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SYNTHESIS, CHARACTERIZATION AND IN VITRO ANTI-INFLAMMATORY ACTIVITY OF SOME SUBSTITUTED 1, 3, 4–ARYL OXADIAZOLE DERIVATIVES

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ABSTRACT

A new series of substituted 1,3,4-aryl Oxadiazoles were synthesized by standard methods. The synthesized compounds were scaled for their spectral studies and the structures of the synthesized compounds were confirmed by IR, NMR, Mass and CHN analysis.The newly synthesized compounds were subjected to anti-inflammatory activity by in vitro protein denaturation method. Some of the synthesized compounds have shown promising anti-inflammatory activities against the standard reference Ibuprofen.

KEYWORDS: 1, 3, 4-aryl-oxadiazole, 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.

% of Inhibition = 100 X [1- Vt / Vc]

Where,

Vt = Mean absorbance of test sample.

Vc = Mean absorbance of control

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 ḍ6 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[12]

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.

Synthesis of 1, 3, 4-aryl Oxadiazoles from Schiff's bases (A_1-A_{12})[13,14]

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 150^0C 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).

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 –CH_3 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 –CH_3 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 –CH_3 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 $–CH_3$ 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 $–CH_3$ 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 $–CH_3$ 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 $–CH_3$ 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 $–CH_3$ str.; 1686.26 –CONH str.; 1570.39 –C=N str.; 1070.38 –C-O-C str.;960.35 –C-Cl bend **^{1}H-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 $–CH_3$ 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 str.; 3025.69 Ar-CH str.; 2846.38 $–CH_3$ 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 –CH_3 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.

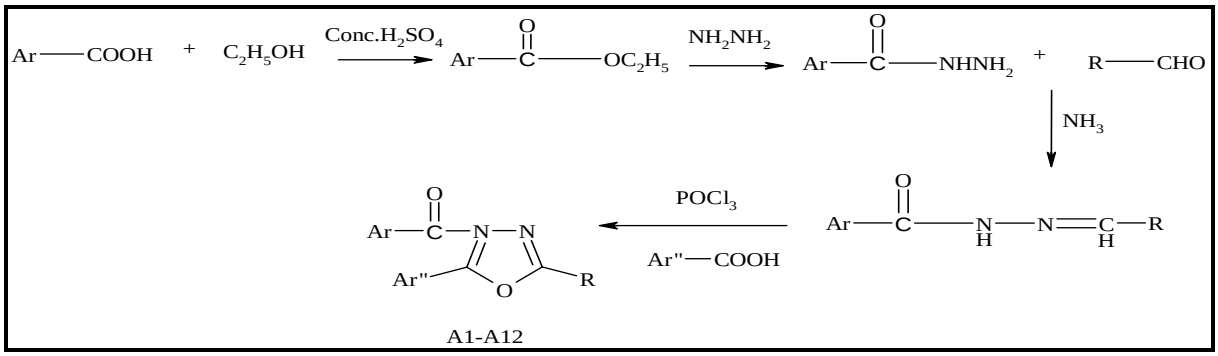
A_{12}: IR (cm^{-1}) KBr disc: 3255.68 –NH str.; 3247.68 –CH=CH str.; 3025.64 Ar-CH str.; 2810.34 –CH_3 str.; 1687.32 –CONH str.; 1576.24 –C=N str.; 1085.25 –C-O-C str.; 976.38 –C-Cl bend **^{1}H-NMR (ppm):** 6.2-7.6 16 H of phenyl; 6.4-6.6 2H of –CH=CH; 6.2 1H of 1,3,4-oxadiazole; 5.0 1H of –NH; 1.2-1.4 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. ^{1}H-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.

Scheme



A1-A12

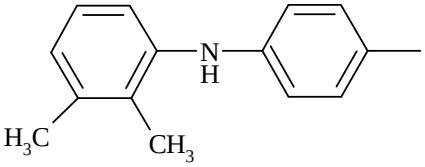
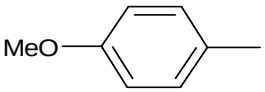
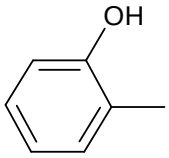
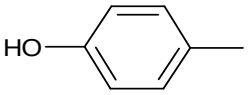
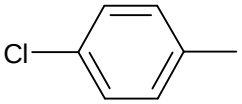
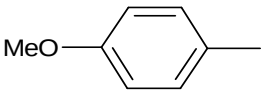
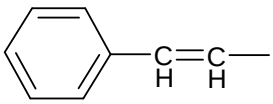
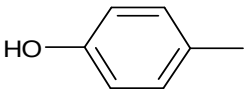
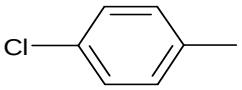
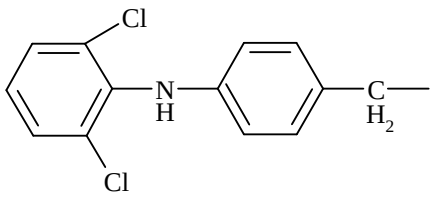
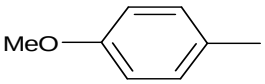
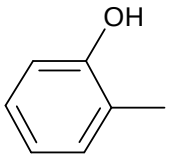
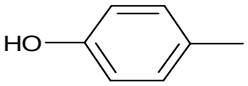
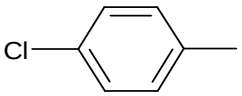
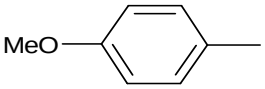
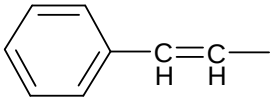
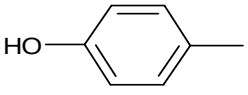
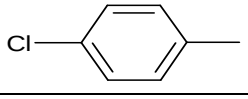
Comp. Code	Ar	R	Ar’
A_1			
A_2			
A_3			
A_4			
A_5			
A_6			
A_7			
A_8			
A_9			
A_{10}			
A_{11}			
A_{12}			

