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Synthesis of Some Newer Derivatives of 2-Amino Benzoic Acid as Potent Anti-inflammatory and Analgesic Agents

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Abstract—Diazotization of *N*-benzylidene anthranilic acids **1a**–**1n** at pH 9 yielded *N*-[α-(phenylazo) benzylidene] anthranilic acids **2a**–**2n** and at pH 3 yielded *N*-benzylidene-5-(phenylazo) anthranilic acids **3a**–**3n**. When compounds **3a**–**3n** were treated with thioglycolic/thiolactic acid in the presence of anhydrous $ZnCl_2$, 2-(4-oxo-2-phenylthiazolidin-3-yl)-5-(phenylazo) benzoic acids **4a**–**4n** were afforded. The newly synthesized compounds were screened for their anti-inflammatory and analgesic activities and were compared with standard drugs, aspirin and phenylbutazone. Out of the compounds studied, the most active compound **4n** showed more potent activity than the standard drugs at all doses tested.

Introduction

Anthranilic acids (2-aminobenzoic acids) constitute an important group of non-steriodal antiinflammatory agents. Some of these anti-inflammatory derivatives were synthesized by several scientists of the world and have been reported as potent anti-inflammatory agents.[1–5] Anthranilic acid, an aromatic nucleus, has gained prominence after the discovery of mefenamic acid and meclofenamate,[6] which are currently useful drugs for the treatment of various inflammatory disorders. Heterocyclic/aliphatic functionalized systematic variation at the 2-position of anthranilic acid nucleus remarkably increases the anti-inflammatory activity. Formazan[7] and thiazolidine[8] derivatives are also well known for their pronounced anti-inflammatory activity. In view of these observations, it was thought worthwhile to synthesize some newer more potent derivatives of anthranilic acid by incorporating formazanyl and thiazolidinyl moieties at the 2-position of anthranilic acid. The structure of these newly synthesised compounds was confirmed by elemental and spectral analysis. Then, these compounds were subjected to screens for their anti-inflammatory, analgesic, antipyretic, cyclo-oxygenase inhibition activity, and acute toxicity.

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Chemistry

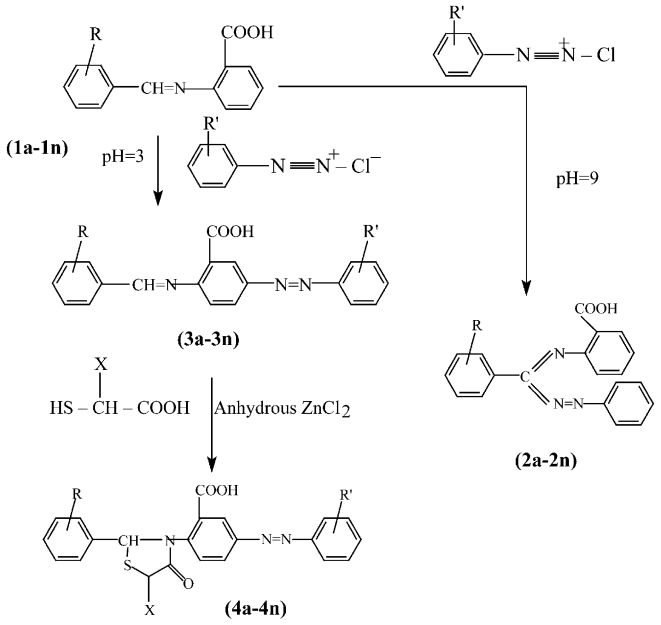
The desired anthranilic acid (2-aminobenzoic acid) derivatives, that is **1a**–**4n** were synthesized as shown in Scheme 1. The reaction of different substituted benzaldehydes and 2-aminobenzoic acid yielded *N*-benzylidene anthranilic acids **1a**–**1n**. Diazotization of **1a**–**1n** at pH adjusted to 9 afforded *N*-[α-(phenylazo) benzylidene] anthranilic acids **2a**–**2n**. When diazonium salt solution was added to **1a**–**1n** at pH adjusted to 3 with constant stirring on mechanical stirrer for 72 h below 0 °C gave *N*-benzylidene-5-(phenylazo) anthranilic acids **3a**–**3n**. 2-(4-Oxo-2-phenylthiazolidin-3-yl)-5-(phenylazo) benzoic acids **4a**–**4n** were synthesized by refluxing **3a**–**3n** with thioglycolic/thiolactic acid in the presence of anhydrous $ZnCl_2$.

Results and Discussion

Anti-inflammatory, analgesic, ulcerogenic, cyclooxygenase activities, and acute toxicity of these new anthranilic acid derivatives **1a**–**1n**, **2a**–**2n**, **3a**–**3n** and **4a**–**4n** are represented in Table 1.

Anti-inflammatory and analgesic activity

The characteristic feature of the first stage compounds is the presence of carbon–nitrogen double bond between two substitued phenyl rings. All the fourteen *N*-benzyl-



1a, R	= 2, 4-Cl_2	2a, R	= 2,4-Cl_2,	R′	= 3-Cl
1b, R	= 3-Cl	2b, R	= 3-Cl,	R′	= 4-Cl
1c, R	= 2-F	2c, R	= 2-F,	R′	= H
1d, R	= 2-CH_3	2d, R	= 2-CH_3,	R′	= 3-Cl
1e, R	= 2-OCH_3	2e, R	= 2-OCH_3,	R′	= 4-Cl
1f, R	= 4-OCH_3	2f, R	= 4-OCH_3,	R′	= 3-Cl
1g,R	= 4-Cl	2g, R	= 4-Cl,	R′	= H
1h,R	= H	2h, R	= H,	R′	= 4-Cl
1i, R	= 2,6-Cl_2	2i, R	= 2,6-Cl_2,	R′	= H
1j, R	= 4-Br	2j, R	= 4-Br.	R′	= 4-OCH_3
1k, R	= 2-Br	2k, R	= 2-Br,	R′	= 2-OCH_3
1l, R	= 4-N-$(CH_3)_2$	2l, R	= 4-N-$(CH_3)_2$,	R′	= H
1m, R	= 4-C_2H_5	2m, R	= 4-C_2H_5,	R′	= 3-Cl
1n, R	= 4-NO_2	2n, R	= 4-NO_2,	R′	= 4-Cl

3a, R	= 2,4-Cl_2,	4a, R	= 2,4-Cl_2,	R′	= 3-Cl,	X=H
3b, R	= 3-Cl,	4b, R	= 3-Cl,	R′	= 4-Cl,	X=H
3c, R	= 2-F,	4c, R	= 2-F,	R′	= H,	X=H
3d, R	= 2-CH_3,	4d, R	= 2-CH_3,	R′	= 3-Cl,	X=H
3e, R	= 2-OCH_3,	4e, R	= 2-OCH_3,	R′	= 4-Cl,	X=H
3f, R	= 4-OCH_3,	4f, R	= 4-OCH_3,	R′	= 3-Cl,	X=H
3g, R	= 4-Cl,	4g, R	= 4-Cl,	R′	= H	X=H
3h, R	= H,	4h, R	= H,	R′	= 4-Cl,	X=CH_3
3i, R	= 2,6-Cl_2,	4i, R	= 2,6-Cl_2,	R′	= H,	X=CH_3
3j, R	= 4-Br,	4j, R	= 4-Br,	R′	= 4-OCH_3,	X=CH_3
3k, R	= 2-Br,	4k, R	= 2-Br,	R′	= 2-OCH_3,	X=CH_3
3l, R	= 4-N-$(CH_3)_2$,	4l, R	= 4-N-$(CH_3)_2$,	R′	= H,	X=CH_3
3m, R	= 4-C_2H_5,	4m, R	= 4-C_2H_5,	R′	= 3-Cl,	X=CH_3
3n, R	= 4-NO_2,	4n, R	= 4-NO_2,	R′	= 4-Cl,	X=CH_3

Scheme 1.

idene anthranilic acids have shown moderate degree (17.3–32.7%) of anti-inflammatory activity while these compounds unexpectedly showed mild degree of analgesic activity. Out of the 14 *N*-benzylidene anthranilic acids, compound **1n** which was substituted with NO_2 group at the *p*-position of phenyl ring elicited maximum inhibition of oedema at a dose of 50 mg/kg po. Being the most active, it was tested at three graded doses (25, 50 and 100 mg/kg po) and was also compared with standard drugs, phenylbutazone and aspirin. The compound showed more potent activity than phenylbutazone and aspirin. However, this compound exhibited very low analgesic activity (16%). Interestingly, compounds **1a**, **1c**, **1g**, **1j** and **1k** which were substituted with chloro atom on positions 2 and 4, fluoro atom on position 2, chloro group on position 4, bromo atom on position 4 and bromo atom on position 2 of phenyl ring, respectively, showed potent anti-inflammatory activity. On the contrary, when phenyl group is substituted with chloro atom on position 3 and ethyl group on position 4 showed lesser degree of activity (i.e., 17.4% in both the compounds).

