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Synthesis, characterization and antibacterial activity of some oxadiazole substituted triazole derivative

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ABSTRACT

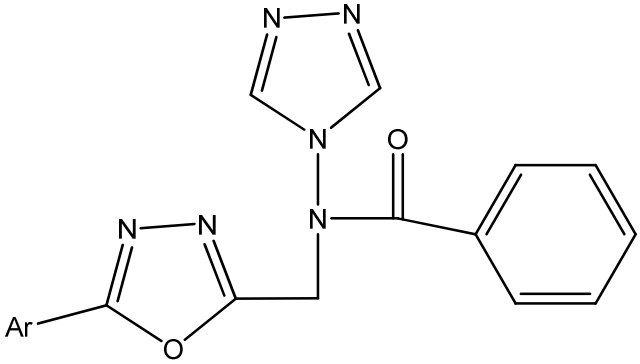
The increasing clinical importance of drug resistance of fungal and bacteria pathogen has lent additional urgency to microbial research and new antimicrobial compound development . For this purpose a series of N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative was synthesized by condensation of 4amino triazole and benzoyl chloride . The treatment of benzoyl derivative of 4-amino Triazole with sodium ethoxide and ethylchloro acetate produce ester derivative of Triazole (2). Subsequently compound (2) was converted to hydrazide by (3) the treatment with hydrazine hydrate after esterification. More over the reaction of compound (3) with aromatic acid in phosphorus oxychloride afforded N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide 4(a-h). The identification and characterization of the synthesized compounds were carried out by Elemental analysis, melting point,Thin Layer Chromatography, FT-IR, NMR data to ascertain that all synthesized compounds were of different chemical nature than the respective parent compound. Antimicrobial and antifungal activities of the final compounds have been evaluated and all the compounds have shown significant inhibition of bacterial and fungal growth.

Key word: 4-amino Triazole, Aromatic acid, Oxadiazole, Antibacterial activity, Antifungal activity.

INTRODUCTION

There is increasing demand for the prepration of new antimicrobial agent due to developing resistance towards conventional antibiotics. A number of biological activity such as antibacterial [1-3] antifungal [4-6] anti-inflammatory, analgesic [7-10] anticonvulsant [11,12] plant growth regulatory activity [13] antitumor [14,15] antiviral[16]anti cancer [17] antileishmanial [18] and potassium channel activators [19] have been associated with N-substituted triazole attached with aromatic nuclei. Therefore in the present study we synthesized

a series of some novel eight derivatives of N-(substituted aryl -1, 3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative and evaluated for antimicrobial and antifungal activites . The structure of synthesized compound were assigned on the basis of elemental analysis and spectral analysis.



MATERIAL AND METHODS

General

All the reagents and solvents used were of laboratory grade Melting point were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Dike miracle FT-IR spectrophotometer from Alkem pharmaceutical Baddi. The ^{1}HNMR were recorded on a Bruker Avance II 400 MHz spectrometer using DMSO-d6 as a solvent and a tetra methyl silane (TMS) as an internal standard and expressed in δ ppm from Panjab University (Chandigarh). Putiry of synthesized compounds were checked by TLC using silica gel G . Spot were exposed in an iodine chamber. The compounds were also subjected to C, H and N analysis (Carlo-Erba) at CDRI Lucknow.

