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Synthesis of some new formazanyl-thiazolyl-indoles and formazanyl-oxazolyl-indoles as inflammation inhibitors

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Various 3-(2-arylideneaminothiazol-4-yl)indoles **3a-e** and 3-(2-arylideneaminooxazol-4-yl)indoles **3a′-e′** on diazotisation with aniline afford 3-[2-(1′-phenyl-3′-substituted-aryl-formazan-4′-yl)thiazol-4-yl] indoles **4a-e** and 3-[2-(1′-substituted-phenyl-3′-substituted aryl-formazan-4′-yl)oxazol-4-yl]indoles **4a′-e′** respectively. All the compounds have shown interesting antiinflammatory activity in carrageenan induced oedema in rats at 50 mg/kg p.o. The most active compound in the series is 3-[2-(*o*-methoxybenzylidene)aminothiazol-4-yl]indole which has shown higher antiinflammatory activity and lower ulcerogenic property than phenylbutazone.

Substituted indoles are associated with psychotropic[1], anti-inflammatory[2-5], CNS depressant[6] and anticonvulsant[7] activities. Besides these, thiazoles[8,9], formazans[10] and oxazoles[11] have also been reported to possess anti-inflammatory activity. These findings prompted us to synthesize some thiazolyl-formazanyl-indoles **4a-e** and oxazolyl-formazanyl-indoles **4a′-e′** with a view to evaluating their anti-inflammatory profiles.

The required 3-chloroacetylindole **1** was prepared by known method[12]. 3-(2-Aminothiazol-4-yl)indole **2** and 3-(2-aminooxazol-4-yl) indole **2′** were prepared by refluxing **1** with thiourea and urea, respectively in absolute ethanol for about 10-12 hr. Structures of both the compounds (**2** and **2′**) were established by elemental analysis and spectral data (IR and ^{1}HNMR). Compounds **2** and **2′** when treated with various aromatic aldehydes separately in dry toluene in the presence of a few drops of glacial acetic acid resulted in the formation of 3-(2-arylideneamino-thiazol-4-yl)indoles **3a-e** and 3-(2-arylideneamino-oxazol-4-yl) indoles **3a′-e′,** respectively.

Diazotisation of **3a-e** and **3a′-e′** with aniline/substituted aniline resulted in the formation of compounds **4a-e** and **4a′-e′**, respectively **(Scheme I).**

Anti-inflammatory activity

The anti-inflammatory activity was done on albino rats of either sex weighing 80-120 g. The animals were divided into groups of six animals each. A freshly prepared suspension of carrageenan (1.0% in 0.9%, saline, 0.05 mL) was injected under the planter aponeurosis of right paw of the rat by the method of Winter *et al*[13]. Following formula was used to calculate the percent anti-inflammatory activity.

$$\% \text{ anti-inflammatory activity} = 1 - \frac{Dt}{Dc} \times 100$$

Where Dt and Dc are the volume of oedema in drug treated and control group, respectively. Phenylbutazone was used as the standard drug for comparision.

Ulcerogenic activity

The ulcerogenic activity was done according to the method of Djahanguiri[14].

Experimental Section

Melting points were taken in open capillaries and are uncorrected. All the compounds were routinely checked for their homogeneity by TLC on silica gel-G plates and spots were located by iodine. IR spectra were recorded on Backman-Acculab-10 spectrophotometer (ν_{max} in cm^{-1}); ^{1}HNMR spectra on Brucker 400-FT instrument and mass spectra on Jeol-JMS D-300 spectrometer. Elemental and spectral analysis of the newly synthesized compounds were obtained from CDRI, Lucknow (U.P.), India.

