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Research Article

Synthesis and Biological Evaluation of Some Novel Substituted 1,3,4 –Aryl Oxadiazole Derivatives

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Abstract

The search for potent bioactive agents in pharmaceutical industry has been directed towards the nitrogen containing heterocycles. In recent days the researchers think about synthesis of bridged derivatives of nitrogen containing heterocycles. The present study reports the synthesis of a library new 1,3,4-Aryl oxadiazole derivatives. The structures of newly synthesized compounds were established using IR, ^{1}H-NMR, Mass and elemental analysis. The newly synthesized compounds were screened for antimicrobial activity using cup-plate agar diffusion method some of the compounds shows promising antibacterial and antifungal activity. Also subjected for in-vitro anti-inflammatory activity using protein denaturation method. Some of the compounds show significant anti-inflammatory activity.

Keywords: 1,3,4-aryl-oxadiazole; Anti-microbial activity; Anti-inflammatory activity; Protein denaturation

Introduction

Mefenamic acid and Diclofenac are the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which are mostly useful for the treatment of pain and threshold. It mostly acts through the inhibition of prostaglandin synthesis by inhibition of Cyclooxygenase (COX). It also exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis. The long-term use of this agents may lead to the development of gastrointestinal ulceration, bleeding and in some cases renal disorders. Chronic use of non-steroidal anti-inflammatory drugs may elicit the appreciable gastro-intestinal toxicity. With the aim of improving safety, profile of NSAIDs chemical modification on these agents had been carried out. It has also been reported that compounds containing some substituted 1,3,4-aryl-oxadiazole moiety possess various biological activities likes antimicrobial activity [1], Anti-inflammatory activity [2], GOT, GPT AND c-GT inhibitory activity [3], Anti-cancer activity [4], Haemolytic activity [5], Antioxidant activity [6], Inhibitors of GSK-3b Kinase [7], Monoamine Oxidase (MAO) inhibitors [8], Anti-tubercular activity [9], Tubulin inhibitors [10], Lipoxygenase inhibitors [11], etc. By considering the above facts in this research, we had replaced the carboxylic acid moiety of Mefenamic acid and Diclofenac by substituted 1,3,4- aryl Oxadiazoles.

Materials and Methods

Material

All the chemicals required for the synthesis were purchased from Modern science, Nashik and are of AR grade.

Methods

***In-vitro* anti-inflammatory activity**

Inhibition of protein denaturation

The standard drug and synthesized compounds were dissolved in minimum quantity of Dimethyl Formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test solution (1mL) containing different concentrations of drug was mixed with 1 mL of 1mM albumin solution in phosphate buffer and incubated at 27° + 1°C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60° + 1°C in water bath for 10 min. After cooling, the turbidity was measured at 660 nm (UV-Visible Spectrophotometer). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average is taken. The Ibuprofen was use as standard drug. The percentage inhibition of denaturation was calculated by using following formula.

$$\% \text{ of Inhibition} = 100 \times [1 - V_t / V_c]$$

Where,

V_t = Mean absorbance of test sample.

V_c = Mean absorbance of control

Antibacterial activity

Anti-bacterial study was carried out by using Cup-plate Agar diffusion method. The synthesized derivatives were tested *in vitro* for their anti-bacterial activity against *E.coli* (NCTC 10418), *S. Aureus* (NCTC 6571) and *B. subtilis*, which are pathogenic to human beings. Leavofloxacin had been used as a standard drug.

Anti-Fungal activity

Anti-fungal activity was carried out by using Cup-Plate Agar diffusion method using nutrient agar as a culture media. The synthesized compounds were tested against *Candida albicans* (ATCC 10231) and *Aspergilus niger* (ATCC 16404). Amphotericin B had been used as a standard drug.

The synthesized compounds were dissolved in DMF and activities were carried out at a concentration of 200 µg/ml.

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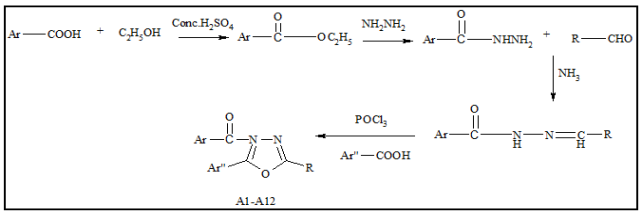