The diazotisation of the *N*-benzylidene anthranilic acids at pH 9 converts them into the corresponding *N*-[α-(phenylazo) benzylidene] anthranilic acids **2a**–**2n** which

Table 1. Anti-inflammatory, analgesic, ulcerogenic, cyclooxygenase, and toxicity data of compounds **1a**–**4n** (Scheme 1)

Compd	R	R'	X	Dose (mg/kg po)	Anti-inflammatory activity % oedema inhibition relative to control	Dose (mg/kg po)	Analgesic activity % decrease of writhes in 25 min after treatment relative to control	Dose (mg/kg po)	Ulcerogenic activity		Cyclo-oxygenase activity assay Inhibitory action of some selected compound% inhibition 10 μ M	ED_{50} (mg/kg po)	ALD_{50} (mg/kg po)
									% of animal with hyperemia	% of animal with ulcer			
1a	2,4-Cl_2	—	—	25	14.8	25	9.0	125	40	10	20	79.4	> 1000
				50	28.6	50	14.0	250	60	20			
				100	54.6	100	30.0	500	100	40			
1b	3-Cl	—	—	50	17.3	50	30	250	50	10	ni		
1c	2-F	—	—	25	15.3	25	10	125	30	10	30	79.4	> 1000
				50	29.3	50	15	250	70	20			
				100	61.3	100	30	500	100	30			
1d	2-CH_3	—	—	50	19.0	50	12.0	250	60	20	ni		> 1000
1e	2-OCH_3	—	—	50	21.1	50	10.1	250	90	30	ni		> 1000
1f	4-OCH_3	—	—	50	20.6	50	9.9	250	10	60	ni		> 1000
1g	4-Cl	—	—	50	28.6	50	15.0	250	20	10	ni		> 1000
1h	H	—	—	50	12.3	50	7.5	250	30	20	ni		> 1000
1I	2,6-Cl_2	—	—	50	30.6	50	16.1	250	100	30	ni		> 1000
1j	4-Br	—	—	50	24.7	50	12.3	250	90	10	ni		> 1000
1k	2-Br	—	—	50	25.1	50	15.2	250	80	20	ni		> 1000
1l	N-$(CH_3)_2$	—	—	50	18.4	50	9.2	250	70	30	ni		> 1000
1m	4-C_2H_5	—	—	50	17.4	50	8.5	250	100	10	ni		> 1000
1n	4-NO_2	—	—	25	16.4	25	10.0	125	50	5	70	79.4	> 1000
				50	32.7	50	16.0	250	70	10			
				100	62.6	100	40.0	500	90	15			
2a	2, 4-Cl_2	3-Cl	—	25	14.2	25	3.0	125	30	10	30	128.8	> 1000
				50	22.2	50	9.8	250	80	20			
				100	42.4	100	20.2	500	100	40			
2b	3-Cl	4-Cl	—	50	24.6	50	11.9	250	70	20	ni		> 1000
2c	2-F	H	—	25	12.8	25	10.2	125	20	15	20	79.4	> 1000
				50	27.4	50	15.3	250	30	30			
				100	52.4	100	30.6	500	50	45			
2d	2-CH_3	3-Cl	—	50	21.2	50	16.2	250	10	40	ni		> 1000
2e	2-OCH_3	4-Cl	—	25	13.7	25	5.0	125	20	15	20	79.4	> 800
				50	22.8	50	10.1	250	60	30			
				100	56.8	100	20.1	500	80	60			
2f	4-OCH_3	3-Cl	—	25	10.8	25	6.7	125	20	20	20	125.9	> 1000
				50	21.7	50	9.7	250	50	40			
				100	44.8	100	20.1	500	70	90			
2g	4-Cl	H	—	50	21.3	50	10.3	250	60	50	ni		> 1000
2h	H	4-Cl	—	50	20.8	50	8.9	250	70	30	ni		> 1000
2I	2,6-Cl_2	H	—	25	19.6	25	9.7	125	70	10	40	63.1	> 1000
				50	28.6	50	14.3	250	90	20			
				100	62.3	100	32.6	500	100	40			
2j	4-Br	4-OCH_3	—	25	14.5	25	10.6	125	20	40	ni	177.8	> 1000
				50	23.5	50	12.6	250	40	60			
				100	46.5	100	24.6	500	60	80			
2k	2-Br	2-OCH_3	—	50	24.9	50	12.2	250	30	40	ni		> 1000
2l	N-$(CH_3)_2$	H	—	50	18.2	50	9.0	250	60	70	ni		> 1000
2m	4-C_2H_5	3-Cl	—	50	15.3	50	7.3	250	50	80			
2n	4-NO_2	4-Cl	—	29	19.7	25	9.6	125	30	5	70	79.4	> 1000
				50	29.7	50	15.3	250	60	10			
				100	59.7	100	30.0	500	90	20			
3a	2, 4-Cl_2	3-Cl	—	50	23.5	50	13.0	250	100	40	ni		> 1000
3b	3-Cl	4-Cl	—	50	19.2	50	10.3	250	50	60	ni		> 1000

(*Continued on next page.*)

Table 1 (*continued*)

Compd	R	R'	X	Dose (mg/kg po)	Anti-inflammatory activity % oedema inhibition relative to control	Dose (mg/kg po)	Analgesic activity % decrease of writhes in 25 min after treatment relative to control	Dose (mg/kg po)	Ulcerogenic activity		Cyclo-oxygenase activity assay Inhibitory action of some selected compound% inhibition 10 μ M	ED_{50} (mg/kg po)	ALD_{50} (mg/kg po)
									% of animal with hyperemia	% of animal with ulcer			
3c	2-F	H	—	50	24.5	50	12.0	250	100	30	ni		> 1000
3d	2-CH_3	3-Cl	—	50	17.2	50	8.0	250	40	30	ni		> 1000
3e	2-OCH_3	4-Cl	—	50	15.7	50	7.0	250	30	60	ni		> 1000
3f	4-OCH_3	3-Cl	—	50	14.6	50	6.8	250	60	60	ni		> 1000
3g	4-Cl	H	—	50	12.2	50	6.2	250	20	60	ni		> 1000
3h	H	4-Cl	—	50	22.9	50	11.3	250	80	50	ni		> 1000
3i	2, 6-Cl_2	H	—	50	21.7	50	10.6	250	70	80	ni		> 1000
3j	4-Br	4-OCH_3	—	50	19.9	50	9.7	250	50	20	ni		> 1000
3k	2-Br	2-OCH_3	—	50	10.1	50	5.0	250	40	30	ni		> 1000
3l	N-$(CH_3)_2$	H	—	50	9.2	50	8.6	250	60	60	ni		> 1000
3m	4-C_2H_5	3-Cl	—	50	26.8	50	9.2	250	100	80	ni		> 1000
3n	4-NO_2	4-Cl	—	25	28.6	25	7.5	125	30	5	ni	90.3	> 1000
				50	33.6	50	13.2	250	70	10			
				100	66.7	100	28.2	500	100	20			
4a	2, 4-Cl_2	3-Cl	H	50	32.2	50	16.0	250	100	40	ni		> 1000
4b	3-Cl	4-Cl	H	50	19.6	50	11.2	250	60	50	ni		> 1000
4c	2-F	H	H	50	31.5	50	15.3	250	90	50	ni		> 1000
4d	2-CH_3	3-Cl	H	50	23.2	50	11.10	250	60	40	ni		> 1000
4e	2-OCH_3	4-Cl	H	25	16.3	25	6.0	125	20	10	ni	79.4	> 1000
				50	28.2	50	12.0	250	60	30			
				100	56.0	100	25.0	500	100	50			
4f	4-OCH_3	3-Cl	H	25	17.2	25	8	125	30	10	ni	79.4	> 1000
				50	29.1	50	15	250	70	20			
				100	54.2	100	45	500	100	30			
4g	4-Cl	H	H	50	19.2	50	10.10	250	80	20	ni		> 1000
4h	H	4-Cl	CH_3	50	36.5	50	18.2	250	100	10	ni		> 1000
4i	2, 6-Cl_2	H	CH_3	25	21.8	25	14.1	125	50	20	90	61.6	> 1000
				50	44.8	50		250	70	30			
				100	76.8	100		500	100	40			
4j	4-Br	4-OCH_3	CH_3	50	22.8	50	13.4	250	100	10	ni		> 1000
4k	2-Br	2-OCH_3	CH_3	50	28.7	50	14.3	250	100	30	ni		> 1000
4l	N-$(CH_3)_2$	H	CH_3	50	31.6	50	15.0	250	90	40	ni		> 1000
4m	4-C_2H_5	3-Cl	CH_3	50	22.8	50	22.2	250	100	4	ni		> 1000
4n	4-NO_2	4-Cl	CH_3	25	29.1	25	10.0	125	30	10	ni	50.1	> 1000
				50	47.2	50	21.3	250	60	20			
				100	93.2	100	40.4	500	90	11			
Phenylbutazone	—	—	—	25	30.42	25	15.25	125	30	30	90	—	—
				50	34.4	50	28.36	250	60	60			
				100	56.4	100	39.43	500	90	90			
Aspirin	—	—	—	25	29.5	25	28.36	125	30	80	100	99.6	—
				50	34.4	50	43.30	250	60	90			
				100	58.8	100	54.30	500	90	90			
Control	—	—	—	25	—	25	—	125	—	—	ni	—	—
				50		50		250					
				100		100		500					

