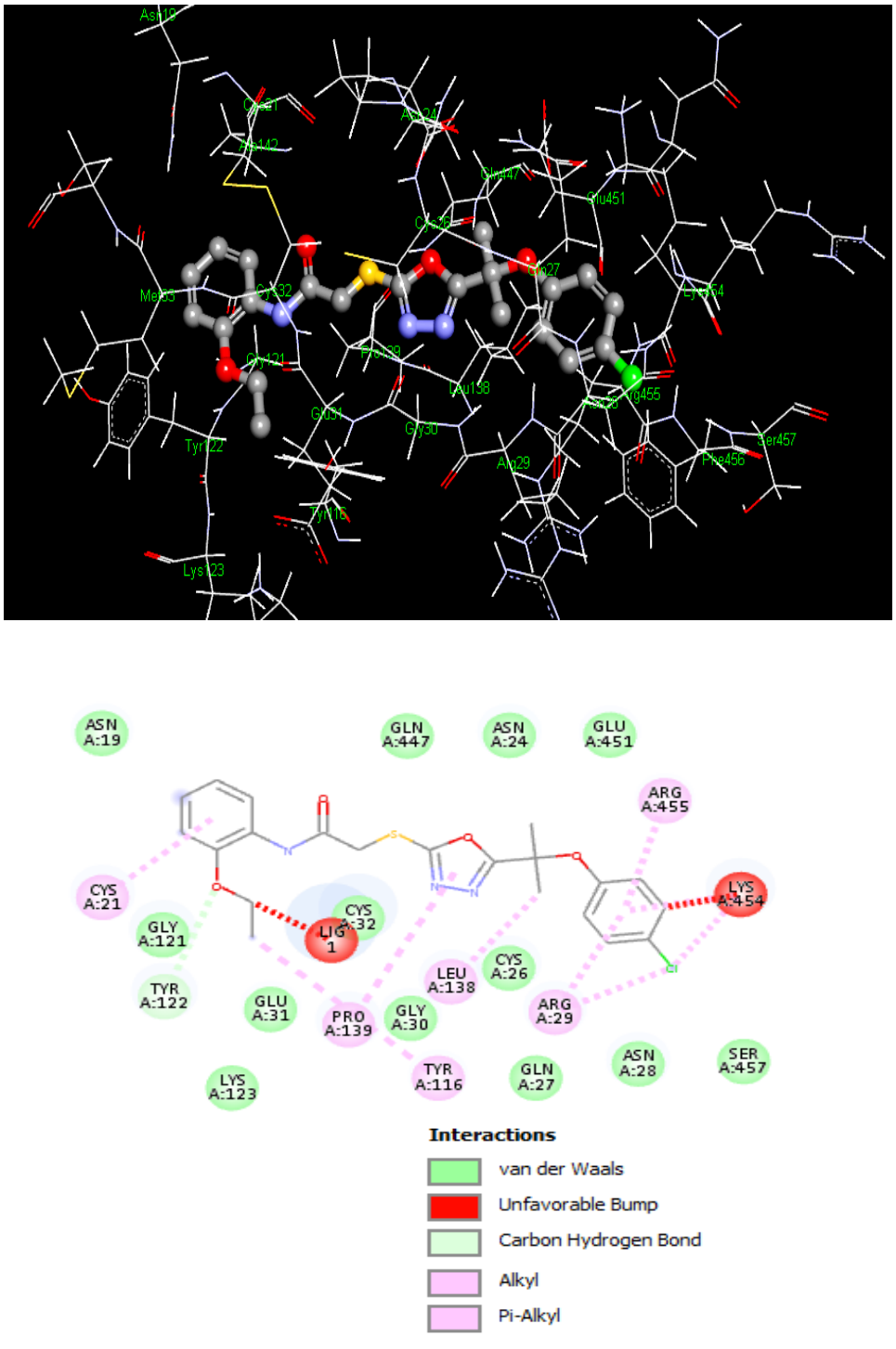


Figure 4.9 3D and 2D binding site interaction of compound 22

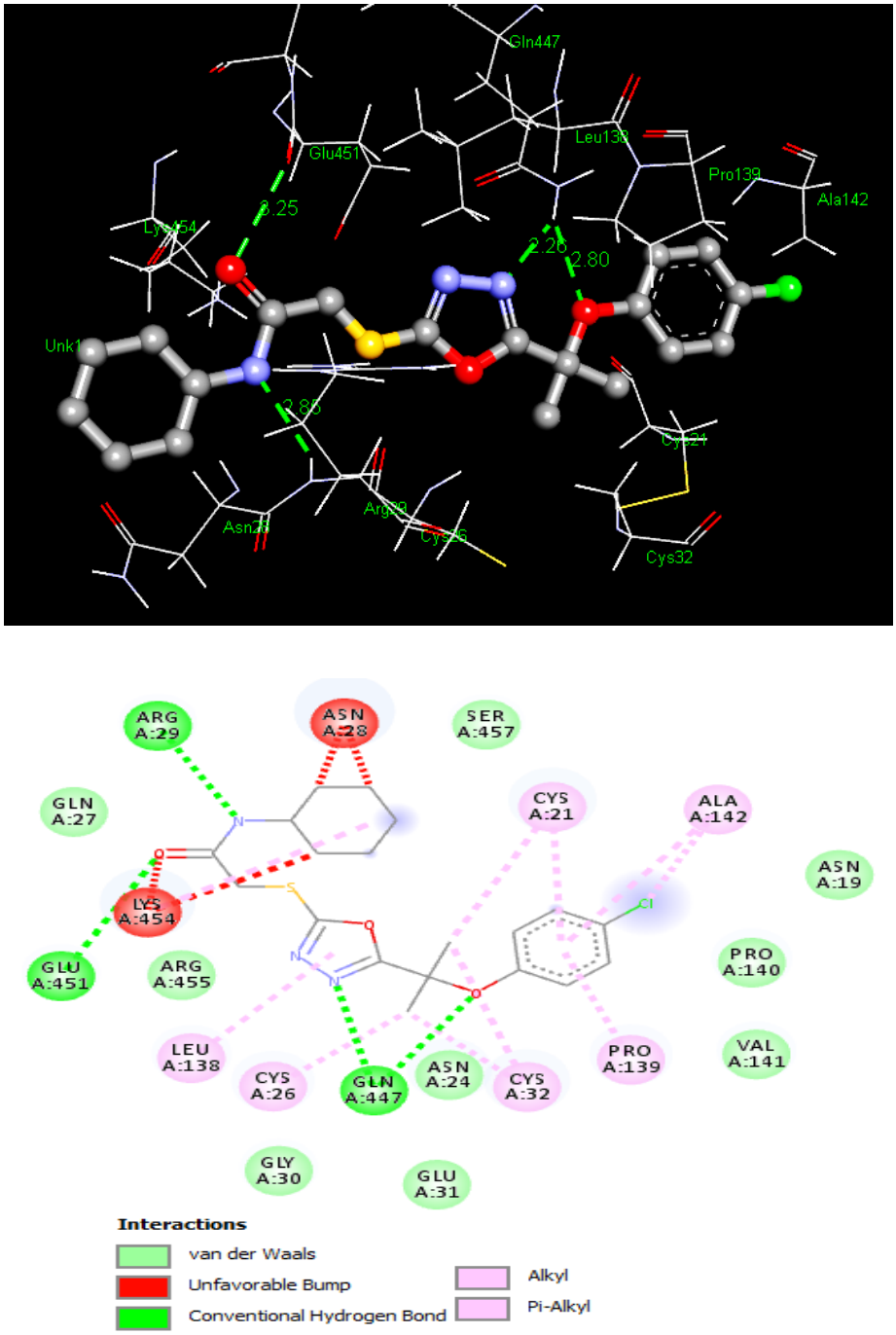


Figure 4.10 3D and 2D binding site interaction of compound 8

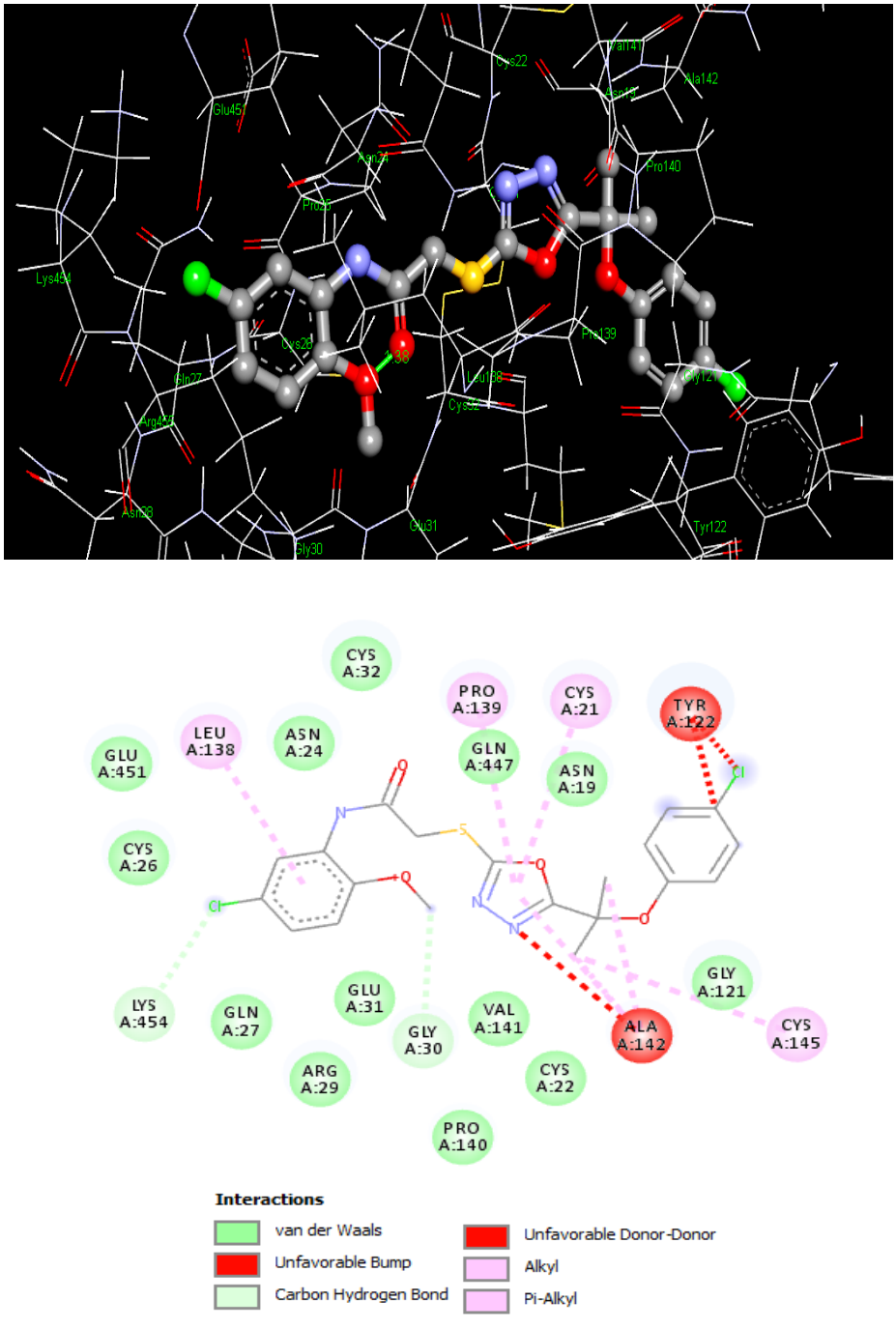


Figure 4.11 3D and 2D binding site interaction of compound 24

The docking results of compounds **5b** and **31-50** showed that ligands **50**, **39** and **38** have excellent docking score. All others compounds also show higher docking score than standard except **5b.**

