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RESEARCH ARTICLE

Synthesis and Biological Evaluation of Novel Oxadiazole Derivatives

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ABSTRACT

A series of novel oxadiazole derivatives 1-2-[2-(3- (trifluromethyl)phenylamino)phenyl)-1,3,4,-oxadiazole-3(2H)-yl]etanones were synthesized and evaluated for their antibacterial and antifungal activity. The structures of the synthesized compounds were determined by IR, NMR, Mass Spectroscopy and elemental analysis.

KEYWORDS

Oxadiazole, Antibacterial, Antifungal

INTRODUCTION

Oxadiazoles belong to an important group of heterocyclic compounds having –N=C-O- linkage. 1,3,4-Oxadiazole is a heterocyclic molecule with oxygen atom at 1 and two nitrogen atoms at 3 and 4 position. 1,3,4-Oxadiazole is a thermally stable aromatic molecule.[1] They have been known for about 80 years it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas viz. drug synthesis, dye stuff industry, heat resistant materials, heat resistant polymers and scintillators. Reviews of the relevant literature prior to 1965 are available.[2] 2,5-Disubstituted-1,3,4-oxadiazole derivatives have been tested for various pharmacological activities, likes Antibacterial[3,] Antiinflammatory[4], Analgesic[5], Antihypertensive[6], Anticonvulsant[7], Antimycobacterial[8], cardiovacular[9], Herbicidal[10] and Insecticidal[11] activity

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In addition, Oxadiazoles derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis[11,12]. Encouraged by the diverse biological activities of Oxadiazoles compounds and in continuation of our work on synthesis of biological active heterocycles containing isoxazoline13, hence it was decided to prepare a new series of 1-2-[2-(3-(trifluromethyl)phenylamino)phenyl)-1,3,4,-oxadiazole-3(2H)-yl]etanones evaluated for their antibacterial and antifungal activities.

Experimental Section

The content was stirred for 30 minutes. Then Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV-254nm light. IR spectra were recorded on Bruker FT-IR-instrument using KBr pellet method. Mass spectra were recorded on Applied Biosystems API 2000 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker 400 MHz spectrometer. Purity of the synthesized compounds was checked by Waters ACQUITY

UPLC H-CLASS. Elemental analysis of the all the synthesized compounds was carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

Synthesis of 2-(3-(Trifluoromethyl)-phenylamino) benzohydrazide

Methyl 2-(3 (trifluoromethyl) phenylamino) benzoate (2.95 gm, 0.01 mol) in absolute ethanol (25 mL) was refluxed with hydrazine hydrate (1.0 mL) for 2 hours. The completion of the reaction was checked by TLC and the reaction mixture was cooled to room temperature. The separated solid was filtered, washed with cold ethanol and crystallized from ethanol. Yield 98%, m.p 136-138°C.

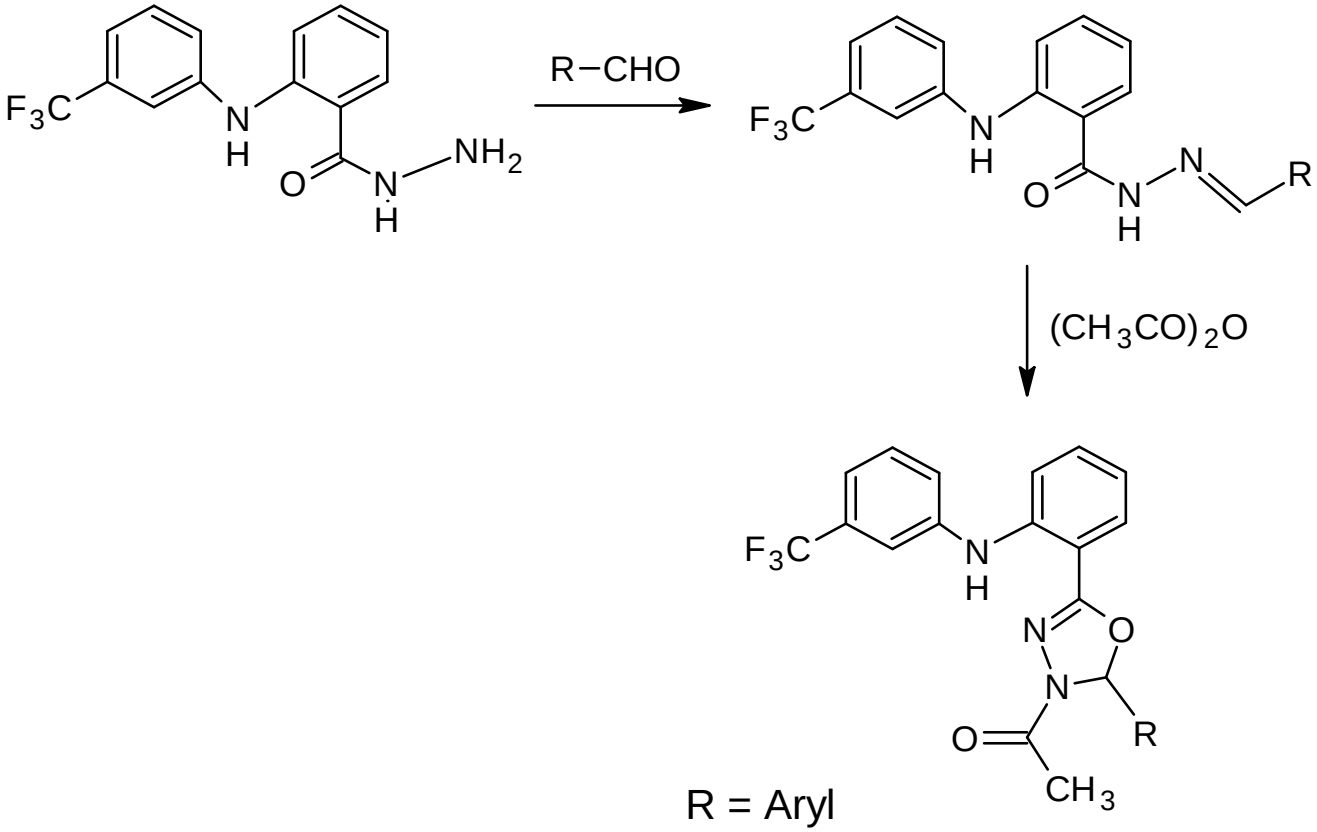
Synthesis of (E)-N'-(Arylidene)-2-(3-(trifluoromethyl)phenylamino)benzohydrazide