ni, no inhibition.

showed more or less similar degree of anti-inflammatory, analgesic and other activities, while the diazotisation at 5-position of **1a–1n** at pH 3 gave *N*-benzylidene-5-(phenylazo)anthranilic acids **3a–3n**. These compounds, however, exhibited varying degree of anti-inflammatory (9.2–33.6%) and analgesic activity (5–13.2%).

Furthermore, cyclocondensation of **3a–3n** with thioglycolic/thiolactic acids resulted into the corresponding five-membered ring compounds, **4a–4n**, which have shown more potent activities than their parent compounds **3a–3n**. The most active compound of **4a–4n** is compound **4n**. This compound **4n** along with other promising compounds **4e** and **4i** were studied in details at three graded doses and have shown dose-dependent activity. Anti-inflammatory activity of potent compounds **4e**, **4i** and **4n** and their comparison with standard drugs, aspirin and phenylbutazone, is given in Scheme 1.

Ulcerogenic activity

Compounds **1a–1n** showed significant lesser degree (10–40%) of ulcer production activity. Moreover, the most active compound **1n** showed lesser ulcerogenic activity than standard drugs, acetylsalicyclic and phenylbutazone. Futhermore, compounds **2a–3n** also exihibited low ulcer production activity ranging between 10 and 50% at 250 mg/kg po. However, compounds **4e**, **4i** and **4n** showed very low degree of ulcerogenic activity.

Cyclooxygenase assay activity

None of the *N*-benzylidene anthranilic acids inhibited the cyclooxygenase activitiy. They, therefore, seems to act through some other mechanism rather than inhibiting prostaglandin synthesis. Cyclooxygenase activity of most of the compounds **2a–3n** did not show any activity suggesting that they might be acting through some other mechanism of their anti-inflammatory action, except compounds **2e**, **2f**, **2n**, **3n** and **4i** which showed good cyclooxygenase activity indicating that these compounds reduces inflammatory response by inhibition of prostaglandins.

ALD_{50} studies

The toxicity study of these compounds indicate their good safety margin.

Conclusion

From the results of the biological activities, we may conclude that diazotisation of **1a–1n** is fruitful as it was found to increase their anti-inflammatory and analgesic activities with decreased ulcer production activity. Moreover, diazotisation of **1a–1n** at pH 3 was found to be more beneficial then their diazotization at pH 9, as compounds **3a–3n** which are formed by the diazotisation at pH 3 were found to be comparatively more potent than compounds **2a–2n** which are formed by diazotisation at pH 9. Furthermore, incorporation of thiazolidine ring in compounds **3a–3n** was found to increase the potency of these compounds and resulted into the formation of **4a–4n** with high anti-inflammatory and analgesic activity with low ulcerogenic activity. These compounds were found to have no suppersive effect on cyclooxygenase which is the prime mechanism of anti-inflammatory activity of anthranilic acid derivatives. Since the analgesic, anti-inflammatory and ulcerogenic activities of **4n** corresponds mostly to the activity shown by **1n** which has got 70% inhibition of cyclooxygenase activity (Table 1). It seems likely that **4n** which is devoid of cyclooxygenase inhibition is converted to **1n** in the body thereby exhibiting the anti-inflammatory, analgesic and ulcerogenic activities through inhibition of cyclooxygenase by **1n**. It is quiet likely that the other anthranilic acid derivatives which do not show cylooxygenase inhibition may be acting for anti-inflammatory, analgesic and ulcerogenic activities by their conversion to metabolites which possess cyclooxygenase inhibition activity.

Experimental

Chemistry

Melting points were determined in open capillaries with the help of thermonic melting point apparatus and are uncorrected. IR spectra (KBr/Nujol) were recorded on Backmann Acculab-10-FTIR spectrometers. ^{1}H NMR spectra were recorded by Bruker WM 400 FT MHz instrument using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal reference standard. All chemical shifts (δ) are in ppm. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel-G plates of 0.5 mm thickness. The elemental analysis (C, H, N) of the compounds were performed on Heracus Carlo Erba 1108 analyser.

***N*-(*p*-Nitrobenzylidene)anthranilic acid (1n).** A mixture of *p*-nitrobenzaldehyde (0.01 mol), anthranilic acid (0.01 mol) and anhydrous $ZnCl_2$ heated on free flame for 10 min. The reaction mixture was cooled, cocentrated and recrystallised from DMF and water to give **1n** (70%): mp 213 °C; IR (Nujol) 1610 (C=N), 3060 (C–C aromatic), 1720 (C=O), 3010 (O–H) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.70 (1H, s), 12.40 (1H, s), 8.55–7.90 (8H, m) (ppm); ms: *m*/*z* (6.7%) M^+ 270. Anal. calcd for $C_{14}H_{10}N_2O_4$; C, 62.22; H, 3.70; N, 10.37. Found: C, 62.51; H, 3.41; N, 10.00.

***N*-(2,4-Dichlorobenzylidene)anthranilic acid (1a).** 90%, mp 176 °C (ethanol); IR (Nujol) 1600 (C=N), 3065 (C–C aromatic), 1715 (C=O), 3000 (O–H) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.68 (1H, s), 12.42 (1H, s), 8.45–7.85 (7H, m) (ppm): ms: *m*/*z* (6.57%) M^+ 294. Anal. calcd for $C_{14}H_9NO_2Cl_2$: C, 57.14; H, 3.06 ;N, 4.76. Found: C, 57.44; H, 3.16; N, 4.80.

***N*-(*m*-Chlorobenzylidene)anthranilic acid (1b).** 80%, mp 158 °C (methanol); IR (Nujol) 1615 (C=N), 3068 (C–C of aromatic C–H), 1717 (C=O), 3012 (O–H) cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 8.70 (1H, s), 12.44 (1H, s), 8.40–7.80 (7H, m) (ppm): ms: *m/z* (7.5%) M^+ 259.5. Anal. calcd for $C_{14}H_{10}NO_2Cl$: C, 64.73; H, 3.85; N, 5.39; Found: C, 64.75; H, 3.76; N, 5.40.

