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Synthesis, characterization, antibacterial and analgesic evaluation of some 1,3,4-oxadiazole derivatives

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ABSTRACT

Research on 1,3,4-oxadiazole and their synthetic analogs have revealed a variety of pharmacological activities including anti-microbial, antitubercular, anticancer, anti-HIV, antioxidant, analgesic, anti-inflammatory and anticonvulsant activities. A series of 1,3,4-oxadiazole derivatives were prepared from isonicotinamide and hydrazide hydrate, characterized by means of IR, $^1\text{H-NMR}$ and mass spectral data. The synthesized compounds were subjected to in-vitro antibacterial activity against *Staphylococcus aureus* (MTCC-87), *Escherichia coli* (MTCC-40), *Staphylococcus epidermidis* (MTCC- 2639), *Pseudomonas aeruginosa* (MTCC-424) and *Proteus vulgaris* (MTCC-426) by cup plate method. The analgesic activity was performed by acetic acid induced writhing in mice. Some of the tested compounds exhibited promising biological activities.

Key words: 1,3,4-oxadiazole, antibacterial, analgesic.

INTRODUCTION

Nitrogen containing heterocycles with an oxygen atom are considered as an important class of compounds in medicinal chemistry because of their interesting diversified biological applications. One such class of biodynamic agent is oxadiazole. Oxadiazole is a cyclic compound containing one oxygen and two nitrogen atoms in a five membered ring. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring. The capacity of 1, 3, 4-oxadiazole nucleus to undergo variety of chemical reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical which made it medicinal backbone on which a number of potential molecules can be constructed. Literature survey reveals that 1,3,4-oxadiazoles have wide range of biological activities [1-9]. The good

biological profile of oxadiazole derivatives prompted us to synthesize some 1,3,4-oxadiazole derivatives, evaluate their antibacterial and analgesic activities by the standard method.

MATERIALS AND METHODS

All the chemicals were procured from S. D Fine Chem. Ltd. The melting points were determined in open capillaries by using a Thomas Hoover melting point apparatus, expressed in °C and are uncorrected. The IR spectra of the compounds were recorded on Shimadzu IR Affinity series-1 in KBr and the values are expressed in cm^{-1} . The $^1\text{H-NMR}$ spectra of the compounds were recorded on a Bruker Advance II 400 MHz spectrophotometer and the values were expressed in δ ppm. The mass spectra of the compounds were recorded on Micromass Q-ToF Micro; in m/z . The purity of the compounds was checked by thin layer chromatography on silica gel G coated plates. The experimental protocol for the acetic acid induced writhing was approved by the institutional animal ethics committee prior to the conduct of the animal experiments.

Experimental

General Procedure for the synthesis of pyridine-4-carbohydrazide (1):

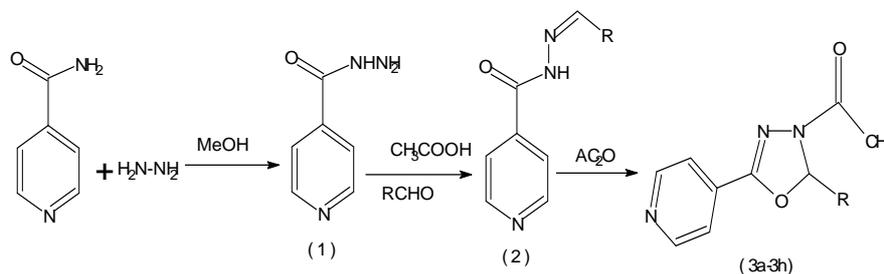
To a solution of isonicotinamide (3.8gm in 20ml ethanol), 3ml of hydrazide hydrate was added and refluxed for 4 hours at 110°C . The reaction mixture was cooled, filtered and recrystallized from ethanol.

General Procedure for the synthesis of Schiff base (2):

Compound 1(0.01mole) was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehyde (0.01mole) was added and the reaction mixture was refluxed for 5 hours at 70°C . The reaction mixture was cooled, poured in crushed ice, filtered and the separated product was purified by recrystallization from ethanol.

