CHAPTER IV

Synthesis of [1, 3, 4] Oxadiazole

Introduction and Literature Survey:

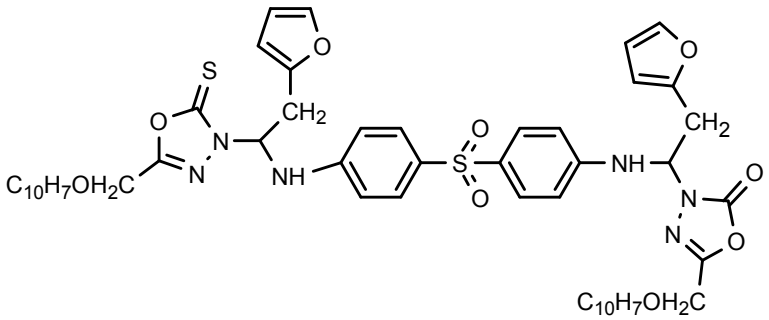
Oxadiazole is important heterocyclic ring present in a large number of biological active molecules of different pharmacological classes It is known to have fungicidal, bacterial and herbicidal activities.

Oxadiazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. This interesting group of compound has diverse biological activities such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, anticancer, anti-HIV, hypoglycemic and genotoxic. Given data represents that oxadiazole being heterocyclic planar five membered ring systems have various pharmacological actions. Results of various derivatives of different oxadiazole and their substitutions are reviewed in present article.

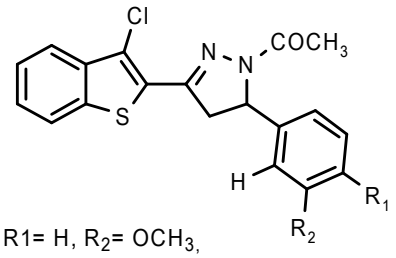
Various methods for synthesizing oxadiazole are discussed with their pharmacological actions. These derivatives of oxadiazole are analyzed here for varying pharmacological activities. Compounds having a five member ring containing one oxygen and two nitrogen are called oxadiazole or in the older literature furadiazole, Name for oxadiazole ring such as ‘Azoxime’ (1, 2, 4 oxadiazole), ‘Furazan’ for (1, 2, 5- oxadiazole) has gained acceptance; as a consequence, the literature is full of multiplicity of name for this molecule. Amongst these or “Oxybiazole”,

"Diazoxole" , "Furo (bb′) diazole and"Biozole". The systematic name of 1, 3, 4-oxadiazole has gradually become prevalent and is used exclusively.

A series of oxadiazole Mannich bases by reaction between oxadiazole derivatives were synthesized [1], dapsone, appropriate aldehydes and was evaluated against Mycobacterium Tuberculosis. Compound 3-{2-furyl[4-(4-{2-furyl [5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxy methyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione from all the synthesized compounds have shown best activity against M. Tuberculosis and isoniazid resistant M. Tuberculosis.

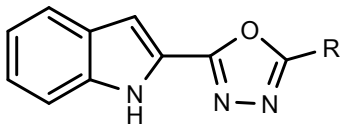


Some new 3-acetyl-5-(3-chloro-1 benzo[6]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles and 2-(3-chloro-1-benzo[6]thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles were synthesized[2] and was evaluated for Antimicrobial activity. Compounds were found to be most potent against activites, even better than the standard drugs i.e. ciprofloxacin.



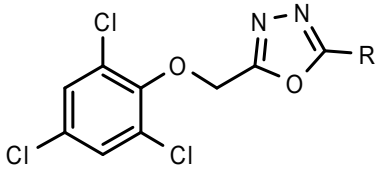
R1= H, R_2= OCH_3,
R_2= H, R_1= OCH_3,

New compounds of 1,3,4-oxadiazole from different compounds were synthesized[3] and was tested for Anti- microbial activity on different strains. A total of four compounds were synthesized out of those only three found to be effective against bacterial strains and none of the strains were found to be effective against fungal strain.



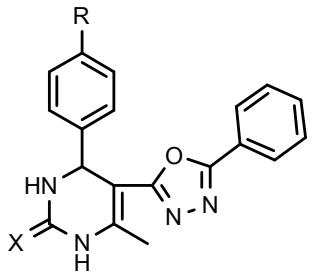
R=H, CH_3,

A series of new 1,3,4-oxadiazole derivatives and 1,2,4-riazine-5-one derivatives were synthesized[4]. All the compounds were screened for their Anti-inflammatory activity by using carrageen in-induced rat paw edema method.



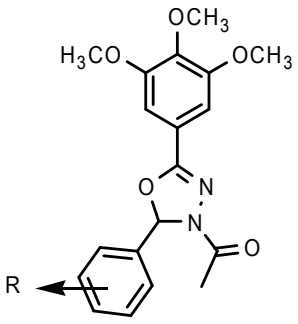
R= 2,4-Dichlorophenyl
R= 1-(4-isobutylphenyl) ethyl

A new compound were synthesized[5] 6-Methyl-4-aryl-5-(5- phenyl-1, 3, 4-oxadiazol-2-yl)-1,2,3,4-tetrahydropyrimidine-2(1*H*)-one significant effect against Streptococcus *pneumonia* (+ve) and 3b has significant activity effect *Escheria coli* (-ve).



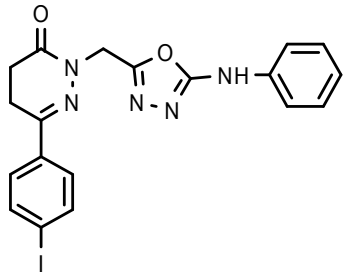
R= OCH_3, X=O
R=NO_2, X=O

Some 3-acetyl-2-substituted phenyl-5-(3,4,5-Tri methoxy phenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives was synthesized [6]. All the synthesized compounds highly active against PC3 cells and are moderately active against Bcap37 and BGC823 cells.



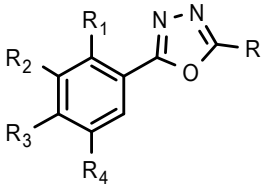
R=2-F, 3-F, 4-F, 2-CF_3,4-CF_3,
2-Cl,3-OCH_3

A series of 5-[3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2i-ylmethyl]-2-substituted 1,3,4-oxadiazole was synthesized [7] and then final compounds were tested for their anti-bacterial activity using cup plate method. All the synthesized compounds found to be most potent derivative as compared to the standard drug.



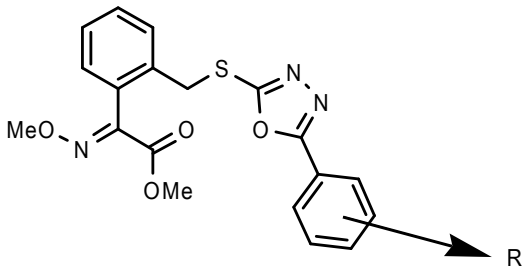
6-(4-Iodo-phenyl) -2-(5-phenylamino-[1,3,4]oxadiazol-2-yl methyl) -4,5-dihydro-2H-pyridazin-3-one

A series of new 1,3,4-oxadiazole with 2-fluoro-4-methoxy moiety was synthesized[8] and are tested for Anti-Microbial activity and all synthesized compounds showed significant anti-bacterial activity against Escherichia coli and Pseudomonas Aeruginosa, showed anti-fungal activity against C. Albicans.



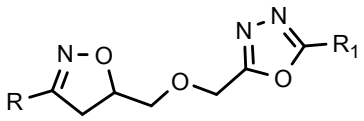
R= 2-flouro-4-methoxyphenyl R_1=CH_3, R_2= Br, R_3=H,R_4= H
R= 2,3,4-triflourophenyl, R_1=F, R_2= H,R_3=OCH_3, R_4= H
R= 2-flouro-4-methoxyphenyl, R_1=H, R_2= H,R_3=H, R_4=Cl

Fifteen novels (E)-methoxy imino-benzene acetate derivatives were synthesized [9]. Bioassays indicated that compound showed potent fungicidal activity against Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Physalospora piricola and Bipolaris mayclis and showed potent fungicidal activity against R. Solani.



R= H, F, 3-Cl, 2,3-Cl, 4-OCH_3,I, NO_2, etc.

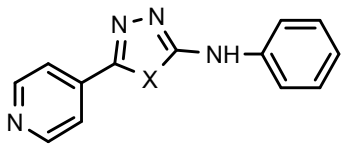
A series of novel ether-linked bis (heterocycles) was synthesized [10] . All the Synthesized compounds were screened for anti-inflammatory and analgesic activities and showed excellent activity against ibuprofen and aspirin.



