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Synthesis and Anti- Inflammatory Activity of Indole Derivatives

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ABSTRACT

The investigation is concerned with synthesis of new substituted indole derivatives 5a'-5e', 6a'-6e' with the potent anti-inflammatory agent. The structure of all new synthesized compound were identified by spectral (IR, 'HNMR and mass) and elemental (C,H,N,) analysis. The obtained compounds were screened for their anti-inflammatory at the dose of 50mg Kg^{-1} p.o.

Keywords: Indole thiadiazolyl, Oxadizole, Anti- inflammatory activity.

INTRODUCTION

Indole derivatives have been reported to posses different biological and pharmacological activities like anti-inflammatory, CNS depressant, psychotropic activities etc. Indomethacin which is indole derivative has been successfully utilized by the clinical for the treatment of inflammatory disorder like different kind of arthritis. The major problem with this drug taken either orally or subcutaneaously, is gasteric ulceration and hemorrhage probably due to systemic or tropical action. As they are more ulcerogenic when administered orally, the primary insult is due to the inhibition of postaglandin biosynthesis at mucosal level and tropical insult might be due to local irritation caused by high drug concentration and erosive property of carboxylic group. Furthermore, various derivatives of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles of different heterocyclic nuclei are well known to exhibit potent ant-inflammatory activity. These findings prompted us to synthesize a new compound by incorporating 1',3',4'-oxadiazolyl, 1,3,4-thiadiazolyl and pyrazolinyl moieties at 3-position of indole nucleus with a hope to develop better anti-inflammatory agents with lesser side effects.

MATERIALS AND METHODS

The melting points were determined in open capillaries with the help of thermonic melting point apparatus, and are uncorrected. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel-G coated plates. Elemental analysis of all compounds was performed on CarloEraba-1108 elemental analyzed, and result were found within the +0.4% of theoritical values.

Infrared spectra: IR (KBr) were recorded on Perkin Elmer-881 and Pargon-500 FTIR (Perkin Elmar, and v was recorded in cm^{-1}.

Nuclear magnetic resonance: ('H-NMR) spectra were recorded on Bruker DRX-300 FTNMR instrument by using $CDCL_3$ or $DMSOD_6$ as a solvent and tetramethylsilane (TMS) was used as internal reference standard. Chemical shift (δ) values were recorded in ppm.

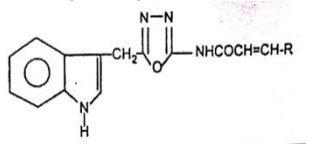
General Procedure for The Preparation of 5-(3'-indolylmethyl)-1,3,4-oxidiazolyl-2-amino-(m-methoxy,p-hydroxypheny) chalkone (5c'). Compound 2-Acetylamino-5-(3'indolylmethyl)-1,3,4-oxadiazole (0.01 mole), in methanol (50 mL), and m-methoxy, p-hydroxybenzaldehyde (0.01 mole) in the presence of 2% NaOH were refluxed for 12 h and the completion of the reaction was monitored on TLC. The reaction mixture were concentrated, cooled and poured into ice water. The separated solid was filtered off and recrystallized from methanol-water to give compound 5c': m.p. 265°C, yield 48% molecular formula $C_{21}H_{18}O_4N_4$(390).

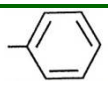
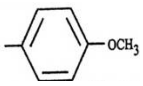
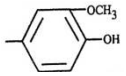
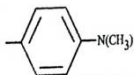
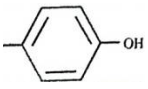
Table 1. Elemental analysis

Element Percentage	Calculated	Found
C	64.62	64.38
H	4.62	4.88
N	14.36	14.72

Spectral Analysis: IR (KBr) v in CM-^{1}:3170 (N-), 3020 (C-H- aromatic), 2930 (C-H alphatic); 1555 (C-C of aromatic ring), 1215 (C-O-C), 1032 (N-N), 1700 (C=O), ^{1}H-NMR ($CDCl_3$) δ in ppm 11.68 (s1H – Ar – OH) 7.70-7.55(m, 8H, Ar-H), 8.20 (s, 1H, NH of indole ring, exchangeable with D_2O (6.90 (s, 2H, CH_2, attached to indole ring), 8.50 (bs, 1H, NHCO, exchangeable with D_2O), 3.40 (s, 3H, -OCH_3.) 5.5 (d, 1H CH=CH-Ar) 6.05 (d, 1H CH=CHCONH).MS :$[M]^+$ at m/z390.

