SYNTHESIS AND ANTI INFLAMMATORY ACTIVITY OF METHYL 2-(2-(DIALKYLAMINO)ACETAMIDO)BENZOXAZOLE-5-CARBOXYLATE

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ABSTRACT:

A new series of Benzoxazole derivatives were synthesized and the structures of these compounds were confirmed by IR, ^{1}H NMR and their Mass Number confirmed by Mass spectroscopy. The title compounds were screened for anti inflammatory activity. Among these some compounds have shown promising Anti inflammatory activity

Key words: Benzoxazole derivatives, Anti-inflammatory activity, Diclofenac.

1.INTRODUCTION:

Benzoxazoles are important heterocyclic systems with varied biological activities. Benzoxazoles exhibit antimicrobial [Sultan Nacak et al.1997], antiviral [Surendra Bahadur et al.1992], antiallergic [Chem. Abstr. 1992], hypoglycemic [Kenji Arakawa et al. 1997], potential agonists of LH hormones [John J Nestor et al. 1984], anti-histaminic [Yousuke Katsura, et al.1992], herbicidal[Peter Paul Wilhelm et al. 1989], inhibitors of immuno complex induced inflammation[Fortuna Haviv et al. 1988], anthelmintic [R.D. Haugwitz et al, 1982], cytotoxic and antitumor [Osvaldo Cox et al. 1982], and anti inflammatory [David W. Dunwell and Delme Evans, 1977].

Based on the above, we have synthesized some new benzoxazole derivatives in hope of getting pharmacological agents with clinical activity.

2. ANTI INFLAMMATORY ACTIVITY:

The title compounds were screened for anti inflammatory activity by paw edema method [C.A. Winter et al. 1962]. All the compounds (Ia –If) have shown promising anti- inflammatory activity when compared with the standard drug Diclofenac.

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Results expressed as mean S.E, as evaluated by student's't' test, values of p were considered statistically significant

3. EXPERIMENTAL WORK:

Melting points were determined in open capillary tubes and are uncorrected. IR spectras were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. Purity of the compounds was checked on Silica Gel T.L.C plates. ^{1} H NMR spectras were recorded on BRUKER AVANCE II 400 NMR spectrometer.

a) SYNTHESIS OF METHYL 4-HYDROXY-3-NITROBENZOATE (II)

To a solution of aluminium nitrate (40gms) in acetic acid- acetic anhydride (1:1) mixture (160ml), was added an appropriate phenol (I, 40gms) in small portions, while cooling and shaking, occasionally. The reaction mixture was left at room temperature for 1.5 hours while shaking the contents, intermittently to complete the nitration. The resulting brown solution was diluted to complete the nitration. The resulting brown solution was diluted with ice-cold water and acidified with concentrated Nitric acid to get a bulky, yellow precipitate. It was filtered washed with small quantity of methanol and purified by recrystallization from alcohol to get a yellow crystalline solid.

b) SYNTHESIS OF METHYL 3-AMINO-4-HYDROXYBENZOATE (III)

Methyl 4-hydroxy-3-nitrobenzoazte (II, 10 grams) was dissolved in boiling alcohol (50%, 100ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colourless. Then the alcohol was reduced to one-third of its volume by distillation and the residual liquid was triturated with crushed ice. The resulting colourless, shiny product was filtered, washed with cold water and dried in the air. Its purification was effected by recrystallization from benzene to get colourless, shiny scales.

c)SYNTHESIS OF METHYL 2-AMINO BENZOXAZOLE-5-CARBOXYLATE (IV)

1.3 moles of Methyl 3-amino-4-hydroxybenzoate (III) was dissolved in 1lit. Methyl alcohol and cooled the solution to $5^{O}C$ by adding chopped ice.

A cold suspension of 1.5 moles of Cyanogenbromide in 1lit.of water was added over a period of 5min with rapid stirring.