Table 4.18 Molecular docking results of compounds 5b and 31-50 against COX-2

Sr.No.	Code	Global Energy	ACE Kcal/mol	Amino acids showing hydrogen bond contacts	Distance (Å)	Amino acids showing van der Waals contacts lie within 4 Å
1	**5b**	4236	-216.19	-	-	Ser_{339}, Phe_{504}, Tyr_{341}, Val_{509}, Ser_{516}, Gly_{512}
2	**31**	5402	-279.85	-	-	Arg_{455}, Arg_{29}, Leu_{138}, Gln_{447}, Pro_{140}, Gly_{121}, Asn_{28}, Gln_{27}, Cys_{26}, Glu_{451}, Cys_{22}, Asn_{19}
3	**32**	5529	-281.50	Asn_{24}	3.17	Asn_{19}, Cys_{22}, Cys_{32}, Gln_{27}, Arg_{455}, Cys_{26}, Glu_{451}, Leu_{138}, Gln_{447}, Gly_{121}
4	**33**	5602	-239.85	Asn_{368}, Tyr_{371}, His_{374}	3.38, 3.34, 2.91	Ala_{185}, Gln_{189}, Trp_{373}, Thr_{198}, Gln_{440}, Leu_{377}
5	**34**	5756	-138.47	Thr_{198}, Thr_{198}, Thr_{198}	2.86, 2.64, 2.64	Gln_{440}, Met_{444}, Ser_{437}, Thr_{369}, Lys_{201}, Phe_{196}, Asn_{368}, Ile_{260}, Val_{277}, Lys_{197}, His_{200}
6	**35**	5862	-104.45	Thr_{198}	2.85	Met_{444}, Ser_{437}, Thr_{369}, Asn_{368}, Phe_{196}, Val_{277}, Lys_{197}, His_{200}
7	**36**	5818	-86.91	-	-	Gln_{275}, Lys_{197}, Val_{277}, Phe_{196}, Ser_{437}, Gln_{440}, Asn_{368}, His_{200},

						Thr_{198}, Asp_{199}, Lys_{201}
8	**37**	5902	-145.27	Thr_{198}, Thr_{198}	2.66, 2.49	Thr_{369}, Phe_{196}, Val_{277}, Ile_{260}, Lys_{197}, His_{200}, Gln_{440}
9	**38**	5946	-333.39	Gln_{447}, Gln_{447}, Pro_{140}	2,92, 2.89, 2.60	Gln_{451}, Lys_{454}, Asn_{28}, Gln_{27}, Arg_{29}, Gly_{30}, Cys_{32}, Gly_{121}, Met_{33}, Ser_{34}, Val_{141}, Asn_{24}
10	**39**	6150	-193.72	Glu_{510}, Glu_{510}	3.27, 3.09	Ser_{516}, Val_{102}, Ser_{105}, Tyr_{101}, Pro_{69}, Ser_{339}, Val_{509}, Gly_{512}, Phe_{504}
11	**40**	5886	-354.31	Arg_{29}	2.82	Arg_{455}, Gln_{27}, Cys_{26}, Gly_{121}, Tyr_{122}, Glu_{31}, Gly_{30}, Gln_{447}, Asn_{24}, Glu_{451}, Ser_{457}, Leu_{458}
12	**41**	5496	-153.13	-	-	Ser_{339}, Glu_{510}, Thr_{70}, Tyr_{101}
13	**42**	5578	-235.53	Asn_{368}, His_{374}	3.09, 2.96	Leu_{377}, Gln_{440}, Thr_{198}, Thr_{192}, Gln_{189}, Ala_{189}
14	**43**	5696	-312.73	Gln_{447}	2.96	Ser_{34}, Met_{33}, Pro_{140}, Val_{141}, Asn_{24}, Leu_{138}, Glu_{451}, Asn_{28}, Gln_{27}, Arg_{29}, Cys_{26}, Gly_{30}, Asn_{19}
15	**44**	5786	-307.62	Tyr_{116}, Lig	1.53, 1.90	Tyr_{122}, Gln_{447}, Gly_{30}, Asn_{24}, Cys_{26}, Glu_{451}, Gln_{27}, Asn_{28}, Arg_{29}, Glu_{31}, Gly_{121}, Asn_{29}
16	**45**	5694	-231.19	Gln_{189}	2.98	Tyr_{134}, Phe_{196}, Tyr_{371}, Leu_{376}, Leu_{377}, Arg_{208}, Gln_{275}
18	**46**	5788	-325.08	Gln_{447}	3.01	Asn_{19}, Asn_{24},

						Gly_{30}, Cys_{26}, Gln_{27}, Asn_{28}, Arg_{455}, Lys_{454}, Glu_{451}, Leu_{138}, Gly_{121}, Met_{33}, Ser_{34}
19	**47**	5498	-108.06	Thr_{198}	3.03	Gln_{440}, Ser_{437}, Asn_{368}, His_{200}, Phe_{196}, Asp_{199}, Val_{277}, Lys_{197}
20	**48**	5732	-267.47	Pro_{140}	2.97	Tyr_{122}, Cys_{32}, Asn_{19}, Arg_{29}, Asn_{28}, Gln_{27}, Lys_{454}, Glu_{451}, Asn_{24}, Leu_{138}, Gln_{447}, Gly_{121}, Ser_{34}, Met_{33}
21	**49**	5794	-272.68	Glu_{451}	3.05	Tyr_{122}, Cys_{32}, Leu_{138}, Arg_{455}, Asn_{28}, Gly_{30}, Gln_{27}, Cys_{26}, Asn_{24}, Gln_{447}, Asn_{19}
22	**50**	6088	-271.53	Tyr_{116}, Lig	1.96, 1.96	Asn_{24}, Gln_{447}, Gly_{30}, Glu_{451}, Cys_{26}, Leu_{138}, Gln_{27}, Asn_{28}, Arg_{455}, Arg_{29}, Gly_{121}, Ala_{142}, Asn_{19}
23	**Diclofenic Sodium**	4612	-242.58	Ser_{516}	1.99	Ser_{339}, Leu_{345}, Val_{102}, Met_{99}, Leu_{517}, Trp_{373}, Phe_{504}

