Int. J. Chem. Sci.: 14(4), 2016, 1877-1885
ISSN 0972-768X
www.sadgurupublications.com

SYNTHESIS OF NOVEL 1, 3, 4-OXADIAZOLE ANALOGUES WITH EXPECTED ANTIBACTERIAL ACTIVITY

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ABSTRACT

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. 1,3,4 Oxadiazole heterocyclic derivatives constitute an important class of heterocyclic compounds. The chemistry of 1,3,4 Oxadiazole heterocyclic derivatives has more than centuries old history. However, the intense search for biologically active substances in 1,3,4 Oxa diazole heterocyclic derivatives began only in the last few cascades. In this present communication, an attempt is made to cover the medicinally active compounds, along with the recent synthesis, which were reported to possess antimicrobial and antifungal activity.

Key words: Synthesis, Isothiocynate, EDC.HCl, Oxadiazoles, Antibacterial and Antifungal activity.

INTRODUCTION

1,3,4-Oxadiazole (**1)** (Fig. 1) is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. It is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogens (-N=)[1,2]. There are three known isomers: 1,2,4-oxadiazole (2), 1,2,3-oxadiazole (3) and 1,2,5-oxadiazole (4) (Fig. 1). However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties.

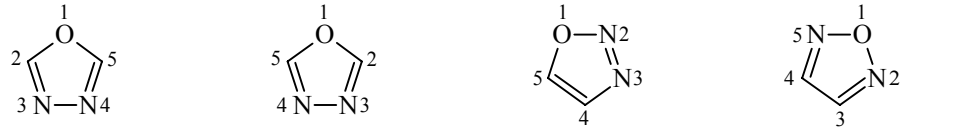

Fig. 1: Isomers of oxadiazole

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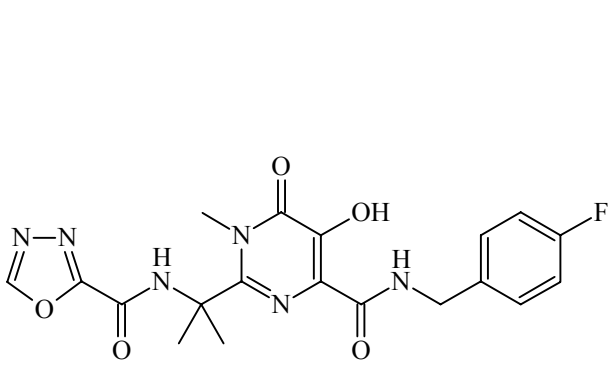
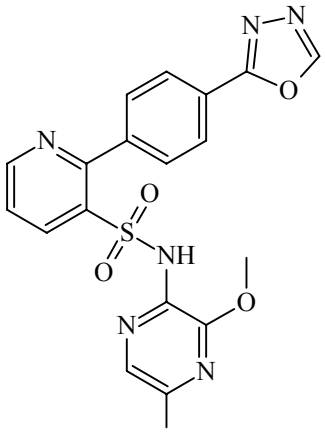
Among heterocyclic compounds, 1,3,4-oxadiazole has become an important construction moiety for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and anti-diabetic properties. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids, esters and carboxamides[2]. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential. Two examples of compounds containing the 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir® (5), an antiretroviral drug[3] and Zibotentan (6) an anticancer agent[4] (Fig. 2).



Raltegravir (5)



Zibotentan (6)

Fig. 2: Structures of raltegravir and zibotentan, drugs that are in late stage clinical development

1,3,4-oxadiazole there is a large amount of compounds exhibiting anti-inflammatory activity[5-7]. 1,3,4-Oxadiazoles are an important class of heterocyclic compound with broad spectrum of biological activities in addition to anti-inflammatory activity such as hypoglycemic[8], antimicrobial[9,10], anti-micro bacterial[11], anticonvulsant[12], anticancer[13], antimalarial[14], etc.