A1-A12

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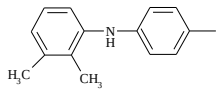
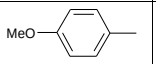
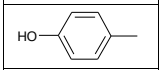
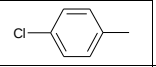
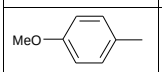
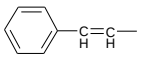
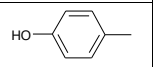
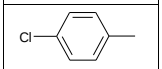
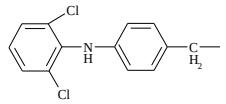
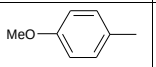
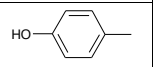
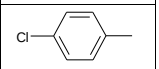
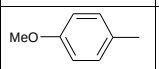
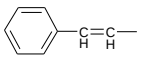
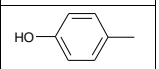
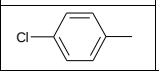
A_1			
A_2			
A_3			
A_4			
A_5			
A_6			
A_7			
A_8			
A_9			
A_{10}			
A_{11}			
A_{12}			

Scheme:

Experimental

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, DMSO d6 as solvent and TMS as internal standard. Combustion analyses were found to be within the limits of permissible errors.

Synthesis of Schiff's bases from acid hydrazide and aromatic aldehyde: 0.01 mole of an acid hydrazide was dissolved in 10 ml of water along with little ammonia and stirred continuously with drop wise addition of 0.01 moles an aromatic aldehyde until a solid mass is obtained. Filter the precipitate and recrystallized from methanol [12].

Synthesis of 1,3,4-aryl Oxadiazoles from Schiff's bases (A_1-A_{12}): 0.01 mole of an aromatic acid was dissolved in $POCl_3$ in a fuming cupboard with continuous stirring until a uniform solution had been formed. After which 0.01 mole a schiffs base is added and temperature of a reaction mixture raised up to 150˚C reflux continued for 2 hrs. Cooled and product is reprecipitated with addition of sodium bicarbonate and recrystallized using methanol to offer title compounds. Purity of synthesized compounds was checked using TLC. (Mobile phase: Toluene: methanol-3:1) [13,14].

Spectral data

Spectral Data: A_1: IR (cm^{-1}) KBr disc: 3250.15 –NH str.; 3256.23 –OH str.; 3002.58 Ar-CH str.; 2854.36 –CH3 str.; 1684.69 –CONH str.; 1556.24 –C=N str.; 1120.36 –C-O-C str.; ^{1}H-NMR (ppm): 6.4-7.2 15H of phenyl; 6.0 1H of 1,3,4-oxadiazole; 5.4 1H of –OH; 5.2 1H of –NH; 1.2-2.6 9H of $–CH_3$, m/e (100%): 493.

A_2: IR (cm^{-1}) KBr disc: 3260.25 –NH str.; 3185.36 –OH str.; 2986.37 Ar-CH str.; 2834.29 –CH3 str.; 1689.28 –CONH str.; 1564.32 –C=N str.; 1089.25 –C-O-C str.; ^{1}H-NMR (ppm): 6.2-7.8 15H of phenyl; 6.2 1H of 1,3,4-oxadiazole; 5.6 2H of –OH; 5.0 1H of –NH; 1.2-2.6 6H of $–CH_3$, m/e (100%): 479.

A_3: IR (cm^{-1}) KBr disc: 3245.25 –NH str3220.23 –OH str.; 3000.14 Ar-CH str.; 2810.37 –CH3 str.; 1685.23 –CONH str.; 1575.24 –C=N str.; 1059.51 –C-O-C str.; ^{1}H-NMR (ppm): 6.1-7.6 15H of phenyl; 6.1 1H of 1,3,4-oxadiazole; 5.4 2H of –OH; 4.8 1H of –NH; 0.8-1.6 6H of $–CH_3$, m/e (100%): 497.

A_4: IR (cm^{-1}) KBr disc: 3245.20 –NH str.; 3110.28 –CH=CH str.; 3025.14 Ar-CH str.; 2836.79 –CH3 str.; 1680.24 –CONH str.; 1556.29 –C=N str.; 1060.58 –C-O-C str.; ^{1}H-NMR (ppm): 6.4-7.8 16H of phenyl; 6.2-6.4 2H of –CH=CH; 6.0 1H of 1,3,4-oxadiazole; 5.0 1H of –NH; 2.1-3.8 9H of $–CH_3$, m/e (100%):503.

A_5: IR (cm^{-1}) KBr disc: 3240.27 –NH str.; 3220.28 –OH str.; 3125.86 –CH=CH str.; 2984.36 Ar-CH str.; 2815.34 –CH3 str.; 1687.24 –CONH str.; 1575.69 –C=N str.; 1035.28 –C-O-C str.; ^{1}H-NMR (ppm): 6.2-7.6 16H of phenyl; 6.2-6.4 2H of –CH=CH; 6.0 1H of 1,3,4-oxadiazole; 5.4 1H of –OH; 5.0 1H of –NH; 2.1-2.6 6H of $–CH_3$, m/e (100%): 489.

