Scholars Academic Journal of Pharmacy (SAJP)
Abbreviated Key Title: Sch. Acad. J. Pharm.
ISSN 2347-9531 (Print)
ISSN 2320-4206 (Online)

A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

Pharmaceutical Chemistry

Design, Synthesis and Pharmacological Evaluation of 2, 5 -Disubtituted-1, 3, 4-Oxadiazole Derivatives as Noval Antibacterial and Antifungal Agent

B.N Thakare*, Dr. R.L Bakal, U.M Kad, S.U Deshmukh
P. Wadhawani College of Pharmacy, Yavatmal (MH), India

Original Research Article

***Corresponding author**
B.N Thakare

Article History
Received: 03.01.2018
Accepted: 14.01.2018
Published:30.01.2018

DOI:
10.21276/sajp.2018.7.1.6

Abstract: The 1, 3, 4-Oxadiazole nucleus is associated with various pharmacological activities and are potential linker moieties. The Schiff base derivatives of 5-arylsubstituted-1, 3, 4-oxadiazole-2-amine were synthesized and the structure of synthesized compound confirmed by TLC and spectroscopic techniques like 1H NMR, IR and mass spectrometry. All the synthesized compounds were screened in vitro for antibacterial and antifungal activity by paper disc diffusion method using Mueller-Hinton agar and cup plate method using Potato dextrose agar respectivly. Penicillin and Ketoconazole were used as standard for antibacterial and antifungal activity respectively. The antimicrobial activity screening reveled that, the compounds are found to be mild to moderate active in the conc. 200 µg/ml , 400 µg/ml , 600 µg/ml and 1000 µg/ml against *Escherichia coli, Staphylococcus aureus, Pseudomonas aerugenosa* and *Klebsiella pneumoniae* bacterial strain, and *Candida albicans,* and *Aspergillus niger* pathogenic fungi. Some of them have good activity at observed concentration.
Keywords: Oxadiazole, Schiff base, 1H NMR, IR, mass spectrometry, antibacterial and antifungal.

INTRODUCTION

The introduction of antibiotics in the chemotherapy of bacterial infections in the middle of the last century revolutionized medicine, causing drastic reduction in mortality from bacterial diseases.

However, the spread and misuse of antibiotics has unfortunately helped the emergence of bacterial resistance, whereby bacteria populations have developed defense mechanisms against most antibiotics [1-3]. The alarming rates of emerging and reemerging microbial threats coupled with the growing emergence of antimicrobial resistance are major concerns to the public health and scientific communities worldwide. Bacterial infection such as food poisoning, rheumatic, salmonellosis and diarrhea are caused by multidrug-resistant Gram-positive and Gram-negative pathogens. Principal players among these problematic organisms are isolates of methicillin-resistant Staphylococcus aureus, Staphylococcus pyogenes, Salmonella typhimurium and Escherichia coli [4].

Similarly there are very few antifungal agents that can be used for life threatening fungal infections. These drugs are amphotericin B, 5-fluorocytosine, azoles such as fluconazole and itraconazole [5], and echinocandins such as caspofungin and micafungin [6]. Because of their high therapeutic index, azoles are first-line drugs for the treatment of invasive fungal infections. Unfortunately, the broad use of azoles has led to development of severe resistance [7, 8] which significantly reduced the efficacy of them.

Thus, these trends have emphasized the urgent need for new, more effective and safe antimicrobial agents. Among the attractive approaches to achieve this goal, the development of structurally new classes of antimicrobial agents with novel mechanism of action and the structural modification or optimization of the existing agents by improving both the binding affinity and spectrum of activity while retaining bioavailability and safety profiles, have provoked special interest in the realm of medical chemistry. However, the increasing prevalence of one such strategy that has been pursued in recent years employs a combination of two different active fragments in one molecule [9]. With this strategy, each drug moiety is designed to bind independently to two different biological targets and synchronously accumulate at both target sites. Such dual-action drugs, or hybrid drugs, offer the possibility to overcome the current resistance and reduce the appearance of new resistant strains.

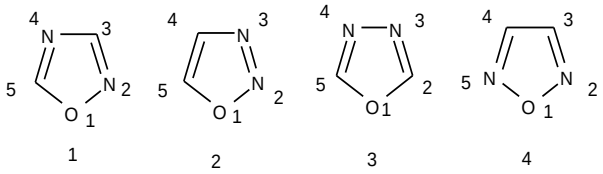
Compounds containing 1, 3, 4-oxadiazole nucleus find unique place in medicinal chemistry and play significant role as, they are associated with immense biological activity [9-15]. Moreover, these

nucleuses are suitable candidate for linking another chemically different compatible moieties [16-17].

In the light of above observation it was decided to carry out synthesis and pharmacological evaluation of 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives as novel antibacterial and antifungal agents.

Chemistry of oxadiazole

Oxadiazole is considered to be derived from furan by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=). There are four possible isomers of oxadiazole **(**1, 2, 3, 4) depending on the position of nitrogen atom in the ring and are numbered as shown as below.