General Procedure for the synthesis of 2-aryl-5-pyridine-1,3,4-oxadiazoles (3a-3h):

A mixture of Schiff base (0.002mole) and acetic anhydride (10ml) was refluxed for 4 hours. The excess of acetic anhydride was distilled off and the residue was poured into ice cold water, filtered and the separated product was purified by recrystallization from ethanol.



Spectral data of the synthesized compounds:

4-(3-acetyl-5-pyridin-4-yl-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (3a): IR (cm^{-1}): 3234 (OH), 1624 (C=N of oxadiazole), 1556 (C=N), 1062 (C-N), 1288 (C-O-C). $^1\text{H-NMR}$ δ (ppm): 10.67 (1H, s, OH), 2.63 (3H, s, CH_3), 6.77-7.71 (8H, m, Ar-H).

4-[4-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]pyridine(3b): IR (cm⁻¹): 1656 (C=N of oxadiazole), 1562 (C=N), 1087 (C-N), 1259 (C-O-C). ¹H-NMR δ (ppm): 2.33(3H, s, CH₃), 7.47-7.81(8H, m, Ar-H). Mass (m/z): 301.72

Table-1: Physical data of the synthesized compounds

Compounds	R	M.F.	M.W.	M.P.(°C)	Yield (%)
3a	4-hydroxyphenyl	C ₁₅ H ₁₃ N ₃ O ₃	283.28	184-185	64.36
3b	4-chlorophenyl	C ₁₅ H ₁₂ ClN ₃ O ₂	301.72	140-141	58.72
3c	3-chlorophenyl	C ₁₅ H ₁₂ ClN ₃ O ₂	301.72	134-135	62.19
3d	2-chlorophenyl	C ₁₅ H ₁₂ ClN ₃ O ₂	301.72	156-157	72.22
3e	3-aminophenyl	C ₁₅ H ₁₄ N ₄ O ₂	282.29	135-136	55.83
3f	3-methoxyphenyl	C ₁₆ H ₁₅ N ₃ O ₃	297.30	179-180	71.31
3g	3,4-dimethoxyphenyl	C ₁₇ H ₁₇ N ₃ O ₄	327.33	120-121	70.12
3h	4-fluorophenyl	C ₁₅ H ₁₂ FN ₃ O ₂	285.27	141-142	73.36

4-[4-acetyl-5-(3-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]pyridine(3c): IR (cm⁻¹): 1660 (C=N of oxadiazole), 1544 (C=N), 1066 (C-N), 1219 (C-O-C). ¹H-NMR δ (ppm): 2.53 (3H, s, CH₃), 7.71-8.11(8H, m, Ar-H). Mass (m/z): 301.72

4-[4-acetyl-5-(2-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]pyridine(3d): IR (cm⁻¹): 1654 (C=N of oxadiazole), 1560 (C=N), 1074 (C-N), 1210 (C-O-C). ¹H-NMR δ (ppm): 2.56 (3H, s, CH₃), 7.42-7.81(8H, m, Ar-H).

3-(3-acetyl-5-pyridin-4-yl-2,3-dihydro-1,3,4-oxadiazol-2-yl)aniline(3e): IR (cm⁻¹): 3270 (N-H), 1620 (C=N of oxadiazole), 1566 (C=N), 1054 (C-N), 1276 (C-O-C). ¹H-NMR δ (ppm): 2.53 (3H, s, CH₃), 6.12 (2H, d, NH₂), 7.22-7.65(8H, m, Ar-H).

4-[4-acetyl-5-(3-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]pyridine(3f): IR (cm⁻¹): 1668 (C=N of oxadiazole), 1538 (C=N), 1064 (C-N), 1278 (C-O-C), 1251(C-O of OCH₃). ¹H-NMR δ (ppm): 2.54 (3H, s, CH₃), 3.95(3H, s, OCH₃), 7.42-7.81(8H, m, Ar-H).