R, R_1= 3-NO_2Ph
R,R_1=2,4-Cl_2Ph

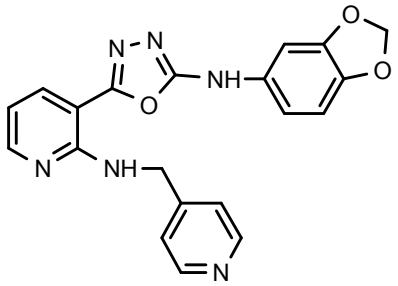
A series of novel 2, 5-disubstituted 1,3,4-oxadiazole derivatives was synthesized[11] and was tested for in. vitro Anti-Microbial activity. 2-

(2-naphthyloxy methyl)-5-phenoxymethyl-1,3,4-oxadiazole exhibited > 90% inhibition among all the synthesized compounds.



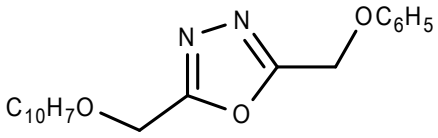
X=S, X=O

Derivatives of oxadiazoles was synthesized[12] and are evaluated for their ability to inhibit tubulin polymerization and to arrest mitotic division of tumor cells. Among the synthesized compounds, 10 showed potent activity.



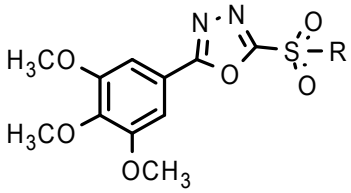
{ 3-[5-(Benzo[1,3]dioxol-5-ylamino)
-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl} -pyridin-4-ylmethyl-amine

A series of five membered heterocyclic were synthesized [13] and was tested for convulsion. From the synthesized compounds (IIf) 2-(4-chlorophenyl) amino-5-(4-pyridyl)-1,3,4-thiadiazole and (IIIf) 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4oxadiazole showed potent activity.



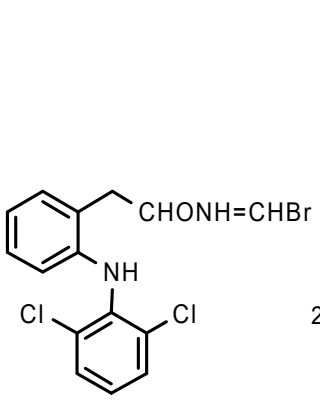
2-(2-naphthyioxymethyl)
-5-phenoxy methyl-1,3,4-oxadiazole

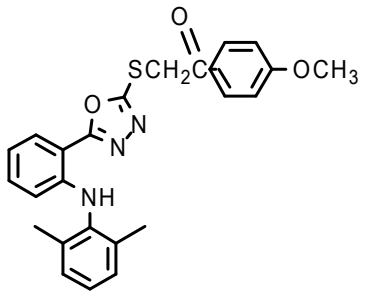
Some compounds using the key intermediates 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol or the oxadiazole analogue were synthesized[14] and tested for fungicidal activity. From all the synthesized compounds can inhibit mycelia growth by approximately 50% *in vitro* against ten kinds of fungus.



R-CH_3, C_2H_5

A series of S-substituted phenacryl 1,3,4-oxadiazole and Schiff bases derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid) [15]. Total eighteen compounds were synthesized and out of those only eight were found to have significant anti-inflammatory activity with significant analgesic activity in acetic acid induced writhing models with no ulcerogenic activity.

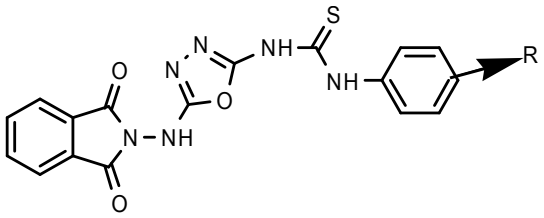




2-{ 5-[2-(2,6-Dimethyl-phenylamino) -phenyl]-[1,3,4]oxadiazol-2-ylsulfanyl} -1-(4-methoxy-phenyl) -ethanone

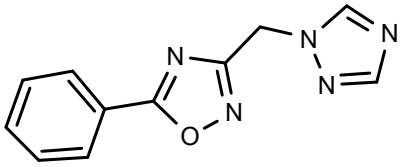
The synthesized some 3-acetyl-2-substituted oxadiazole derivatives by cyclization reaction of N'-substitutedbenzylidene-3,4,5- trimethoxy benzohydrazide in acetic anhydride[16]. The antitumor activities *in vitro* of these compounds were evaluated against PC3, BGC823, and Bcap-37 cells by MTT method.

A series of novel 1,3,4-oxadiazole derivatives of Phthalimide synthesized and evaluated for their anticonvulsant and neurotoxicity studies. Oxadiazole derivatives were synthesized by reacting phthalic anhydride with semicarbazide[17] and hydrazine hydrate in presence of sodium hydroxide. Among the compounds synthesized by him with para methoxy substituent demonstrated that distal hydrophobic center could be made more lipophilic than phenyl ring thus displaying the highest anticonvulsant activity.



R= 4-OCH_3

A series of 3- and 5-aryl-1,2,4-oxadiazole derivatives and tested for anticonvulsant activity in a variety of models. These 1,2,4-oxadiazoles derivatives exhibit considerable activity in both pentylene tetrazole (PTZ) and maximal electroshock seizure (MES) models. Compound 10 was protective in the PTZ model with an oral ED50 of 25.5 mg/kg and in the MES model with an oral ED50 of 14.6 mg/kg. Several oxadiazoles were synthesized that act as a selective GABA potentiating compounds with no interaction to the benzodiazepine binding site.

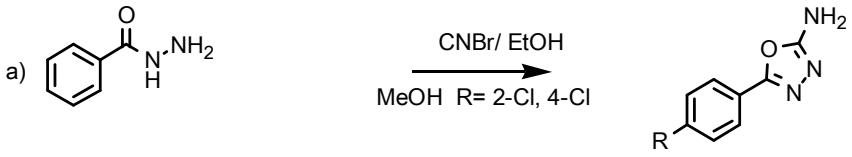


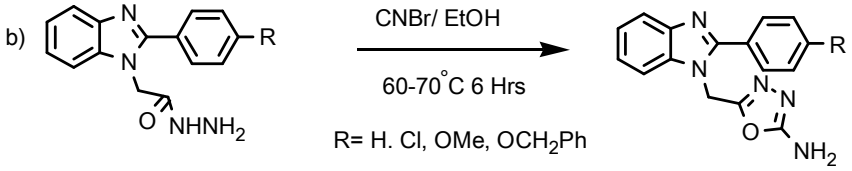
5-Phenyl-3-[1,2,4]triazol-1-ylmethyl-
[1,2,4]oxadiazole

The synthesis 5-aryl-2-amino-1,3,4-oxadiazole compounds in yields of 62 to 70%. These compounds were used as intermediates for the synthesis of new quinazolinone derivatives [18]. A new series of 2-amino-1,3,4-oxadiazoles carrying a benzimidazole moiety in 33%–60% yield

from the reaction between2-(2-(4-substituted-phenyl)-1*H*-benzo[d]imidazol-1-yl)aceto hydrazide and cyanogen bromide.

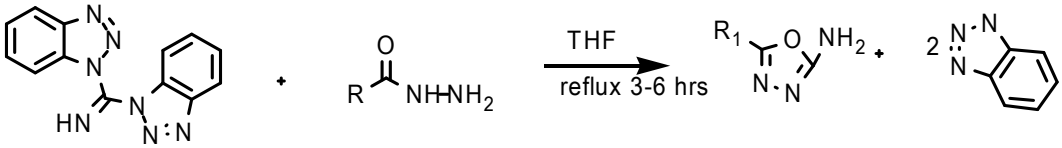
Synthesis of 5-Aryl-2-amino-1,3,4-oxadiazole obtained from acyl hydrazides and cyanogen bromide.





The synthesis of 5-aryl-2-amino-1,3,4-oxadiazole compounds in excellent yields from the reaction between di(benzotriazol-1-yl)methanimine and arylhydrazides using approach[19].

Synthesis of 5-Aryl-2-amino-1,3,4-oxadiazole obtained from acylhydrazides and di(benzotriazol-1-yl) methanimine.