1 2 3 4

Isomers of oxadiazole

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophillic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp2 carbon atom [11].

EXPERIMENTAL WORK

Synthesis of N-{4-(substituted-amino) phenyl}-5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-amine

Practical Procedure (*See* Fig-1: Scheme of synthesis)

Synthesis of ethyl 4-nitrobenzoate (2)

4-nitrobenzoic acid (10 g, 0.059 mol) was taken in a 250 ml round bottom flask fitted with a reflux condenser and a calcium chloride guard tube. Absolute ethanol (25 ml) and 1-1.5 ml of concentrated sulphuric acid were added and the reaction mixture was refluxed for 12 hours. After completion of reaction, the reaction mixture was poured into ice-cold water; the oily layer that deposited was extracted with diethyl ether and on evaporation of solvent yields pure mass.

Synthesis of 4-nitrobenzohydrazide (3)

The *ethyl 4-nitrobenzoate* (10g, 0.051 mol) was suspended in ethanol and hydrazine hydrate (98%, 2.65 ml, 0.051 mol) was added and refluxed the solution for 6 hours. Excess ethanol was distilled out and the contents were allowed to cool. The crystals formed were filtered, washed thoroughly with water and dried. On recrystalisation from ethanol, colourless needles were obtained.

Synthesis of 5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-amine (4)

To a stirring solution of *4-nitrobenzohydrazide (3)* (10g, 0.055 mol) in ethanol, sodium bicarbonate (4.62g, 0.055 mol) in water (10 ml) was added at room temperature. The mixture was stirred at room temperature for five minute and ethanolic solution of cyanogen bromide (5.83g, 0.055 mol) was added. The mixture was stirred with heating at 50^0C-55^0C for 14-16 hours and reaction mixture was added to 100 ml of cold water. If suspension was found to be acidic then neutralize with dilute solution of sodium bicarbonate. The precipitate obtained was filtered, dried and crystallized from ethanol.

Synthesis of N-[5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-ylbenzene-1, 4-diamine (5)

An ethanolic solution of p-chloroaniline (3.06g, 0.024 mol) was added to solution of compound (4) (5g, 0.024 mol) in 10% aqueous sodium hydroxide (5 ml) and the mixture was sonicated on a sonication bath for 60-90 min. The reaction mixture was poured in ice cold water (50 ml) and the solid thus separated out was filtered, washed with water, dried and recrystallized from ethanol.

N-{4-(substituted-amino) phenyl}-5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-amine (6a-6g)

To an ethanolic solution of compound (5) (0.0067 mol) the equimolar quantity of respective aldehyde or ketone (0.0067 mol) in ethanol (10 ml) was added. The suspension was heated until a clear solution was obtained. A few drops of glacial acetic acid (GAA) were added as a catalyst and the solution was refluxed for 3 h on a steam bath. The precipitated solid was filtered off, wash with water and recrystallized from ethanol.

Physical data of synthesised compounds

The synthesised intermediates and final derivatives were characterized by physical data like

nature, coloure, percentage practical yield (% P.Y.) melting point, retention factor (Rf) and solubility.

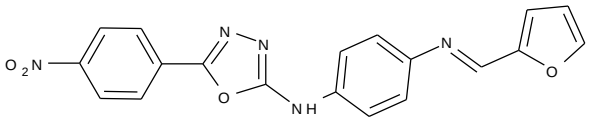
Molecular formula and formula weight were calculated by using ChemSktech (version 12). All compounds were solid in nature except ester.

(*See* Table-1)
(*See* Figure-2)
(*See* Table-2)

Solubility of compound: All compounds were found to be insoluble in water, sparingly soluble in chloroform and freely soluble in dimethylsulfoxide.

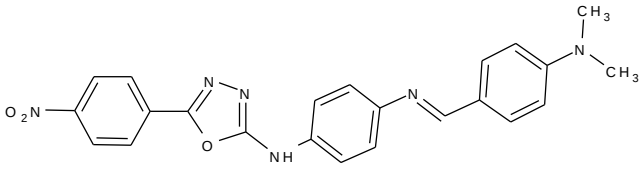
Spectral Data

N-[4-[(E)-2-furylmethyleneamino]phenyl]-5-(p-tolyl)-1,3,4-oxadiazol-2-amine (6a).



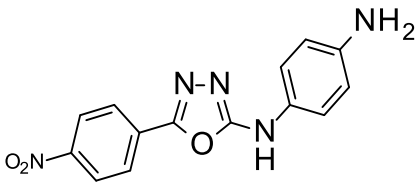
(*See* Figure 3)
(*See* Table 3)

IR Spectral study of N-{4-((E)-(4-dimethylaminophenyl) methyleneamino) phenyl}-5-(p-tolyl)-1,3,4-oxadiazol-2-amine (6d).