Encouraged by the diverse biological activities of 1,3,4 oxadiazole heterocyclic compounds, it was decided to prepare a new series of 1,3,4 oxadiazole derivatives. In the present communication, 1,3,4 oxadiazole derivatives 4 (a-f) were prepared by the action of substituted isocynates (1) with acid hydrazides (2) in the presence of TEA at room temperature to obtained intermediate derivative (3). The intermediate derivative (3) was

reacted with EDC.HCl, in NMP to afford novel 1,3,4 Oxadiazole derivatives 4(a-h) (Scheme 1). The structures of all synthesized compounds were assigned on the basis of IR, Mass, ^{1}H NMR spectral data Further these compounds were subjected for antifungal and antibacterial activity.

EXPERIMENTAL

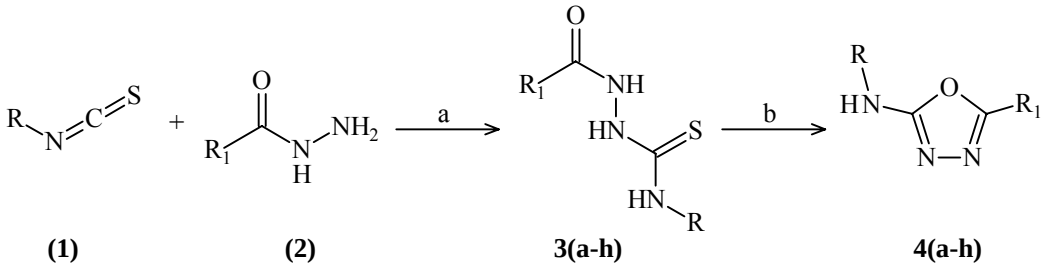
Materials and methods

Laboratory chemicals were provided by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are not correct. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene:ethyl acetate (8:2). The spots were observed by exposure to iodine Vapours or by UV light or p-Anisaldehyde stain solution. The IR spectra were received by Perkine Elmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H NMR & ^{13}C NMR spectra were obtained by Bruker Advance II 400 spectrometer using TMS because the internal standard in $CDCl_3$. Elemental analysis of the new synthesized compounds were obtained by Carlo Erba 1108 analyzer. General Information. Commercial chemicals were treated as follows: DMF, distilled from CaH_2 and degassed (freeze and thaw) three times prior to use; THF, ether, hexanes distilled from Na/benzophenone.

The synthesis of the compounds is as per the following **Scheme 1** given below.

The synthetic route is depicted in Scheme 1.

The title compounds **4(a-h)** were synthesised in two sequential steps using different reagents and reaction conditions, the **4(a-h)** were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass).



(1) **(2)** **3(a-h)** **4(a-h)**

Scheme 1

Reagents & reaction conditions: (a) TEA, Dry THF, RT (b) EDC·HCl, DMSO, 80°C, 3 hrs.

Compd.	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
R	Bn	Bn	Bn	Bn	Ph	-4-OCH_3-Bn	-4-CF_3-Bn	2,4 Di methoxy Bn
R_1	Ph	-4-OCH_3-Ph	-4-F-Ph	-4-NO_2-Ph	-Ph	-Ph	-Ph	-4-NO_2-Ph

Experimental section

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20-30 Torr). Flash chromatography was performed with silica gel (200-300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz for ^1H for ^{13}C, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-d or DMSO-d_6 as the internal standard (^1H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

General procedure for the preparation of Thiosemicarbazide (3a-3h)

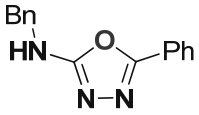
Benzyl-isothiocyanate 1 (2.40 m.mol) was added to a stirred solution of benzoylhydrazide 2 (2.00 m.mol) and triethylamine (2.00 m.mol) in 10 mL of THF. The reaction mixture was stirred at room temperature for 16 h, and then the solvents were removed via a rotary evaporator. The residue was triturated with diethyl ether/ethyl acetate (95:5) to afford 95% yield, of the desired thiosemicarbazide.