3-(2-Aminothiazol-4-yl)indole 2. To a solution of compound **1** (0.01 mole) in absolute ethanol (250mL), was added thiourea (0.01 mole). The reaction mixture

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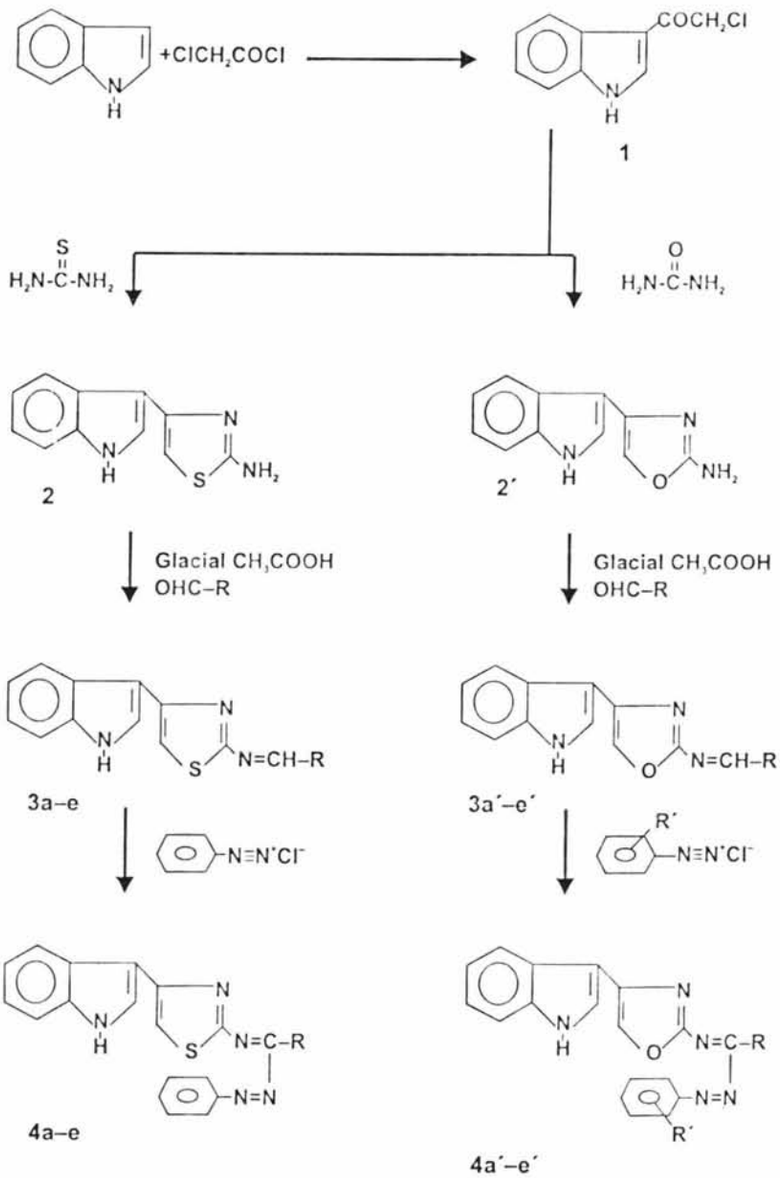

Scheme I

was refluxed for 10-12 hr, concentrated, filtered off and crystallised from methanol. The solid thus obtained was washed with Na_2CO_3 solution and then with water to liberate the base completely, dried and recrystallised from ethanol/water to get compound **2,** mp 255°C, yield 82% (Found: C, 61.43; H, 4.22; N, 19.49. $C_{11}H_9N_3S$ requires C, 61.39; H, 4.18; N, 19.53%); IR (Nujol): 3340 (NH_2), 3160 (NH), 3050 (aromatic C-H), 1670 (C=N), 1550 (C=C of aromatic ring), 1230 (C–N), 1130cm^{-1} (C—S); ^{1}HNMR ($CDCl_3$ + DMSO-d_6): δ 9.50 (s, 1H, NH of indole exchangeable with D_2O), 7.25-6.40 (m, 6H, Ar-H), 6.10 (s, 2H, -NH_2); MS:m/z 215 [M$^+$].