Continued the stirring for 0.75hrs at room temperature, 1.3 moles of solid Sodium bicarbonate in small portions over a period of 1.5 hrs was added to bring the p^{H} 6.5 -7.0. Stirring was continued for another 1hour. The solid was separated by filtration, washed with cold water and recrystallized from ethyl alcohol.

d) SYNTHESIS OF METHYL 2-(2-CHLOROACETAMIDO) BENZOXAZOLE-5-CARBOXYLATE (V)

Methyl 2-aminobenzoxazole-5-carboxylate (IV) was treated with Chloroacetyl chloride. Both Methyl 2-aminobenzoxazole-5-carboxylate (IV) and Chloroacetyl chloride were taken in equimolar ratios and the reaction was refluxed for 5hrs in dry benzene. The reaction mixture was then evaporated and washed first with benzene and then with Petroleum ether.

e) SYNTHESIS OF METHYL 2-{(2-(DIALKYLAMINO)ACETAMIDO)}-BENZOXAZOLE-5-CARBOXYLATE (VI)

To a solution of Methyl 2-(2-chloroacetamido) benzoxazole-5-carboxylate (V) in dry Acetone, N,N-dialkylamine has been added and the reaction mixture was refluxed for 5hrs, the colorless product formed has been recrystallized by suitable solvents.

SPECTRAL DATA:

Ia: IR (cm^{-}) : 3364 (NH), 1683 (C=O), 1616 (C=C), 1442 (C=N), 1284 (C-OC)

^{1}H NMR(δ,ppm) 9.3 (s, 1H, NH) 7.5-8.8 (m, 3H, Ar-H), 3.89 (s, tH, CH_3), 3.29 (1s, 2H, CH_2) , 2.69 (qs, 4H, CH_2), 1.02 (ts, 6H, CH_3)

If: IR (cm^{-}): 3368 (NH), 1682 (C=O), 1610 (C=C), 1442 (C=N), 1283 (C-O-C)

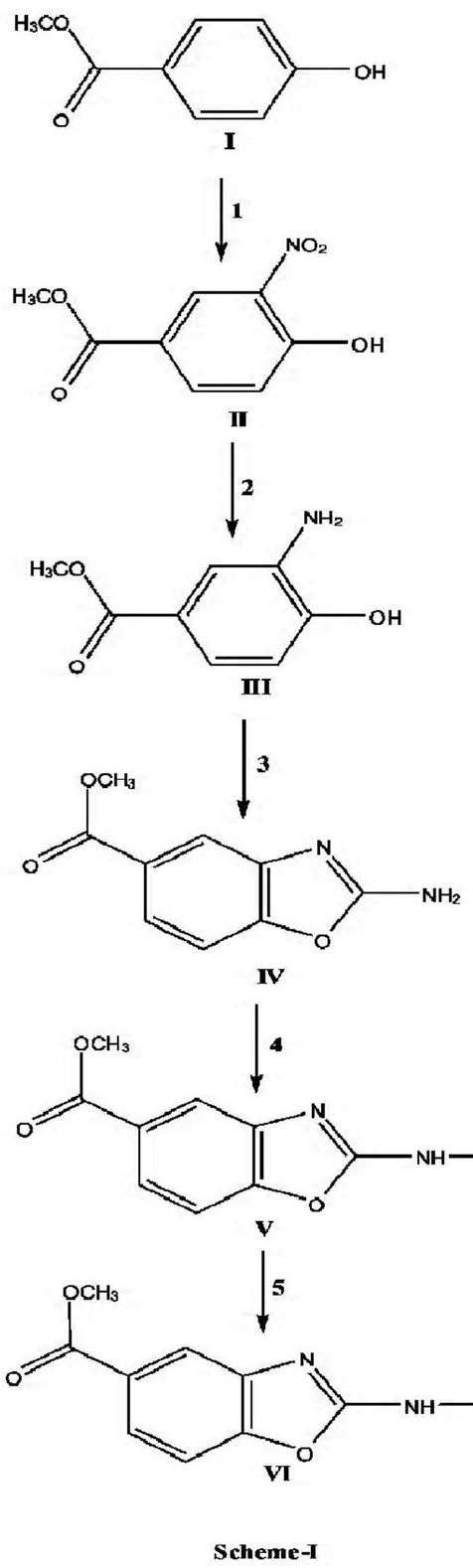
^{1}H NMR: (δ,ppm) 9.0 (s, 1H, NH) 7.2-8.8 (m, 3H, Ar-H), 3.69 (s, 3H, CH_3), 4.09 (1s, 2H, CH_2) , 2.75 (ts, 6H, CH_3)..