General procedure for the preparation of 2-amino1,3,4-oxadiazole derivatives (4a-4h)

EDC·HCl (0.6 m.mol) was added to a stirred solution of thiosemicarbazide 3a (0.50 m.mol) in 1 mL of DMSO. The reaction mixture was stirred at 60^OC for 3 h and extracted with dichloromethane (DCM, 15 mL) and distilled water (20 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with DCM (3 × 15 mL). The combined organic layers were dried over Na_2SO and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/THF) to afford 89% yield, white solid of the desired 2-amino-1,3,4-oxadiazole 4a.

N-benzyl-5-phenyl-1,3,4-oxadiazol-2-amine (4a)

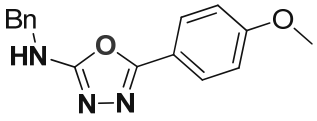
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.86 (m, 2H), 7.51−7.28 (m, 8H), 5.05 (s, 1H), 4.62 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 159.3, 137.4, 130.6, 128.9, 128.9, 128.1, 127.8, 125.9, 124.5, 47.8; M.p 178-179^{o}C; LC/MS (ESI): m/z = 250.0 [M^{-1}].



4a

N-benzyl-5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine(4b)

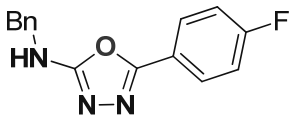
Yield, 80%, white solid, M.p. 167-169^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 8.23 (s, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.44−7.23 (m, 5H), 7.08 (d, J = 8.9 Hz, 2H), 4.44 (d, J = 6.2 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 163.8, 161.4, 158.2, 139.3, 128.9, 127.9, 127.6, 127.4,117.2, 115.2, 55.9, 46.6. LC/MS (ESI): m/z = 280.0 [M^{-1}].



4b

N-benzyl-5-(4-fluorophenyl)-1,3,4-oxadiazol-2-amine (4c)

Yield, 87%, Mp 172-173°C, white solid; ^{1}H NMR (400 MHz, DMSO) δ 8.34 (t, J = 6.1 Hz, 1H), 7.91−7.81 (m, 2H), 7.47−7.21 (m, 7H), 4.46 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 169.0, 163.2 (d, 1JCF = 248.5 Hz), 155.6, 139.0, 129.0 (d, 3JCF = 9.1 Hz), 128.9, 128.0, 127.9 (d, 4JCF = 3.0 Hz), 127.6, 116.7 (d, 2JCF = 22.2 Hz), 48.52; LC/MS (ESI): m/z = 268.0 [M^{-1}].

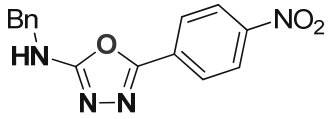


4c

N-benzyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (4d)

Yield, 75%, yellow solid, Mp 191-193^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 8.62 (t, J = 6.2 Hz, 1H), 8.37 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 9.0 Hz, 2H), 7.43−7.25 (m, 5H),

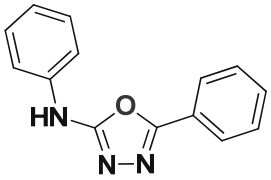
4.50 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO**)** δ 164.8, 157.0, 148.5, 139.0, 130.1, 128.9, 127.9, 127.7, 126.6, 125.1, 46.6; LC/MS (ESI): m/z = 295.0 [M^{-1}].