***N*-(*o*-Fluorobenzylidene)anthranilic acid (1c).** 90%, mp 223 °C (DMF/water); IR (Nujol) 1612 (C=N), 3065 (C–C of aromatic), 1716 (C=O), 3010 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (1H, s), 12.41 (1H, s), 8.35–7.75 (7H, m) (ppm): ms: *m/z* (8.50%) M^+ 243. Anal. calcd for $C_{14}H_{10}NO_2F$: C, 69.13; H, 4.11; N, 5.76; Found: C, 69.23; H, 3.99; N, 5.81.

***N*-(*o*-Methylbenzylidene)anthranilic acid (1d).** 70%, mp 186 °C (ethanol); IR (Nujol) 1610 (C=N), 3066 (C–C of aromatic), 1717 (C=O), 3014 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 8.66 (1H, s), 12.42 (1H, s), 8.38–7.76 (7H, m) (ppm): ms: *m/z* (9.69%) M^+ 239. Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.43; N, 5.85; Found: C, 75.33; H, 5.95; N, 5.90.

***N*-(*o*-Methoxybenzylidene)anthranilic acid (1e).** 90%, mp 177 °C, (ethanol/water); IR (Nujol) 1611 (C=N), 3064 (C–C of aromatic), 1715 (C=O), 3011 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (3H, s), 8.64 (1H, s), 12.40 (1H, s), 8.40–7.70 (8H, m) (ppm): ms: *m/z* (9.01%) M^+ 255. Anal. calcd for $C_{15}H_{13}NO_3$: C, 70.61; H, 5.19; N, 5.49; Found: C, 70.58; H, 5.09; N, 5.40.

***N*-(*p*-Methoxybenzylidene)anthranilic acid (1f).** 80%, mp 104 °C, (benzene); IR (Nujol) 1612 (C=N), 3062 (C–C of aromatic C–H), 1711 (C=O), 3010 (O–H)cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (3H, s), 8.60 (1H, s), 12.43 (1H, s), 8.38–7.65 (8H, m) (ppm): ms: *m/z* (8.60%) M^+ 255. Anal. calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.09; N, 5.49; Found: C, 70.63; H, 5.23; N, 5.33.

***N*-(*p*-Chlorobenzylidene)anthranilic acid (1g).** 60%, mp 196 °C (methanol); IR (Nujol) 1608 (C=N), 3060 (C–C of aromatic C–H), 1710 (C=O), 3015 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62 (1H, s), 12.41 (1H, s), 8.35–7.70 (8H, m) (ppm): ms: *m/z* (8.95%) M^+ 259.5. Anal. calcd for $C_{14}H_{10}NO_2Cl$: C, 64.73; H, 3.85; N, 5.39; Found: C, 64.77; H, 3.99; N, 5.17.

***N*-benzylidene anthranilic acid (1h).** 70%, mp 201 °C (ethanol); IR (Nujol) 1600 (C=N), 3015 (C–C of aromatic C–H), 1710 (C=O), 3015 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (1H, s), 12.38 (1H, s), 8.30–7.70 (9H, m) (ppm): ms: *m/z* (9.22%) M^+ 225. Anal. calcd for $C_{14}H_{11}NO_2$: C, 74.46; H, 4.88; N, 6.22; Found: C, 74.76; H, 4.90; N, 6.31.

***N*-(2,6-Dichlorobenzylidene)anthranilic acid (1i).** 90%, mp 203 °C (ethanol); IR (Nujol) 1612 (C=N), 3061 (C–C of aromatic C–H), 1712 (C=O), 3016 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (1H, s), 12.43 (1H, s), 8.33–7.73 (7H, m) (ppm): ms: *m/z* (8.76%) M^+ 294. Anal. calcd for $C_{14}H_9NO_2Cl_2$: C, 57.14; H, 3.06; N, 4.76. Found: C, 57.43; H, 3.16; N, 4.77.

***N*-(*p*-Bromobenzylidene)anthranilic acid (1j).** 70%, mp 198 °C (methanol); IR (Nujol) 1615 (C=N), 3063 (C–C of aromatic C–H), 1714 (C=O), 3015 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.61 (1H, s), 12.43 (1H, s), 8.30–7.72 (8H, m) (ppm): ms: *m/z* (5.67%) M^+ 304. Anal. calcd for $C_{14}H_{10}NO_2Br$: C, 55.26; H, 3.28; N, 4.60; Found: C, 55.23; H, 3.33; N, 4.68.

***N*-(*o*-Bromobenzylidene)anthranilic acid (1k).** 80%, mp 192 °C (ethanol/water); IR (Nujol) 1618 (C=N), 3061 (C-C of aromatic C–H), 1715 (C=O), 3012 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (1H, s), 12.42 (1H, s), 8.30–7.70 (8H, m) (ppm): ms: *m/z* (4.30%) M^+ 304. Anal. calcd for $C_{14}H_{10}NO_2Br$: C, 55.26; H, 3.28; N, 4.60; Found: C, 55.30; H, 3.39; N, 4.23.

***N*-(*p*-*N*,*N*-Dimethylbenzylidene)anthranilic acid (1l).** 90%, mp 178 °C (ethanol/water); IR (Nujol) 1620 (C=N), 3068 (C–C of aromatic C–H), 3015 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (6H, s), 8.68 (1H, s), 12.45 (1H, s), 8.35–7.80 (8H, m) (ppm): ms: *m/z* (5.01%) M^+ 268. Anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.44; Found: C, 71.90; H, 5.66; N, 10.61.

***N*-(*p*-Ethylbenzylidene)anthranilic acid (1m).** 80%, mp 155 °C (ethanol); IR (Nujol) 1615 (C=N), 3066 (C–C of aromatic C–H), 3015 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.66 (1H, s), 12.46 (1H, s), 8.38–7.75 (8H, m) (ppm): ms: *m/z* (6.32%) M^+ 253. Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.88; H, 5.92; N, 5.53; Found: C, 76.13; H, 5.63; N, 5.51.

***N*-[α-(*p*-Chlorophenylazo)-*p*-nitrobenzylidene] anthranilic acid (2n).** Concd HCl (3 mL) was added to a solution of *p*-chloroaniline (0.02 mol) in glacial acetic acid (5 mL). A solution of sodium nitrite (1 gm in 5 mL of water) was then added drop by drop in this solution. The diazonium salt solution of *N*-(*p*-nitrobenzylidene) anthranilic acid (0.02 mol) was added dropwise with constant stirring in methanol (50–70 mL) at below 0 °C. The reaction mixture was kept at room temperature for 3–6 days and then poured into cold water. The solid thus obtained was washed with water and recrystallised from methanol to afford **2n**. 70%, mp 260 °C (methanol); IR (Nujol) 1600 (C=N), 3090 (C–C of aromatic C–H), 1720 (C=O), 3010 (OH), 1430 (*N*=*N*) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.45 (1H, s), 8.60–7.00 (12H, m) (ppm): ms: *m/z* (4.35%) M^+ 408.5. Anal. calcd for $C_{20}H_{13}N_4O_4Cl$: C, 58.75; H, 3.18; N, 13.70; Found: C, 58.63; H, 3.26; N, 13.86.

***N*-[α-(*m*-Chlorophenylazo)-2,4-dichlorobenzylidene] anthranilic acid (2a).** 70%, mp 223 °C (methanol); IR (Nujol) 1610 (C=N), 3092 (C–C of aromatic C–H), 1723 (C=O), 3008 (OH), 1432 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.44 (1H, s), 8.62–7.05 (12H, m) (ppm): ms: *m/z* (3.67%) M^+ 432.5. Anal. calcd for $C_{20}H_{12}N_3O_2Cl_3$: C, 55.49; H, 2.77; N, 9.71; Found: C, 55.50; H, 3.01; N, 10.03.

***N*-[*m*-Chloro-α-(*p*-Chlorophenylazo) benzylidene] anthranilic acid (2b).** 50%, mp 240 °C (benzene); IR (Nujol) 1602 (C=N), 3095 (C–C of aromatic C–H), 1722 (C=O), 3013 (OH), 1432 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.44 (1H, s), 8.62–7.00 (12H,

m) (ppm): ms: *m/z* (4.12%) M^+ 398. Anal. calcd for $C_{20}H_{13}N_3O_2Cl_2$: C, 60.30; H, 3.26; N, 10.55; Found: C, 60.41; H, 3.31; N, 10.60.