4-[4-acetyl-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]pyridine(3g): IR (cm⁻¹): 1662 (C=N of oxadiazole), 1524 (C=N), 1036 (C-N), 1266 (C-O-C), 1246(C-O of OCH₃). ¹H-NMR δ (ppm): 2.50 (3H, s, CH₃), 3.76(6H, s, (OCH₃)₂), 7.22-7.65(7H, m, Ar-H).

4-[4-acetyl-5-(4-fluorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]pyridine(3h): IR (cm⁻¹): 1623 (C=N of oxadiazole), 1065 (C-O-C), 1521 (C=N), 1086 (C-F). ¹H-NMR δ (ppm): 2.53 (3H, s, CH₃), 7.71-8.11(8H, m, Ar-H). Mass (m/z): 285.27

Determination of Antibacterial activity: The synthesized compounds were screened *in-vitro* for their antibacterial activity against *Staphylococcus aureus* (MTCC-87), *Escherichia coli* (MTCC-40), *Staphylococcus epidermidis* (MTCC-2639), *Pseudomonas aeruginosa* (MTCC-424) and *Proteus vulgaris* (MTCC-426) using cup plate method [10]. The compounds were tested at 500 µg concentration in DMSO, using nutrient agar as the medium. After 24 hr of incubation at 37 °C, the zone of inhibition formed were measured in mm against standard drug Tetracycline and the data were presented in Table-2.

Determination of Analgesic activity: The synthesized compounds were screened for the evaluation of analgesic activity by acetic acid induced writhing [11]. In this model the animals were divided into different groups (n = 6). Group I served as control (1% Carboxy Methyl Cellulose as vehicle, 1ml/kg, p.o.), group II served as standard (Indomethacin, 10 mg/kg, p.o.) and other groups were served as test groups and received the test compounds each at the dose of 200 mg/kg/p.o. The vehicle, standard and test compounds were administered in the suspension form in Carboxy Methyl Cellulose to the respective groups, 30 min before the induction of pain by acetic acid.

Table-2: Antibacterial activity of the synthesized compounds

Compounds	Diameter of zone of inhibition (mm)				
	<i>P. vulgaris</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>S. epidermidis</i>
3a	18.33 ± 1.52	12.00 ± 1.00	22.33 ± 1.52	13.66 ± 1.52	12.33 ± 1.52
3b	15.00 ± 1.00	13.00 ± 1.00	17.00 ± 1.00	15.66 ± 0.57	15.33 ± 0.57
3c	13.33 ± 0.57	15.00 ± 1.00	13.00 ± 1.00	13.33 ± 0.57	11.66 ± 0.57
3d	19.66 ± 0.57	18.33 ± 0.57	24.00 ± 1.00	20.00 ± 1.00	20.66 ± 0.57
3e	20.00 ± 1.00	18.00 ± 1.00	24.00 ± 1.00	18.00 ± 1.00	20.66 ± 0.57
3f	11.33 ± 0.57	14.00 ± 1.00	13.33 ± 0.57	16.33 ± 0.57	11.66 ± 0.57
3g	12.33 ± 0.57	09.66 ± 0.57	10.33 ± 0.57	09.00 ± 1.00	09.33 ± 0.57
3h	14.00 ± 1.00	06.33 ± 0.57	14.00 ± 1.00	13.33 ± 1.52	13.00 ± 1.00
Control	-	-	-	-	-
Standard	24.33 ± 0.57	22.00 ± 1.00	28.33 ± 1.52	21.66 ± 0.57	22.33 ± 1.52

Results were expressed as Mean ± S.D. (n = 3), "-" indicates no zone of inhibition.