4d

N,5-diphenyl-1,3,4-oxadiazol-2-amine (4e)

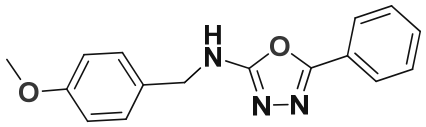
Yield 84%, Mp 215-216°C, white solid; ^{1}H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 8.01-7.86 (m, 2H), 7.72−7.51 (m, 5H), 7.38 (t, J = 7.9 Hz, 2H), 7.02 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 160.4, 158.2, 139.1, 131.4, 129.8, 129.6, 126.0, 124.4, 122.4, 117.6. LC/ MS (ESI): m/z = 236.0 [M^{-1}].



4e

N-(4-methoxybenzyl)-5-phenyl-1,3,4-oxadiazol-2-amine (4f)

Yield, 69%, white solid, Mp 184-187°C; ^{1}H NMR (400 MHz, DMSO) δ 8.25 (t, J = 6.1 Hz, 1H), 7.86-7.77 (m, 2H), 7.57−7.49 (m, 3H), 7.32 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.38 (d, J = 6.1 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 164.1, 159.0, 158.1, 131.2, 130.9, 129.7, 129.3, 125.6, 124.7, 114.2, 55.6, 46.1. LC/MS (ESI): m/z = 280.0 [M^{-1}].

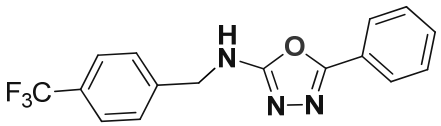


4f

5-phenyl-N-(4-(trifluoromethyl)benzyl)-1,3,4-oxadiazol-2-amine (4g)

Yield 50%, white solid, Mp 192-195°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.85 (m, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.48-7.40 (m, 3H), 5.31 (s, 1H), 4.69 (d, J = 2.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 164.0, 158.4, 144.1, 131.0, 129.7,

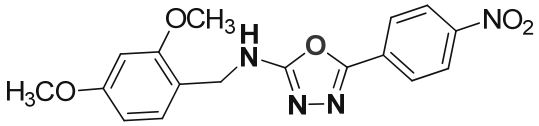
128.5, 128.3 (q, 2JCF = 31.3 Hz), 125.7 (q, 3JCF = 3.0 Hz), 125.7, 124.7 (q, 1JCF = 273.1 Hz) 124.7, 46.1; LC/MS (ESI): m/z = 318.0 [M^{-1}].



4g

N-(2,4-Dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-oxadiazol2-amine (4h)

Yield 70% white solid, Mp 183-184°C; ^{1}H NMR (400 MHz, DMSO) δ 8.41−8.29 (m, 3H), 8.04 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 6.50 (dd, J = 8.3, 2.4 Hz, 1H), 4.38 (d, J = 5.9 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 164.8, 160.6, 158.4, 156.8, 148.5, 130.2, 129.9, 126.5, 125.1, 118.5, 104.8, 98.8, 56.0, 55.7, 41.5; LC/MS (ESI): m/z = 355.0 [M^{-1}].



4h

Biological activity

The samples of synthesized novel 1,3,4 Oxadiazole derivatives **(4a-4h)** for antimicrobial activity were prepared at concentration 40 μg/mL in DMSO solvent. In case of anti-bacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked against Gram positive bacteria Staphylococcus aureus (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*), Gram negative bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Escherichia coli* (*E. coli*). The antifungal activity was checked against fungi *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*). The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole.

The 1,3,4 Oxadiazole derivates **4h**, **4g** and **4e** showed more activity than other substituent's.

The order of activity was:

4h > 4g > 4e > 4f > 4c > 4d > 4b > 4a

Table 2: Antimicrobial screening data of novel 1,3,4 Oxadiazole derivatives (4a-4h)

Compounds	Antibacterial activity (Zone of inhibition in mm)				Antifungal activity (Zone of inhibition in mm)	
	S. aureus	***B. subtilis***	***P. aeruginosa***	***E. coli***	***A. niger***	***C. albicans***
4a	09	07	10	08	11	17
4b	10	08	07	09	09	21
4c	13	15	13	11	10	06
4d	11	12	09	12	19	18
4e	15	12	12	13	12	13
4f	14	16	09	12	24	11
4g	18	14	17	12	16	25
4h	20	24	19	14	27	23
Sparfloxacin	24	25	22	22	---	---
Benzyl penicillin	19	18	16	16	---	---
Fluconazole	---	---	---	---	25	30