***N*-[*o*-Fluoro-α-(phenylazo) benzylidene] anthranilic acid (2c).** 60%, mp 246 °C (ethanol); IR (Nujol) 1605 (C=N), 3096 (C–C of aromatic C–H), 1725 (C=O), 3015 (OH), 1434 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.43 (1H, s), 8.60–7.05 (12H, m) (ppm): ms: *m/z* (5.95%) M^+ 347. Anal. calcd for $C_{20}H_{14}N_3O_2F$: C, 69.16; H, 4.03; N, 12.10; Found: C, 69.21; H, 4.13; N, 12.19.

***N*-[α-(*m*-Chlorophenylazo)-*o*-methoxybenzylidene] anthranilic acid (2d).** 55%, mp 211 °C (methanol); IR (Nujol) 1608 (C=N), 3097 (C–C of aromatic C–H), 1725 (C=O), 3015 (OH), 1435 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.40 (3H, s),12.46 (1H, s), 8.62–7.02 (12H, m) (ppm): ms: *m/z* (6.11%) M^+ 377.5. Anal. calcd for $C_{21}H_{16}N_3O_2Cl$: C, 66.75; H, 4.23; N, 11.12; Found: C, 66.80; H, 4.26; N, 11.22.

***N*-[α-(Chlorophenylazo)-*o*-methoxybenzylidene] anthranilic acid (2e).** 45%, mp 233 °C (DMF/water); IR (Nujol) 1610 (C=N), 3095 (C–C of aromatic C–H), 1728 (C=O), 3018 (OH), 1436 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.45 (3H, m), 12.48 (1H, s), 8.68–7.10 (12H, m) (ppm): ms: *m/z* (5.87%) M^+ 393.5. Anal. calcd for $C_{21}H_{16}N_3O_3Cl$: C, 64.04; H, 4.06; N, 10.67; Found: C, 64.13; H, 4.16; N, 10.66.

***N*-[α-(*m*-Chlorophenylazo)-*p*-methoxybenzylidene] anthranilic acid (2f).** 40%, mp 217 °C (benzene/hexane); IR (Nujol) 1608 (C=N), 3090 (C–C of aromatic C–H), 1730 (C=O), 3020 (OH), 1432 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.39 (3H, m), 12.50 (1H, s), 8.70–7.10 (12H, m) (ppm): ms: *m/z* (6.01%) M^+ 393.5. Anal. calcd for $C_{21}H_{16}N_3O_3Cl$: C, 64.04; H, 4.06; N, 10.67; Found: C, 64.00; H, 4.26; N, 10.59.

***N*-[*p*-Chloro-α-(phenylazo)benzylidene]anthranilic acid (2g).** 60%, mp 222 °C (methanol); IR (Nujol) 1605 (C=N), 3098 (C–C of aromatic C–H), 1728 (C=O), 3018 (OH), 1435 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.44 (1H, s), 8.65–7.10 (12H, m) (ppm): ms: *m/z* (5.54%) M^+ 363.5. Anal. calcd for $C_{20}H_{14}N_3O_2Cl$: C, 66.02; H, 3.85; N, 11.55; Found: C, 66.12; H, 3.87; N, 11.75.

***N*-[α-(*p*-Chlorophenylazo)benzylidene] anthranilic acid (2h).** 60%, mp 186 °C (Ethanol) ; IR (Nujol) 1608 (C=N), 3095 (C–C of aromatic C–H), 1726 (C=O), 3020 (OH), 1438 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.45 (1H, s), 8.68–7.12 (12H, m) (ppm): ms: *m/z* (5.17%) M^+ 363.5. Anal. calcd for $C_{20}H_{14}N_3O_2Cl$: C, 66.02; H, 3.85; N, 11.55; Found: C, 66.32; H, 3.40; N, 11.26.

N-[2,6-Dichloro-α-(phenylazo)benzylidene]anthranilic acid (2i). 60%, mp 254 °C (ethanol); IR (Nujol) 1605 (C=N), 3096 (C–C of aromatic C–H), 1727 (C=O), 3022 (OH), 1440 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.42 (1H, s), 8.70–7.08 (12H, m) (ppm): ms: *m/z* (4.95%) M^+ 398. Anal. calcd for $C_{20}H_{13}N_3O_2Cl_2$: C, 60.30; H, 3.26; N, 10.55; Found: C, 60.45; H, 3.25; N, 10.57.

***N*-[*o*-Bromo-α-(*p*-methoxyphenylazo)benzylidene]anthranilic acid (2j).** 70%, mp 229 °C (benzene); IR (Nujol) 1608 (C=N), 3094 (C–C of aromatic C–H), 1724 (C=O), 3020 (OH), 1442 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.39 (3H, s) 12.40 (1H, s), 8.72–7.10 (12H, m) (ppm): ms: *m/z* (7.01%) M^+ 438. Anal. calcd for $C_{21}H_{16}N_3O_3Br$: C, 57.53; H, 3.65; N, 9.58; Found: C, 57.13; H, 3.70; N, 9.66.

***N*-[*o*-Bromo-α-(*o*-methoxyphenylazo)benzylidene]anthranilic acid (2k).** 70%, mp 236 °C (benzene/hexane); IR (Nujol) 1606 (C=N), 3092 (C–C of aromatic C–H), 1720 (C=O), 3021 (OH), 1444 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.40 (3H, s) 12.42 (1H, s), 8.70-7.08 (12H, m) (ppm): ms: *m/z* (6.89%) M^+ 438. Anal. calcd for $C_{21}H_{16}N_3O_3Br$: C, 57.53; H, 3.65; N, 9.58; Found: C, 57.61; H, 3.55; N, 9.67.

***N*-[*p*-*N*,*N*-Dimethyl-α-(phenylazo)benzylidene]anthranilic acid (2l).** 60%, mp 217 °C (ethanol); IR (Nujol) 1606 (C=N), 3092(C–C of aromatic C–H), 1722 (C=O), 3020 (OH), 1440 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 1.30 (6H, s), 12.38 (1H, s), 8.74–7.12 (12H, m) (ppm): ms: *m/z* (5.25%) M^+ 372. Anal. calcd for $C_{22}H_{20}N_4O_2$: C, 70.96; H, 5.37; N, 15.05; Found: C, 71.20; H, 5.22; N, 15.19.

***N*-[*p*-Ethyl-α-(*m*-chlorophenylazo)benzylidene]anthranilic acid (2m).** 50%, mp 198 °C (ethanol); IR (Nujol) 1605 (C=N), 3090 (C–C of aromatic C–H), 1718 (C=N), 3020 (OH), 1441 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.75 (2H,q), 2.05 (3H, t), 12.38 (1H, s), 8.67–7.05 (12H, m) (ppm): ms: *m/z* (4.87%) M^+ 391.5. Anal. calcd for $C_{22}H_{18}N_3O_2Cl$: C, 67.43; H, 4.59; N, 10.72; Found: C, 67.42; H, 4.60; N, 11.58.

5-(*p*-Chlorophenylazo)-*N*-(*p*-nitrobenzylidene)anthranilic acid (3n). To a solution of *N*-(*p*-nitrobenzylidene)anthranilic acid (0.15 mol) in ethanol (abs. 50 mL) containing glacial acetic acid; pH adjusted to 3, a diazonium salt solution of *p*-chloroaniline was added dropwise with constant vigorous stirring on mechanical stirrer for 72 h below 0 °C. The reaction mixture was kept at room temperature for 24 h and the solvent was removed and the solid thus obtained was recrystallized from acetone to yield **3n** (45%): mp 278 °C; IR (Nujol) 1580 (C=N), 3060 (C–C of aromatic C–H), 1700 (C=O), 3020 (OH), 1420 (N=N), 765 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.40 (1H, s), 8.80 (1H, s) 8.60–7.80 (11H, m) (ppm): ms: *m/z* (7.65%) M^+ 409. Anal. calcd for $C_{20}H_{13}N_4O_4Cl$: C, 58.75; H, 3.18; N, 13.70; Found: C, 58.63; H, 3.22; N, 13.51.