3-(2-Aminooxazol-4-yl)indole 2′. A mixture of compound **1** (0.01 mole) in ethanol and urea (0.01 mole) were refluxed for 10 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was filtered off and crystallised from methanol. The precipitate obtained was thoroughly washed with Na_2CO_3 solution and water. When the base was completely liberated from the ppt, the ppt was dried and recrystallised from

ethanol/water to yield compound **2′**, mp 240°C, yield 65% (Found: C, 66.29; H, 4.48; N, 21.14. $C_{11}H_9N_3O$ requires C, 66.33; H, 4.52; N, 21.10%): IR (Nujol): 1070 (C-O-C), 3140 (NH), 3350 (NH_2), 1685 (C=N), 3040 (aromatic C-H), 1220 (C-N), 1530cm^{-1} (C=C of aromatic ring); ^{1}HNMR ($CDCl_3$ + DMSO-d_6): δ 9.50 (s, 1H, NH of indole exchangeable with D_2O), 7.20-6.50 (m, 6H, Ar-H), 6.15 (bs, 2H,-NH_2); MS: m/z 199 [M^+]

3-(2-Arylideneaminothiazol-4-yl)indoles 3a-e. Compound **2** (0.01 mole) in ethanol in the presence of 2-3 drops of glacial acetic acid was refluxed with various aromatic aldehydes for 6 hr. The solvent was distilled off. The cooled reaction mixtures were poured onto ice, filtered off and recrystallised from appropriate solvents. The characterization data of compounds **3a-e** are given in **Table I**. Compound **3a**: IR (Nujol): 1580 (C=N), 3150 (NH), 3050 (aromatic C-H), 1230 (C-N), 1560 (C=C of aromatic ring), 1150cm^{-1} (C-S); ^{1}HNMR ($CDCl_3$ + DMSO-d_6): δ 8.2 (s, 1H, N=CH-Ar), 7.60-6.20 (m, 11H, Ar-H), 9.45 (s, 1H, NH of indole exchangeable with D_2O); MS: m/z 303 [M^+].

3-(2-Arylideneaminooxazol-4-yl)indoles 3a′-e′. Compound **2** (0.01 mole) in ethanol and various aldehydes (0.01 mole) were refluxed in the presence of a few drops of glacial acetic acid for about 4-6 hr. The reaction mixtures were concentrated, cooled and poured onto crushed ice. The separated solids were filtered off and recrystallised from appropriate solvents. The characterization data of compounds **3a′-e′** are given in **Table II**. Compound **3a′:** IR (Nujol) : 1580 (C=N), 3130 (NH), 3040 (aromatic C-H), 1220 (C-N), 1560 (C=C of aromatic ring), 1060cm^{-1} (C-O-C); ^{1}HNMR ($CDCl_3$ + DMSO-d_6): δ 8.2 (s, 1H, N=CH-Ar) 7.30-6.25 (m, 11H, Ar-H), 9.50 (s, 1H, NH of indole exchangeable with D_2O); MS: m/z 287 [M^+].

3-[2-(1′-Phenyl-3′-substituted-aryl-formazan-4'-yl)-thiazol-4-yl]indoles 4a-e. To aniline (0.01 mole) dissolved in glacial acetic acid (5mL) was added conc. HCl (3mL) at 0-5°C. A solution of sodium nitrite (1g in 5mL of water) was then added dropwise. The diazonium salt solution thus prepared was added in a solution of compounds **3a-e** (0.01 mole) in ethanol dropwise with stirring in pyridine (50 mL) below 0°C. The reaction mixtures were kept at room temperature for 2-3 days and then poured into cold water (250mL). The resulting solids were washed with water and recrystallised from appropriate solvents to yield compounds **4a-e**. The characterization data of compounds **4a-e** are given in **Table I**. Compound **4a**: IR (Nujol): 1420 (N=N), 1680 (C=N), 3160 (NH) 3060 (aromatic C-H), 1560 (C=C of aromatic ring), 1250 (C-N), 1140cm^{-1} (C-S); ^{1}HNMR ($CDCl_3$ + DMSO-d_6): δ 7.28-6.45 (m, 16H, Ar-H), 9.45 (, 1H, NH of indole exchangeable with D_2O); MS: m/z 407 [M^+].