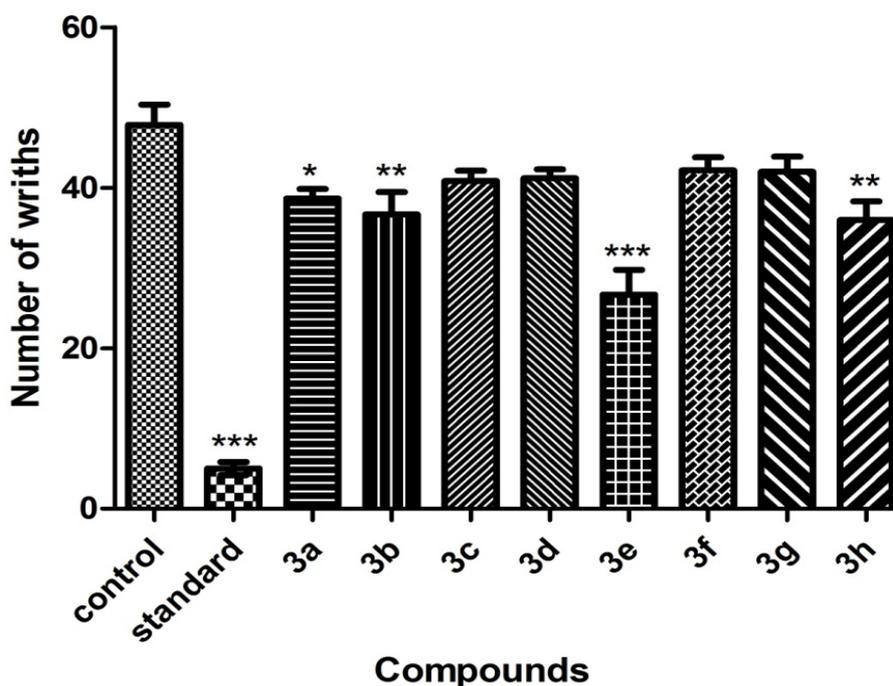


Fig.1: Effects of the synthesized compounds on acetic acid induced writhing in mice.

Results were expressed as Mean ± SEM (n = 6). *p < 0.05, **p < 0.01, *** p < 0.001 as compared to control (One way ANOVA followed by Dunnet's multiple comparison test).

Healthy Swiss albino mice (20-30 gm) were placed into individual restraining cages. The animals were then allowed to adapt in the cages for 30 minutes before testing. Writhing was induced in mice by administration of 0.6% acetic acid (10 ml/kg body weight, i.p.). The numbers of writhes were calculated over the period of 20 min after acetic acid injection. A writh is indicated by an abdominal constriction followed by full extension of hind limb. The data represents the total numbers of writhes observed over the 20 min period (Fig-1).

RESULTS AND DISCUSSION

The physical and spectral data proved the structure and purity of the synthesized compounds. The synthesized compounds were evaluated for *in-vitro* antibacterial activity by cup plate method. The results were summarized in Table-3 including the activity of standard. The compound 3e exhibited highest activity against *E. coli*, *S. epidermidis* and *P. vulgaris*. It has also been observed that compound 3d showed highest activity against *S. aureus*. But the activity was less than the standard drug Tetracycline.

The analgesic activity of the synthesized compounds was evaluated using chemical method. Acetic acid induced writhing test used for detecting both central and peripheral analgesia. Intraperitoneal administration of acetic acid releases prostaglandins and mediators like PGE₂ and PGF_{2 α} and their levels were increased in the peritoneal fluid of the acetic acid induced mice [12]. The compound 3e was found to be significant ($p < 0.001$) in reducing the number of wriths. The compounds 3b and 3h were also found significant ($p < 0.01$) in reducing the number of wriths, but the activity was comparatively less than that of 3e. The standard drug Indomethacin was found to be more potent than the test compounds (Fig.1).

CONCLUSION

From the results, it could be concluded that all the synthesized compounds were effective against both gram positive and gram negative microorganisms shows broad spectrum of antibacterial activity. The compound 3e was found to be most effective against *E. coli*, *S. epidermidis* and *P. vulgaris* and significant analgesic activity in the acetic acid induced writhing in mice; it might be due to the presence of amino group.

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