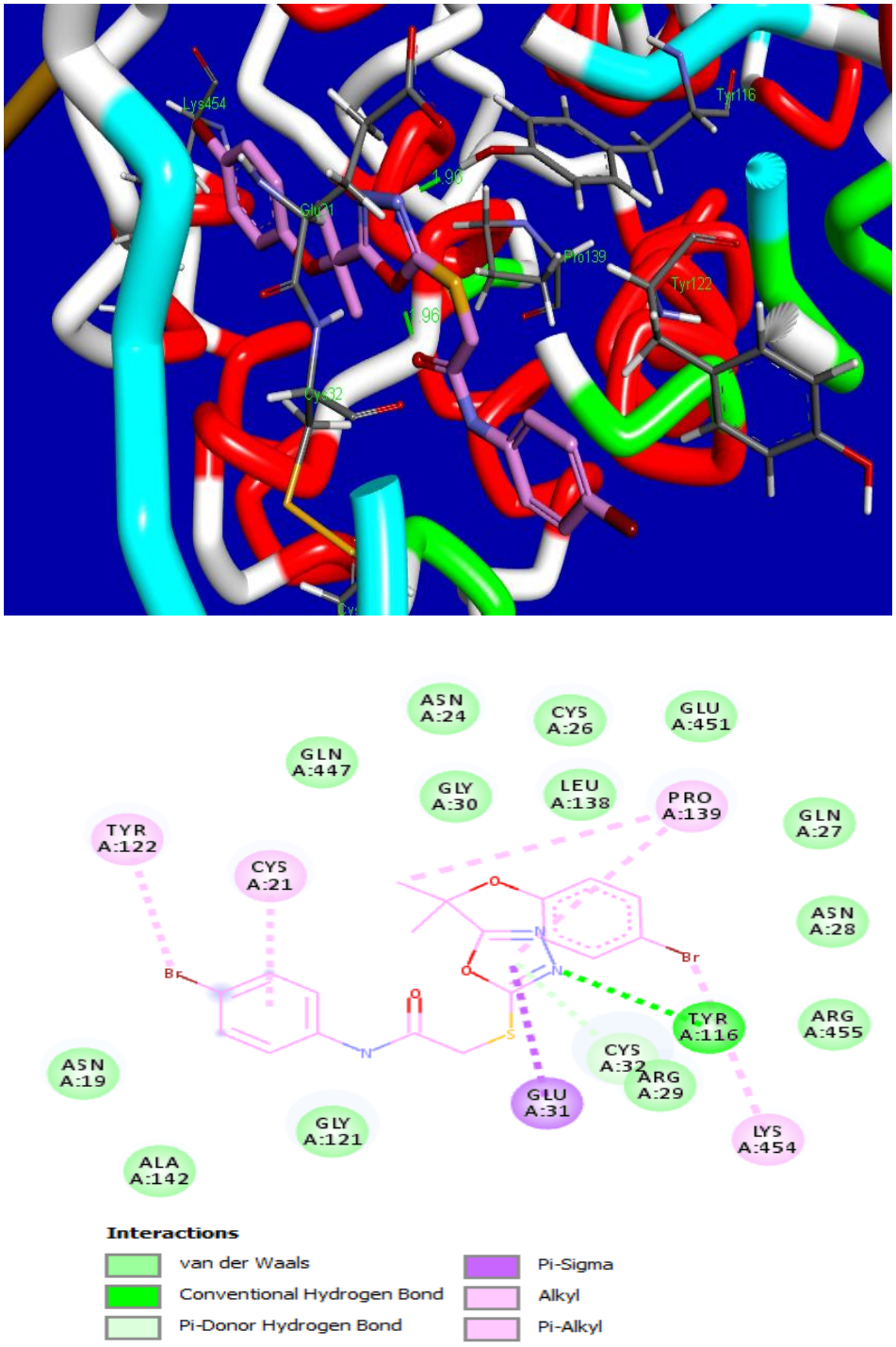
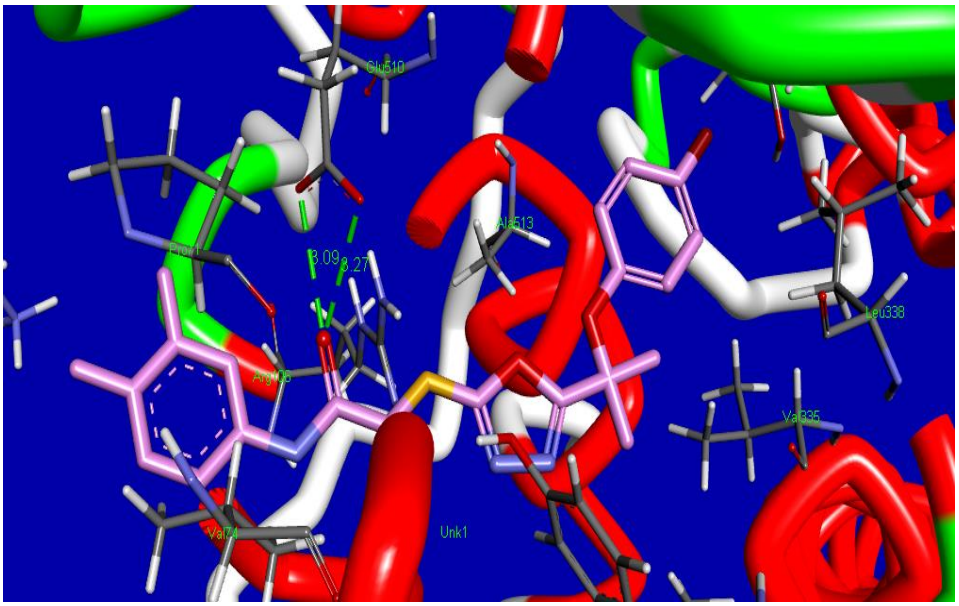