3-[2-(1'-Substitutedphenyl-3'-substituted-aryl-formazan-4'-yl)oxazol-4-yl]indoles 4a'-e'. Concentrated HCl (3mL) at 0-5°C was added to aniline/ substituted aniline (0.01 mole) dissolved in glacial acetic acid (5mL). A solution of sodium nitrite (1g in 5 mL of water) was then added dropwise. The diazonium salt solution thus obtained was added to a solution of compounds **3a'-e'** (0.01 mole) in ethanol dropwise with stirring in pyridine (50 mL) below 0°C. The reaction mixtures were kept at room temperature for 2-3 days and poured onto ice. The separated solids were washed with water and recrystallised from appropriate solvents. The characterization data of compounds **4a'-e'** are given in **Table II**. Compound **4a'**: IR (Nujol): 3150 (NH), 1690 (C=N), 1440 (N=N), 3040 (aromatic C-H), 1550 (C=C of aromatic ring), 1270 (C-N), 1065cm^{-1} (C-O-C); ^{1}HNMR ($CDCl_3$ + DMSO-d_6): δ 7.25-6.50 (m, 16H, Ar-H), 9.50 (s, 1H, NH of indole exchangeable with D_2O); MS: m/z 391 [M^+].

Anti-inflammatory activity

The anti-inflammatory activity of all the newly synthesized compounds are given in **Tables I** and **II**. All the compounds were subjected to preliminary screening for anti-inflammatory activity by carrageenan-induced rat paw oedema test and tested at a dose of 50 mg/kg oral.

All the compounds of the present series showed activity varying from 16.92 to 50.76%. However, compound **3e** was found to be most potent which showed 50.76% inhibition of oedema, which was more than the activity of the standard drug phenyl butazone (38.9% inhibition at 50 mg/kg p.o.).

Ulcerogenic activity

The most active compound **3e** had much less ulcerogenic liability as compared to phenyl butazone (UD_{50} of compound **3e** = 187.4 mg/kg i.p. and UD_{50} of phenyl butazone = 66.6 mg/kg i.p.).

Table I—Characterisation data and anti-inflammatory activity of compounds **3a-e** and **4a-e**

Compd	R	mp °C	Yield (%)	Recrystallisation Solvent	Mol. formula	Mol. wt.	Found (Calcd) (%)			Dose mg/kg	% Anti-inflammatory activity*	Mean increase in ± S.E.
							C	H	N			
3a	Phenyl	152	50	Ethanol	$C_{18}H_{13}N_3S$	303	71.32 (71.28	4.25 4.29	13.82 13.86)	50	27.69	
3b	Furfural	204	30	Ethanol/water	$C_{16}H_{11}N_3OS$	293	65.56 (65.52	3.71 3.75	14.29 14.33)	50	16.92	
3c	*p*-N,Ndimethyl aminophenyl	80	40	Ethanol/water	$C_{20}H_{18}N_4S$	346	69.32 (69.36	5.16 5.20	16.22 16.18)	50	23.07	
3d	*p*-methoxyph-enyl	126	35	Ethanol	$C_{19}H_{15}N_3OS$	333	68.50 (68.46	4.46 4.50	12.65 12.61)	50	30.77	
3e	*o*-methoxyph-enyl	104	40	Ethanol	$C_{19}H_{15}N_3OS$	333	68.50 (68.46	4.54 4.50	12.65 12.61)	25 50 100	36.92 50.76 66.15	0.41±0.009 0.32±0.011 0.22±0.018
4a	phenyl	220	20	Benzene/pet.ether	$C_{24}H_{17}N_5S$	407	70.80 (70.76	4.21 4.17	17.15 17.19)	50	18.52	
4b	Furfural	154	22	Ethylacetate/Pet ether	$C_{22}H_{15}N_5OS$	397	66.53 (66.49	3.81 3.77	17.59 17.63)	50	9.26	
4c	*p*-N,Ndimethyl aminophenyl	208	15	Methanol/water	$C_{26}H_{22}N_6S$	450	69.37 (69.33	4.84 4.88	18.70 18.66)	50	20.37	
4d	*p*-methoxyph-enyl	110	23	Ethanol/water	$C_{25}H_{19}N_5OS$	437	68.68 (68.64	4.30 4.34	16.05 16.01)	50	22.22	
4e	*o*-methoxyph-enyl	188	30	Methanol	$C_{25}H_{19}N_5OS$	437	68.60 (68.64	4.30 4.34	15.97 16.01)	50	24.07	
Phenyl Butazone	-	-	-	-	-	-	-	-	-	25 50 100	15.00 38.90 65.20	0.45±0.015 0.31±0.02 0.26±0.011