6d

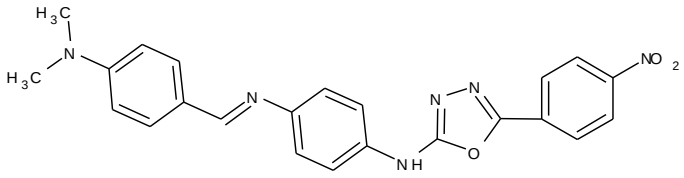
(*See* Figure 4)
(*See* Table 4)



Comp.5

(*See* Figure 5)

8 Ar-**H** (6.2-8.2)
1 N**H** (3.71)
2 N**H$_2$** (3.01)



Comp. 6d

1 N=C**H** (9.86)
12 Ar-**H** (6.2-8.2)
2 O-C**H$_2$**-Ar (5.16)
6 N-(C**H$_3$**)$_2$ (2.91)
1 N**H** (3.38)
(*See* Figure 6)

RESULTS AND DISCUSSION

Chemistry

A novel series of *5-aryl (nitro-substituted)-1, 3, 4-oxadiazole-2-amine (6a-6f)* derivatives were synthesized as outlined in scheme (Figure 1).

Hydrazide (3) is important intermediates in the synthesis of 1, 3, 4-oxadiazoles. Hydrazide of 4-nitrobenzoic acid (1) was synthesized from ester (2) as reported in ~~literature~~ method and ester was synthesized by usual method of esterification.

The compound 4 was synthesized from potassium salt of (3). Aromatic alkylation of 4 was carried out by sonication. Finally Schiff bases of 5 were synthesized.

The reactions and purity of the compounds were confirmed by TLC using silica gel G as stationary phase and suitable solvent system as mobile phase and by melting point. The physical data of compounds are tabulated in table 1.

Structures of all final derivatives are well supported by the spectral data such as IR and 1H NMR. N=C stretching between 1700-1600 and singlet at 9.8-10.2 ppm downfield are characteristics in final derivatives of 6a-6g.

Antimicrobial Results

All the synthesized compound were screened for anti-bacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aerugenosa* and *Klebsiella pneumoniae* bacterial strain, at various concentration such as 200 µg/ml, 400 µg/ml, 600 µg/ml, 800 µg/ml and 1000 µg/ml. According to antibacterial screening by paper disc diffusion method using Mueller-Hinton agar, also include the activity of reference compound penicillin.

All the synthesized compound were screened for anti-fungal activity against *Candida albicans*, and *Aspergillus niger* at various concentration such as 200 µg/ml, 400 µg/ml, 600 µg/ml, 800 µg/ml and 1000 µg/ml. According to antibacterial screening by cup plate method using Potato dextrose agar, also include the activity of reference compound Ketoconazole.

Antibacterial Screening

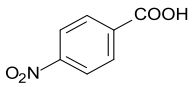
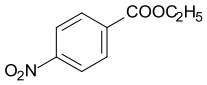
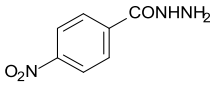
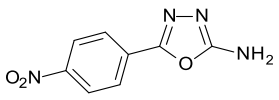
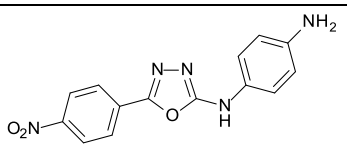
The diameter of the zone of inhibition were measured in mm of each organism, Penicillin was used as a standard drug
(*See* Table-5)

Anti-fungal Screening

The diameter of the zone of inhibition were measured in mm of each organism, ketoconazole was used as a standard drug.
(*See* Table 6)

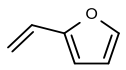
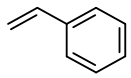
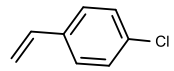
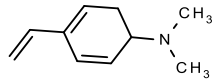
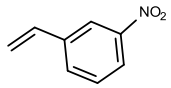
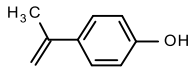
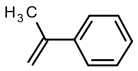
It has been observed that the entire tested compound's showed mild to moderate activity against tested bacteria and fungi, some of them have good activity at observed concentration.

Table-1: Physical data of synthesised compounds 1-5.

Comp. code	Structure	MF MW	Rf value*^	% Yield	M.P. (^oC)#
1		$C_7H_5NO_4$ 167.12	0.26	-	237-240
2		$C_9H_9NO_4$ 195.17	0.95	72	-
3		$C_7H_7N_3O_3$ 181.14	0.67	85	258-260
4		$C_8H_6N_4O_3$ 206.15	0.78	68	272-274
5		$C_{14}H_{11}N_5O_3$ 297.16	0.83 (0.48)	70	261-263

*Mobile phase Chloroform: Acetone (4:1), ^Moble phase Chlorofprm: Benzene (1:1), #Recrystallised from ethanol.