To a mixture of 2-(3-(trifluoromethyl) phenylamino) benzohydrazide (2.95 gm, 0.01 mol) in methanol (20 mL) was stirred for 5 minutes. Then added different aryl aldehydes (0 heat to reflux for 2-3 hours. Solvent was distilled out under *vacuo* to get solid, crystallized from methanol.

General procedure for the Preparation of 1-[2-(Aryl)-5-(2-(3-(trifluoro methyl) phenylamino)phenyl)-1,3,4-oxadiazol-3(2H)-yl]ethanones

A mixture of (*E*)-*N*'-(Arylidene)-2-(3-(trifluoromethyl)phenylamino)benzo hydrazide (0.01 mol) in acetic anhydride (10 mL) was heated to reflux for 3 hours. (monitoring by TLC), then distilled out acetic anhydride under *vacuo*. Neutralized with sodium bicarbonate solution. Then product was extracted with ethyl acetate and washed with water (2 x 10 mL), dried with Na_2SO_4, solvent was removed in *vacuo* and the resulting crude product was purified by column chromatography to give the pure compounds. The physical constants of the products are recorded in Table-1.

Reaction Scheme



RESULT AND DISCCUSION

Synthesis of 1,3,4-oxadiazole derivatives has attracted considerable attention in view of therapeutic applications. Looking to this, the synthesis of 1,3,4 oxadiazoles was undertaken by the condensation of different aryl aldehydes with 2-(3-(trifluoro methyl) phenylamino) benzohydrazide in presence of acetic anhydride as shown in reaction scheme .

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

Analytical Data

1-(2-(4-Chlorophenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone (3a): mp 150-152°C; Purity by UPLC: 98.8%. IR (KBr): 3334(N-H str), 3062(Ar, C-H str), 2922(CH_3, C-H str), 1668(C=O str), 1621(C=N str), 1579(Ar, C=C str), 1343(CF_3, C-F str), 1048(C-O, str of oxadiazole ring), 765(C-Cl str) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.36 (s, 3H, CH_3), 6.90-6.94(t, *J*=6.8 Hz, 1H, ArH), 7.05(s, 1H, ArH), 7.34-7.51(m, 10H, ArH), 7.79-7.81(d, *J*=6.8 Hz, 1H, ArH), 8.78(s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.52, 89.91, 108.40, 114.11, 117.52, 119.19, 119.89, 124.18, 128.00, 129.07, 129.26, 130.18, 132.76, 134.63, 136.02, 141.46, 143.24, 155.73, 167.44; MS: *m/z* = 459.4 $[M]^+$; Anal. Calcd for $C_{23}H_{17}ClF_3N_3O_2$: C, 60.07; H, 3.73; N, 9.14% Found: C, 59.80; H, 3.52; N, 9.00%.