5-(*m*-Chlorophenylazo)-*N*-(2,4-dichlorobenzylidene)anthranilic acid (3a). 50%, mp 246 °C (ethanol); IR (Nujol) 1578 (C=N), 3059 (C–C of aromatic C–H), 1708 (C=O), 3018 (OH), 1422 (N=N), 762 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.36 (1H, s), 8.76 (1H, s), 8.62–7.84 (10H, m) (ppm): ms: *m/z* (4.66%) M^+ 432.5. Anal.

calcd for $C_{20}H_{12}N_3O_2Cl_3$: C, 55.49; H, 2.77; N, 9.71; Found: C, 55.60; H, 2.63; N, 9.76.

***N*-(*m*-Chlorobenzylidene)-5-(*p*-chlorophenylazo)anthranilic acid (3b).** 30%, mp 266 °C (benzene); IR (Nujol) 1582 (C=N), 3056 (C–C of aromatic C–H), 1706 (C=O), 3021 (OH), 1418 (N=N), 760 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.34 (1H, s), 8.77 (1H, s), 8.60–7.80 (11H, m) (ppm): ms: *m*/*z* (6.39%) M^+ 398. Anal. calcd for $C_{20}H_{13}N_3O_2Cl_2$: C, 60.30; H, 3.26; N, 10.55; Found: C,60.33; H, 2.99; N, 10.35.

***N*-(*o*-Fluorobenzylidene)-5-(phenylazo)anthranilic acid (3c).** 40%, mp 280 °C (methanol); IR (Nujol) 1581 (C=N), 3063 (C–C of aromatic C–H), 1769 (C=O), 3016 (OH), 1425 (N=N), 760 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.41 (1H, s), 8.78 (1H, s), 8.62–7.85 (11H, m) (ppm): ms: *m*/*z* (7.03%) M^+ 347. Anal. calcd for $C_{20}H_{14}N_3O_2F$: C, 69.16; H, 4.03; N, 12.10; Found: C,69.26; H, 3.95; N, 12.11.

5-(*m*-Chlorophenylazo)-*N*-(*o*-methylbenzylidene)anthranilic acid (3d). 35%, mp 282C (DMF/water); IR (Nujol) 1580 (C=N), 3060 (C–C of aromatic C–H), 1710 (C=O), 3020 (OH), 1420 (N=N), 756 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (3H, s), 12.38 (1H, s), 8.82 (1H, s), 8.60–7.82 (11H, m) (ppm): ms: *m*/*z* (6.79%) M^+ 377.5. Anal. calcd for $C_{21}H_{16}N_3O_2Cl$: C, 66.75; H, 4.23; N, 11.12; Found: C,66.77; H, 4.46; N, 11.23.

5-(*p*-Chlorophenylazo)-*N*-(*o*-methoxybenzylidene)anthranilic acid (3e). 20%, mp 276 °C (benzene/pet.ether); IR (Nujol) 1585 (C=N), 3061 (C–C of aromatic C–H), 1700 (C=O), 3017 (OH), 1423 (N=N), 758 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (3H, s), 12.40 (1H, s), 8.86 (1H, s), 8.62–7.82 (11H, m) (ppm): ms: *m*/*z* (6.98%) M^+ 393.5. Anal. calcd for $C_{21}H_{16}N_3O_3Cl$: C, 64.04; H, 4.06; N, 10.67; Found: C,64.08; H, 4.03; N, 11.00.

5-(*m*-Chlorophenylazo)-*N*-(*p*-methoxybenzylidene)anthranilic acid (3f). 25%, mp 278 °C (chloroform); IR (Nujol) 1581 (C=N), 3058 (C–C of aromatic C–H), 1712 (C=O), 3017 (OH), 1419 (N=N), 757 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.43 (3H, s), 12.41 (1H, s), 8.85 (1H, s), 8.61–7.85 (11H, m) (ppm): ms: *m*/*z* (7.11%) M^+ 393.5. Anal. calcd for $C_{21}H_{16}N_3O_3Cl$: C, 64.04; H, 4.06; N, 10.67; Found: C,64.13; H, 4.11; N, 10.93.

***N*-(*p*-Chlorobenzylidene)-5-(phenylazo)-anthranilic acid (3g).** 40%, mp 263C (ethanol); IR (Nujol) 1583 (C=N), 3060 (C–C of aromatic C–H), 1705 (C=O), 3015 (OH), 1420 (N=N), 759 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.42 (1H, s), 8.84 (1H, s), 8.60–7.84 (11H, s) (ppm): ms: *m*/*z* (8.75%) M^+ 263. Anal. calcd for $C_{20}H_{14}N_3O_2Cl$: C, 66.02; H, 3.85; N, 11.55; Found: C, 66.22; H, 3.90; N, 11.32.

5-(*p*-Chlorophenylazo)-*N*-(benzylidene)anthranilic acid (3h). 30%, mp 268 °C (methanol); IR (Nujol) 1582 (C=N), 3061 (C–C of aromatic C–H), 1702 (C=O), 3017 (OH), 1421 (N=N), 760 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.40 (1H, s), 8.82 (1H, s), 8.62–7.86 (12H, m) (ppm): ms: *m*/*z* (8.70%) M^+ 263. Anal. calcd for $C_{20}H_{14}N_3O_2Cl$: C, 66.02; H, 3.85; N, 11.55; Found: C,66.22; H, 3.70; N, 11.29.

***N*-(2,6-Dichlorobenzylidene)-5-(phenylazo)anthranilic acid (3i).** 50%, mp 274 °C (hexane); IR (Nujol) 1580 (C=N), 3060 (C–C of aromatic C–H), 1701 (C=O), 3018 (OH), 1420 (N=N), 752 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.81 (1H, s), 8.60–7.82 (11H, m) (ppm): ms: *m*/*z* (6.67%) M^+ 398. Anal. calcd for $C_{20}H_{13}N_3O_2Cl_2$: C, 60.30; H, 3.26; N, 10.55; Found: C, 60.31; H, 3.06; N, 10.65.

***N*-(*p*-Bromobenzylidene)-5-(*p*-methoxyphenylazo)anthranilic acid (3j).** 60%, mp 284 °C (ethanol); IR (Nujol) 1578 (C=N), 3063 (C–C of aromatic C–H), 1698 (C=O), 3017 (OH), 1422 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (3H, s), 8.79 (1H, s), 8.58–7.80 (11H, m) (ppm): ms: *m*/*z* (3.65%) M^+ 438. Anal. calcd for $C_{21}H_{16}N_3O_3Br$: C, 57.53; H, 3.65; N, 9.58; Found: C,57.77; H, 3.80; N, 9.76.

N-(*o*-Bromobenzylidene)-5-(*o*-methoxyphenylazo)anthranilic acid (3k). 60%, mp 263 °C (ethanol); IR (Nujol) 1580 (C=N), 3061 (C–C of aromatic C–H), 1699 (C=O), 3016 (OH), 1421 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (3H, s), 8.80 (1H, s), 8.60–7.80 (11H, m) (ppm): ms: *m*/*z* (4.00%) M^+ 438. Anal. calcd for $C_{21}H_{16}N_3O_3Br$: C, 57.53; H, 3.65; N, 9.58; Found: C, 57.69; H, 3.80; N, 9.23.

***N*-(*p*-*N*,*N*-Dimethylbenzylidene)-5-(phenylazo)anthranilic acid (3l).** 40%, mp 260 °C (ethanol); IR (Nujol) 1583 (C=N), 3062 (C–C of aromatic C–H), 1700 (C=O), 3018 (OH), 1425 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (6H, s) 8.81 (1H, s), 8.64–7.81 (12H, m) (ppm): ms: *m*/*z* (5.35%) M^+ 372. Anal. calcd for $C_{22}H_{20}N_4O_2$: C, 70.96; H, 5.37; N, 15.05; Found: C, 70.77; H, 5.40; N, 15.01.

5-(*m*-Chlorophenylazo)-*N*-(*p*-ethylbenzylidene)anthranilic acid (3m). 30%, mp 266 °C (DMF/water); IR (Nujol) 1584 (C=N), 3065 (C–C of aromatic C–H), 1703 (C=O), 3020 (OH), 1422 (N=N), 760 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.40 (5H, s), 8.80 (1H, s), 8.61–7.80 (11H, m) (ppm): ms: *m*/*z* (6.71%) M^+ 391.5. Anal. calcd for $C_{22}H_{18}N_3O_2Cl$: C, 67.43; H, 4.59; N, 10.72; Found: C, 67.63; H, 4.71; N, 10.63.