Synthesis and Characterization of Compounds

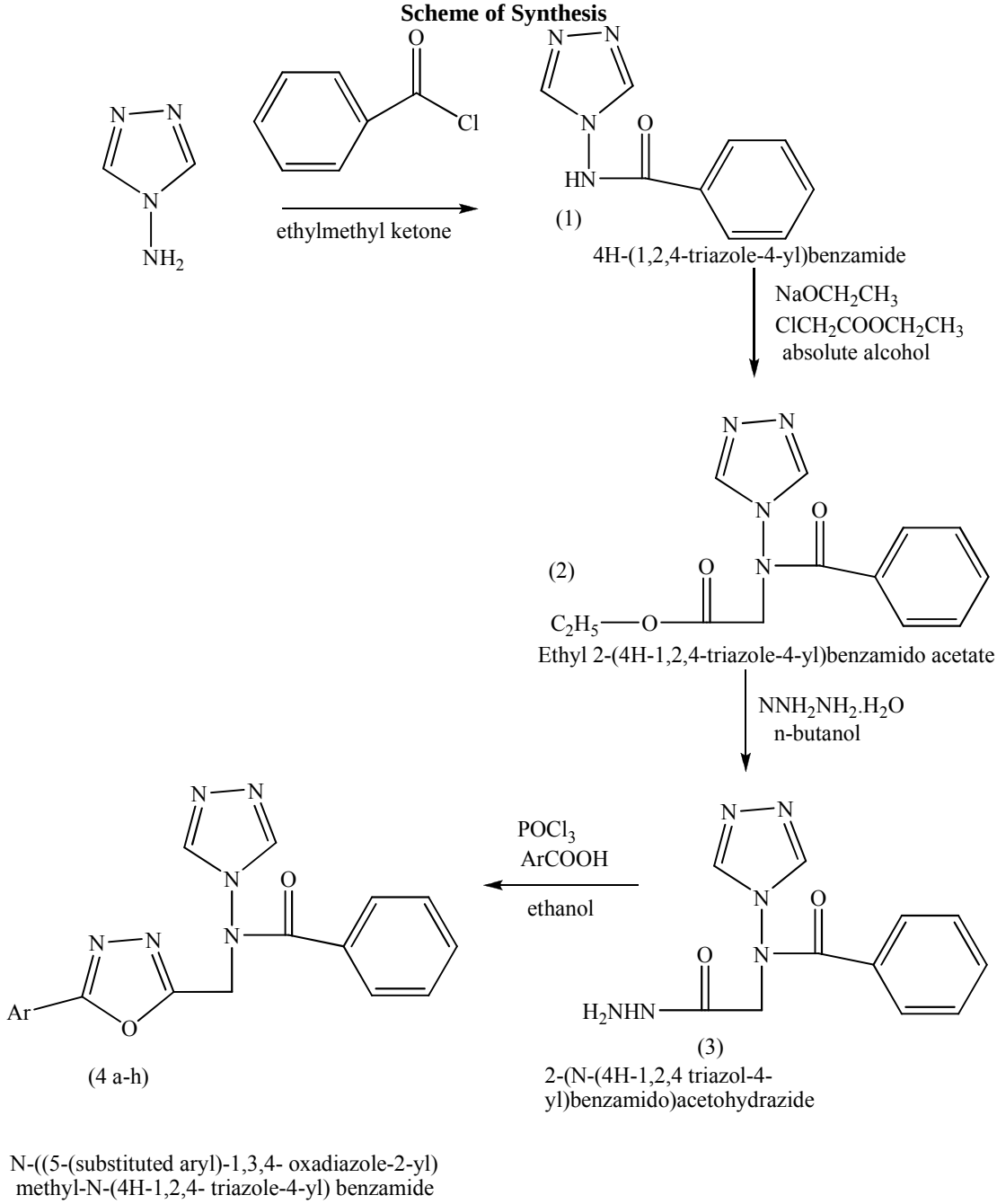
4H-(1,2,4-triazole-4-yl)benzamide (1)

4-Amino triazole (0.01mole) was dissolved in ethyl methyl ketone. Benzoyl chloride (0.01mole) and 10% NaOH solution was added dropwise with constant stirring for 2 hrs on ice bath.The reaction mixture was poured in ice cold water.The product was filtered , dried and recrystallized from ethanol to give compound **(1).** The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3).Percentage Yield-78%, M.P. 82^{0}C, Rf-0.86, IR cm-1: 3252-3500 (N-H), 1680, 1712 (C=O), ^{1}HNMR δ 7.2 (s, 1H, NH), 7.5-8.0 (m, Ar-H) , 8.6-8.7(s, H, CH-triazole).

Ethyl 2-(4H-1,2,4-triazole-4-yl)benzamido acetate (2)

4H-(1,2,4-triazole-4-yl)benzamide (0.01 mole) dissolve in absolute ethanol, sodium ethoxide(0.01mole) and ethylchloroacetate(0.01mole) was added dropwise and refluxed for 30 hrs. The resulting mixture was poured in cold water. The crude product was filtered , dried and recyrstallized from ethanol to furnish compound **(2)**. The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-68%, M.P. 70^{0}C, Rf-0.57, IR cm-1:1680, 1740 (C=O), 1690 (ester), 1598 (C=N), 3000-3100 (CH2),^{1}HNMR δ 8.0-8.2(s,1 H, CH triazole), 3.5 (s, 2H, CH2) , 4.2 (q, 2H, $\underline{CH_2}$ CH_3), 2.0 (t, 3H, CH_3), 7.5-8.0(m, Aromatic ring).