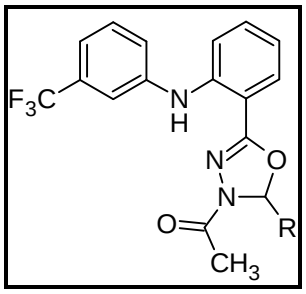
4-(3-Acetyl-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-2,6-dimethoxyphenyl acetate(3b): mp 132-135°C; UPLC Purity; = 98.96%. IR (KBr): 3314(N-H str), 2941(CH_3, C-H str), 2846(-OCH_3, C-H str), 1767(-$OCOCH_3$, C=O str), 1675(-$COCH_3$, C=O str), 1608(C=N str), 1501(Ar, C=C str), 1333(CF_3, C-F str), 1049(C-O str. of oxadiazole ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.34(s, 3H, CH_3), 2.39(s, 3H, -$OCOCH_3$), 3.83 (s, 6H, -OCH_3), 6.77(s, 2H, ArH), 6.92-6.95(t, *J*=6.4 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 7.32-7.52(m, 6H, ArH), 7.82-7.84(d, *J*=8.0 Hz, 1H, ArH), 8.81(s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 20.47, 21.64, 56.28, 90.34, 103.13, 108.46, 114.13, 117.38, 117.43, 119.28, 119.80, 119.84, 124.11, 129.29, 130.19, 132.77, 134.38, 141.49, 143.20, 152.48, 155.79, 167.80, 168.52; MS: *m/z* = 543.3 $[M]^+$; Anal. Calcd for $C_{27}H_{24}F_3N_3O_6$: C, 59.67; H, 4.45; N, 7.73% Found: C, 59.30; H, 4.25; N, 7.40%.

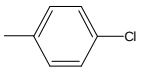
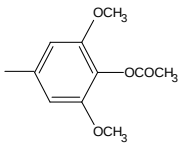
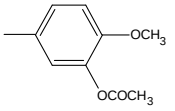
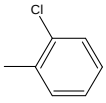
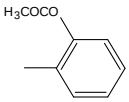
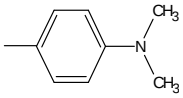
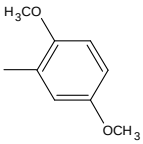
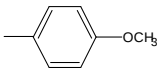
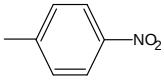
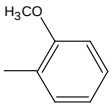
5-(3-Acetyl-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-2-methoxyphenyl acetate(3c): mp 130-133 °C; IR (KBr): 3318, 2945, 2830, 1766, 1675, 1610, 1515. 1330, 1050 cm^{-1}; MS: *m/z* = 513.9 $[M]^+$; Anal. Calcd for $C_{26}H_{22}F_3N_3O_5$: C, 60.82; H, 4.32; N, 8.18% Found: C, 60.60; H, 4.09; N, 8.00%.

1-(2-(2-Chlorophenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone(3d): mp 148-150°C; IR (KBr): 3330, 3060, 2924, 1670, 1622, 1580, 1343, 1050, 765 cm^{-1}; MS: *m/z* = 459.4 $[M]^+$; Anal. Calcd for $C_{23}H_{17}ClF_3N_3O_2$: C, 60.07; H, 3.73; N, 9.14% Found: C, 59.80; H, 3.52; N, 9.00%.

2-(3-Acetyl-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate(3e): mp 128-130 °C; IR (KBr): 3315, 2926, 2835, 1689, 1539, 1331, 1070 cm^{-1}; MS: *m/z* = 484.1 $[M]^+$; Anal. Calcd for $C_{25}H_{20}F_3N_3O_4$: C, 62.11; H, 4.17; N, 8.69% Found: C, 61.90; H, 4.01; N, 8.42%.

Table-1: Physical constant of 1-[2-(Aryl)-5-(2-(3-(trifluoromethyl)phenylamino) phenyl) -1,3,4-oxadiazol-3(2*H*)-yl]ethanones



Sr. No.	Substitution R	M.F.	M.W.	Yield (%)
3a		$C_{23}H_{17}ClF_3N_3O_2$	459.85	94
3b		$C_{27}H_{24}F_3N_3O_6$	543.49	88
3c		$C_{26}H_{22}F_3N_3O_5$	513.47	77
3d		$C_{23}H_{17}ClF_3N_3O_2$	459.85	91
3e		$C_{25}H_{20}F_3N_3O_4$	483.44	89
3f		$C_{25}H_{23}F_3N_4O_2$	468.47	72
3g		$C_{25}H_{22}F_3N_3O_4$	485.46	76
3h		$C_{24}H_{20}F_3N_3O_3$	455.43	78
3i		$C_{23}H_{17}F_3N_4O_4$	470.40	83
3j		$C_{24}H_{20}F_3N_3O_3$	455.43	79

TLC solvent system: - Ethyl Acetate: Hexane = 3: 7

1-(2-(4-(Dimethylamino)phenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone(3f): mp 140-142 °C; IR (KBr) : 3315, 2915, 2803, 2790, 1671, 1540, 1057 cm^{-1}; MS: *m/z* = 469.1 $[M]^+$; Anal. Calcd for $C_{25}H_{23}F_3N_4O_2$: C, 64.10; H, 4.95; N, 11.96% Found: C, 63.93; H, 4.78; N, 11.73%.