5-(*p*-Chlorophenylazo)-2-[4-oxo-2-(*p*-nitrophenyl)thiazolidin-3-yl]benzoic acid (4n). To a solution of 5-(*p*-chlorophenylazo)-*N*-(*p*-nitrobenzylidine)anthranilic acid (0.01 mol) in benzene (dry, 50 mL) thiolactic acid/thioglycolic acid (0.01 mol) was added separately and the reaction mixture was refluxed for 48 h and the completion of the reaction was monitored by TLC. The excess of solvent was distilled off, and the product was recrystallised from DMF/water to afford **4n**. 50%; mp 196 °C; IR (Nujol) 1510 (C–N), 3040 (C–C of aromatic C–H), 1700 (C=O), 3000 (O–H), 1420 (N=N), 760 (C–Cl), 1760 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.40 (1H, s), 6.95 (1H, s), 8.65–7.20 (11H, m), 2.15 (3H, d), 5.95 (1H, q) (ppm): ms: *m*/*z* (3.75%) M^+ 469. Anal. calcd for $C_{23}H_{17}N_4O_5SCl$: C, 55.59; H, 3.42; N, 11.28; Found: C, 55.53; H, 3.55; N, 11.53.

5-(*p*-Chlorophenylazo)-2-[4-oxo-2-(2,4-dichlorophenyl)-thiazolidin-3-yl]benzoic acid (4a). 80%; mp 222 °C (methanol); IR (Nujol) 1509 (C–N), 3042 (C···C of aromatic C–H), 1701 (C=O), 3010 (OH), 1420 (N=N), 761 (C–Cl), 1762 (C=N of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.38 (1H, s), 6.96 (1H, s), 8.68–7.28 (10H, m), 3.68 (2H, s) (ppm); ms: *m*/*z* (2.60%) M^+ 506.5. Anal. calcd for $C_{22}H_{14}N_3O_3SCl_3$: C, 52.12; H, 2.76; N, 8.29; Found: C, 52.32; H, 2.90; N, 8.41.

5-(*p*-Chlorophenylazo)-2-[2-(*m*-chlorophenyl)-4-oxo-thiazolidin-3-yl]benzoic acid (4b). 70% ; mp 210 °C (ethanol); IR (Nujol) 1507 (C–N), 3041 (C···C of aromatic C–H), 1705 (C=O), 3012 (OH), 1425 (N=N), 763 (C–Cl), 1764 (C=N of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.36 (1H, s), 6.92 (1H, s), 8.65–7.26 (11H, m), 3.65 (2H, s) (ppm); ms: *m*/*z* (3.21%) M^+ 472. Anal. calcd for $C_{22}H_{15}N_3O_3SCl_2$: C, 55.93; H, 3.17; N, 8.89; Found: C, 55.71; H, 3.10; N, 9.01.

2-[2-(*o*-Fluorophenyl)-4-oxo-thiazolidin-3-yl]-5-(phenylazo)benzoic acid (4c). 60%; mp 264 °C (benzene/pet.ether); IR (Nujol) 1505 (C–N), 3040 (C–C of aromatic C–H), 1702 (C=N), 3015 (OH), 1426 (N=N), 1768 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.36 (1H, s), 6.90 (1H, s), 8.68–7.30 (12H, m), 3.62 (2H, s) (ppm); ms: *m*/*z* (2.95%) M^+ 421. Anal. calcd for $C_{22}H_{16}N_3O_3SF$: C, 62.70; H, 3.80; N, 9.97 ; Found: C, 62.83; H, 3.93; N, 10.02.

5-(*m*-Chlorophenylazo)-2-[2-(*o*-methoxyphenyl)-4-oxo-thiazolidin-3-yl]benzoic acid (4d). 50%; mp 256 °C (methanol); IR (Nujol) 1508 (C–N), 3045 (C···C of aromatic C–H), 1705 (C=O), 3018 (OH), 1428 (N=N), 765 (C–Cl), 1770 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.30 (1H, s), 6.95 (1H, s), 8.60–7.10 (11H, m), 2.35 (3H, s), 3.60 (2H, s) (ppm); ms: *m*/*z* (4.26%) M^+ 451.5. Anal. calcd for $C_{23}H_{18}N_3O_3SCl$: C, 61.12; H, 3.98; N, 9.30; Found: C, 61.28; H, 3.91; N, 9.56.

5-(*p*-Chlorophenylazo)-2-[2-(*o*-methoxyphenyl)-4-oxo-thiazolidin-3-yl]benzoic acid (4e). 60%; mp 223 °C (ethanol); IR (Nujol) 1510 (C–N), 3042 (C···C of aromatic C–H), 1708 (C=O), 3016 (OH), 1430 (N=N), 760 (C–Cl), 1772 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.32 (1H, s), 6.98 (1H, s), 8.62–7.20 (11H, m), 3.41 (3H, s), 3.65 (2H, s) (ppm); ms: *m*/*z* (3.23%) M^+ 467.5. Anal. calcd for $C_{23}H_{18}N_3O_4SCl$: C, 59.03; H, 3.85; N, 8.98; Found: C, 59.13; H, 3.45; N, 8.64.

5-(*m*-Chlorophenylazo)-2-[2-(*p*-methoxyphenyl)-4-oxo-thiazolidin-3-yl]benzoic acid (4f). 65%; mp 221 °C (chloroform); IR (Nujol) 1505 (C–N), 3040 (C···C of aromatic C–H), 1700 (C=O), 3014 (OH), 1428 (N=N), 762 (C–Cl), 1771 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.30 (1H, s), 6.95 (1H, s), 8.65–7.20 (11H, m), 3.44 (3H, s), 3.64 (2H, s) (ppm); ms: *m*/*z* (2.75%) M^+ 467.5. Anal. calcd for $C_{23}H_{18}N_3O_4SCl$: C, 59.03; H, 3.85; N, 8.98; Found: C, 59.29; H, 3.76; N, 8.76.

2-[2-(*p*-Chlorophenyl)-4-oxo-thiazolidin-3-yl]-5-(phenylazo)benzoic acid (4g). 55%; mp 210 °C (ethanol); IR (Nujol) 1502 (C–N), 3048 (C–C of aromatic C–H), 1700 (C=O), 3020 (OH), 1425 (N=N), 763 (C–Cl), 1772 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.32 (1H, s), 6.92 (1H, s), 8.58–7.10 (12H, m), 3.63 (2H, s), 5.90 (1H, q) (ppm); ms: *m*/*z* (3.26%) M^+ 437.5. Anal. calcd for $C_{22}H_{16}N_3O_3SCl$: C, 60.34; H, 3.65; N, 9.60 ; Found: C, 60.48; H, 3.71; N, 10.00.

5-(*m*-Chlorophenylazo)-2-[5-methyl-4-oxo-2-phenylthiazolidin-3-yl]benzoic acid (4h). 40% mp 195 °C (methanol); IR (Nujol) 1512 (C–N), 3044 (C···C of aromatic C–H), 1702 (C=O), 3002 (OH), 1422 (N=N), 761 (C–Cl), 1761 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.41 (1H, s), 6.94 (1H, s), 8.68–7.24 (12H, m), 2.14 (3H, d), 5.98 (1H, q) (ppm); ms: *m*/*z* (2.67%) M^+ 451.5. Anal. calcd for $C_{23}H_{18}N_3O_3SCl$: C, 61.12; H, 3.98; N, 9.30 ; Found: C, 61.42; H, 3.71; N, 9.20.

2-[2-(2,3-Dichlorophenyl)-5-methyl-4-oxo-thiazolidin-3-yl]-5-(phenylazo)benzoic acid (4i). 50%; mp 178 °C (methanol); IR (Nujol) 1511 (C–N), 3043 (C–C of aromatic C–H), 1703 (C=O), 3005 (OH), 1425 (N=N), 762 (C–Cl), 1760 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.44 (1H, s), 6.92 (1H, s), 8.66–7.22 (11H, m), 2.15 (3H, d), 5.95 (1H, q) (ppm); ms: *m*/*z* (2.30%) M^+ 487. Anal. calcd for $C_{23}H_{17}N_3O_3SCl_2$: C, 56.79; H, 3.50; N, 8.64 ; Found: C, 56.73; H, 3.85; N, 8.56.