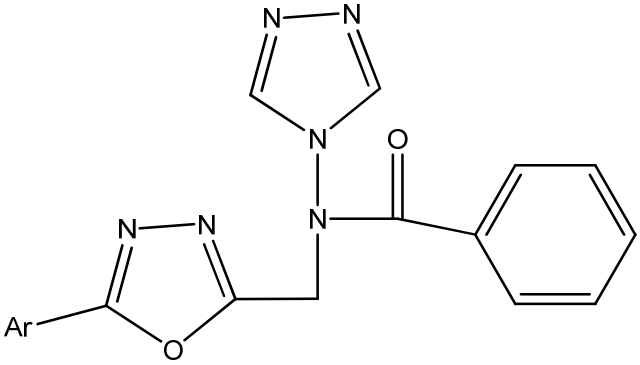
Scheme of Synthesis

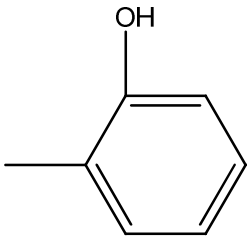
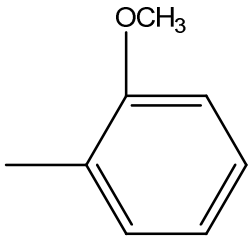
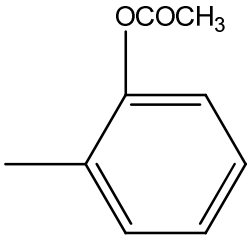
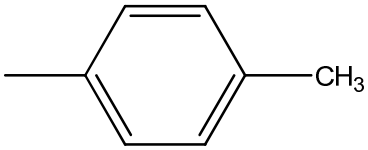
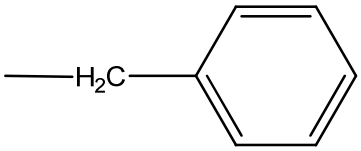
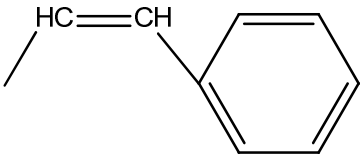
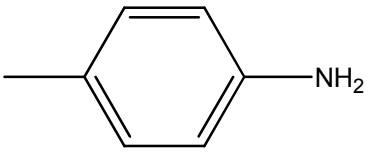
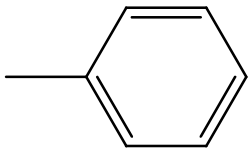


Synhesis of 2-(N-(4H-1,2,4 triazol-4-l)benzamido)acetohydrazide (3)

Ethyl 2-(4H-1,2,4-triazole-4-yl)benzamido acetate (0.01mole) was dissolve in n-butanol 25 ml and refluxed with hydrazine hydrate (0.01 mole) for 18 hrs.After cooling at room temperature , a white solid appeared the crude product was filtered , dried and recrystallized with absolute ethanol . The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-65%, M.P. 240^0C, Rf-0.70, IR cm-1:1680, 1715 (C=O),1660-1674 (C=O,hydrazide), 3338,3320,3321 (NH_2+NH) ,2989-3000 (CH2), 1400-1600 (Aromatic), ^{1}HNMR δ 8.2-8.4 (s, 1H, CH triazole), 3.8 (s, 2H, CH2) , 5.2 (s,1H,$\underline{NHNH_2}$), 3.0(s, 2H, $NH\underline{NH_2}$).

Table No.1: Lead Nucleus with Different substituents (Ar)



S.N.	Ar	S.N.	Ar
4a		4e	
4b		4f	
4c		4g	
4d		4h	

Procedure (4a-4f)

Compound (3) was refluxed with different aromatic acid(0.01mole) in the presences of phosphorus oxychloride(10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . Then the separated solid was filtered and recrystallised from ethanol to give derivative (4a-4h).

N-((5-(2 Hydroxy phenyl)-1,3,4- oxadiazole-2-yl) methyl-N-(4H-1,2,4- triazole-4-yl) benzamide (4a)

Compound (3) 0.01 mole was refluxed with salicylic acid (0.01mole) in the presences of phosphorus oxy chloride (10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B1.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-60%, M.P. 170^{0}C, Rf-0.65, IR cm-1:1684, 1716 (C=O), 3649,

3687 (CH2), 1156 (C-O-C), 1412-1606 (Aromatic), 3200 (OH) ,^{1}HNMR δ 7.4-7.6 (s, 1H, CH triazole), 3.2 (s, 2H, CH2) , 4.8-5.1(s, 1H, OH), 8.1-8.7(m, Ar-H).

