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SYNTHESIS, ANTIMICROBIAL ANTIINFLAMMATORY ACTIVITIES OF OXADIAZOLE DERIVATIVES

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ABSTRACT : A new series of ten compounds of 1,3,4 oxadiazoles were synthesized by ring closure reactions of different acid hydrazides with carbon disulphide and aromatic acids separately. Further, the 2-thio oxadiazoles were treated with aromatic amines to get mannich bases. The structures of the synthesized compounds were consistent with IR, 1H NMR and MASS spectroscopy. The synthesized compounds were screened by disc diffusion method for their antibacterial and antifungal activity. Among the compounds synthesized 3d, 3e and 5b shown significant antimicrobial activity against both bacterial and fungal strains.

Keywords: 1, 3, 4-oxadiazole, Mannich bases, Antibacterial and Antifungal activity.

INTRODUCTION

1, 3, 4 oxadiazoles possess multi-range of biological actions such as antibacterial [1], anifungal [2], anti-inflammatory [3 - 4], herbicidal, anticonvulsant, ant tubercular [5] and anticancer activity, etc. In the present study newer analogs of 2, 5-disubstituted oxadiazoles were synthesized from various acid hydrazides, which are obtained by reacting respective esters with hydrazine hydrate. The acid hydrazides were reacted with different aromatic acids to get 2, 5- disubstituted 1, 3, 4-oxadiazoles (3a-e). Mannich bases of oxadiazoles were synthesized by converting acid hydrazide into 2-thio oxadiazoles followed by subjecting into mannich reaction (5a-e). All the synthesized compounds were screened for in vitro antimicrobial activity by disc diffusion method.

EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on pre-coated silica gel GF 254 plates. IR spectra were recorded through KBr pellet method in Perkin-Elmer FTIR spectrophotometer. 1H NMR spectra was recorded on BRUKER ADVANCE II 400 NMR spectrometer with tetramethyl silane as an internal standard. The mass spectrum of compounds was recorded on JEOL GC Mate spectrophotometer.

Synthesis of 4-substituted acid hydrazides (2):

The starting material 4-substituted ethyl benzoate (1) was prepared by esterifying corresponding aromatic acids with ethanol in the presence of concentrated sulphuric acid [6]. A mixture of 4-substituted ethyl benzoate (0.01 mol), hydrazine hydrate (0.15 mol) and 30ml of ethanol was refluxed for 4 hr and the excess of ethanol was distilled off and the contents were poured into ice cold water and the precipitated hydrazides were filtered, dried and recrystallized from ethanol.

Synthesis of 2, 5-disubstituted-1, 3, 4-oxadiazoles (3a-e):

The acid hydrazide (2) (0.01 mol) and aromatic acid (0.01 mol) were refluxed in POCl3 (5 ml) for 8 h, cooled and poured into crushed ice and neutralised with sodium bicarbonate solution. The precipitate was filtered off, dried and recrystallized from ethanol [7].

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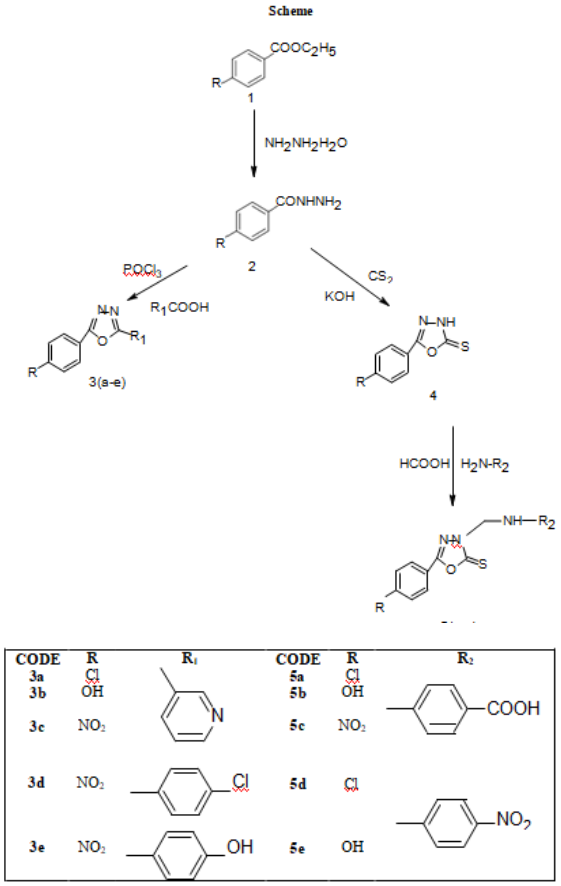

Synthesis of 5-(substituted)-2-thio-1, 3, 4-oxadiazoles (4):

The acid hydrazides (2) (0.01 mol) was dissolved in cold ethanol (15 ml) followed by added carbon disulphide (2 ml) and potassium hydroxide (0.6 g). The reaction mixture was refluxed until the evolution of hydrogen sulphide gas ceased (around 12 h). Excess solvent was evaporated and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%) to pH~5. The precipitate was filtered off, dried and recrystallized from ethanol.