1-(2-(2,5-Dimethoxyphenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone(3g): mp 135-137 °C; IR (KBr): 3316, 2940, 2829, 1678, 1510, 1332, 1075 cm^{-1}; MS: *m/z* = 485.9 $[M]^+$; Anal. Calcd $C_{25}H_{22}F_3N_3O_4$: C, 61.85; H, 4.57; N, 8.66% Found: C, 61.60; H, 4.40; N, 8.40%.

1-(2-(4-Methoxyphenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone(3h): mp 133-134 °C; IR (KBr): 3316, 2939, 2840, 1680, 1512, 1332, 1075 cm^{-1}; MS: *m/z* = 455.9 $[M]^+$; Anal. Calcd for $C_{24}H_{20}F_3N_3O_3$: C, 63.29; H, 4.43; N, 9.23% Found: C, 63.00; H, 4.12; N, 9.04%.

1-(2-(4-Nitrophenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone(3i): mp 148-150 °C; IR (KBr): 3320, 2935, 2836, 1675, 1515, 1334, 1079 cm^{-1}; MS: *m/z* = 471.2 $[M]^+$; Anal. Calcd for $C_{23}H_{17}F_3N_4O_4$: C, 58.73; H, 3.64; N, 11.91% Found: C, 58.00; H, 3.47; N, 11.37%.

1-(2-(2-Methoxyphenyl)-5-(2-(3-(trifluoromethyl)phenylamino)phenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone(3j): mp 130-132 °C; IR (KBr): 3316, 2939, 2840, 1680, 1512, 1332, 1075 cm^{-1}; MS: *m/z* = 455.9 $[M]^+$; Anal. Calcd for $C_{24}H_{20}F_3N_3O_3$: C, 63.29; H, 4.43; N, 9.23% Found: C, 63.00; H, 4.12; N, 9.04%.

Biological Activity

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeuroginosa and Streptococcus pyogenes (recultured) bacterial strains by disc diffusion method14, 15. Discs measuring 6.25 mm in diameter were punched from Whatman no.1filter paper. The test compounds were prepared with different concentrations using dimethylformamide. One milliliter containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37^0 C for 24 h. ciprofloxacin was used as a standard drug. Solvent and growth controls were prepared and kept. Zones of inhibition and minimum inhibition concentrations (MICs) were noted. The results of antibacterial studies are given in Table 2.

Antifungal Activity

Newly prepared compounds were screened for their antifungal activity against Aspergillus flavus, Aspergillus fumigatus, Candida albicans and Penicillium marneffei (recultured) in DMSO by serial plate dilution method16, 17. Sabourands agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lowning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Agar media (20 mL) were poured into each petri dish. Excess of suspensions was decanted and the plates were dried by placing in an incubator at 37o C for 1 h using an agar punch, wells were made and each well were labeled. A control was also prepared in triplicate and maintained at 37o C for 3-4 days. Zone of inhibition and minimum inhibitory concentration (MIC) were noted. The activity of each compound was compared with flucanazole as the standard drug. The results of antifungal studies are given in Table 2.

CONCLUSIONS

All synthesized 1,3,4 oxadiazole compounds are novel compounds with electron relrasing group such as methoxy and compounds having pharmacophores such as chloro and both this group are present in one moiety exhibited best antimicrobial activity the deta reported in this article may be helpful guide for the medicinal chemist who is working in this area.

Table-2: Antimicrobial activity 1-[2-(Aryl)-5-(2-(3-(trifluoromethyl) phenyl amino) phenyl -1,3,4-oxadiazol-3(2*H*)-yl]ethanones

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/mL				Minimal fungicidal concentration µg/mL		
	Gram +*Ve* Bacteria		Gram -*Ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
3a	500	250	62.5	125	500	500	1000
3b	200	250	125	100	>1000	500	500
3c	250	500	200	62.5	>1000	250	500
3d	125	250	100	200	500	1000	>1000
3e	250	250	250	250	250	500	500
3f	200	125	200	100	1000	>1000	>1000
3g	500	250	100	100	500	>1000	>1000
3h	125	125	200	125	1000	>1000	>1000
3i	100	100	125	200	1000	>1000	>1000
3j	200	200	250	250	>1000	500	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S. Aureus	S. Pyogenus	E. Coli	P. Aeruginosa
	(microgramme/mL)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C. Albicans	A. Niger	A. Clavatus
	(microgramme/mL)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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