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Synthesis and characterization of some newer 1,3,4- oxadiazoles

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ABSTRACT

Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 4-chlorobenzylidine- 1,3,4-oxadiazoles are associated with diverse biological activities by the virtue of -N = C-O- grouping. In the view of wide range of biological properties associated with 1,3,4-oxadiazole, we have synthesized substituted derivatives of 1,3,4-oxadiazole.

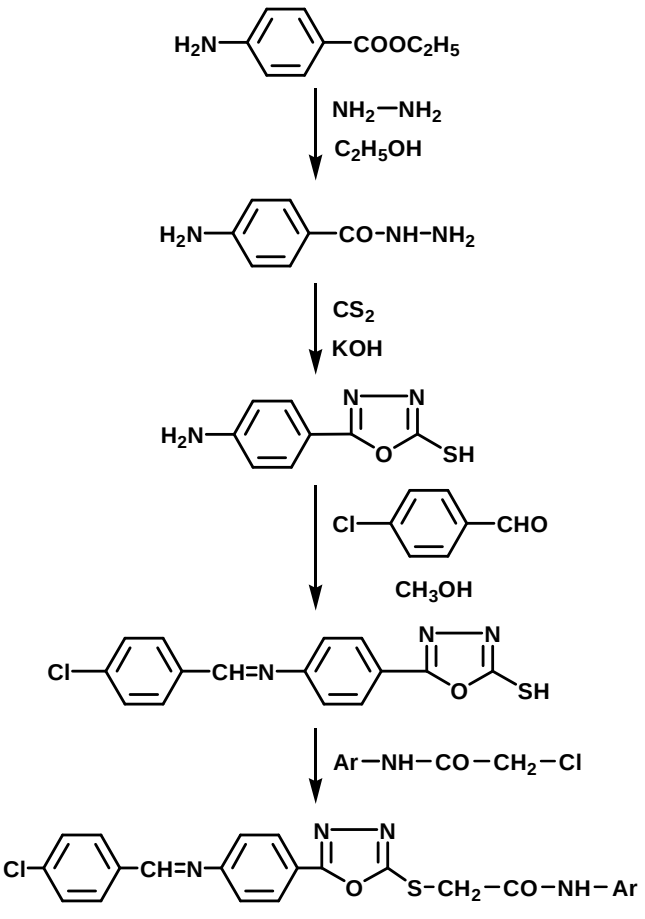
INTRODUCTION

This work aims at the development of a newer isoniazid-based oxadiazole ring system. 1,3,4-Oxadiazole derivatives show a broad spectrum of biological activities, which include analgesic and anti-inflammatory, antimicrobial, anticonvulsant, antifungal, anticancer, antimycobacterial[1,2], etc. The research envisages a meaningful exploration of this lead molecule for novel analgesic, anti-inflammatory activities with minimum toxicity and high potency[5]. The lead compound was structurally modified by incorporating various substitutions at the second and fifth position of the heterocyclic ring system. From a review of the literature it is clear that 2,5 disubstituted 1,3,4-oxadiazole derivatives of oxadiazole possess remarkable analgesic, anti-inflammatory activity[5,6].

EXPERIMENTAL

Chemicals were procured from E. Merck (India) and S. D. Fine Chemicals (India). Melting points were taken in open capillary tubes and are uncorrected. Microanalysis of the compounds was done on a Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA) and

REACTION SCHEME



the values were found within ± 0.4 % of the theoretical values. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (*n*max in cm–1) (Perkin-Elmer, USA) and 1H NMR spectra were recorded on a Varian E-360 MHz (Perkin-Elmer, USA) or Bruker spectrometer DPX-300MHz (Bruker, Germany) with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS-D 300 instrument (Jeol, Japan) fitted with a JMS 2000 data system at 70 eV. Spectral data are consistent with the assigned structures. The progress of the reactions was monitored on silica gel G plates using iodine vapour as visualizing agent. All solvents were distilled prior to use.