A_6: IR (cm^{-1}) KBr disc: 3250.48 –NH str.; 3184.26 –CH=CH str.; 3025.38 Ar-CH str.; 2826.38 –CH3 str.; 1690.27 –CONH str.; 1558.34 –C=N str.; 1039.34 –C-O-C str.; 987.25 –C-Cl bend ^{1}H-NMR (ppm): 6.4-7.8 16H of phenyl; 6.2-6.4 2H of –CH=CH; 6.2 1H of 1,3,4-oxadiazole; 5.0 1H of –NH; 2.0-2.6 6H of $–CH_3$, m/e (100%): 532.

A_7: IR (cm^{-1}) KBr disc: 3286.84 –NH str.; 3220.54 –OH str.; 3058.48 Ar-CH str.; 2856.37 –CH3 str.; 1694.25 –CONH str.; 1556.32 –C=N str.; 1025.39 –C-O-C str.;965.38 –C-Cl bend ^{1}H-NMR (ppm): 6.2-7.8 15H of phenyl; 6.2 1H of 1,3,4-oxadiazole; 5.4 1H of –OH; 5.0 1H of –NH; 1.2-1.6 5H of $–CH_3$, m/e (100%): 548.

A_8: IR (cm^{-1}) KBr disc: 3265.28 –NH str.; 3226.48 –OH str.; 3012.35 Ar-CH str.; 2825.36 –CH3 str.; 1686.26 –CONH str.; 1570.39 –C=N str.; 1070.38 –C-O-C str.;960.35 –C-Cl bend 1H-NMR (ppm): 6.4-7.8 15H of phenyl; 6.0 1H of 1,3,4-oxadiazole; 5.6 2H of –OH; 5.0 1H of –NH; 1.2-1.6 2H of $–CH_2$, m/e (100%): 534.

A_9: IR (cm^{-1}) KBr disc: 3265.24 –NH str.; 3225.69 –OH str.; 2986.37 Ar-CH str.; 2830.35 –CH3 str.; 1684.38 –CONH str.; 1572.35 –C=N str.; 1085.34 –C-O-C str.;968.35 –C-Cl bend ^{1}H-NMR (ppm): 6.4-7.6 15H of phenyl; 6.0 1H of 1,3,4-oxadiazole; 5.4 1H of –OH; 5.0 1H of –NH; 1.2-1.4 2H of $–CH_2$, m/e (100%): 552.

A_{10}: IR (cm^{-1}) KBr disc: 3245.68 –NH str.; 3226.35 –CH=CH

Table 1: Analytical data of synthesized compounds (A_1-A_{12}).

Comp. Code	Molecular formula	Mole. Wt.	M.P. (˚C)	Elemental analysis Found (Cald.)			Rf Value	% Yield
				C	H	N		
A_1	$C_{30}H_{27}N_3O_4$	493.6	271-273	73.01 -72.89	5.51-5.21	7.51 -7.23	0.48	54
A_2	$C_{29}H_{25}N_3O_4$	479.5	236-241	72.64 -72.38	5.25-4.96	8.76 -8.39	0.61	51
A_3	$C_{29}H_{24}ClN_3O_3$	498	238-242	69.95 -69.68	4.86-4.39	8.44 -8.25	0.64	62
A_4	$C_{32}H_{29}N_3O_3$	503.6	268-273	76.32 -76.03	5.8-5.58	8.34 -8.13	0.49	64
A_5	$C_{31}H_{27}N_3O_3$	489.6	301-305	76.05 -75.89	5.56-5.28	8.58 -8.31	0.58	68
A_6	$C_{32}H_{28}ClN_3O_2$	532	318-323	73.62 -73.26	5.41-5.12	8.05 -7.86	0.61	64
A_7	$C_{29}H_{23}C_{l2}N_3O_4$	548.4	308-313	63.51 -63.21	4.23-3.98	7.66 -7.38	0.6	78
A_8	$C_{28}H_{21}Cl_2N_3O_4$	534.4	287-293	62.93 -62.59	3.96-3.68	7.86 -7.64	0.54	58
A_9	$C_{28}H_{20}Cl_3N_3O_3$	552.9	309-315	60.83 -60.59	3.65-3.29	7.6 -7.38	0.57	53
A_{10}	$C_{31}H_{25}Cl_2N_3O_3$	558.5	278-283	66.67 -66.31	4.51-4.25	7.52 -7.21	0.48	57
A_{11}	$C_{30}H_{23}Cl_2N_3O_3$	544.4	272-277	66.18 -65.98	4.26 -3.98	7.72 -7.28	0.57	59
A_{12}	$C_{30}H_{22}Cl_3N_3O_2$	562.9	269-273	64.02-63.85	3.94 -3.58	7.47 -7.14	0.53	61