* $p < 0.05$

Table II—Characterisation data and anti-inflammatory activity of compounds **3a′-e′** and **4a′-e′**

Compd	R	R′	mp °C	Yield (%)	Recrystallisation Solvent	Mol. formula	Mol. wt.	Found (Calcd) (%)			Dose mg/kg p.o.	% Anti-inflammatory activity*
								C	H	N		
3a′	Phenyl	-H	182	50	Methanol	$C_{18}H_{13}N_3O$	287	75.30 (75.26	4.49 4.53	14.67 14.63)	50	18.31
3b′	Furfural	-H	172	48	Ethanol	$C_{16}H_{11}N_3O_2$	277	69.27 (69.31	3.93 3.97	15.20 15.16)	50	19.72
3c′	*p*-N,N-dimethyl aminophenyl	-H	110	55	Ethanol/water	$C_{20}H_{18}N_4O$	330	72.68 (72.72	5.49 5.45	16.93 16.97)	50	21.12
3d′	*p*-methoxyphenyl	-H	198	30	Ethanol/water	$C_{19}H_{15}N_3O_2$	317	71.96 (71.92	4.77 4.73	13.21 13.25)	50	22.53
3e′	*o*-methoxyphenyl	-H	162	46	Ethanol/water	$C_{19}H_{15}N_3O_2$	317	71.96 (71.92	4.69 4.73	13.29 13.25)	50	30.98
4a′	Phenyl	-H	190	20	Ethanol/water	$C_{24}H_{17}N_5O$	391	73.69 (73.65	4.30 4.34	17.86 17.90)	50	18.84
4b′	Furfural	-H	126	15	Methanol/water	$C_{22}H_{15}N_5O_2$	381	69.33 (69.29	3.89 3.93	18.33 18.37)	50	17.39
4c′	*p*-N,N-dimethyl aminophenyl	2-Cl	202	20	Ethanol/water	$C_{26}H_{21}N_6OCl$	468.5	66.63 (66.59	4.52 4.48	17.88 17.92)	50	11.59
4d′	*p*-N,N-dimethyl aminophenyl	2-OCH_3	156	25	Methanol	$C_{27}H_{24}N_6O_2$	464	69.78 (69.82	5.13 5.17	18.14 18.10)	50	20.20
4e′	*o*-methoxyphenyl	-H	129	30	Methanol/water	$C_{25}H_{19}N_5O_2$	421	71.21 (71.25	4.55 4.51	16.66 16.62)	50	23.19

* $p < 0.05$

Structure-Activity Relationship

SAR studies of these compounds revealed that when the compound is substituted with an *o*-methoxyphenyl group (*cf.* compound **3e**), it is most active (50.76%) and when it is substituted with a furfural group (*cf.* compound **3b**), it is least active (16.92%). Furthermore, when the compound is substituted with a *p*-dimethylaminophenyl group **(3c)**, then it showed noticeable anti-inflammatory activity (23.07%). But compound **3c** is less active than compound **3a** (27.69%) which has got phenyl group as substituent.

The corresponding arylidene-oxazolyl-indoles **3a'-e'** exhibited lesser degree (18.31 to 30.98%) of inhibition of oedema. However, thiazolyl-formazans generally showed less degree (9.26 to 24.07%) of activity. In general, oxazolyl-formazans **4b'-e'** were found to be less active than the corresponding arylidene-oxazolyl-indoles **3b'-e'** but compound **4a'** showed slight increase in the activity. Hence, in general, it may be concluded— (i) Formazans are less active than the corresponding arylidenes; (ii)Oxazoles, in general showed less % of inhibition than the corresponding thiazoles; (iii) Compounds having *o*-methoxyphenyl moiety as substituent **(3e** and **4e)** are more potent than the compounds having *p*-methoxyphenyl moiety (**3d** and **4d**) as substituent.

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