Synthesis of Mannich bases of 1, 3, 4-oxadiazoles (5a-e):

Equimolar quantity of 5-(4-substituted) phenyl-1, 3, 4-oxadiazol-2(3H)-thione (4) (0.01 mol) and different amines were dissolved in ethanol (20 ml) and followed by added drop by drop of formaldehyde solution (0.01 mol). Stirred the contents for 1 h at room temperature and then refluxed for 2-3 hours. Then the content was kept at overnight at the temperature of 5-80C. The reaction mixture was concentrated and the product was filtered, dried and recrystallized from ethanol [8].

Table 1- Physical data of the compounds

Code	Molecular formula	Molecular Weight	Yield (%)	Melting Point (°C)	*Rf value
3a	C13H8N3OCl	257.67	70.81	162	0.50
3b	C13H9N3O2	239.22	63.02	186	0.55
3c	C13H8N4O3	268.22	73.30	210	0.52
3d	C14H8N3O3Cl	301.68	77.07	190	0.46
3e	C14H9N3O4	283.23	65.37	205	0.35
5a	C16H12N3O3SCl	361.80	78.45	180	0.58
5b	C16H13N3O4S	343.35	86.87	196	0.56
5c	C16H12N4O5S	372.35	92.21	189	0.38
5d	C15H11N4O3SCl	362.79	91.16	175	0.79
5e	C15H12N4O4S	344.34	84.58	182	0.75

* Solvent system: Ethylacetate : Hexane (1:4)

Antimicrobial activity:

The synthesized compounds were tested for their in vitro antibacterial activity against Bacillus cereus, Staphylococcus aureus (gram positive) and Pseudomonus aeruginosa, Klebsiella pneumonia (gram negative) and the antifungal activity was screened against Candida albicans and Aspergillus fumigatus at the concentrations of 50, 100 and 150 µg/ml by disc diffusion method. Ciprofloxacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively. Dimethyl sulfoxide was used as a control and the zone of inhibition of the compounds are presented in the table.

Sterile disc of 5 mm in diameter made from Whatmann filter paper which is previously sterilized in U.V. lamp was dipped in solution of different concentrations of synthesized compounds, standard and blank and placed the disc on the surface of agar plates. Allowed the plates to stand for 1 h at room temperature as a period of pre-incubation to minimize the effects of variation in time between the applications of different solutions. Then the plates were incubated for 24 h at 37o C ± 1o C for bacteria and 72 h at 25oC± 1oC for fungi. The diameter of zone of inhibition was measured.

RESULTS AND DISCUSSION

Five derivatives of each of 2, 5-disubstituted and mannich bases of 1, 3, 4-oxadiazole were synthesized from acid hydrazides. The structures of the synthesized compounds were confirmed on the basis of IR, 1H NMR and Mass spectroscopy. All the compounds were screened for their in vitro antibacterial and antifungal activities. The compounds 3d, 3e, 5b and 5d shown good antibacterial activity against gram positive organisms and the compounds 3c, 3d, 3e and 5b could show better action against gram negative organisms. About

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antifungal screening, the compounds 3d, 3e, 5a and 5b shown significant activity.

To conclude, 3d, 3e and 5b are fruitful compounds among the series synthesized for both bacterial and fungal inhibition.

Spectral data:

(3a): IR (cm^{-1}): 3085.09 (Ar CH str), 1479.44 (C=C, C=N str), 1106.94 (C-O-C str), 735.76 (C-Cl str). **^{1}H NMR (δ ppm):** 9.31 (m, 4H, pyridine), 7.53 (d, 4H, Ar). **m/z:** 257 (M^+), 212, 185.

(3b): IR (cm^{-1}): 3052.32(Ar CH str), 2844.75(Ar OH str), 1494.93(C=C,C=N str), 1096.86(C-O-C str). **^{1}H NMR (δ ppm):** 8.70 (m, 4H, pyridine), 6.94-7.82 (d, 4H, Ar), 5.07(s, 1H, OH). **m/z:** 239(M^+), 210, 185.

(3c): IR (cm^{-1}): 3063.24 (Ar CH Str), 1552.81(Ar NO_2 Str), 1481.84(C=C, C=N Str), 1085.23(C-O-C Str). **^{1}H NMR (δ ppm):** 9.35(m, 4H, pyridine), 8.44-8.46(d, 4H, Ar). **m/z:** 268(M^+), 212, 198.

(3d): IR (cm^{-1}): 2925.72 (Ar CH Str), 1556.18 (Ar NO_2 Str), 1480.13(C=C,C=N Str), 1071.64 (C-O-C Str), 732.80 (C-Cl bend). **^{1}H NMR (δ ppm):** 8.46(m, 4H, Nitrobenzene), 7.59 (m, 4H, Chlorobenzene). **m/z:** 301 (M^+), 219, 185.