Table No.2: Physical and analytical data of compounds

S.N.	Molecular formula	Molecular weight	% Analysis Found (calcd)		
			C%	H%	N%
4a	$C_{18}H_{14}N_6O_3$	362	58.67(58.63)	3.62(3.60)	22.19(22.17)
4b	$C_{20}H_{16}N_6O_4$	404.37	58.40(58.37)	3.78(3.75)	19.78(19.76)
4c	$C_{19}H_{16}N_6O_2$	360.36	62.22(62.20)	3.48(3.46)	22.36(22.32)
4d	$C_{18}H_{15}N_7O_2$	361.35	58.62(58.60)	3.28(3.26)	26.33(25.30)
4e	$C_{19}H_{16}N_6O_3$	376.36	59.63(58.61)	3.28(3.25)	21.32(21.30)
4f	$C_{19}H_{16}N_6O_2$	360.36	62.32(62.30)	3.38(3.36)	22.31(22.28)
4g	$C_{20}H_{16}N_6O_2$	372.38	63.51(63.48)	3.33(3.31)	21.42(21.40)
4h	$C_{18}H_{14}N_6O_2$	346.34	61.42(61.40)	3.07(3.05)	23.27(23.25)

2-(5-((N-(4H-1,2,4- triazole-4-yl) benzamido)methyl-1,3,4-oxadiazol-2yl)phenylacetate (4b)

Compound (3) 0.01mole was refluxed with acetyl salicylic acid (0.01mole) in the presences of phosphorus oxy chloride (10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B2.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-65%, M.P. 120^{0}C, Rf-0.46, IR cm-1:1683, 1716 (C=O), 3849-3919 (CH2), 1150 (C-O-C), 1203 (C-O ester),1479-1592 (Aromatic), 3000(alkyl) ,^{1}HNMR δ 8.0-8.2 (s, 1H, CH triazole), 4.4(s, 2H, CH2) , 7.6-7.8(m, Ar-H), 2.1(s, 3H, CH3).

N-((5-benzyl-1,3,4- oxadiazole-2-yl) methyl)-N-(4H-1,2,4- triazole-4-yl) benzamide (4c)

Compound (3) 0.01mole was refluxed with phenyl acetic acid (0.01mole) in the presences of phosphorus oxy chloride (10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B3.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-64%, M.P. 153^{0}C, Rf-0.42, IR cm-1:1586-1653 (C=O), 2925-3194 (CH2), 1194 (C-O-C), 1434-1482 (Aromatic),^{1}HNMR δ 8.2-8.4 (s, 1H, CH triazole), 3.8-4.3 (s, 2H, CH2) , 7.3-7.8 (m, Ar-H).

N-((5-(4-amino phenyl)-1,3,4- oxadiazole-2-yl) methyl)-N-(4H-1,2,4- triazole-4-yl) benzamide (4d)

Compound (3) 0.01mole was refluxed with para amino benzoic acid (0.01mole) in the presences of phosphorus oxychloride (10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B4.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-70%, M.P. 220^{0}C, Rf-0.67, IR cm-1:1684-1716 (C=O), 3649-3698 (CH2), 1179 (C-O-C), 1320-1507 (Aromatic), 3420 (NH2),1360-1180 (C-N) ^{1}HNMR δ 7.5-7.9 (s, 1H, CH triazole), 3.6 (s, 2H, CH2) , 7.2-7.4 (m, Ar-H) ,5.8-6.0(s, 2H, NH2) m/z

N-((5-(2 methoxy phenyl)-1,3,4- oxadiazole-2-yl) methyl)-N-(4H-1,2,4- triazole-4-yl) benzamide (4e)

Compound (3) 0.01mole was refluxed with 2 methoxy benzoic acid (0.01mole) in the presences of phosphorus oxychloride(10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised

from ethanol to give derivative B5.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-68%, M.P. 210^0C, Rf-0.92, IR cm-1:1621-1653 (C=O), 3566,3628 (CH3), 1165 (C-O-C), 1457-1558 (aromatic), ^{1}HNMR δ 8.9 (s, 1H, CH triazole), 4.0-4.2 (s, 2H, CH2) , 7.0-8.2 (m, Ar-H) , 3.8 (t, 3H, OCH3).