TABLE 1

Sr.No.	R	Molecular Formula	M.V.	Yield %	M.P.°C	% of N		% of S	
						Found	Reqd.	Found	Reqd.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	-3-CH_3-C_6H_4	$C_{24}H_{19}O_2N_4SCI$	462.5	43	150	12.04	12.10	6.89	6.91
2	-4-CH_3-C_6H_4	$C_{24}H_{19}O_2N_4SCl$	462.5	46	138	12.12	12.10	6.92	6.91
3	-2-OCH_3-C_6H_4	$C_{24}H_{19}O_3N_4SCl$	478.5	50	162	11.66	11.70	6.70	6.68
4	-3-OCH_3-C_6H_4	$C_{24}H_{19}O_3N_4SCl$	478.5	53	198	11.72	11.70	6.65	6.68
5	-4-OCH_3-C_6H_4	$C_{24}H_{19}O_3N_4SCl$	478.5	42	175	11.71	11.70	6.66	6.68
6	-2-4$(Cl)_2$-C_6H_3	$C_{23}H_{15}O_2N_4SCl_3$	517.5	45	152	10.79	10.82	6.15	6.18
7	-2-4-$(CH_3)_2$-C_6H_3	$C_{25}H_{21}O_2N_4SCl$	477.5	42	161	11.71	11.72	6.73	6.70
8	-2-NO_2-4-Cl- C_6H_3	$C_{23}H_{15}O_4N_4SCl_2$	514	41	149	11.90	11.89	6.20	6.22
9	-2-Cl-4-NO_2- C_6H_3	$C_{23}H_{15}O_4N_4SCl_2$	514	47	178	11.85	11.89	6.25	6.22

Preparation of p-amino benzoyl hydrazine

Benzocaine (33.0 g, 0.2 mole) was dissolved in ethanol (70ml, 95%) with stirring. Hydrazine hydrate (80ml, 99%) was added dropwise and contents were refluxed on waterbath for four hours. Excess of solvent was distilled off and the reaction mixture was cooled to 4-5 ° C. The separated product was filtered, washed with chilled ethanol and dried in oven at 105° C. Recrystallised from ethanol. Yield, 23.5 g; 78% m.p. 209-10 ° C; Found: N, 27.78% $C_7H_9N_3O$; Required: N, 27.81%

Preparation of 5-(4-amino phenyl)-1,3,4-oxadiazol-2-thione

p-Amino benzoyl hydrazine (15.1 g, 0.1 mole) ws dissolved in solution of potassium hydroxide (5.6 g; 0.1 mole) in 100 ml water with constant stirring. Methanol (100 ml) was added dropwise and a clear solution was obtained. CS2(6ml, 0.1 mole) was added dropwise with constant stirring. The resulting solution was refluxed for six hours and then concentrated. Residual solution was poured in water and filtered. The filtrate was acidified with dilute HCl. The product thus obtained ws filtered washed with water and dried. Recrystallised from ethanol. Yield, 16.51 g; 86 % m.p. 259-10 ° C; Found: N, 21.80% ; S 16.60% C_8H_7 ON_3S; Required: N, 21.87% S 16.66%

Preparation of 5-[4-(4-chloro benzylidin)-amino] – phenyl 1,3,4-oxadiazole -2-thione

5-(4-Amino phenyl)-1,3,4-oxadiazole – 2 – thione (19.2 g; 0.1 mole) was dissolved in spirit. p-chloro benzaldehyde (14.05g ; 0.1 mole) was added dropwise with constant strring. Resultant solution was refluxed on a waterbath for three hours. Excess of solvent was distilled off. The contents were allowed to cool at room temperature. The separated product was filtered, washed with water and dried. Recrystallized from ethanol. Yield, 25.25 g; 81 % m.p. 156 ° C; Found: N, 13.26% ; S 10.09% $C_{15}H_{10}$ ON_3SCl; Required: N, 13.31% S 10.14%

Preparation of 2-[(N (3–Methyl phenyl) carboxamido-methyl thio)]-5- [4- (4- chloro benzylidin) amino] - phenyl 1,3,4-oxadiazole.

5-[4-(4-chloro benzylidin) –amno) –phenyl 1,3,4-oxadiazol-2-thione (3.15 g. 0.01 mole) was dissolved in solution of potassium hydroxide (5 g) in water (20 ml). α- Chloro 4-chloro acetanilide (0.014 mole) was added with constant stirring at 80 ° C. Stirring was con-

tinued and the reaction mixture maintained at 80° C for two hours.

The contents were left overnight. The crystals were filtered. washed with water and dried. Recystallised from ethanol. Yield, 43 % m.p. 150 ° C; Found: N, 12.04% ; S 6.89% $C_{24}H_{19}O_2N_4SCI$; Required: N, 12.10% S 6.91%

Similarly different substituted 1,3,4 – oxadiazoles have been prepared by using substituted α-chloro acetanilide.

CONCLUSIONS

A new class of oxadiazoles was synthesized by cyclization of the terminal carboxylic group of an aroyl propionic acid with the objective to develop better anti-inflammatory and analgesic molecules with or without ulcerogenic activity. The results of biological tests make novel oxadiazoles interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly hold great promise for discovering safer anti-inflammatory agents.

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