str.; 3025.69 Ar-CH str.; 2846.38 –CH3 str.; 1684.37 –CONH str.; 1576.34 –C=N str.; 1065.48 –C-O-C str.;967.28 –C-Cl bend ^{1}H-NMR (ppm): 6.2-7.8 16H of phenyl; 6.2-6.6 2H of –CH=CH; 6.2 1H of 1,3,4-oxadiazole; 5.4 1H of –OH; 5.0 1H of –NH; 1.2-1.6 5H of $-CH_3$, m/e (100%): 558.

A_{11}: IR (cm^{-1}) KBr disc: 3246.85 –NH str.; 3235.36 –CH=CH str.; 3226.34 –OH str.; 3025.61 Ar-CH str.; 2856.30 –CH3 str.; 1685.64 –CONH str.; 1565.32 –C=N str.; 1075.30 –C-O-C str.; 986.25 –C-Cl bend ^{1}H-NMR (ppm): 6.4-7.8 16 H of phenyl; 6.4-6.6 2H of –CH=CH; 6.2 1H of 1,3,4-oxadiazole; 5.4 1H of –OH; 5.0 1H of –NH; 1.2-1.4 2H of $-CH_2$, m/e (100%): 544.

A_{12}: IR (cm^{-1}) KBr disc: 3255.68 –NH str.; 3247.68 –CH=CH str.; 3025.64 Ar-CH str.; 2810.34 –CH3 str.; 1687.32 –CONH str.; 1576.24 –C=N str.; 1085.25 –C-O-C str.; 976.38 –C-Cl bend ^{1}H-NMR (ppm): 6.2-7.6 16 H of phenyl; 6.4-6.6 2H of –CH=CH; 6.2 1H of 1,3,4-oxadiazole; 5.0 1H of –NH; 1.2-1.4 2H of $-CH_2$, m/e (100%): 562.

Results and Discussion

The structures of the synthesized derivatives of 1, 3, 4-aryl-oxadiazoles (A_1-A_{12}) were established by IR, ^{1}H-NMR, Mass spectra and elemental analysis. The purity of synthesized compounds had been checked on TLC plates using Toluene: Methanol (3:1) as a mobile phase. The IR, ^{1}H-NMR and Mass data reported in manuscript under section of spectral data. The IR spectra shows absorption bands like 3250-3280cm-1 (-NH str.), 3220-3250 cm-1 (-OH str.), 2980-3050 cm-1 (Aromatic –CH str.), 2840-2880 cm^{-1} (aliphatic –CH str.), 1685-1695 cm^{-1} (-CONH str.), 1550-1585 cm^{-1} (-C=N str.), 1030-1080 (-C-O-C str.) which are characteristic feature of 1,3,4-aryl-oxadiazoles. 1H-NMR shows the peaks in 6.4-7.8 (Aromatic H), 6.0-6.2 (H of 1,3,4-oxadiazole), 5.4-5.6 (H of –OH group), 5.0 (H of –NH), 1.2-2.6 (H of $-CH_3$ substituent of phenyl ring).

The synthesized compounds were subjected for in vitro anti-inflammatory activity. Out of twelve compounds, the compounds A_2, A_4 and A_{10} had shown significant anti-inflammatory activity. The structural features of the compounds like presence of electron donating group likes $-CH_3$, $-OCH_3$ along with hydroxyl (-OH) group was thought to increase the biological activity. While other compounds which possess electron withdrawing substituents like –Cl, -OH might be responsible for decrease in activity. Some derivatives which contains a –CH=CH linkage due to impartation of unsaturation character in the compounds also responsible for increase in biological activities.

The synthesized compounds were subjected for anti bacterial activity. Out of twelve compounds the compounds A_3, A_4,A_5 and A_{10} had shown significant antibacterial activity. The structural features of the compounds like presence of electron donating group likes $-CH_3$, $-OCH_3$ along with hydroxyl group was thought to increase the biological activity. While other compounds which possess electron withdrawing substituents like –Cl, might be responsible for decrease in activity. In case of anti fungal compounds A_1, A_2,A_6 and A_{11} shows significant activity as they posses higher percentage of electron donating groups like $-CH_3$, $-OCH_3$ which might increase the antifungal activity of these derivatives beside this these derivatives also contains a chloride linkage which increases the binding of drugs to the receptors this also responsible for increase in biological activities. Mostly Diclofenac derivatives shows significant antimicrobial activity as it brings inhibition of bacterial DNA synthesis.

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