N-(-p-tolyl-1,3,4- oxadiazole-2-yl) methyl)-N-(4H-1,2,4- triazole-4-yl) benzamide (4f)

Compound (3) 0.01mole was refluxed with 4-tolic acid (0.01mole) in the presences of phosphorus oxy chloride(10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B6.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-63%, M.P. 150^0C, Rf-0.69, IR cm-1:1645-1716 (C=O), 2922,3566 (CH2), 1120 (C-O-C), 1311-1557 (aromatic), 2922 (CH3), ^{1}HNMR δ 7.9 (s, 1H, CH triazole), 4.2-4.4 (s, 2H, CH2) , 7.3-7.8 (m, Ar-H) ,2.34 (s, 3H, CH3) m/z

N-(5-styryl-1,3,4- oxadiazole-2-yl) methyl)-N-(4H-1,2,4- triazole-4-yl) benzamide (4g)

Compound (3) 0.01mole was refluxed with cinnamic acid (0.01mole) in the presences of phosphorus oxychloride(10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B7.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-52%, M.P. 90^0C, Rf-0.72, IR cm-1:1684-1716 (C=O), 3566, 3649 (CH2), 1153 (C-O-C), 1446-1576 (aromatic), 3168 (=CH), ^{1}HNMR δ 8.0 (s, 1H, CH triazole), 4.3(s, 2H, CH2) , 7.3-7.6(m, Ar-H) ,7.0(s, H, CH=CH).

N-(5-phenyl-1,3,4- oxadiazole-2-yl) methyl)-N-(4H-1,2,4- triazole-4-yl) benzamide (4h)

Compound (3) 0.01mole was refluxed with benzoic acid (0.01mole) in the presences of phosphorus oxy chloride(10ml) for 8 hrs. The content then was poured into ice cold water and bacify with sodium bicarbonate solution . The separated solid was filtered and recrystallised from ethanol to give derivative B8.The completion of the reaction was monitored by TLC and purified by coloumn chromatography on silica gel (60-120 mesh) eluting with ethylacetate : methanol (5:3). Percentage Yield-58%, M.P. 122^0C, Rf-0.66, IR cm-1:1551-1607 (C=O), 3566, 3462 (CH2), 1175 (C-O-C), 1291,1445-1484 (aromatic ring), 3050-3000 (Ar-H), ^{1}HNMR δ 7.6-7.8 (s, 1H, CH triazole), 4.1 (s, 2H, CH2) , 7.5-8.2 (m, Ar-H).

RESULTS AND DISCUSSION

N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative have been synthesized by reaction between 4- amino 1,2,4 triazole and benzoyl chloride in ethyl methylketone at ice bath for 2 hrs which afforded 4H-1,2,4-Trizole-4-yl)benzamide (1). In the IR spectrum of compound (1) bands in the range of 1712 and1680 cm-1 were obtained due to C=O stretching in C6H5COCl group and the appearance of a new band at 775-740cm-1due to C-Cl bond. Compound (1) on treatment with ethylchloroacetate in absolute ethanol yielded Ethyl-(4H-1, 2, 4-Triazole-4-yl) benzamido acetate (2). In the IR spectrum of compound (2) bands in the range of 3000-3100 due to CH_2 and C=O stretching was observed at 1680,1740. 1H NMR spectrum signals were found at δ 4.2 (CH2) and 2.0 (CH3).Compound (2) on reaction with Hydrazine hydrate in butanol gave N-(4H-1, 2, 4 triazol- 4-) benzamido) acetohydrazide (3). In the IR spectrum of compound (3) bands in the range 3338, 3320, 3321 for

($NH+NH_2$). ^1H NMR spectrum signals were found at δ 3-5.2($NH+NH_2$).The final compounds (4a-h) were produced by the reaction of compound (3) and various Aromatic acid in phosphorus oxy chloride. These reactions are summarized in Scheme of synthesis. The structure of synthesized compound was confirm by IR and ^{1}HNMR The purity and homogeneity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected), thin-layer chromatography.

Table No.3: Antibacterial activity of N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative against gram (+ve bacteria) . Zone of inhibition is expressed in mm.