(3e): IR (cm^{-1}): 2918.46 (Ar CH Str), 2849.42 (Ar OH Str), 1521.88 (Ar NO_2 Str), 1491.47 (C=C,C=N Str), 1074.39 (C-O-C Str). **^{1}H NMR (δppm):** 5.10 (s, 1H, OH), 6.79 – 8.20 (m, 8H, Ar). **m/z:** 283(M^+), 216, 188.

(5a): IR (cm^{-1}): 3316.90 (NH Str), 3027.53 (Ar CH Str), 1606.74 (Ar C=C str), 1252.83 (C=S str), 1074.39 (C-O-C Str), 722.19 (C-Cl str) **^{1}H NMR (δ ppm):** 2.57(s, H, COOH), 5.78 (t, H, NH), 6.94 (d, 2H, CH_2), 7.57-7.86 (m, 8H, Ar). **m/z:** 362(M+), 240, 129.

(5b): IR(cm^{-1}): 3325.16 (NH Str), 3298.94 (OH Str), 3016.25 (Ar CH Str), 1605.71 (Ar C=C Str), 1280.14 (C=S Str), 1076.66(C-O-C Str). **^{1}H NMR (δ ppm):** 2.59 (s, H, COOH), 5.06 (s, 1H, OH), 5.50 (m, H, NH), 6.73 (d, 2H, CH_2), 6.82 - 7.85 (m, 8H, Ar). **m/z:** 343(M^+), 250, 193.

(5c): IR (cm^{-1}): 3423.41 (NH Str), 3054.28 (Ar CH Str), 1604.98 (Ar C=C Str), 1526.19 (Ar NO_2 Str), 1255.17 (C=S Str), 1111.19 (C-O-C Str). **^{1}H NMR (δ ppm):** 2.56 (s, H, COOH), 5.42 (t, H, NH), 6.11 (d, 2H, CH_2), 7.87-8.35 (m, 8H, Ar). **m/z:** 372(M^+), 251, 129.

(5d): IR (cm^{-1}): 3366.10 (NH Str), 3089.73 (Ar CH Str), 1603.53 (Ar C=C Str), 1531.18 (Ar NO_2 Str), 1258.31(C=S Str), 1111.69 (C-O-C Str), 752.59 (C-Cl str). **^{1}H NMR (δ ppm):** 5.96 (t, H, NH), 6.79 (d, 2H, CH_2), 7.53-8.05 (m, 8H, Ar). **m/z:** 363 (M^+), 251, 129.

(5e): IR (cm^{-1}): 3398.14 (NH Str), 3251.27 (OH Str), 3021.39 (Ar CH Str), 1609.75 (Ar C=C Str), 1559.75 (Ar NO_2 Str), 1253.17 (C=S Str), 1089.96 (C-O-C Str). **^{1}H NMR (δ ppm):** 5.59 (t, H, NH), 6.07 (d, 2H, CH_2), 6.75 (m, 4H, Hydroxybenzene), 8.15 (m, 4H, Nitrobenzene). **m/z:** 344(M^+), 222, 176.

Table 2-Antibacterial activity

Code	Zone of Inhibition (in mm)											
	Gram positive						Gram negative					
	Bacillus Cereus (µg/ml)			Staphylococcus aureus (µg/ml)			Pseudomonus aeruginosa (µg/ml)			Klebsiella Pneumonia (µg/ml)		
	50	100	150	50	100	150	50	100	150	50	100	150
3a	13	16	20	12	14	19	14	16	20	13	15	19
3b	13	15	18	13	15	18	12	15	19	12	14	16
3c	14	16	19	11	14	18	16	18	22	16	18	21
3d	15	18	20	15	18	20	13	19	24	12	18	23
3e	16	19	21	15	19	22	15	18	25	14	17	24
5a	14	16	19	14	17	20	13	15	18	12	15	17
5b	15	18	21	15	17	21	15	18	21	13	16	20
5c	12	15	19	12	15	18	12	16	20	12	15	18
5d	13	15	21	16	18	21	12	14	16	12	14	17
5e	14	17	19	12	15	18	12	15	18	13	16	18
Ciprofloxacin (10 µg/ml)	39			38			38			39		

Table 3- Antifungal activity

CODE	Zone of Inhibition (in mm)					
	Candida albicans (µg/ml)			Aspergillus fumigates (µg/ml)		
	50	100	150	50	100	150
3a	15	18	20	14	19	21
3b	12	16	19	13	18	20
3c	15	18	21	15	20	22
3d	17	21	23	16	22	24
3e	14	18	22	15	19	23
5a	17	20	23	20	24	26
5b	15	20	22	16	21	22
5c	16	19	22	15	18	20
5d	15	18	21	16	18	20
5e	13	17	20	15	19	22
Ketoconazole (10 µg/ml)	38			39		

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