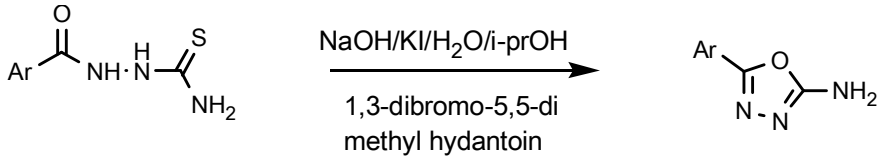


R_1= Ph, 4-t-BuC_6H_5,4-NH_2-C_6H_5,4-$NO_2C_6H_5$,4-OHC_6H_5,4-ClC_6H_5,4-PyridylC_6H_5

1,3-dibromo-5,5-dimethylhydantoin is an effective oxidizing agent for cyclization reactions of acylthiosemicarbazide were cyclized to 5-aryl-

2-amino-1,3,4-oxadiazoles in excellent yield[20]. The main advantage of this method was that the reagents used are commercially cheap and safe to work with. Further, it is applicable to large scale synthesis where other oxidizing agents cannot be used.

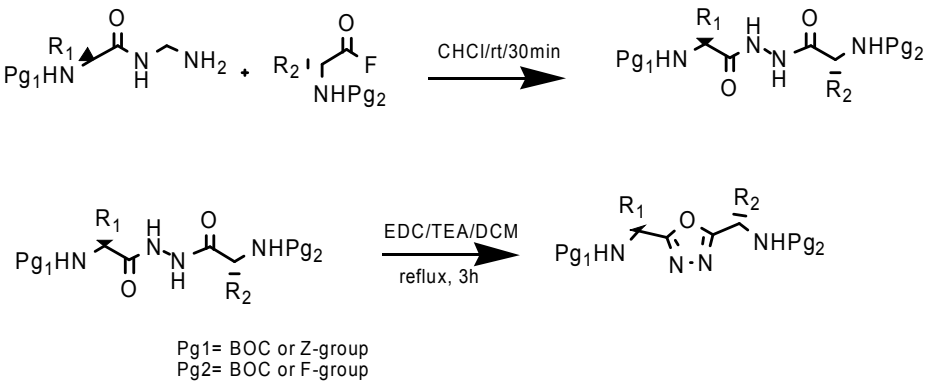
Synthesis of 5-aryl-2-amino-1,3,4-oxadiazole from acylthiosemicarbazide and 1,3-dibromo-5,5-dimethylhydantoin.



Ar= Ph, 4-ClC_6H_4, 4-$OMeC_6H_4$

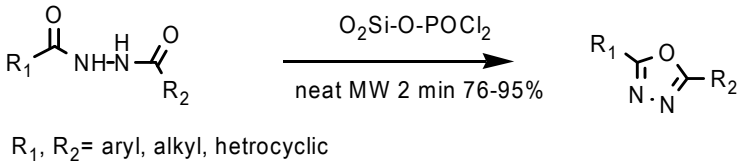
The synthesis of novel orthogonally protected 1,3,4-oxadiazole[21], tethered dipeptide mimetics, by cyclodehydration of diacylhydrazine using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) as a dehydration agent, obtaining a 70%–92% yields.

Synthesis of Cyclodehydration reaction of diacylhydrazines using EDC.



The silica-supported dichlorophosphate is an efficient cyclodehydration agent for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from 1,2-diacylhydrazines in solvent-free medium under microwave irradiation. This protocol was suitable for the synthesis of alkyl, aryl, and heterocyclic substituted symmetrical and unsymmetrical 1,3,4-oxadiazoles, and has the specific advantages of no corrosion or environmental pollution, an accelerated rate, high yield and a simple work-up procedure [22].

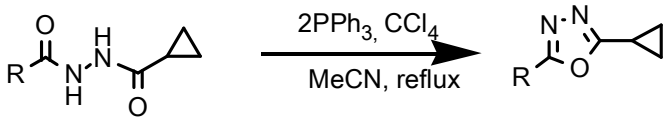
Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from 1,2-diacylhydrazines and silica-supported dichlorophosphate.



The effect of halogens in a Robinson-Gabriel type reaction of Cyclo propane-carboxylic acid *N*′-substituted-hydrazides with PPh3/CX4 (X =

Cl, Br, I) as dehydration agents resulting in the formation of 1,3,4-oxadiazoles [23].

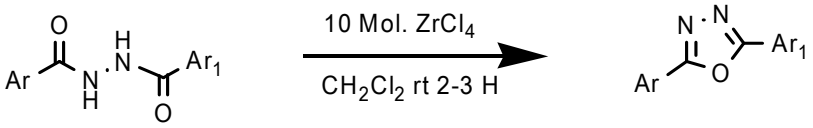
Synthesis of Effect of halogens in the formation of 1,3,4-oxadiazoles.



R= $Me_2C_6H_5$, C_6H_5,P-BuC_6H_4, Benzyl, etc.

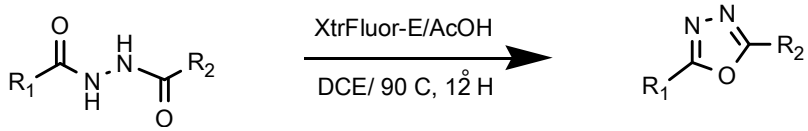
A simple generalized method for the synthesis of 1,3,4-oxadiazoles from diacylhydrazines using inexpensive ZrCl4 as a catalyst. Advantages over the existing methods include higher yields, shorter reaction times, and a simple experimental procedure[24].

Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from 1,2-diacylhydrazines and Zirconnium(IV) chloride.



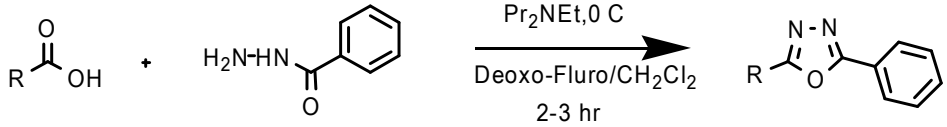
The use of di ethyl amino di fluoro sulfinium tetrafluoroborate ([Et2NSF2] BF4), XtalFluor-E, as a new cyclo dehydration agent for the preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines[25].

Synthesis of Preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using XtalFluor-E.



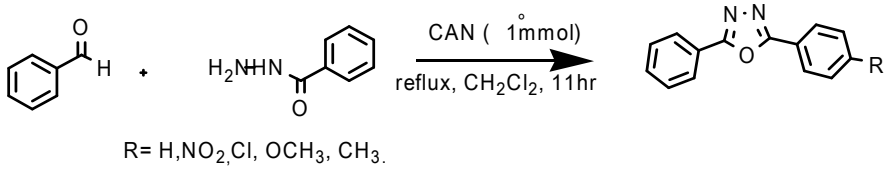
A one-pot direct synthesis of 1,3,4-oxadiazoles in excellent yields from carboxylic acids (1 equiv) and benzohydrazide (2.2 equiv) using Deoxo-Fluor reagent[26].

Synthesis of 1,3,4-oxadiazoles using Deoxo-Fluor.



A new procedure for the synthesis of disubstituted oxadiazoles 68 through a one-pot reaction of benzohydrazide, and *para* substituted aromatic aldehydes in the presence of an cerium ammonium nitrate (CAN) and dichloromethane solvent[27].

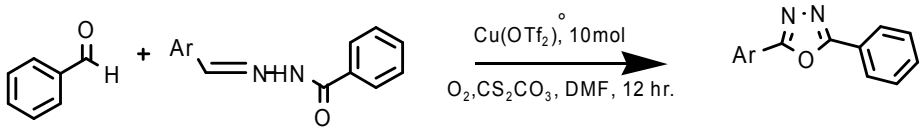
Synthesis of 2,5-diaryl-1,3,4-oxadiazoles from benzohydrazide and aromatic aldehydes.



R= H,NO_2,Cl, OCH_3, CH_3.

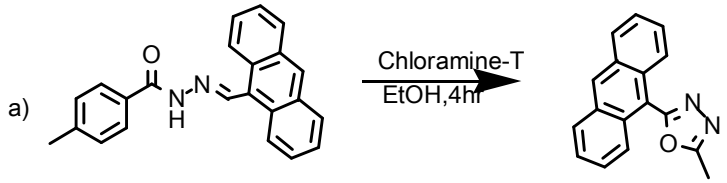
A direct route to both symmetrical and unsymmetrical 2,5-disubstituted-1,3,4-oxadiazoles 70 by means of an imine C-H functionalization of *N*-arylidenearoylhydrazide 69 using Cu(OTf)2 as catalyst[28].