Table-2: Physical data of compounds 6a-6g

Comp Code	R	Colour	MF MW	Rf value*	% Yield	M.P. (^{o}C)#
6a		Faint yellow	$C_{19}H_{13}N_5O_4$ 375.34	0.75	65	252-254
6b		Brick red	$C_{21}H_{15}N_5O_3$ 385.38	0.74	71	286-288
6c		Yellow	$C_{21}H_{14}ClN_5O_3$ 419.82	0.75	80	264-266
6d		Orange	$C_{23}H_{20}N_6O_3$ 428.44	0.78	74	278-280
6e		Yellow	$C_{21}H_{14}N_6O_3$ 430.37	0.79	74	298-300
6f		Yellow	$C_{22}H_{17}N_5O_4$ 415.40	0.70	85	258-260
6g		Yellow	$C_{22}H_{17}N_5O_3$ 399.40	0.71	71	272-274

* Mobile phase: Chloroform: Benzene (1:1)

Table-3: IR Spectral Data of comp. 6a.

Vibration Mode Type	***Frequency in cm^{-1}***	
	Observed	**Reported**
N-O stretch	1526,1336	1550-1470, 13601290
	1597,1492,1406	1600, 1500, 1400
Ar-C-H stretch	3108	3100-3000
2^0N-H stretch	3285	3350-3310
Ar-C-N stretch	1292	1335-1250
Aliphatic C-N stretch	1048	1250-1020
Schiff C=N stretch	1662	1700-1600

Table-4: IR Spectral Data of comp. 6d.

Vibration Mode Type	**Frequency in cm-1**	
	Observed	**Reported**
N-O stretch	1528,1336	1550-1470,1360-1290
Ar-C-C stretch	1602,1484	1600-1585,1500 -1400
Ar-C-H stretch	3084	3100-3000
2^0N-H stretch	3270	3350-3310
Ar-C-N stretch	1291	1335-1250
Aliphatic C-N stretch	1165	1250-1020
Schiff C=N stretch	1656	1700-1600

Table-5: Zone of inhibition of compounds at various concentrations against bacteria.

Code	Conc. (µg/ml)	Zone of inhibition (in mm)				Code	Zone of inhibition (in mm)			
		EC	SA	PA	KP		EC	SA	PA	KP
6a	200	13	11	9	-	6e	13	12	12	11
	400	14	-	12	9		-	**18**	14	-
	600	14	13	-	12		-	**18**	-	13
	800	-	12	-	15		17	-	15	**16**
	1000	17	15	14	16		18	19	16	17
6b	200	12	-	-	9	6f		10	13	10
	400	12	12	16	-		8	13	12	-
	600	17	**18**	17	-		-	12	18	-
	800	-	-	18	**16**		17	-	-	15
	1000	23	19	-	18		18	17	19	17
6c	200	8	13	10	10	6g	10	-	9	12
	400	-	-	12	16		-	-	16	-
	600	-	14	12	16		18	14	16	13
	800	16	15	13	-		18	18	-	13
	1000	18	17	-	16		20	12	18	15
6d	200	11	9	9	**14**	**Pen**	**13**	**-**	**14**	**12**
	400	16	11	13	-		**-**	**16**	**16**	**14**
	600	-	11	14	14		**14**	**17**	**18**	**-**
	800	**18**	14	14	**18**		**17**	**19**	**-**	**15**
	1000	19	16	16	17		**23**	**20**	**21**	**18**

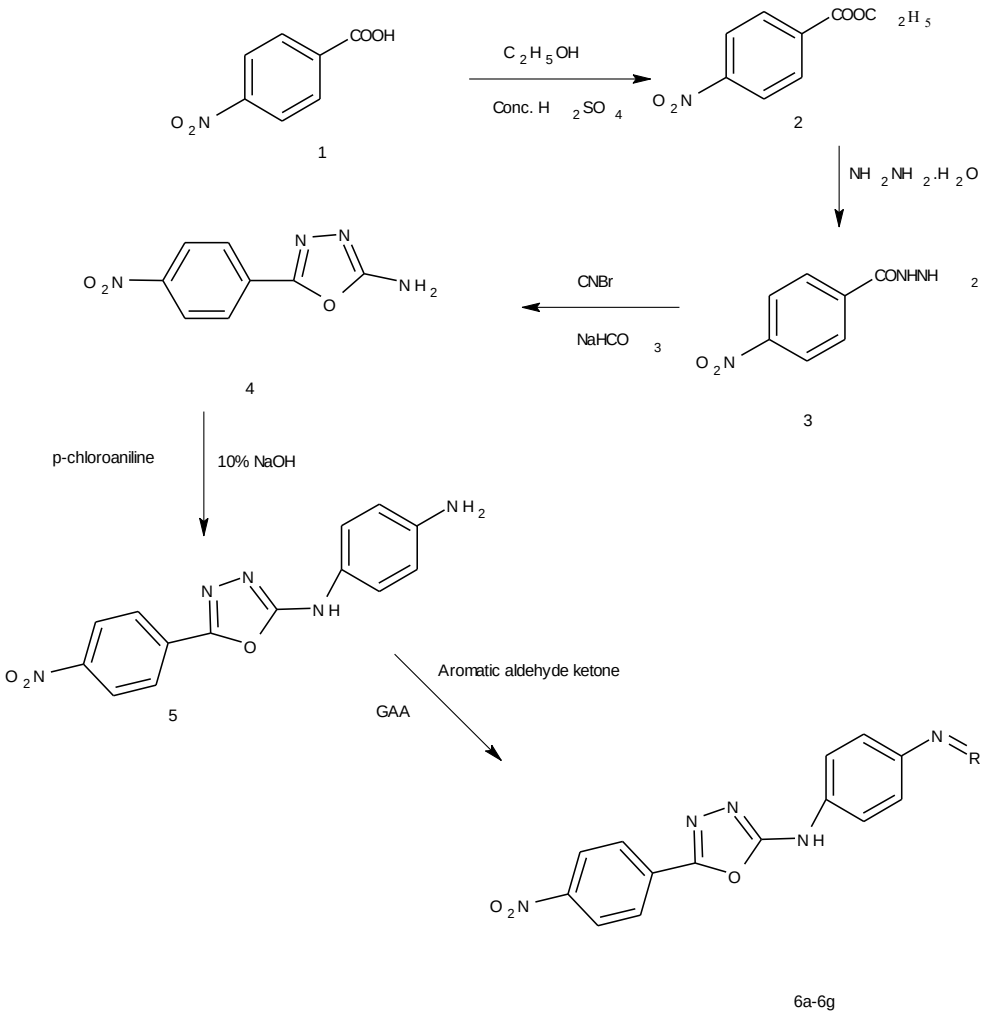
*No antimicrobial activity was found for DMSO.