RESULTS AND DISCUSSION

NMR Spectra

Aromatic protons were observed 6.68-8.43 δ ppm. Readily available starting materials and simple synthesizing procedures make this method is very attractive and convenient for the synthesis of 1,3,4 Oxadiazole derivatives. Formation of products was confirmed by recording their ^{1}H NMR, ^{13}C, FT-IR, mass spectra.

Antimicrobial screening

The results of antimicrobial studies of newly synthesized compounds reveal that the compounds possess significant antibacterial and antifungal activities. The results of these studies are given in (Table 2). From Antibacterial screening results, it has been observed that compounds **4h**, **4g** and **4e** possess good activity.

CONCLUSION

The newly synthesized 1,3,4 Oxadiazole derivatives **(4a-4h)** exhibited moderate to promising antimicrobial activity against standard strains. This class of compounds certainly holds great promise to discover novel classes of antimicrobial agents. All these reactions are

very easy to carry out giving high yield. These results make interesting lead molecule for further synthetic and biological evaluation.

REFERENCES

1. Nagaraj, K. C. Chaluvaraju, M. S. Niranjan and S. Kiran, 1,3,4-Oxadiazole: A Potent Drug Candidate with Various Pharmacological Activities, Int. J. Pharm. Pharm. Sci., **3**, 9 (2011).
2. J. Boström, A. Hogner, A. Llinàs, E. Wellner and A. T. Plowright, Oxadiazoles in Medicinal Chemistry, J. Med. Chem., **55**, 1817 (2012).
3. A. Savarino, A Historical Sketch of the Discovery and Development of HIV-1 Integrase Inhibitors, Expert Opin. Investig. Drugs, **15**, 1507 (2006).
4. N. D. James and J. W. Growcott, Zibotentan, Drugs Future, **34**, 624 (2009).
5. V. Jakubkiene, M. M. Burbuliene, G. Mekuskiene, E. Udrenaite, P. Gaidelis and P. Vainilavicius, Farmaco, **58**, 323 (2003).
6. D. H. Boschelli, D. T. Connor, D. A. Bornemeier, F. D. Dyer, J. A. Kennedy et al., J. Med. Chem., **36**, 1802 (1993).
7. A. Husain, F. J. Ahmad, M. Ajmal and P. Ahuja, J. Serb. Chem. Soc., **73**, 781 (2008).
8. M. M. Girges, Arzneimittelforschung, **44**, 490 (1994).
9. G. Sahin, E. Palaska, M. Ekizoglu and M. Ozalp, Farmaco, **57**, 539 (2002).
10. H. K. Misra, Arch. Pharm., **316**, 487 (1983).
11. G. Navarrete-Vazquez, G. M. Molina-Salinas, Z. V. Duarte-Fajardo, J. Vargas-Villarreal, S. Estrada-Soto et al., Bioorg. Med. Chem., **15**, 5502 (2007).
12. S. V. Bhandari, K. G. Bothara, M. K. Raut, A. A. Patil, A. P. Sarkate and V. J. Mokale, Bioorg. Med. Chem., **16**, 1822 (2008).
13. A. Zarghi, S. A. Tabatabai, M. Faizi, A. Ahadian, P. Navabi, V. Zanganeh and A. Shafiee, Bioorg. Med. Chem., **15**, 1863 (2005).
14. A. S. Aboraia, H. M. Abdel-Rahman, N. M. Mahfouz and M. A. EL-Gendy, Bioorg. Med. Chem., **14**, 1236 (2006).

Revised : 02.10.2016 *Accepted : 05.10.2016*