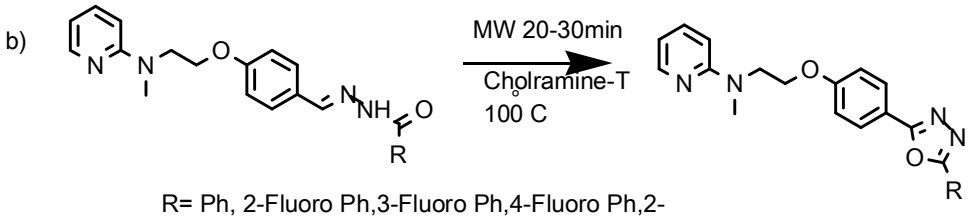
Synthesis of 1,3,4-oxadiazoles from *N*-arylidenearoylhydrazides and Cu(OTf)2.



Ar= Ph,4-MeC_6H_4, 4-t-BuC_6H_4, 4-$OMeC_6H_4$, 3,4-$OMeC_6H_4$, 4-t-$BuOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-FC_6H_4, 4-BrC_6H_4, 4-$AcOC_6H_4$, Etc.

The synthesis of 1,3,4-disubstituted oxadiazoles from the oxidative cyclization of *N*-acylhydrazones with chloramine-T under microwave irradiation[29].Synthesis of oxidative cyclization of *N*-acylhydrazones using chloramine-T.

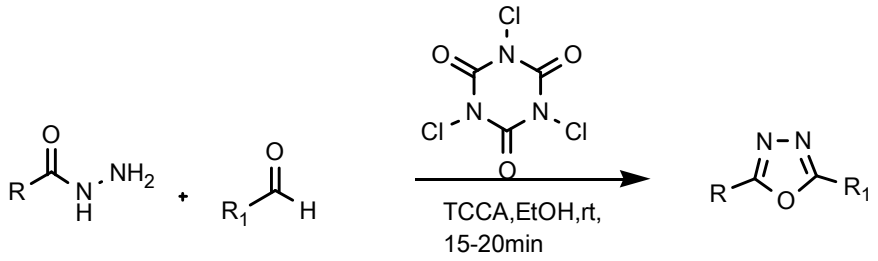




R= Ph, 2-Fluoro Ph,3-Fluoro Ph,4-Fluoro Ph,2-Chloro Ph,etc>

An efficient method for one-pot synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles using trichloroisocyanuric acid (TCCA) at ambient temperatures[30]. The main advantages of this method are the mild nature of the synthesis, and the short reaction time.

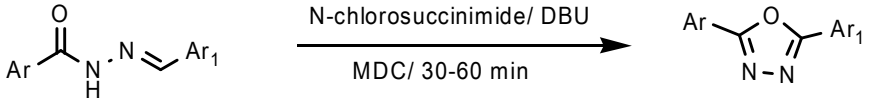
Synthesis of 1,3,4-oxadiazoles using trichloroisocyanuric acid (TCCA).



R=Ph, 4-ClC_6H_4,4-$OCH_3IC_6H_4$,4-$CH_3C_6H_4$,
R_1= Ph,4-$CH_3C_6H_4$,4-ClC_6H_4,4-$CH_3C_6H_4$,

A mixture of *N*-chlorosuccinimide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) oxidatively cyclized structurally diverse acyl hydrazones thereby providing an efficient and convenient method for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles[31]. The salient features of this method are the mild reaction conditions, short reaction time, excellent yields, and a simple workup procedure.

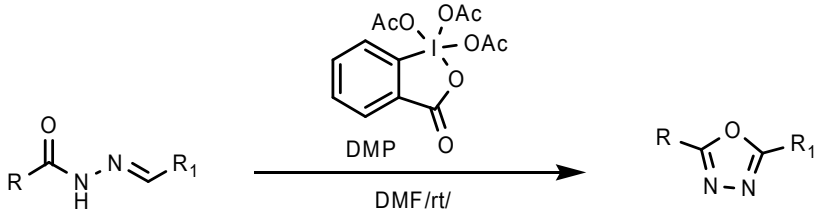
Synthesis of Oxidative cyclization of acylhydrazones using N-chlorosuccinimide and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU).



Ar =Ph, 4-$NO_2C_6H_4$,4-$OCH_3C_6H_4$,4-$CH_3C_6H_4$,3,5-$CF_3C_6H_3$
Ar_1 = Ph, 4-$OCH_3C_6H_4$,4-ClC_6H_4 ,4-$CH_3C_6H_4$,

The synthesis of 2,5-disubstituted-1,3,4-oxadiazoles, conveniently prepared by oxidative cyclization of *N*-acylhydrazones through use of an excess of Dess-Martin periodinane under mild conditions[32].

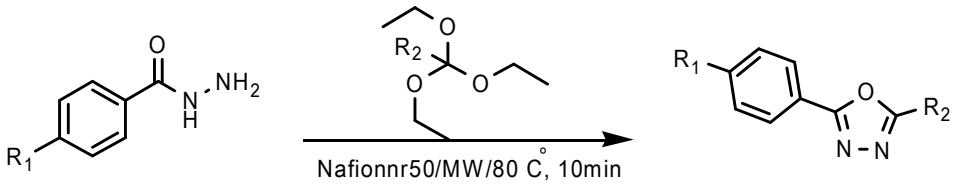
Synthesis of Oxidative cyclization of *N*-acylhydrazones using Dess-Martin periodinane.



R =Ph, 4-$NO_2C_6H_4$,4-$OCH_3C_6H_4$,4-$CH_3C_6H_4$,3,5-$CF_3C_6H_3$
R_1 = Ph, 4-$OCH_3C_6H_4$,4-ClC_6H_4 ,4-$CH_3C_6H_4$,

A novel one-pot solvent-free synthesis of 1,3,4-oxadiazole by condensation of benzohydrazide and triethylorthoalkanates under microwave irradiation,and efficiently catalyzed by Nafion®NR50 (solid supported), and phosphorus pentasulfide in alumina (P4S10/Al2O3) with excellent yields[33].

Synthesis of Nafion catalized 1,3,4-oxadiazole.



R_1 = H, F, OMe,
R_2 = H, Et. Ph

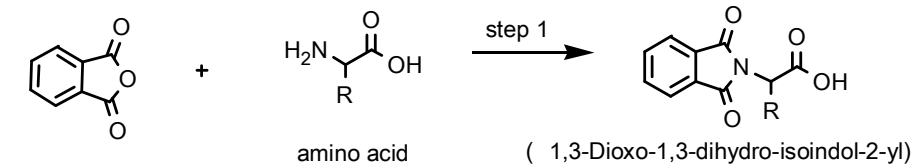
Experimental and spectral studies:

Materials and methods:

Melting points were determined using open capillary method and are uncorrected. The compounds were checked for homogeneity by TLC on silica gel G. The IR spectra were recorded by using JASCO FTIR spectro photometer using KBr-disc method.

Scheme I

Step I Preparation of phthalyl amino acid from phthalic anhydride and alpha amino acids.



phthalic anhydride

amino acid

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) -acetic acid
PHTHALYL AMINO ACID

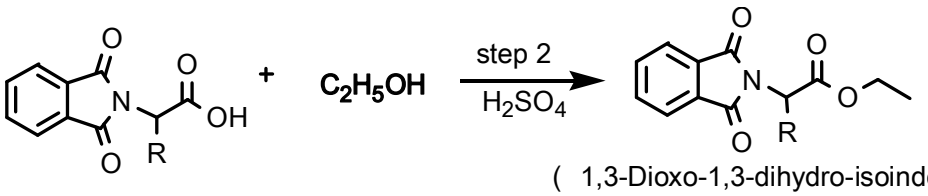
[4a-d]

A mixture of (0.06 moles) of appropriate amino acids in NaoH and (0.06moles) of finely powered phthalic anhydride was heated for 30 mints with stirring in an oil bath at 145-150 ˚c. after 30 mints reaction mixture was cooled and solid obtained was dissolved in 40ml hot methanol. The filtrate was diluted with 40 ml cold water the product allowed to crystallize to give phthalyl amino acids (4a-d).