Figure 4.12 3D and 2D binding site interaction of compound 50



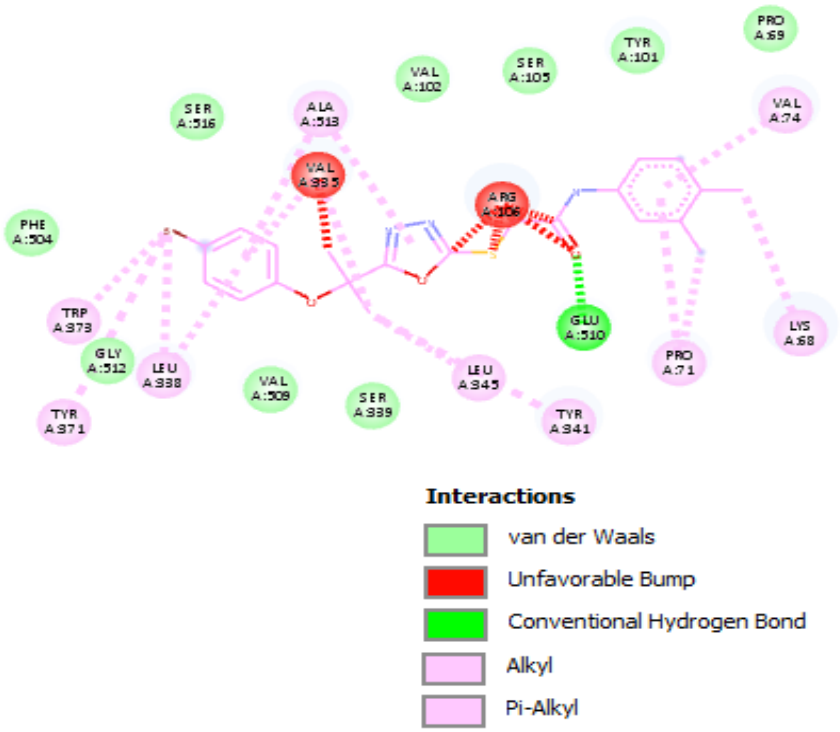
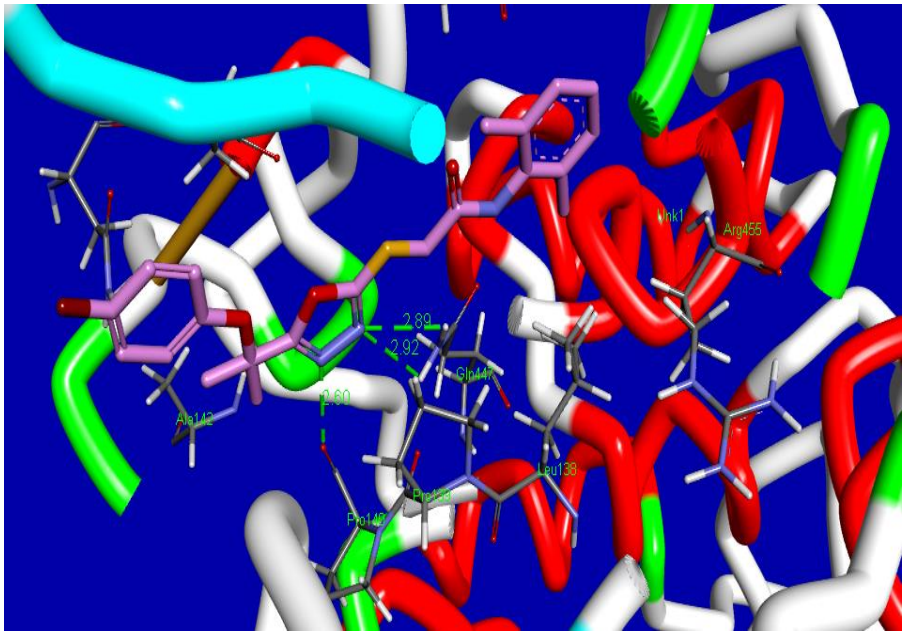


Figure 4.13 3D and 2D binding site interaction of compound 39



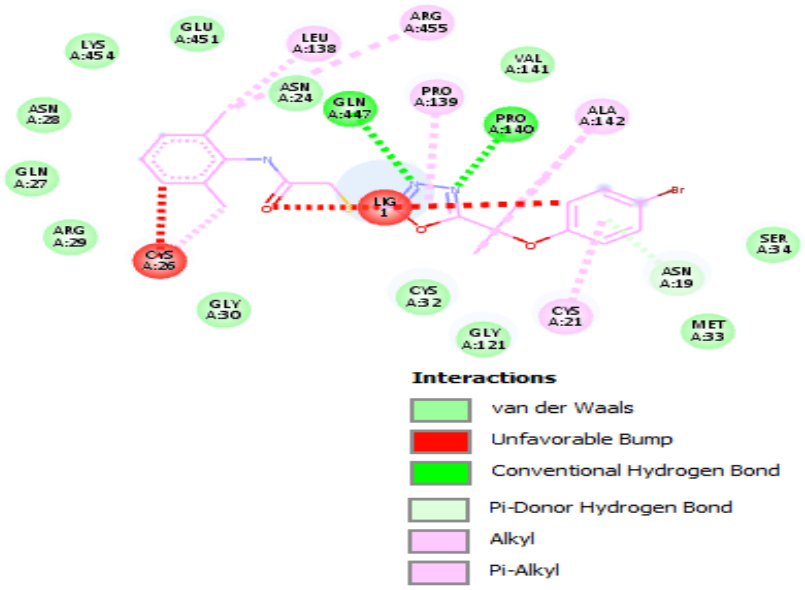


Figure 4.14 3D and 2D binding site interaction of compound 38

From these results it can be concluded that majority of our target compounds have good COX-2 inhibitory potential as compared to standard diclofenic sodium except **5a, 5b** and **13**.

4.5 Computational investigations

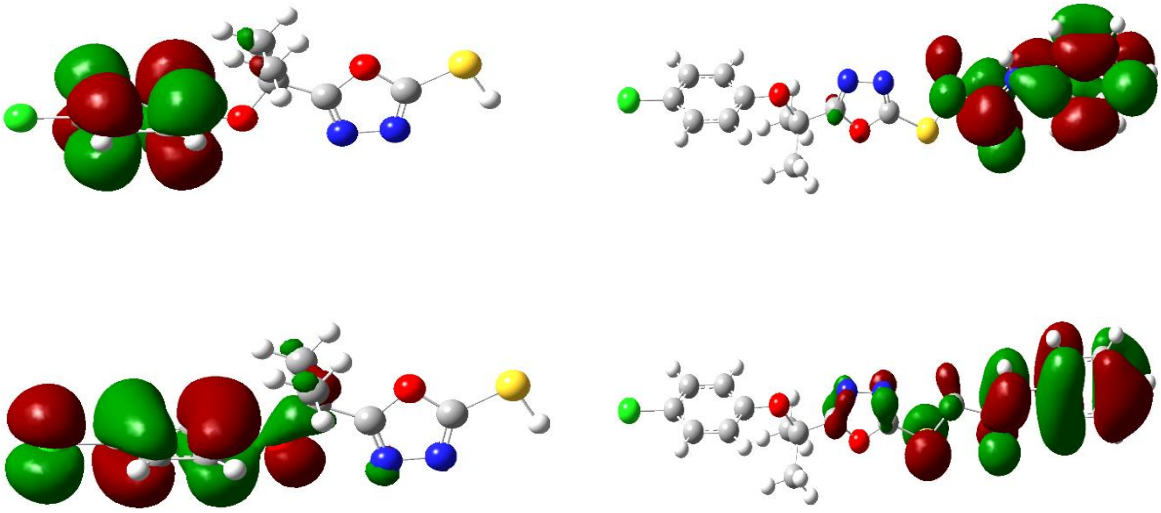
4.5.1 Frontier molecular orbital (FMO) analysis