Table-6: Zone of inhibition of compounds at various concentrations against fungi

Code	Conc (µg/ml)	Zone of inhibition (in mm)		Code	Zone of inhibition (in mm)	
		CA	AN		CA	AN
6a	200	-	-	6e	5	8
	400	14	10		10	12
	600	13	10		11	-
	800	15	14		10	17
	1000	16	-		15	18
6b	200	-	10	6f	-	9
	400	-	10		12	12
	600	13	13		13	13
	800	17	15		-	16
	1000	18	18		14	17
6c	200	9	-	6g	-	-
	400	10	12		9	-
	600	-	12		10	13
	800	15	16		12	12
	1000	17	17		-	20

*No antimicrobial activity was found for DMSO.

Figures



Where R

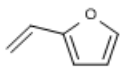
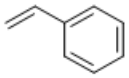
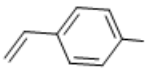
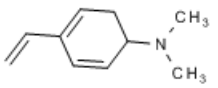
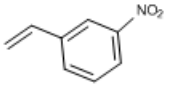
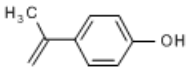
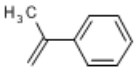
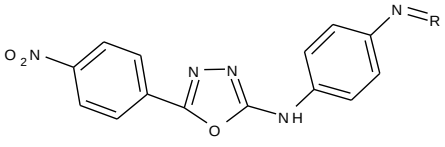
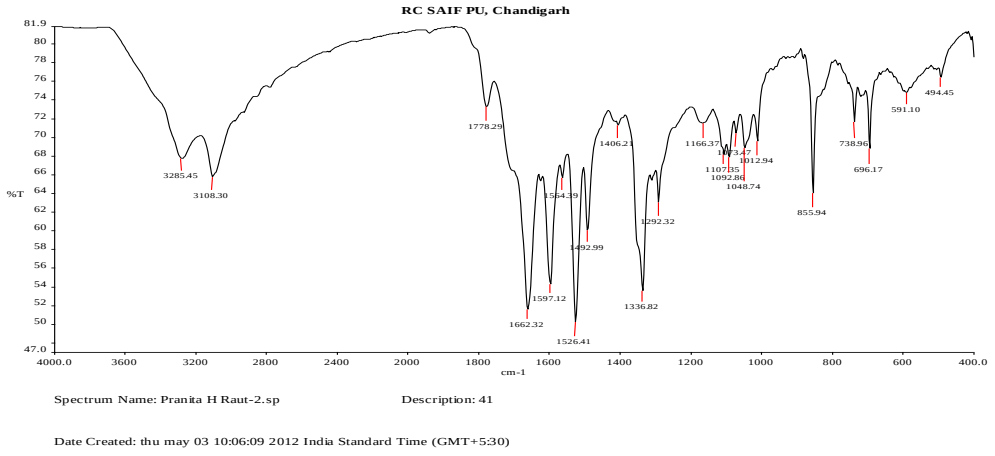
a		b		c		d	
e		f		g			----