4. RESULTS AND DISCUSSION:

In the present work the series of benzoxazole derivatives were synthesized. The synthesized compounds all were characterized by analytical and spectral studies. All the compounds synthesized were screened for anti inflammatory activity against Diclofenac as standard drug. Among all the compounds screened for anti inflammatory activity Ic ,Id and Ie showed good activity.

5.ACKNOWLEDGEMENT:

The author was very thankful to Prof. M.Sarangapani, Principal, University College of Pharmaceutical Sciences, Kakatiya University, and supervisor to carry out this work. Under his supervision I learned a lot.

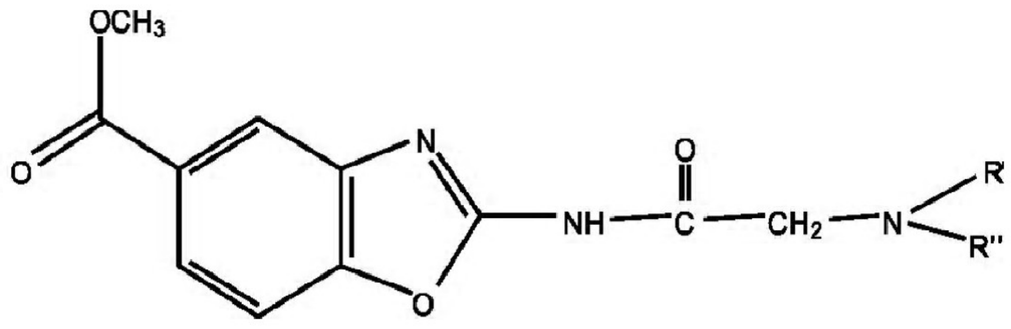


Scheme-I

1) $Al_2(NO_3)_3$ CH_3COOH & $(CH_3CO)_2O$ 2) $Na_2S_2O_4$ – 50% alcohol 3) CNBr – Methanol &Water 4) $ClCH_2COCl$ -Dry Benzne 5) Secondary amine – Dry Acetone

Table-1

Physical data of Methyl 2-{[2-(dialkylamino)acetamido}-benzoxazole-5-carboxylate



S.No	Compound	R^I	R^{II}	Molecular Formula	M.P(^OC)	Yeild (%)
1.	Ia	CH_3	CH_3	$C_{13}H_{15}N_3O_4$	228	67
2.	Ib	C_2H_5	C_2H_5	$C_{15}H_{19}N_3O_4$	239	65
3.	Ic	(CH_2CH_2)	(OCH_2CH_2)	$C_{15}H_{17}N_3O_5$	226	72
4.	Id	(CH_2CH_2)	$(HNCH_2CH_2)$	$C_{15}H_{18}N_4O_4$	198	68
5.	Ie	(CH_2CH_2)	$(CH_2CH_2CH_2)$	$C_{16}H_{19}N_3O_4$	248	75
6.	If	(C_6H_{11})	(C_6H_{11})	$C_{23}H_{31}N_3O_4$	202	71

Table-2

Anti inflammatory activity of Methyl 2-{2-[(dialkylamino)acetamido}-benzoxazole-5-carboxylate

Initial *Mean ±SD) (1.65± 0.1)*	*1hr*		*2hr*		*3hr*		*4hr*	
	Mean ±SD	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*
Control	3.42±0.16	NA	3.57±0.16	NA	3.63±0.1	NA	3.47±0.1	NA
Standard	2.38±0.13	30.40*	2.13± 0.12	40.33*	1.93±0.12	46.83*	1.73± 0.13	50.43*
Ia	3.25±.0.16	4.97	3.10±.0.12	13.16	2.98±0.11	17.90	2.82±0.07	18.73
Ib	3.15±0.16	7.89	3.03±0.15	15.12	2.88±0.14	20.66	2.72±0.13	21.61
Ic	2.98±0.13	12.86	2.83±0.13	20.72	2.72±0.09	25.06*	2.58±0.07	25.64*
Id	2.9±0.11	15.20	2.78±0.07	22.12	2.68±0.07	26.17*	2.55±0.10	26.51*
Ie	2.93±0.15	14.32	2.83±0.1	20.72	2.72±0.07	25.06*	2.57±0.08	25.93*
If	3.35±0.15	2.04	3.28±0.13	12.53	3.13±0.15	13.77	3.05±0.13	12.10

* Significant Protection at P<0.05(n=6) red= Reduction

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