Table 2. Physical and analytical data of 5-(3'-indolylmethyl)-1,3,4-oxadiazolyl-2-aminosubstitutedchalkones (5'a-5'e)



Comp No.	R	M.P (C°)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental Analysis					
						%C		%H		%N	
						Calcd	Found	Calcd	Found	Calcd	Found
5'a		230	50	Ethanol-water	$C_{20}H_{16}O_2N_4$	69.77	69.91	4.65	4.92	16.28	16.47
5'b		232	60	DMF	$C_{21}H_{18}O_3N_4$	67.38	67.09	4.81	4.53	14.97	14.63
5'c		265	48	Methanol-water	$C_{20}H_{16}O_4N_4$	64.62	64.38	4.62	4.88	14.36	14.72
5'd		290	56	Methanol-water	$C_{22}H_{21}O_2N_5$	68.22	68.45	5.43	5.22	18.09	18.32
5'e		270	45	Acetic acid	$C_{20}H_{16}O_3N_4$	66.67	66.84	4.44	4.15	15.56	15.78

General Procedure for The Preparation of 1-acetyl-5(m-methoxy, p-hydroxphenyl)3-[5'-(3"-indolelmethyl)-2'-amino-1',3',4'-oxadiazol-2'N-yl-2-pyrazoline (6'c). To the solution of compound 5-(3'indolylmethyl)-1,3,4-oxadiazole-2-aminosubstitutedchalkones) (0.02 mole) in ethanol (40 mL), hydrazine hydrate (99%, 0.04) and few drops of glacial acetic acid were added. Then, the reaction mixture was refluxed for 12 hours. The excess of solvent was removed through distillation and

separated product was recrystallized from methanol- water to furnish the compound 6c':m.p. 286°C, yield 50% molecular formula $C_{23}H_{22}O_4N_6S$(446).

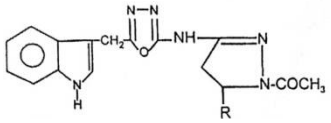
Table 3. Elemental Analysis

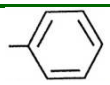
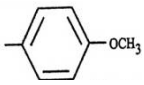
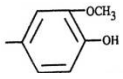
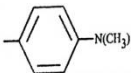
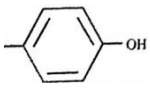
Element Percentage	Calculated	Found
C	61.99	61.49
H	4.93	4.58
N	18.83	18.69

Spectral analysis: IR (KBr) v in cm^{1}-:3250 (O-H), 3150 (N-H), 3070 (C-H aromatic), 3945 (C-H aliphatic); 1710 (C=O)1590 (C=O); 1035 (N-N), 1120(C-O-C). ^{1}H-NMR ($CDCl_3$) δ in ppm: 7.60-7.15 (m, 8H, Ar-H) 8.15 (s, 1H, NH of indole ring, exchangeable with (D_2O), 6.85 (s, 2H, CH_2 attached to indole ring), 6.55 (t, 1H, CH-Ar of pyrazoline ring), 5.30 (d, 2H, CH_2 of pyrazoline ring), 3.45 (s, 3H, OCH_3), 11.15 (ss, 1H, OH exchangeable with D_2O), (s, 3H, $COCH_3$). MS:[M]+ at m/z 446.

A number of 1-acetyl-5-substitutedaryl-3-[5-(3'-indolylmethyl)-2'-amino -1',3',4'-oxadiazol-2'N-yl]-2-pyrazolines (6a'6'b, 6'd and 6'e) have been synthesized in the similar way.

Table 4. Physical and analytical data of 1- -acetyl-5-substitutedaryl-3(3"-indolylmethyl)-2' -amino-1',3',4'-oxadiazol-2'N-yl]2-pyrazolines (6'a-6'e)



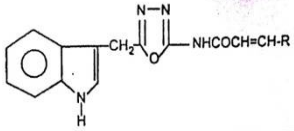
Comp No.	R	M.P (C°)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental Analysis					
						%C		%H		%N	
						Calcd	Found	Calcd	Found	Calcd	Found
6'a		210	48	Ethanol-water	$C_{22}H_{20}O_2N_6$	66.00	63.33	5.00	5.21	21.53	21.28
6'b		190	55	Methanol-water	$C_{22}H_{23}O_3N_6$	64.19	64.02	5.12	5.00	19.53	19.26
6'c		286	50	Methanol-water	$C_{23}H_{22}O_4N_6$	61.88	61.49	4.93	4.58	18.83	18.69
6'd		240	54	Methanol-water	$C_{24}H_{25}O_2N_7$	65.01	65.32	5.64	5.34	22.12	22.27
6'e		277	65	Acetic acid	$C_{22}H_{20}O_3N_6$	63.46	63.72	4.81	4.66	20.19	20.02