S.N.	Kp		St		Pa		Sm		Pv	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
4a	26	31	25	28	22	30	18	20	18	22
4b	22	25	24	24	26	28	16	18	18	19
4c	20	24	20	22	23	25	12	16	16	17
4d	28	30	25	28	22	28	18	20	18	22
4e	20	24	24	26	22	24	15	17	16	19
4f	24	26	26	28	23	26	16	18	15	18
4g	23	25	20	22	21	22	16	18	15	16
4h	25	27	22	24	20	24	14	16	16	18
standard	30	35	28	30	25	32	20	24	22	24

Streptococus pyrogen (Sp), *Bacillus aureus* (Ba), *Micrococus leuteus* (Ml), *Streptococus epidermis* (Se), *Clostridium sporogen* (Cs)

Table No.4: Antibacterial activity of N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative against gram (- ve bacteria) . Zone of inhibition is expressed in mm.

S.N.	Sp		Ba		Ml		Se		Cs	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
4a	15	18	20	23	18	20	20	22	16	19
4b	20	24	22	25	20	22	22	24	20	22
4c	18	20	21	23	15	18	15	19	15	17
4d	21	23	23	27	18	23	21	23	19	21
4e	20	21	21	25	18	20	16	21	12	16
4f	18	20	22	22	15	18	18	20	18	20
4g	20	22	18	20	15	17	16	21	16	20
4h	17	21	18	21	19	22	18	20	15	19
standard	27	28	26	30	28	24	21	25	18	24

Klebsiella pneumonia (Kp), *Salmonella typhimurium* (St) , *Pseudomonas aeruginosa* (Pa) , *Serratia marcesens* (Sm) and *Proteus vulgaris* (Pv)

Antimicrobial activity

The antimicrobial activity of the synthesized compound 4(a-h) were determined by agar diffusion technique[20]. The organism tested were *Streptococus pyrogen* (NCIM-2608), *Bacillus aureus* (NCIM-2797), *Micrococus leuteus* (NCIM-2704), *Streptococus epidermis* (NCIM-2493),*Clostridium sporogen*(NCIM-2559), *Klebsiella pneumonia* (NCIM-2957), *Salmonella typhimurium* (NCIM-2501), *Pseudomonas aeruginosa* (NCIM-2863), *Serratia marcesens* (NCIM-2078) and *Proteus vulgaris* (NCIM-2813) for antibacterial activity and *Gibberella fujikuroi* (NCIM-655), *Rhizopus oligosporus* (NCIM-1215), *Neurospora crassa* (NCIM-908), *Aspergillus niger* (NCIM-618), *Candida albican* (NCIM-3557) for antifungal activity. The agar media were inoculated with test organism and a solution of test compound 50 µg/ml and 100

µg/ml in DMSO. DMSO 10 µg/ml was separately in cups (8 mm diameter) in the agar medium. Streptomycin (50 µg /ml), Ampicillin (50 µg /ml), and fluconazole (5 µg /ml) were used as a reference for antibacterial and antifungal activity respectively. The zone of inhibition were measured after 24 hrs incubation. The results of the microbial activity tests are summarized in table . Most of the synthesized compounds were found to possess varied antimicrobial activities towards the entire microorganism used with minimum inhibitory concentration (MIC).

Table No.5: Antifungal activity of N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative against fungi. Zone of inhibition is expressed in mm.

S.N.	Zf		Ro		Nc		An		Ca	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
4a	22	24	20	21	20	22	15	18	18	24
4b	20	25	16	22	18	23	12	16	22	25
4c	23	26	20	23	24	25	14	18	20	213
4d	23	24	18	20	24	26	11	22	22	26
4e	22	23	20	22	18	22	18	20	20	22
4f	22	23	22	23	20	23	12	21	18	20
4g	23	25	20	24	16	20	16	18	20	24
4h	20	25	22	25	16	18	20	22	21	25
standard	23	26	22	25	24	26	26	24	22	26

Gibberella fujikuroi (Gf), *Rhizopus oligosporus* (Ro), *Neurospora crassa* (Nc), *Aspergillus niger* (An), *Candida albican* (Ca) .

CONCLUSION

A new series of N-(substituted aryl -1,3,4-oxadiazole -2 yl) methyl-N-(4H-1,2,4 –triazol-4 yl) benzamide derivative were synthesized by the steps mentioned in experimental part. The structure of the synthesized compounds was confirmed by IR and 1HNMR method. All the compounds were evaluated for antibacterial and antifungal activity. Compounds have shown promising antibacterial and antifungal activity. And all the synthesized compounds promising good to moderate biological activity comparable to standard.