The energy of frontier orbital's, namely, the "Highest Occupied Molecular Orbital HOMO and "Lowest Unoccupied Molecular Orbital" LUMO are very popular parameters from quantum chemistry calculations provide valuable information about molecular systems. The energy gap between HOMO and LUMO (E_{gap}) measures the kinetic stability of the molecule [183]. A large value of the energy gap implies high kinetic stability and low chemical reactivity. Furthermore, the energy gap between HOMO and LUMO explains the intermolecular charge transfer (ICT) within the molecule, which is responsible for the bioactivity of the molecule. The distribution pattern of the FMOs has been illustrated in Figure 4.15. In all the studied derivatives **9-17**, except **5a** in which HOMOs delocalized on 4-chlorophenoxy group, the HOMOs had leading contribution from *N*-arylacetamide and the adjacent Sulfur atom. Similarly, LUMOs had also dominating contribution from *N*-arylacetamide moiety except **15, 16** and **5a** in which major contribution from 4-chlorophenoxy group. However in case of **17** HOMOs delocalized on both benzene rings along with acetamide groups. The ICT has been observed from *N*-arylacetamide to the 4-chlorophenoxy group units in **15** and **16**.

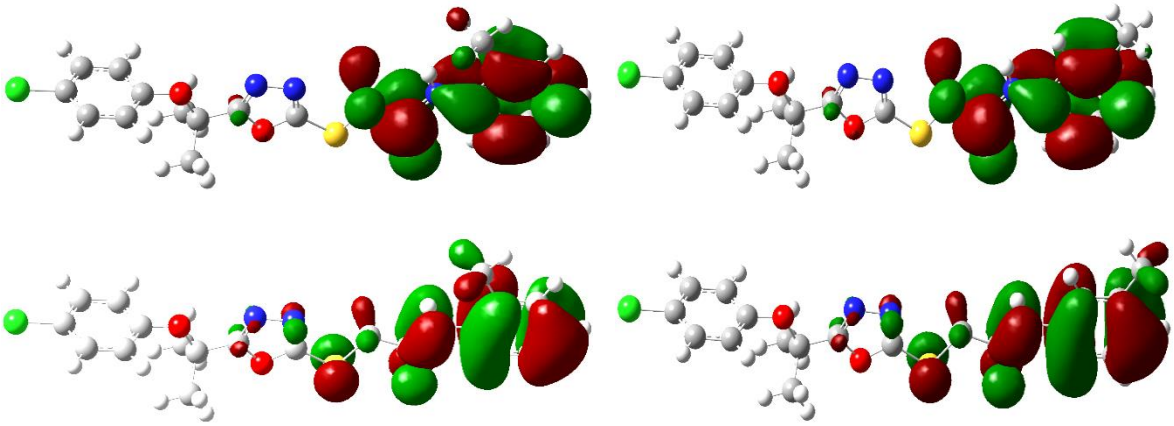
The E_{HOMO}, E_{LUMO} and HOMO–LUMO energy gaps (E_{gap}) at the B3LYP/6-31G** level of theory has been tabulated in Table 4.19. The highest E_{gap} in **5a** and **15** decrease their biological activity. While the low energy gap in **9, 13, 12, 17** and **16** makes them potent

inhibitor of F-Xa due to which they show high anti-coagulant activity. Other electronic parameters such as Ionization potential (I), Electron affinity (A), hardness (η), softness (s),

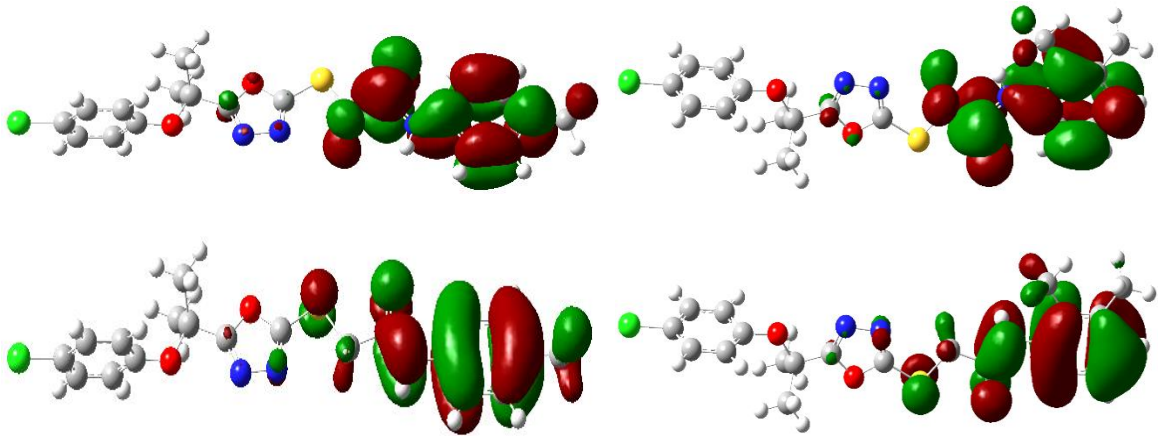
Chemical potential (μ), absolute electronegativity (χ), electrophilicity index (ω) and dipole moment (D) of the synthesized compounds were also calculated which were represented in Table 4.19. The electrophilicity index will be useful to explain the binding capacity with biomolecules [184].