TableNo. 4.1 Synthesis of phthalyl amino acid from phalic anhydride and α-aminoacids [4a-4d]

Comp. No.	R	M.P. ℃	% Yield	Mol. Formula/ Mol.Wt	IR (KBr)		
					C=O amide	C=O Acid	-OH
4a	H	193	85	$C_{10}H_7O_4N$ 205	1672	1700	3300
4b	HO-C6H4-CH2	180	90	$C_{17}H_{14}O_5N$ 312	1660	1716	3000
4c	HO-CH2-	112	83	$C_{11}H_9O_5N$ 235	1682	1720	3225
4d	HS-CH2	126	87	$C_{11}H_9O_4NS$ 251	1081	1765	3200

Step II preparation of phthalyl amino ester from phthalyl amino acids.



(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) - acetic acid ethyl ester

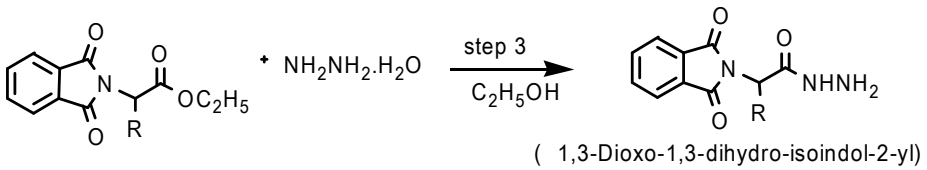
[5a-d]

A mixture of (4a-d) was taken (0.04 moles) in excess of ethanol (50 ml) was added (2ml) conc. H_2SO_4. The reaction mixture was refluxed for 6 hours. The product obtained, filtered, washed and dried, then recrystalised from ethanol. The yield was recorded (5a-d).

Table No. 4.2 Physical properties of phthalyl amino ester (5a-d):

Comp. NO.	R	M.P. ˚C	% Yield	Mol. Formula/ Mol.wt	IR(KBr)		
					C-O-C	-C=o amide	-COO
5a	H	102	69	$C_{12}H_{11}O_4N$/ 233	1021	1086	1725
5b	HO-C_6H_4-CH2	153	62	$C_{19}H_{17}O_5N$/ 339	1190	1670	1710
5c	HO-CH_2-	Oily	73	$C_{13}H_9O_5N$/ 261	1165	1650	1730
5d	HS-CH_2	Oily	82	$C_{13}H_{13}O_4NS$ 279	1030	1675	1740

Step III preparation of phthalyl amino substituted acetic acid hydrazide from phthalyl amino esters.



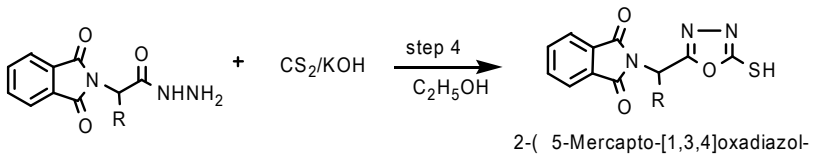
(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)
-acetic acid hydrazide
[6a-d]

The solution of (5a-d) (0.04 mole) was taken in 50 ml of ethanol and 99% hydrazine hydrate (0.1 mole) 5ml added to the reaction mixture was refluxed for 3 hours. After cooling the solid material neutralize with alkali NaOH, and filtered, washed with ethanol and diethyl ether. The yield was recorded (6a-d).

Table No. 4.3 Physical properties of phthalyl amino acetic hydrazide(6a-d):

					IR (KBr)		
Comp. No	R	M.P.	% Yield	Mol. Formula	C=O Amide	NH_2	C=C
6a	H	241	81	$C_{10}H_9O_4N_3$	1625	3200	1600
6b	HO-C_6H_5-CH2	250	70	$C_{17}H_{16}O_5N_3$	1680	3300	1650
6c	HO-CH_2	237	65	$C_{12}H_{11}O_4N_3$	1660	3350	1610
6d	SH-CH_2	225	72	$C_{11}H_{11}O_4N_3S$	1670	3300	1615

Step IV preparation of phthalyl-1-(5-thio-1, 3, 4-oxadiazole-2-yl)-alkane from phthalyl amino substituted acetic acid hydrazide.



2-(5-Mercapto-[1,3,4]oxadiazol-2-ylmethyl) -isoindole-1,3-dione

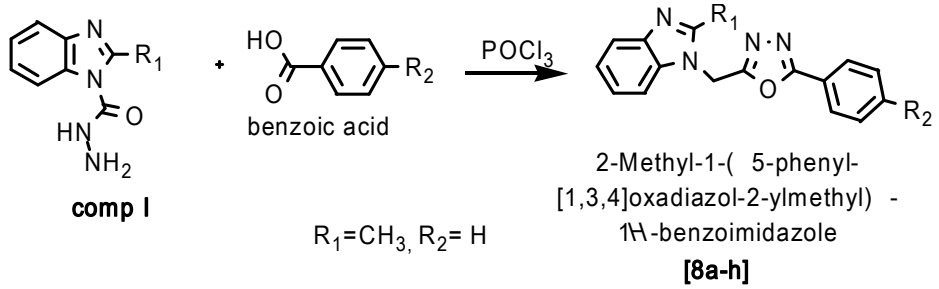
[7a-d]

The solution of (6a-d) (0.01 mole) was taken in 40ml of ethanol, (0.2 mole) of KOH and (0.2 mole), 2ml CS_2 added to the reaction mixture was refluxed for 6 hours and concentrate to a small volume. The content was poured into ice cold water and acidified with dil HCl to give the desired product which was recrystalised from ethanol. The yield was recorded (7a-d).

Table No. 4.4 Physical properties of [1,3,4]-Oxadiazole (7a-d):

					IR(KBr)				
COMP	R	%YLD	MP℃	Mol.Form/ Mol.Wt	C-H	S-H	C=N	C=O	C-O-C
7a	H	75	288	$C_{11}H_7O_3N_3S$ 261	3000	2595	1600	1710	1160
7b	HO-C_6H_4-CH_2	82	299	$C_{18}H_{14}O_4N_3S$ 368	3025	2550	1610	1716	1040
7c	HO-CH_2	70	293	$C_{12}H_{19}O_4N_3S$ 291	3040	2520	1600	1720	1040
7d	SH-CH_2	70	307	$C_{12}H_9O_3N_3S_2$ 307	3050	2589	1610	1716	1030

Scheme II



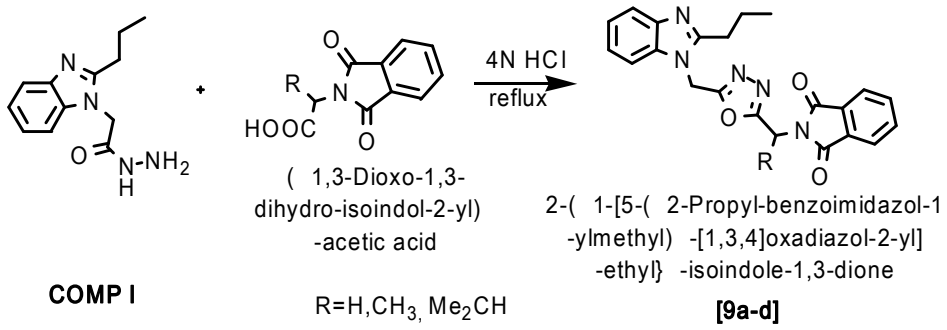
Synthesis of [1,3,4] Oxadiazole:

The product obtained from 2-propyl benzimidiazole-yl-acetahydrizide [0.04mole] was mixed with aromatic /aliphatic acids [0.03mole] and add 1ml of $POCl_3$. The mixture was stirred to get homogeneous mixture then it was heated in a beaker under microwave at 160W for 5 mints. Completion of heating TLC was checked. The product was cooled at room temperature then excess of ice cold water was added. The product formed was filtered and recrystalised from ethanol and m.p. recorded.