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REFERENCES

[1] Holla, B, S., Mahalinga, M., Karthikeyan, M, S., Poojary, B., Akberali, P, M., Kumari, N, S., **2005**, *European Journal of Medicinal Chemistry*, 40: 1173–1178.
[2] Gumrukcuglu, N., Serdar, M., Celik, E., Sevim, A., Demirbas, N., **2007**, *Turk J Chem* 31: 335 – 348.
[3] Shiradkar, M., Pandit, U., Akula, K, C., Maheta, A., Suresh Kumar, G, V., **2006**, *ARKIVOC*, xiv: 141-154.
[4] Singh, R, J., Singh, D, K., **2009**, *E-Journal of Chemistry*, 6(S1): S219-S224.
[5] Rezaei, Z., Khabnadideh, S., Pakshir, K., Hossaini, Z., Amiri, F., Assadpour, E., **2009**, *European Journal of Medicinal Chemistry*, 44: 3064–3067.
[6] Uchida, T., Kagoshima, Y., Konosu, T., **2009,** *Bioorganic & Medicinal Chemistry Letters*,19: 2013–2017.

[7] Braccio, M, D., Grossi. G., Roma, G., Piras, D., Mattioli, F., Gosmar, M., **2008**, *European Journal of Medicinal Chemistry*, 43: 584-594.
[8] Goksen, U, S., Kelekci,N, G., Goktas, O., Koysal, Y., Kılıc, E., Isık, S., Aktay,G., Ozalp, M., **2007**, *Bioorganic & Medicinal Chemistry*, 15: 5738–5751.
[9] Karthikeyan, M, S., **2009**, *European Journal of Medicinal Chemistry*, 44: 827-833.
[10] Tozkoparan, B., Kupeli, E., Yesiladac, E., Ertan, M., **2007**, *Bioorgan*ic *& Medicinal Chemistry*, 15: 1808–1814.
[11] Shiradkar, M, R., Ghodake, M., Bothara, K, G., Bhandari, S, V., Nikalje, A., Akula, K, C., Desai, N, C., Burange, P, J., **2007**, *ARKIVOC*, xiv: 58-74
[12] Shalini, M., Yogeeswari, P., Sriram, D., Stables, J, P., **2009**, *Biomedicine & Pharmacotherapy*, 63: 187-193.
[13] Qin, X., Yu, H., Liu, J., Dai, H., Bing, G., Qin, Z., Zhang, X., Wang, T., Fang, J., **2009**, *ARKIVOC*, ii: 201-210.
[14] Shiradkar, M, R., Murahari, K, K., Gangadasu, H, R., Suresh, T., Kalyan, C, A., Panchal, D., Kaur, R., Burange, P., Ghogare, J., Mokale, V., Raut, M., **2007**, *Bioorganic & Medicinal Chemistry*,15: 3997–4008.
[15] Joshi, S, D., Vagdevi, H., M., Vaidya, V, P., Gadaginamath, G, S., **2008**, *European Journal of Medicinal Chemistry*, 43: 1989-1996.
[16] Jordao, A, K., Afonso, P, P., Ferreira, V, F., Desouza, M, C, B, V., Almeida, M, C, B., Beltrame, C, O., Paiva, D, P., Wardell, S, M, S, V., Wardell, J, L., Tiekink, E, R, T., Damaso, C, R., Cunha, A, C., **2009**, *European Journal of Medicinal Chemistry*, 44: 3777–3783.
[17] Sztanke, K., Tuzimski, T., Rzymowska, J., Pasternak K., Szerszen, M, K., **2008**, *European Journal of Medicinal Chemistry*, 43: 404-419.
[18] Rodriguez, L, V., Dedet, J, P., Paredes, V., Mendoza, C., Cardenas, F., **1995**, *Mem Inst Oswaldo Cruz, Rio de Janeiro*, Vol. 90(4): 525-528.
[19] Calderone, V., Giorgi, I., Livi, O., Martinotti, E., Mantuano, E., Martelli, A., Nardi, A., 2**005**, *European Journal of Medicinal Chemistry* 40: 521–528
[20] Dr. M.K. Lalitha, Manual on Antimicrobial Susceptibility Testing. Department of Microbiology, Christian Medical College Vellore, Tamil Nadu.