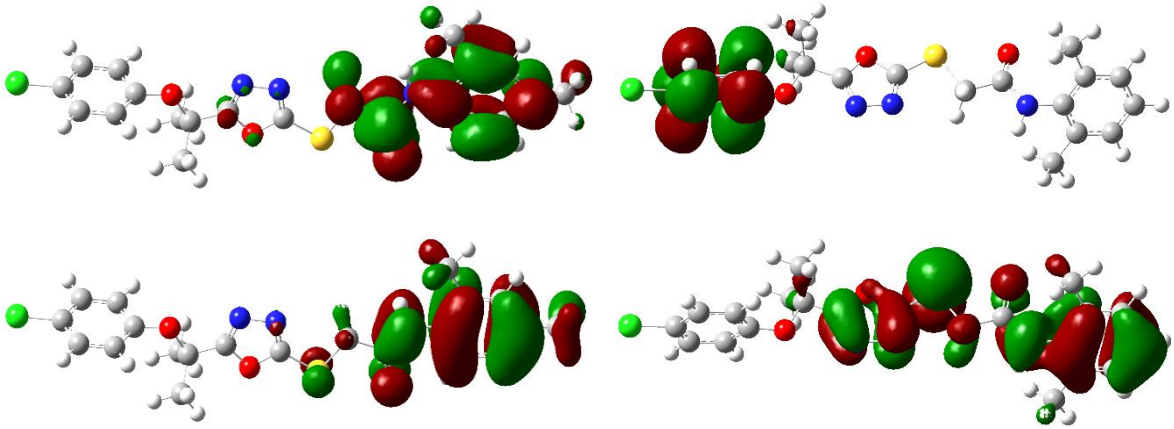
5a **9**



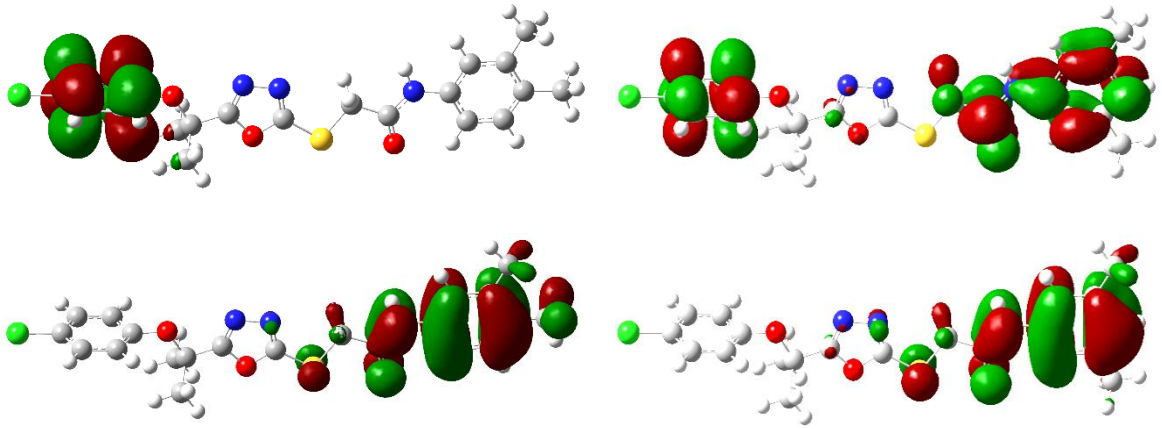
10 **11**



12 **13**



14 **15**



16 **17**

Figure 4.15 The charge density distribution of the HOMOs (bottom) and LUMOs (top) of the compounds 5a and 9-17.

Table 4.19 DFT computed molecular properties (all in eV, except dipole moment which is in the units of Debye) for oxadiazoles derivatives obtained at B3LYP/6-31G level of theory**

Sr. No.	Compound name	E_{HOMO}	E_{LUMO}	E_{gap}	Ionisation potential (I)	Electron affinity (A)	Chemical hardness (η)	Chemical softness (S)	Chemical potential (μ)	Electronegativity (χ)	Electrophilicity (ω)	Dipole moment (D)
1	**5a**	-6.60	-0.58	6.02	6.60	0.58	3.01	0.17	-3.59	3.59	2.14	3.66
2	**9**	-6.25	-0.64	5.61	6.25	0.64	2.80	0.18	-3.44	3.44	2.12	1.84
3	**10**	-6.14	-0.64	5.51	6.14	0.64	2.75	0.18	-3.39	3.39	2.09	1.83
4	**11**	-6.15	-0.60	5.54	6.15	0.60	2.77	0.18	-3.37	3.37	2.06	2.20
5	**12**	-6.05	-0.57	5.48	6.05	0.57	2.74	0.18	-3.31	3.31	1.99	2.39
6	**13**	-6.07	-0.58	5.49	6.07	0.58	2.75	0.18	-3.32	3.32	2.01	2.19
7	**14**	-5.95	-0.57	5.39	5.95	0.57	2.69	0.19	-3.26	3.26	1.97	2.36
8	**15**	-6.41	-0.54	5.87	6.41	0.54	2.94	0.17	-3.47	3.47	2.05	2.14
9	**16**	-5.97	-0.53	5.43	5.97	0.53	2.72	0.18	-3.25	3.25	1.94	2.67
10	**17**	-6.08	-0.54	5.54	6.08	0.54	2.77	0.18	-3.31	3.31	1.98	2.37

4.5.2 Molecular Electrostatic Potential (MEP)

Undoubtedly MEP is a very useful tool to understand the molecular interactions. Especially its 3-D mapping is widely used to explain the relative reactive sites for the electrophilic (negative region) and nucleophilic (positive region) attack in a molecule. It also provides visual understanding of the relative polarity of the molecule. To predict reactive sites for electrophilic and nucleophilic attack of all synthesized compounds, the MEP surface maps have been calculated and illustrated in Figure 4.16. The different colors represent the different values of the electrostatic potential at the surface. Negative and positive Electrostatic Potential (EP) regions indicated by red and blue color respectively, while the neutral potential regions represented by green color.

Careful analyses of the MEP revealed that oxadiazole moiety would be favorable site for electrophile attack in all the studied compounds. Further in all synthesized derivatives, the carboxamide group showed both positive and negative potential that makes them good F-Xa inhibitors and anti-coagulants.