RESULTS AND DISCUSSION

Acute toxicity study (ALD_{50} mg/Kg p.o).All the compounds have shown ALD_{50}>1000 mg/kg p.o.
Anti inflammatory activity against carrageenan induced rat's paw oedema Twenty indole derivatives and reference drug have been screened for their anti-inflammatory activity at a dose of 50 mg kg^{-1} p.o. Most of these congeners showed statistically significant anti-inflammatory activity ranging from 24.3% to 49%. The most active compounds of the present series 6'c exhibited more potent ant-inflammatory activity (47.6% and 49%, respectively). By considering their potentiality, compounds 6'c were further tested for their anti-inflammatory activity at three different graded i.e 25, 50 and 100 mg kg^{-1} p.o. Ulcerogenic Activity (UDso mg kg^{-1} i.p) Only compounds 6'c and reference drug,

phenylbutazone were tested for their liability, Compound 6'c and phenylbutazone produced ulcers in 50% animals at a dose of 168.2 and 66.6 mg kg^{-1} i.p.

Table 5. Biological data of 5-(3'-indolylmethyl)-1'3'4'-oxadiazolyl-2'-aminosubstituted chalkones (5'a-5'e)



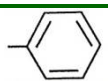
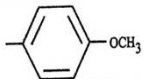
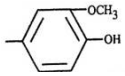
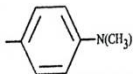
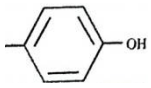
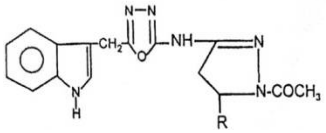
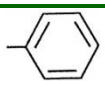
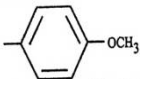
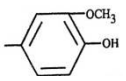
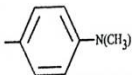
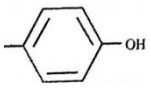
Comp No.	R	Dose (mg Kg^{-1} p.o.)	Anti-inflammatory activity (%)	Acute toxicity (ALD50 mg Kg^{-1} p.o.)
5'a		50	28.12**	>1000
5'b		50	40.6*	>1000
5'c		50	42.0*	>1000
5'd		50	30.13*	>1000
5'e		50	34.2*	>1000

Table 6. Biological data of 1-acetyl-5-substitutedaryl-3-[5'-(3"-indolylmethyl)-2'-amino-1',3',4'-oxadiazole-2'N-yl]-2-pyrozolines (6'a-6e') .



Comp No.	R	Dose (mg Kg^{-1} p.o.)	Anti-inflammatory activity (%)	Ulcerogenic activity (UD50 mg Kg^{-1} i. p.)	Acute toxicity (ALD50 mg Kg^{-1} p.o.)
6'a		50	33.3	--	>1000
6'b		50	43.6*	--	>1000
6'c		25 50 100	30.3* 49.0*** 69.47**	168.2	>1000
6'd		50	32.13*	--	>1000
6'e		50	37.25*	--	>1000
Phynyl buta zone		25 50 100	26.5* 45.6** 65.1**	66.6	--

SAR study of indole nucleus has revealed that substitution at 3-position of indole nucleus markedly enhanced the anti-inflammatory activity. Furthermore, indole was substituted with thiadiazolyl oroxadiazolyl moieties at its 3-position. These compounds further converted into different substituted chalkones and finally cyclized into their corresponding pyrazoline congeners. From the result obtained Table-5 and Table-6,it was noticed that these substituted chalkones showed mild to moderate anti-inflammatory activity. Furthermore, anti-inflammatory activity increased an cyclization of chalkone congeners (5a'5'e) into their corresponding pyrazoline congeners (6'a-6'e). Moreove, it has been observed that when compounds 6'c were substituted at 5-position of pyrazoline ring with m-methoxy,p-hydroxylphenyl group. Then they showed maximum percentage inhibition of rat's paw oedema (49.0%).

Compounds 6'b, substituted at 5-position of pyrazoline ring with p-methoxyphenyl group, have also shown interesting anti-inflammatory activity (43.6%). Furthermore, it is evident from the results obtained that the compounds (6'a-6'e), having oxadizolyl moiety exhibited better anti-inflammatory activity.

CONCLUSION

a) Chalkone congeners (5'a'5'e) and pyrazoline congeners (6'a-6'e) substituted with m-methoxy, p-hydroxylphenyl group show maximum anti-inflammatory activity.
b) Chalkone congeners (5'a-5'e)andpyroazoline congeners (6'a-6'e) substituted with phenyl group posses minimum anti-inflammatory activity.
c) Compound, 6'a-6'e, which contains oxadizolyl moiety, exhibit better inflammation inhibiting property.
d) Cyclization of chalkone congeners into their corespoding pyrazoline congeners enchances the anti-inflammatory activity.

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