Fig-1: Scheme of synthesis



6a -6g

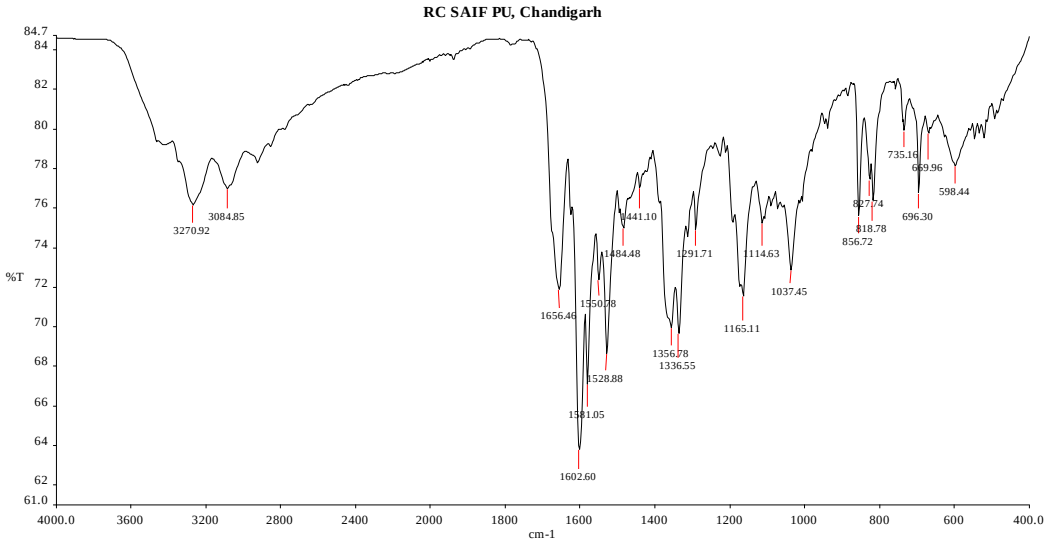
Fig-2: Structure of compounds 6a-6g



Spectrum Name: Pranita H Raut-2.sp Description: 41

Date Created: thu may 03 10:06:09 2012 India Standard Time (GMT+5:30)

Fig-3: Structure and *IR Study* of 6a



Spectrum Name: Pranita H Raut-17.sp Description: 44

Date Created: thu may 03 10:35:22 2012 India Standard Time (GMT+5:30)