Table No. 4.5 Physical properties of [1,3,4]Oxadiazole (8a-d):

Comp.	R_1	R_2	M.P.	Mol. formula [mol.wt]	Found %				
					C	H	N	O	Cl
8a	CH_3	H	152˚	$C_{17}H_{14}N_4O$ 290	70	5.2	19.3	5.5	-
8b	CH_3	NH_2	200˚	$C_{16}H_{14}N_5O$ 292	65.73	4.85	24	5.4	
8c	CH_3	CH_3	135˚	$C_{15}H_{16}N_4O$ 304	71	5.3	18.4	5.2	
8d	CH_3	Cl	205˚	$C_{17}H_{13}N_4OCl$ 325	62.8	4.0	17	5.2	11
8e	C_6H_5	H	170˚	$C_{22}H_{16}N_4O$ 352	75.0	5.0	15.9	4.1	
8f	C_6H_5	NH_2	183˚	$C_{22}H_{17}N_5O$ 367	72.0	4.7	19.0	4.3	
8g	C_6H_5	CH_3	158˚	$C_{23}H_{18}N_4O$ 366	75.0	5.0	15.0	5.0	
8h	C_6H_5	Cl	169˚	$C_{22}H_{15}N_4OCl$ 386	68.0	4.0	15.0	4.0	9.0

Scheme III



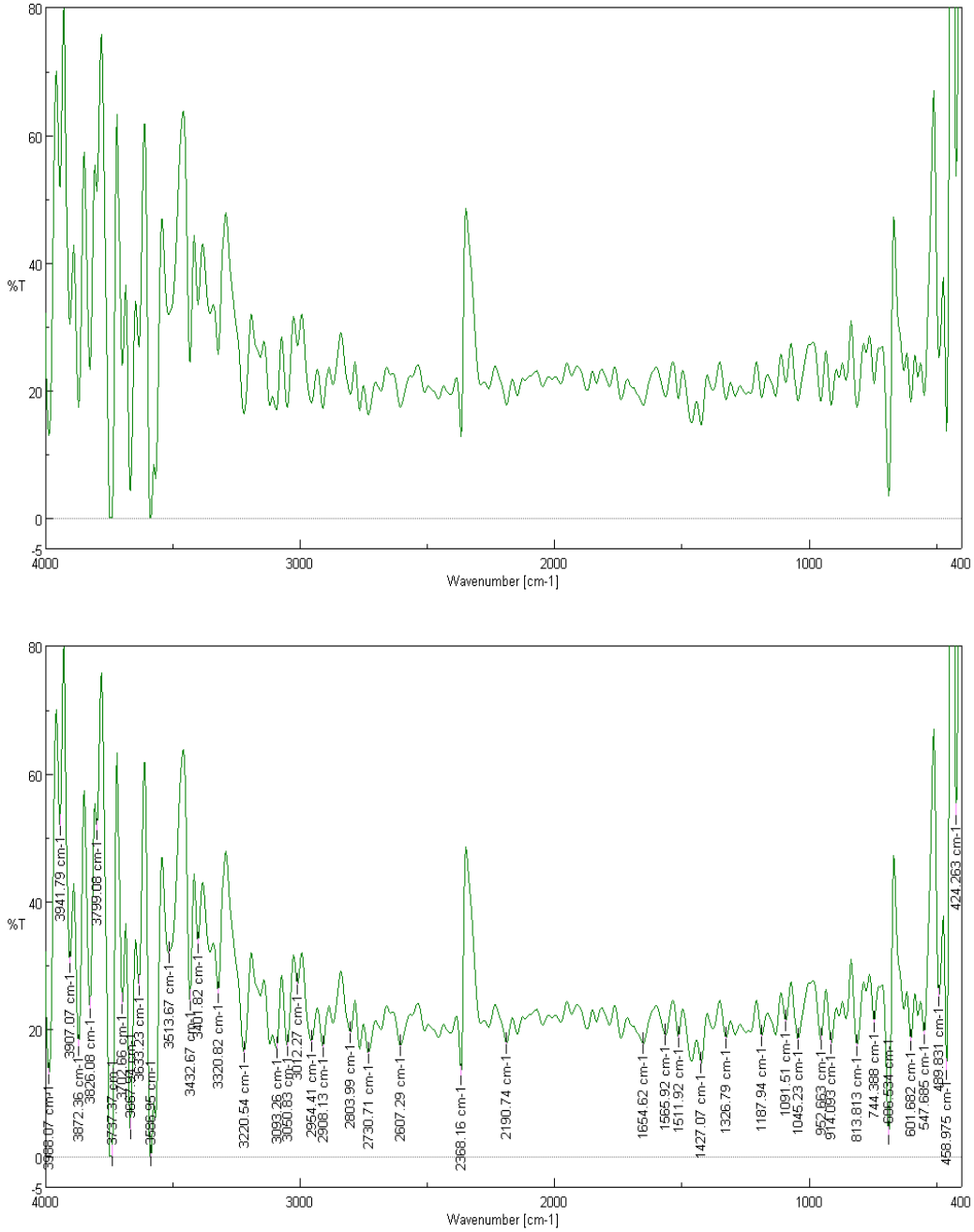
A mixture of 2-(2propyl-1H-benzimidiazol-yl) acetic acid hydrazide (0.002 mole), (0.003 mole) phthalyl amino acid (1,3-Dioxo-1,3-dihydro-isoindole-2-yl)-acetic acid and (1ml) phosphoryl chloride was heated for 30 min. Completion of reaction was monitored by TLC, the content were cooled to room temperature and added excess of ice cold water. The solid product was separated was collected and neutralized with dil NaOH solution, the solid product separated was collected and filtered. Further purification was done by recrystalization from ethanol DMF mixture (2:1) the yield and m.p. was recorded.

Table No. 4.6 Physical properties of [1,3,4]oxadiazole

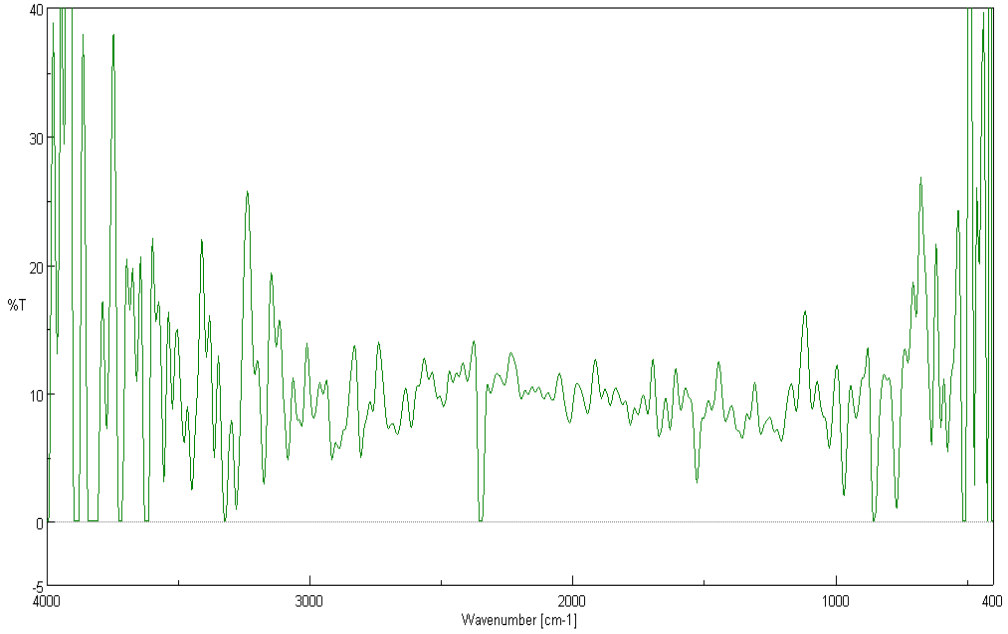
	R	Mol for/ Mol Wt	C	H	N	O
9a	H	$C_{22}H_{19}N_5O_3$ 401	65.83	4.77	17.45	11.96
9b	C_6H_4-CH_2	$C_{29}H_{25}N_5O_3$ 491	70.86	5.13	14.25	09.76
9c	CH-Me_2	$C_{25}H_{25}N_5O_3$ 443	67.70	5.68	15.79	10.82
9d	CH_3	$C_{23}H_{21}N_5O_3$ 415	66.49	5.09	16.86	11.55