Table no. 01: Analytical data of synthesized compounds (A_1-A_{12})

Comp.code	Molecular formula	Mole. Wt.	M.P. (^{0}C)	Elemental analysis Found (Cald.)			Rf Value	% Yield
				C	H	N		
A_1	$C_{30}H_{27}N_3O_4$	493.57	271-273	73.01 (72.89)	5.51 (5.21)	7.51 (7.23)	0.48	54
A_2	$C_{29}H_{25}N_3O_4$	479.54	236-241	72.64 (72.38)	5.25 (4.96)	8.76 (8.39)	0.61	51
A_3	$C_{29}H_{24}ClN_3O_3$	497.99	238-242	69.95 (69.68)	4.86 (4.39)	8.44 (8.25)	0.64	62
A_4	$C_{32}H_{29}N_3O_3$	503.61	268-273	76.32 (76.03)	5.80 (5.58)	8.34 (8.13)	0.49	64
A_5	$C_{31}H_{27}N_3O_3$	489.58	301-305	76.05 (75.89)	5.56 (5.28)	8.58 (8.31)	0.58	68
A_6	$C_{32}H_{28}ClN_3O_2$	532.02	318-323	73.62 (73.26)	5.41 (5.12)	8.05 (7.86)	0.61	64
A_7	$C_{29}H_{23}C_{l2}N_3O_4$	548.43	308-313	63.51 (63.21)	4.23 (3.98)	7.66 (7.38)	0.60	78
A_8	$C_{28}H_{21}Cl_2N_3O4$	534.40	287-293	62.93 (62.59)	3.96 (3.68)	7.86 (7.64)	0.54	58
A_9	$C_{28}H_{20}Cl_3N_3O_3$	552.85	309-315	60.83 (60.59)	3.65 (3.29)	7.60 (7.38)	0.57	53
A_{10}	$C_{31}H_{25}Cl_2N_3O_3$	558.47	278-283	66.67 (66.31)	4.51 (4.25)	7.52 (7.21)	0.48	57
A_{11}	$C_{30}H_{23}Cl_2N_3O_3$	544.44	272-277	66.18 (65.98)	4.26 (3.98)	7.72 (7.28)	0.57	59
A_{12}	$C_{30}H_{22}Cl_3N_3O_2$	562.89	269-273	64.02 (63.85)	3.94 (3.58)	7.47 (7.14)	0.53	61

Table no: 02: In-vitro anti-inflammatory activity of Synthesized compounds (A_1-A_{12})

Treatment	Mean increase in paw volume (ml)±SEM									
	Time in minute									
	0	% inhibition	30	% inhibition	60	% inhibition	90	% inhibition	120	% inhibition
Carrageenan (Control	0.24±0.01		0.48±0.03		0.78±0.09		0.85±0.12		0.89±0.14	
Ibuprofen	0.24±0.03	0	0.31±0.07	35.41	0.30±0.07	61.53	0.27±0.06	68.23	0.26±0.13	70.78
A_1	0.24±0.01	0	0.34±0.03	29.16	0.35±0.01	55.12	0.33±0.01	61.17	0.30±0.01	66.29
A_2	**0.24±0.02**	**0**	**0.33±0.03**	**31.25**	**0.32±0.01**	**58.97**	**0.30±0.01**	**64.70**	**0.28±0.02**	**68.53**
A_3	0.23±0.01	4.16	0.34±0.01	29.16	0.38±0.01	51.28	0.38±0.02	55.29	0.32±0.02	64.04
A_4	**0.24±0.02**	**0**	**0.33±0.01**	**31.25**	**0.33±0.02**	**57.69**	**0.31±0.02**	**63.52**	**0.29±0.01**	**67.41**
A_5	0.23±0.01	4.16	0.32±0.01	33.33	0.34±0.01	56.41	0.32±0.01	62.35	0.30±0.02	66.29
A_6	0.24±0.02	0	0.35±0.01	27.08	0.39±0.02	50	0.38±0.01	55.29	0.32±0.03	64.04
A_7	0.23±0.02	4.16	0.33±0.01	31.25	0.35±0.02	55.12	0.34±0.02	60	0.30±0.01	66.29
A_8	0.24±0.02	0	0.33±0.02	31.25	0.35±0.03	55.12	0.31±0.02	63.52	0.30±0.02	66.29
A_9	0.23±0.03	4.16	0.33±0.02	31.25	0.34±0.01	56.41	0.32±0.02	62.35	0.30±0.02	66.29
A_{10}	**0.24±0.01**	**0**	**0.32±0.02**	**33.33**	**0.34±0.02**	**56.41**	**0.33±0.01**	**61.17**	**0.29±0.01**	**67.41**
A_{11}	0.24±0.02	0	0.34±0.03	29.16	0.34±0.03	56.41	0.35±0.01	58.82	0.31±0.02	65.16
A_{12}	0.23±0.03	4.16	0.33±0.04	31.25	0.35±0.01	55.12	0.33±0.02	61.17	0.30±0.03	66.29

CONCLUSION

The present study is innovative and novel. Total 12 new compounds are synthesized and structures of these are confirmed by IR, NMR, mass and elemental analysis. These compounds were screened for anti-inflammatory activity by in vitro protein denaturation method. Some of these derivatives have shown promising activity. With suitable molecular modification and manipulations these compounds will prove as potent anti-inflammatory compounds in future.

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