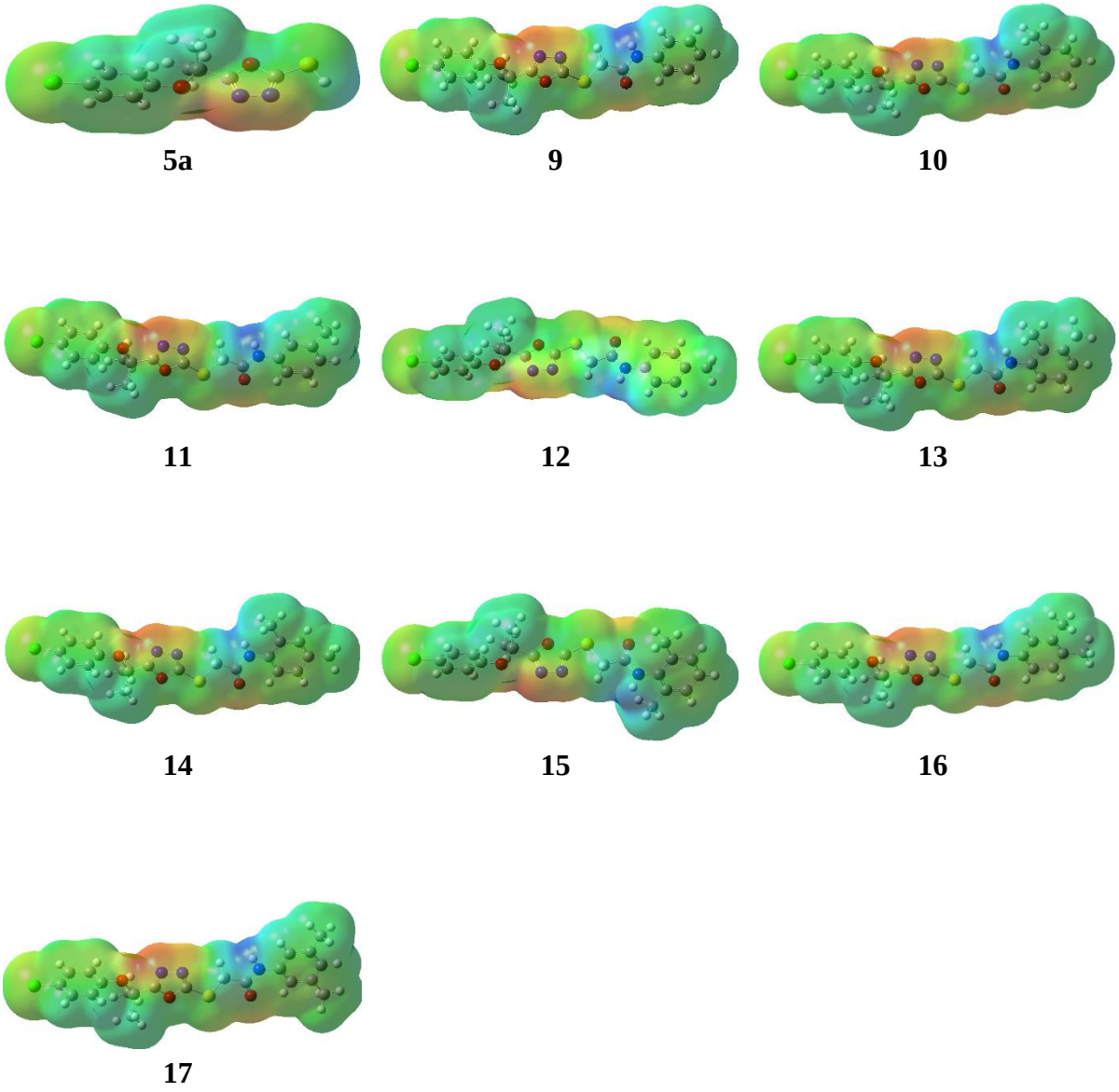


Figure 4.16 The molecular electrostatic potential surfaces of compounds 5a &9-17

CONCLUSION

The objectives of present study were successfully achieved by working on three main parts of thesis (**1**) Synthesis of fibric acids derivatives (**2**) Biological screening and (**3**) In *silicio* studies. In the first part of research work four schemes were applied to synthesize fibric acid derived oxadiazoles and their hybrids with acetamides. For this purpose two fibric acids (**2a & 2b**) were synthesized from two phenols (**1a & 1b**) by refluxing them with acetone, chloroform and sodium hydroxide. Further these acids were converted into corresponding esters (**3a & 3b**) and carbohydrazides (**4a & 4b**). Cyclization of these carbohydrazides was carried out to synthesize 1,3,4-oxadiazoles (**5a & 5b**). In 2nd scheme *N*-substituted-2-bromoacetamides (**7a-7y**) were prepared by reacting 2-bromoacetylbromide with various anilines (**6a-6y**). Two main series of compounds **8-30** and **31-50** were synthesized (scheme 3 & scheme 4) successfully by reacting 5-(2-aryloxypropan-2-yl)-1.3.4-oxadiazol-2thiols (**5a & 5b**) with *N*-substituted-2-bromoacetamides (**7a-7y**). Characterization of compounds was carried out through spectroscopic analysis.

After the successful completion of synthesis of acetamide derivatives we diverted our attention towards the biological activities of target compounds. For this purpose protocols of anti-thrombotic activity (*in vitro* and *in vivo*) and anti-inflammatory (*in vitro* and *in vivo*) were followed. The anti-thrombotic activity (in *vitro* and *vivo*) was performed for selective compounds to evaluate their FXa inhibition potential. *In vitro* compounds **17, 27** and **36** showed higher % age of clot lysis than standard drug streptokinase but remaining compounds showed moderate to good activity. In *vivo* activity results for compounds **9, 12, 13, 16, 17, 24, 27, 32, 36, 39, 41** and **48** enhanced clotting times (even better than standard drug heparin) were observed. Anti-inflammatory activity was also performed for the compounds to

evaluate their COX-2 enzyme inhibition potential. *In vitro* all compounds showed moderate to better activity while in vivo compounds **8, 9, 11, 12, 16, 17, 24, 34** and **48** showed greater than standard drug diclofenic sodium. Compounds **14**, **15**, **19**, **21**, **31, 38** and **42** results were comparable to that of standard drug while all remaining compounds exhibited moderate activity. In last part of research work *in silico* studies were performed for selected compounds. Molecular docking of compounds **5a & 5b** and **8-50** was carried out against COX-2 protien. All the compounds except **5a & 5b, 13** and **25** showed higher docking score than standard. In case of antithrombotic activity compounds **9-17** were docked against FXa protein. Except the compound **5a** all others showed higher docking score than control ligand. DFT computed molecular properties of compounds **9-17** was also calculated by computational methodology. Our experimental and computational results suggest that these newly synthesized 5-[2-(4-chloro/bromophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol derivatives **(8-50)** compounds are good COX-2 and F-Xa inhibitors and might be used as effective anti-inflammatory and anti-coagulant agents. In future these compounds might be evaluated at molecular level.

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