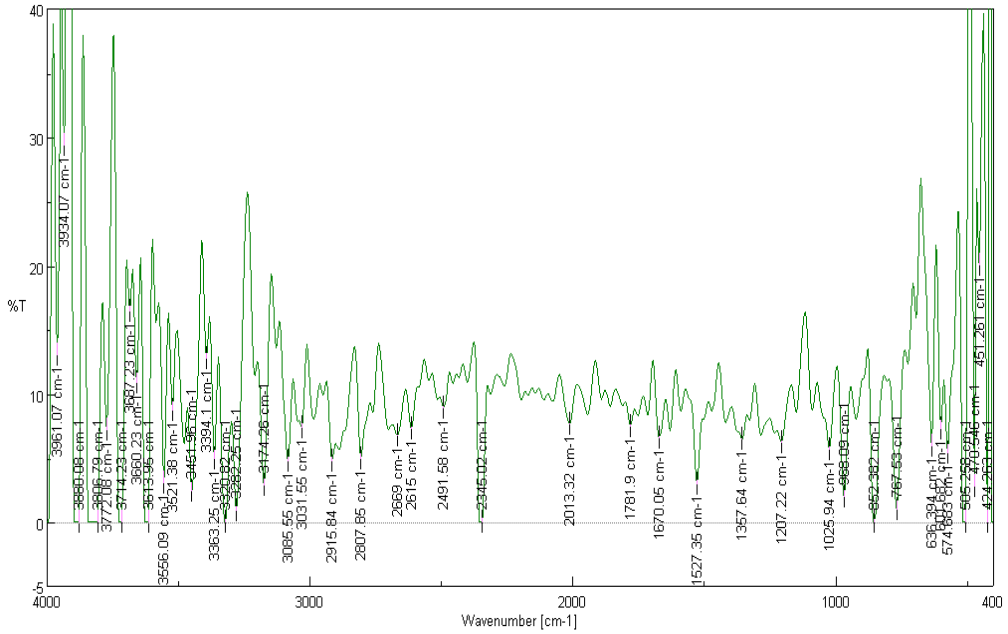
Table No. 4.7 Physical properties of synthesized compound (9a-d):

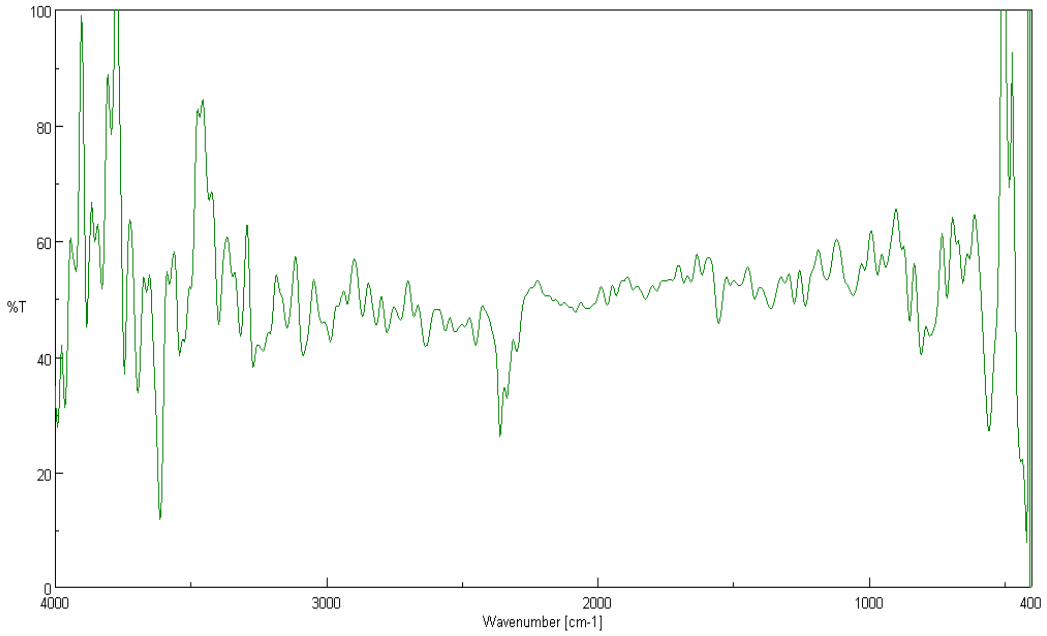
					IR(KBr)			
COMP	R	%YLD	MP℃	Mol.Form/ Mol.Wt	C-H	C=N	C=O	C-O-C
9a	H	62	193-195	$C_{11}H_7O_3N_3S$ 261	3000	1600	1710	1160
9b	C_6H_4-CH_2	65	182-185	$C_{18}H_{14}O_4N_3S$ 368	3025	1610	1716	1040
9c	CH-Me_2	62	142-145	$C_{12}H_{19}O_4N_3S$ 291	3040	1600	1720	1040
9d	CH_3	68	123-126	$C_{12}H_9O_3N_3S_2$ 307	3050	1610	1716	1030

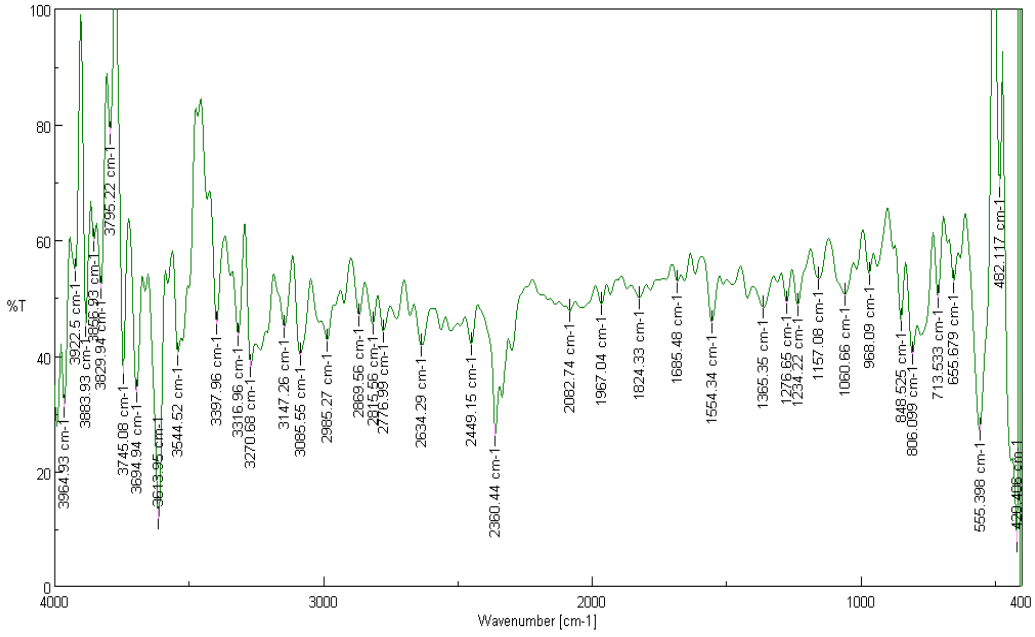


2-(5-marcapto- (1, 3, 4) oxadiazole-2-ylmethyl]-isoindole-1, 3- dione.

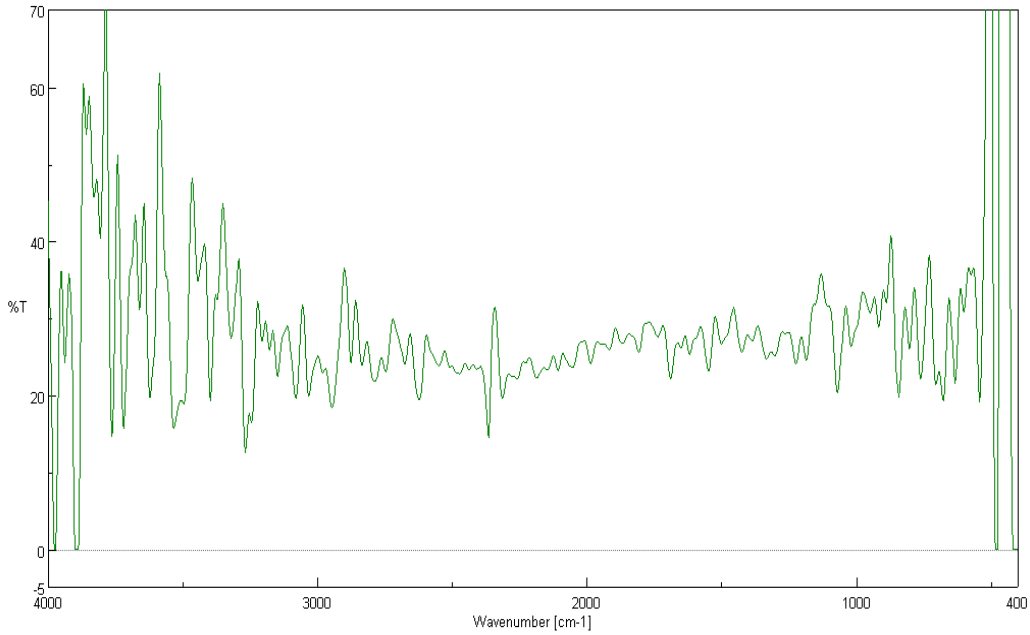

%T
Wavenumber [cm-1]