Fig-4: Structure and *IR Study* of 6d

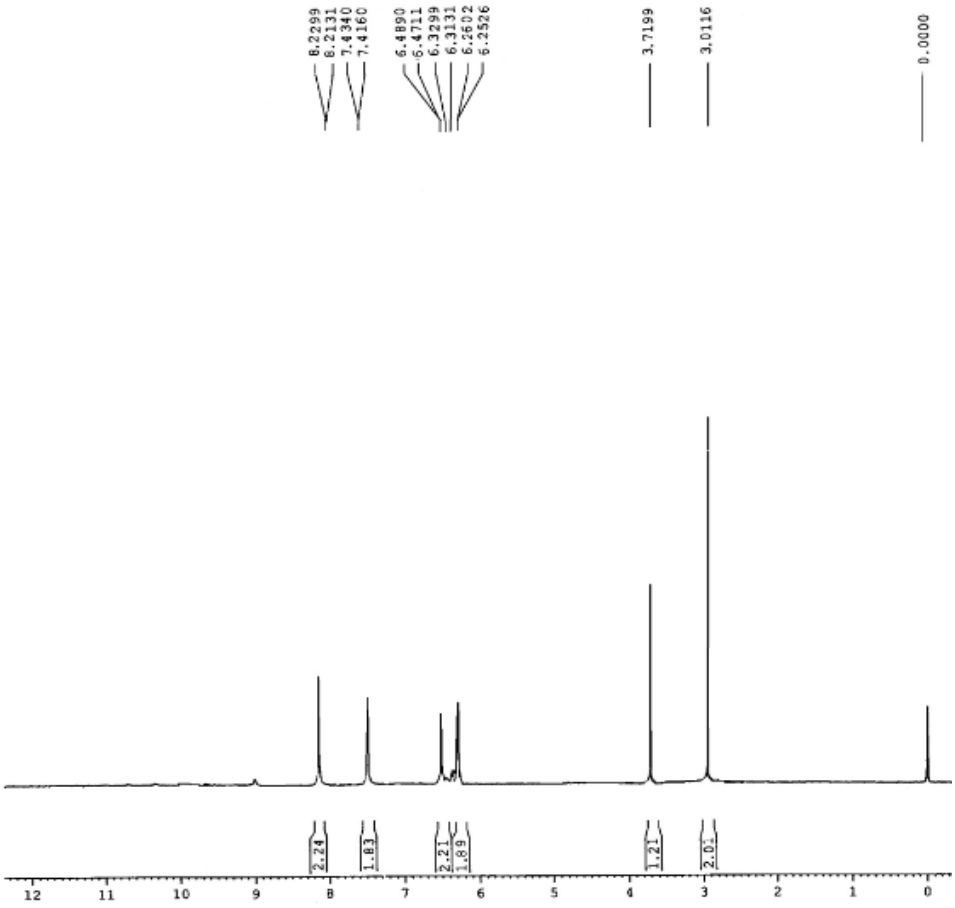


Fig-5: structure and ^{1}H NMR Spectra of compound 5

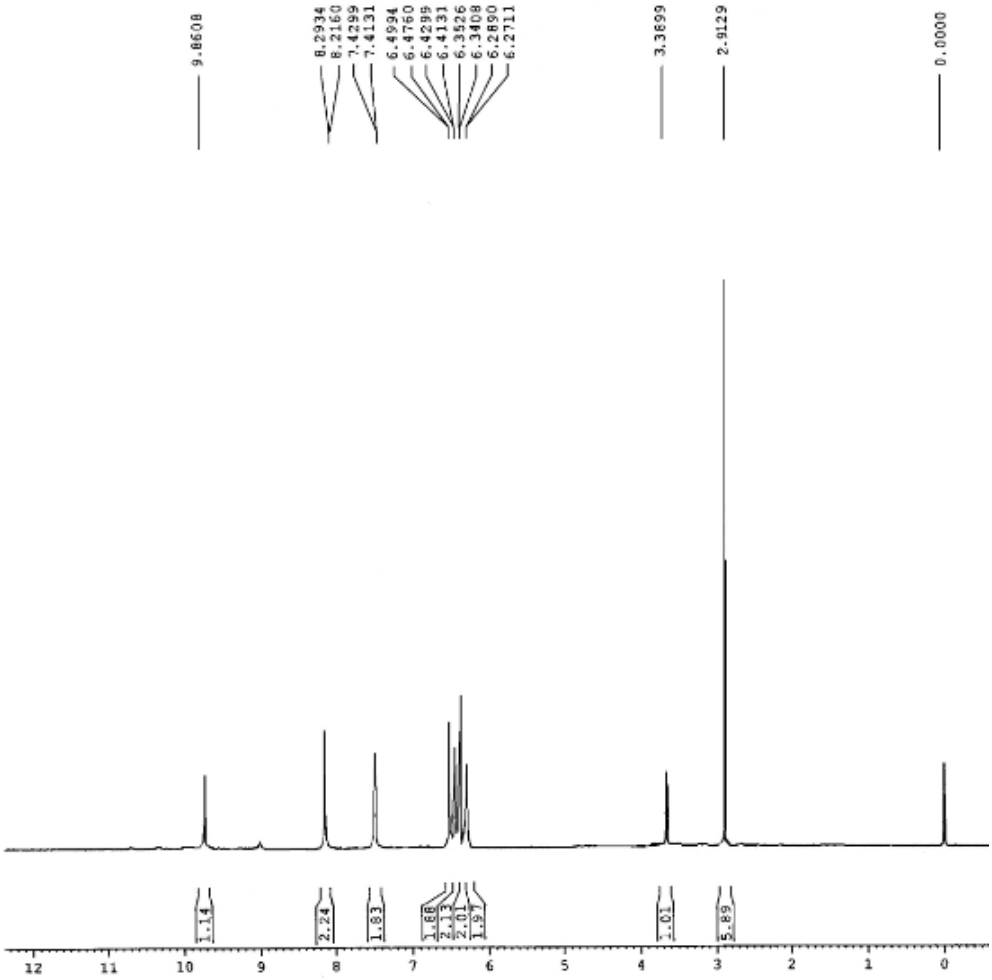


Fig-6: structure and ^{1}H NMR Spectra of compound 6d

CONCLUSION

The present work, which has undertaken is benefited and novel for the synthesis of 5-aryl(nitro-substituted)-1,3,4-oxadiazole-2-amine derivatives. In light of the above, for the synthesis of 5-aryl(nitro-substituted)-1,3,4-oxadiazole-2-amine derivatives. Scheme was established based on literature survey. The method can be successfully used for the synthesis of some other analogs.

In the synthesis of ester dry alcohol was required for increasing the yield. Also care should be taken after the formation of acid hydrazide remove the excess of hydrazine by distillation otherwise it involve in cyclization. Seven compounds were synthesized with standard chemicals and procedure. The synthesized compounds were tested for the preliminary test, physical constant and TLC etc. The structure of final compounds was confirmed by IR, ^{1}H NMR.

All the synthesized compounds were screened in vitro for antibacterial and antifungal activity by paper disc diffusion method and Cup-plate method respectivly. The antimicrobial activity screening reveled that, the compound are found to be active in the conc. 200 µg/ml, 400 µg/ml, 600 µg/ml and 1000 µg/ml against *Escherichia coli*, *Staphylococcus aureus, Pseudomonas aerugenosa, Klebsiella pneumoniae, candida albicans* and *Aspergillus niger*.

The entire proposed compound shows mild to moderate activity against *Escherichia coli, staphylococcus aureus, Pseudomonas aerugenosa, Klebsiella pneumoniae, candida albicans* and *Aspergillus niger*.

Acknowledgement

"From small beginnings come great things"
"Be not afraid anything. You will do marvelous work, the moment you fear, you are no buddy."