2-[2-(*p*-Bromophenyl)-5-methyl-4-oxo-thiazolidin-3-yl]-5-(p-Methoxyphenylazo)benzoic acid (4j). 65%; mp 203 °C (ethanol); IR (Nujol) 1514 (C–N), 3042 (C–C of aromatic C–H), 1705 (C=N), 3002 (OH), 1424 (N=N), 1762 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.42 (1H, s), 6.95 (1H, s), 8.64–7.20 (11H, m), 3.41(3H, s) 2.12 (3H, d), 5.96 (1H, q) (ppm); ms: *m*/*z* (1.67%) M^+ 526. Anal. calcd for $C_{24}H_{20}N_3O_4SBr$: C, 54.75; H, 3.80; N, 7.98 ; Found: C, 54.80; H, 3.72; N, 8.02.

2-[2-(*o*-Bromophenyl)-5-methyl-4-oxo-thiazolidin-3-yl]-5-(*o*-Methoxyphenylazo)benzoic acid (4k). 70%; mp 226 °C (methanol); IR (Nujol) 1510 (C–N), 3041 (C···C of aromatic C–H), 1708 (C=O), 3005 (OH), 1426 (N=N), 1765 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.40 (1H, s), 6.90 (1H, s), 8.66–7.26 (11H, m), 3,43 (3H, s) 2.14 (3H, d), 5.98 (1H, q) (ppm); ms: *m*/*z* (2.01%) M^+ 526. Anal. calcd for $C_{24}H_{20}N_3O_4SBr$: C, 54.75; H, 3.80; N, 7.98 ; Found: C, 54.94; H, 3.67; N, 7.70.

2-[2-(*p*-*N*,*N*-Dimethylphenyl)-5-methyl-4-oxo-thiazolidin-3-yl]-5-(phenylazo)benzoic acid (4l). 50%; mp 203 °C (ethanol); IR (Nujol) 1515 (C–N), 3045 (C–C of aromatic C–H), 1700 (C=O), 3006 (OH), 1427 (N=N), 1768 (C=O of β-thialactum) cm^{-1}, ^1H NMR ($CDCl_3$) δ 12.41 (1H, s), 6.88 (1H, s), 8.65–7.25 (12H, m), 1.48 (6H, s), 2.15 (3H, d), 5.96 (1H, q) (ppm); ms: *m*/*z* (3.56%) M^+ 447. Anal. calcd for $C_{24}H_{23}N_4O_3S$: C, 64.42; H, 5.12; N, 12.52; Found: C, 64.62; H, 5.13; N, 12.56.

5-(*m*-Chlorophenylazo)-2-[2-(*p*-ethylphenyl)5-methyl-4-oxo-thiazolidin-3-yl]benzoic acid (4m). 35%; mp 212 °C (benzene); IR (Nujol) 1512 (C–N), 3044 (C···C of aromatic C–H), 1705 (C=O), 3002 (OH), 1426 (N=N),

1769 (C=O of β-thialactum), 764 (C–Cl) cm^{-1}, ^1H NMR ($CDCl_3$) δ (5H, s), 12.38 (1H, s), 6.90 (1H, s), 8.66–7.28 (11H, m), 2.18 (3H, d), 5.98 (1H, q) (ppm); ms: *m*/*z* (3.52%) M^+ 479.5. Anal. calcd for $C_{25}H_{22}N_3O_3SCl$: C, 62.56; H, 4.58; N, 8.75; Found: C, 62.63; H, 4.92; N, 8.80.

Pharmacological evaluation

Anti-inflammatory activity. Paw edema inhibition test was used on albino rats of charles foster species by adopting the method of Winter et al.[9] Groups of five rats of both sexes (body weight 120–160 g), pregnant females excluded, were given a dose of a test compound. 30 min later, 0.2 mL of 1% carrageenan suspension in 0.9% NaCl solution was injected subcutaneously, into the plantar aponeurosis of the hind paw and the paw volume was measured by a water plethysmometer socrel and then measured again 3 h later. The mean increase of paw volume at each time interval was compared with that of control group (five rats treated with carrageenan, but not treated with test compounds) at the same time intervals and percent inhibition values were calculated by the formula given below:

$$\%\ \text{anti-inflammatory activity} = 1 - \frac{D_t}{D_c} \times 100$$

where D_t and D_c are tested and control groups, respectively.

Analgesic activity. Acetic acid writhing test was performed on mice by following the method of Davis et al.[10] Groups of five mice body weight (20–30 g) of both sexes, pregnant female excluded, were given a dose of a test compound. 30 min later, the animals were injected intraperitoneally with 0.25 mL/mouse of 0.5% acetic acid during the following 25 min. The mean number of writhes for each experimental groups and percentage decrease compared with the control group (five mice not treated with test compounds) were calculated after 60 min.

Ulcerogenic activity. Groups of 10 rats (body weight 200–250 g) of both sexes, pregnant females excluded, fasted for 24 h, were treated with an oral dose of a test compound, except control group. All animals were sacrificed 6 h after dosing and their stomachs and small intestines were microscopically examined to assess the incidence of hyperaemia, shedding of epithelium, petechial and frank haemorrhages and erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.[11]

Acute toxicity study. Approximate 50% lethal dose (ALD_{50}) of the compounds were determined in albino mice. The mice of either sex 20–25 g were used. The test compounds were injected intraperitoneally at different dose levels in groups of 10 animals. After 24 h of drug administration, percent mortality in each group was observed from the data obtained ALD_{50} was calculated by the method of Smith.[12]

Cyclooxygenase activity. This test was carried out in vitro on the microsomal fraction of mucosal preparations of rabbit distal colon in order to search out the possible mechanism of the compounds. The preparation was based on the method of Calderano et al.[13] Colonic mucosa (≅2–3 g), stripped as previously described was minced and homogenized Potter homogenizer in 3 vols of Tris buffer 0.1, pH 8.0. The homogenate was centrifused for 30 min at 10,000*g*. The resulting supernatent was centrifused for 1 h at 100,000*g*. The precipitate was suspended in Tris buffer 0.1 M, pH 8.0, and recentrifused for 1 h at 100,000*g*. The microsomal pellet was used immediately for enzyme assay cyclooxygenase activity was assayed by measuring the rate of conversion of arachidonic acid to PGE_2. Microsomal fractions (50 μL) were incubated with test agents for 5 min at 37 °C in 30 μL Tris–HCl, pH 8.0 containing 2 mM reduced glutathione, 5 mM L-tryptophan, 1 μM hematin. The substrate 20 μM arachidonic acid with tracer amount of [1-^{14}C] arachidonic acid [≅200 (xx) cpm] was then added and the reaction proceeded for 3 min at 37 °C. The reaction was stopped by addition of 0.2 mL of ethyl ether/methanol/citric acid 0.2 M (30:4:1), which was precooled at −25 °C PGE_2, was extracted twice into the same mixture. The solvent was evaporated under an N_2 stream and radiolabelled arachidonic acid was separated from radiolabelled acid was separated from radiolabelled PGE_3 by RP-HBLC. HPLC analysis was performed on a Hitachi spectrophotometer equipped with a flow cell. the sample was injected on an ultra sphere column (Beckman) ODS 5 mm×4.6 mm×25 cm. with 2 nmol unlabelled PGE_2 as an interval standard, PG chromatographic profile was obtained by isocratic elution with 150 mM H_3PO_4 in water, pH 3.5, containing 30% acetonitrile, a flow rate of 1 mL/min monitoring the uv absorption at 214 nm. Radioactivity that co-eluted with autheutic PGE_2 was quantified by liquid scintillation spectrometry. Test samples were compared to paired control incubations. The percentage of inhibition was calculated as follows.

$$[(\text{cpm control} - \text{cpm test}/\ (\text{cpm control})) \times 100]$$

Statistical analysis. This was carried out using Student *t*-test.

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