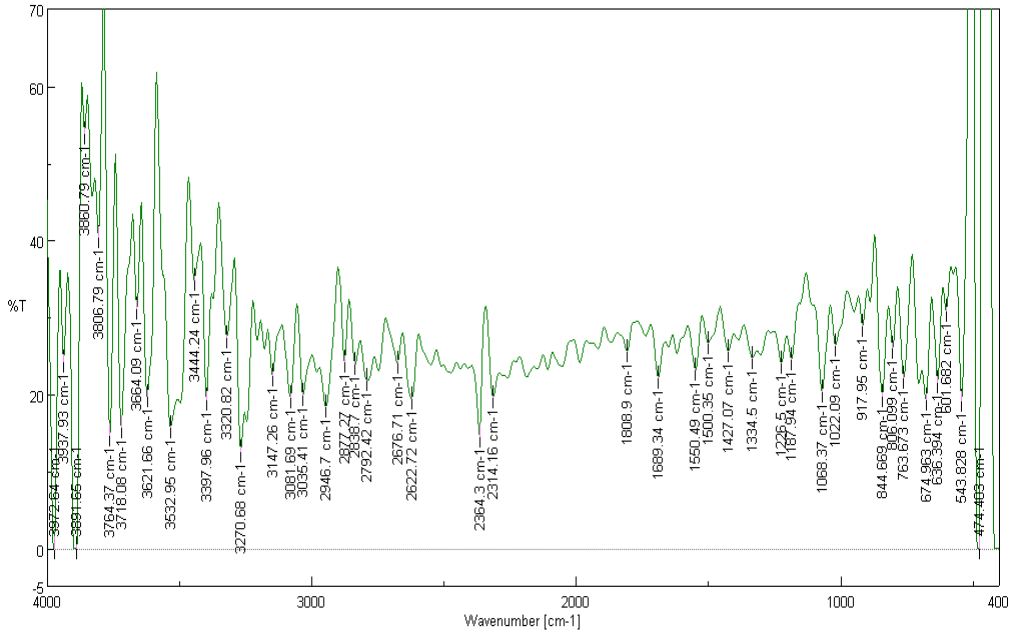

%T
Wavenumber [cm-1]





2-[2-Marcapto-1-(5-marcapto- (1, 3, 4) oxadiazole-2-yl)-ethyl]-isoindole-1, 3- dione.





2-[4-hydroxy- phenyl-1-(5-marcapto- (1, 3, 4) oxadiazole-2-yl)-ethyl]-isoindole-1, 3- dione.

Result and Discussion:

SchemeI

Phthalic acid and appropriate amino acid were fused together afforded corresponding phthalyl amino acid [4a-d] scheme I. the structure of the prepared compounds have been identified by their IR spectra in which two bands [1665-1680]cm^{-1} [3350-3400] indicates the presence of C=O, and –OH respectively. Treatment of phthalylamino acid with absolute ethanol in presence of conc.H_2SO_4 gave the corresponding ester Ethyl-N-phthalyl -1-alkyl /phenyl glycinate [5a-d]. Then ester was heated with hydrazine hydrates in presence of ethanol, N- phthalyl amino substituted acetic acid hydrazide synthesized [6a-d]. Finally oxadiazole [7a-d] derivative have been synthesized by the cyclization reaction of the acid hydrazide with CS_2/KOH in ethanol. The formation of these condensation products was confirmed by measuring their m.p. and spectral analysis.

Scheme II

The preparation of 1, 3, 4 oxadiazole derivative followed by four steps. The structure of the final compound was confirmed on the basis of spectra and analytical data. The IR spectra of 1, 3, 4 oxadiazole derivatives carrying benzimidiazole showed absorption bands in the region of 3066-2965 cm^{-1} which is characteristic of C-H stretching. The C=N absorption band was observed around 1580-1600cm^{-1}.

Scheme III

The mixture of 2-[2-propyl-1H-benzimidiazole carbohydrazide and phthalyl amino acid was heated in presence of phosphorus oxychloride for 30 hrs. after completion of the reaction monitored by TLC. The reaction mixture was cooled and neutralized with alkali NaOH. The solid product separated was collected by filtration and recrystalised by ethanol and DMF [2:1]

Biological Screening Antimicrobial Activity:

The newly synthesized compounds were screened for their antimicrobial activity in vitro against Gram positive (Bacillus cereus) and Gram negative bacteria (E.coli) yeast (Saccharomyces cerevisae) and Fungi (Aspergillus Niger).

The test was performed by disc diffusion method adopted with some modification for the prepared compound using Gentamycin and Ampicillin as reference. Whatmann filter paper No.1 disk of 5 of diameter were sterilize by autoclaving for 10 minutes at 120℃. The sterile discs were impregnated with different (600µg/disc).

Agar plates were surface inoculated uniformly from the broth culture of the tested microorganism. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5℃ for 45 minutes to permit good diffusion and then transferred to an incubator at 37℃ for 24 hours, for bacteria incubator 27℃ for 48 hours. The inhibition caused by the various compounds on the microorganism was examined.

The results of the preliminary screening test in table. The antibacterial and antifungal activity compounds [4a- 4d] were tested and found that compound 4a, 5b and 4b,5d was highly active against Bacillus cereus but slightly active against Escherichia Coli while compound 4c

found slightly active and compound 1c and 1d were found moderately active against B.Cereus . All compounds were inactive against Saccharomyces cerevisae and Aspergillus Niger.

Table No. 4.8 Results of antimicrobial activity of the tested compounds.

Comp.No.	B. cereus	E.Coli	S.cerevisae	A.niger
Gentamycin	+++	+++	–	–
Ampicillin	+++	+++	–	–
4 a	+++	++	–	–
4b	+++	++	–	–
4c	++	++	–	–
4d	++	++	–	–

Table No. 4.9 Results of antimicrobial activity of the tested compounds**.**

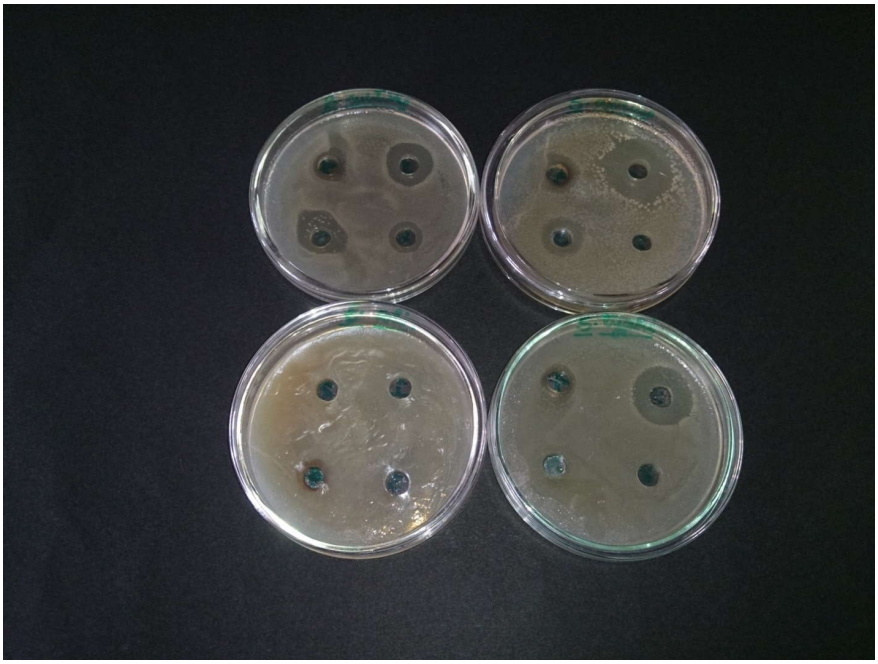
Comp. No.	B. cereus	E.Coli	S.cerevisae	A.niger
Gentamycin	+++	+++	_	_
Ampicillin	+++	+++	_	_
5a	_	+	_	_
5b	+++	+	_	_
5c	--	_	_	_
5d	++	++	_	_
5 e	+	+	_	_
5f	_	_	_	_
5e	-	-	-	-
5h	-	-	-	-

Key to symbols

Highly active = +++ (inhibition zone>12mm)

Moderately active = ++ (inhibition zone 9-12mm)

Slightly active = + (inhibition zone 6-9mm)



Conclusion:

All the newly synthesized compounds (8a-h) and (9a-d) were screened for antibacterial activity studies at a concentration of 600ug/disc as a control and Gentamycin used as standard against gram +ve and gram –ve bacteria. All the newly synthesized compounds showed moderate to mild antimicrobial activity. These findings concluded that the titled compounds have the property to kill the microbes in some extent when compared with standard drugs.

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