Very first I respectfully acknowledge this project work to my parents who made me and allowed me to do post graduation in Pharmacy with love and all the pains they have taken for me.

I would love to express my love and gratitude to my mother Mrs. Triveni N. Thakare, my father Mr. Namdeo S. Thakare, my brother Dr. Gopal, Gajanan, all my family members and teachers and friends without

their efforts, unbelievable support, encouragement and sacrifice, I would never been come so far. They gave me lot of courage to reach at this stage of life. Their trusts in me gave new strength to live such a beautiful life.

It gives me an immense pleasure to thank my esteem Guide Dr. Bakal Sir, lecturer, P. Wadhwani College of Pharmacy, Yavatmal [now he is Principal, College Of Pharmacy, Bhusaval (MS) India]

I am thankful to him for giving me freedom to work and also for providing all facilities. It gives me an immense pleasure to thank Respected Dr. Anil V. Chandewar Sir, Principal, P. Wadhwani College of Pharmacy, Yavatmal for their valuable support and guidance.

My sincere thanks to Asst. Prof. Mrs. Madhuri Lahule, Dr. K.V. Ingole and Lab. technician Mrs. Vijaya T. Jadhav for their kind moral support to provide bacterial and fungal strain which needed for antimicrobial study.

I also thanks to Mr. Avtar Singh SAIF Panjab University for providing Spectral Facility.

There are many others whose names flashed across my mind when I enlist those who have given grateful to me. It would rather impracticable to mention each of them separately, but I am conscious my obligation and thanks them collectively.

REFERENCES

1. Cohen FL, Tartasky D. Microbial resistance to drug therapy: a review. American Journal of Infection Control. 1997 Feb 1; 25(1):51-64.
2. Simoens S. Health economics of antibiotics. Pharmaceuticals. 2010 Apr 29; 3(5):1348-59.
3. McBride WJ. Chemoprophylaxis of tropical infectious diseases. Pharmaceuticals. 2010 May 18; 3(5):1561-75.
4. Booth C. Chapter II Fungal Culture Media. Methods in microbiology. 1971 Dec 31; 4: 49-94.
5. Sheehan DJ, Hitchcock CA, Sibley CM. Current and emerging azole antifungal agents. Clinical microbiology reviews. 1999 Jan 1; 12(1):40-79.
6. Denning DW. Echinocandins: a new class of antifungal. Journal of Antimicrobial Chemotherapy. 2002 Jun 1;49(6):889-91.
7. Casalinuovo IA, Di Francesco P, Garaci E. Fluconazole resistance in Candida albicans: a review of mechanisms. European review for medical and pharmacological sciences.. 2004;8:69-78.
8. Hoffman HL, Ernst EJ, Klepser ME. Novel triazole antifungal agents. Expert opinion on investigational drugs. 2000 Mar 1;9(3):593-605.
9. Bremner JB, Ambrus JI, Samosorn S. Dual action-based approaches to antibacterial agents. Current medicinal chemistry. 2007 Jun 1;14(13):1459-77.
10. Bhatia S, Gupta M. 1, 3, 4-Oxadiazole as antimicrobial agents: An overview. J. Chem. Pharm. Res. 2011;3(3):137-47.
11. Somani RR, Shirodkar PY. Oxadiazole: A biologically important heterocycle. ChemInform. 2011 Mar 8;42(10):no.
12. Singh AK, Sahu VK, Yadav D. biological Activities of 2, 5-disubstituted-1, 3, 4-oxadiazoles. International Journal of Pharma Sciences and Research. 2011;2(6):135-47.
13. Kulkarni VS. Oxadiazole: A New Profile of Biological Activities. International Journal of Drug Formulation & Research. 2010;1:134-66.
14. Mukesh B, Vandana S, Rakesh K. Biological activities of 1, 3, 4-oxadiazole: a review. Int Res J Pharm. 2011;2(12):84-9.
15. Singhal N, Sharma PK, Dudhe R, Kumar N. Recent advancement of triazole derivatives and their biological significance. J. Chem. Pharm. Res. 2011;3(2):126-33.
16. Bhandari SV, Parikh JK, Bothara KG, Chitre TS, Lokwani DK, Devale TL, Modhave NS, Pawar VS, Panda S. Design, synthesis, and evaluation of anti-inflammatory, analgesic, ulcerogenicity, and nitric oxide releasing studies of novel indomethacin analogs as non-ulcerogenic derivatives. Journal of enzyme inhibition and medicinal chemistry. 2010 Aug 1;25(4):520-30.
17. De Oliveira CS, Lira BF, dos Santos Falcão-Silva V, Siqueira-Junior JP, Barbosa-Filho JM, de Athayde-Filho PF. Synthesis, molecular properties prediction, and anti-staphylococcal activity of N-acylhydrazones and new 1, 3, 4-oxadiazole derivatives. Molecules. 2012 May 3;17(5):5095-107.