Synthesis and Pharmacological Evaluation of 1-(1-((Substituted)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(substituted pyridin-2-yl)thiosemicarbazide

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Some novel Mannich base isatin derivatives were synthesized by reacting 1-(5-methyl-2-oxoindolin-3-ylidene)-4-(substitutedpyridin-2-yl)thiosemicarbazide with formaldehyde and several secondary amines. Their chemical structure was elucidated by means of spectral (FT-IR, ^{1}H- and ^{13}C-NMR and mass) analysis. Investigation of anti-inflammatory activity of synthesized compounds was done by carrageenan induced paw oedema method using diclofenac sodium as standard drug and analgesic activity was done by acetic acid induced writhing method. The synthesized compounds showed significant anti-inflammatory and analgesic activity.

Key words isatin; schiff base; mannich base; anti-inflammatory; analgesic

Isatin (indole-2,3-dione) is an endogenous compound, widely distributed in mammalian tissues and body fluids.[1)] In the brain the highest levels have been found in the hippocampus[2)] (0.1 μg/g) and an immunocytochemical staining revealed specific localization within particular cells. *In vivo* isatin administration causes a range of dose-dependent behavioral effects[3)] including angiogenesis and increased water retention. *In vitro*, isatin is a potent inhibitor of both atrial natriureticpeptide (ANP) stimulated membrane bound guanylate cyclase and nitric oxide-stimulated soluble guanylate cyclase.[4)] It is an inhibitor of monoamine oxidase B (IC503-8 lM) and of atrial natriuretic peptide receptor binding (0.4 lM) at levels that may be in the physiological range.[5)] Isatin is well known as pharmacological agent having a range of action in the brain and to be protective against certain types of infections. Isatin (indolin-2,3-dione) derivatives are reported to show other biological activities like antibacterial,[6—8)] antifungal,[9—11)] antiviral,[12—14)] anti HIV,[15—17)] antiprotozoal,[18,19)] muscle relaxant,[20)] antiallergic[21)] and anti-inflammatory[22)] activities. Prompted by the biological properties of 2,3-dioxindole derivatives and its Schiff and Mannich bases, it was decided to synthesize various Mannich bases of isatin and its derivatives with pyridine and to screen them for their anti-inflammatory and analgesic properties. The results of such studies are discussed in this paper.

The N-Mannich bases of isatin derivatives were synthesized by condensing 1-(5-methyl-2-oxoindolin-3-ylidene)-4-(substitutedpyridin-2-yl)thiosemicarbazide with formaldehyde and various secondary amines (Chart 1). All the compounds gave satisfactory elemental analysis. IR, ^{1}H-, ^{13}C-NMR and mass spectra were consistent with the assigned structures. All the synthesized compounds were screened for anti-inflammatory and analgesic activity.

MATERIAL AND METHODS

General Experimental Procedure All protocols of animal experiments have been approved by the Institutional Animal Ethics Committee (IAEC). Melting points were determined in open capillary tubes and are uncorrected. The physical constants of the synthesized compounds are given in Table 1. The purity of the synthesized compounds was routinely checked by TLC on silica gel G. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL GSX 400 spectrometer using TMS as an internal standard (chemical shifts in δ, ppm), IR spectra on a Shimadzu FT 8300 infrared spectrophotometer (ν_{max} cm^{-1}) and mass spectra on a JEOL MSMATE spectrometer. Microanalyses for C, H and N were performed in a Heraeus CHN Rapid Analyser.

Synthesis of 5-Methyl Isatin (1) To 65 ml of concentrated sulphuric acid at 50 °C was added 15 g of dry isonitrosoacetanilide derivative. The solution was heated to 80 °C and was kept at this temperature for about 10 min. Then it was cooled to room temperature and poured upon cracked ice. After 90 min, the 5-methyl isatin was filtered, washed several times with cold water to remove sulphuric acid and then dried in air.

Synthesis of 4-(Substituted pyridin-2-yl)thiosemicarbazide (2) To a solution of substituted 2 amino pyridine (0.01 mol) in DMF (10 ml) was added sodium hydroxide (0.01 mol) and carbon disulphide (0.75 ml). The mixture was stirred at 15—20 °C for 1 h, to the stirred mixture was added hydrazine hydrate (0.01 mol) and stirring continued at 60 °C for 1 h. On adding water a pale yellow solid separated out which is recrystallized from DMF-ethanol.

Synthesis of 1-(5-Methyl-2-oxoindolin-3-ylidene)-4-(substituted pyridin-2-yl)thiosemicarbazide (3) Equimolar quantities of 5-methyl isatin and 4(substituted pyridin-2-yl)thiosemicarbazide were dissolved in warm ethanol containing 1 ml of glacial acetic acid. The reaction mixture was refluxed for 10 h and set aside. The resultant solid was washed with dilute ethanol dried and recrystallized from ethanol and chloroform mixture.

Synthesis of (4a—j) A slurry consisting of 1-(5-methyl-2-oxoindolin-3-ylidene)-4-(substituted pyridin-2-yl)thiosemicarbazide (0.002 mol), THF (3 ml) and 37% formalin (1 ml) was made. To this was added amine (0.003 mol) drop wise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 h with occasional shaking after, which it was warmed on a steam bath for 15 min. At the end of the period the contents were cooled and the product obtained was recrystallized from chloroform

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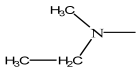
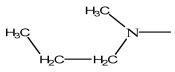
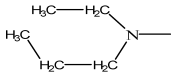
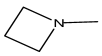
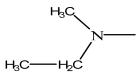
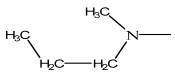
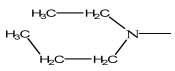
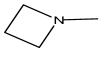
Table 1. Physical Data of the Synthesized Compounds

Compounds	R	R_1	R_2	Yield (%)	mp (°C)	Mol. formula
4a		CH_3	H	68	160	$C_{20}H_{24}N_6OS$
4b		CH_3	H	74	172	$C_{21}H_{26}N_6OS$
4c		CH_3	H	71	182	$C_{22}H_{28}N_6OS$
4d		CH_3	H	78	164	$C_{19}H_{20}N_6OS$
4e		CH_3	H	81	150	$C_{20}H_{22}N_6OS$
4f		H	CH_3	71	162	$C_{20}H_{24}N_6OS$
4g		H	CH_3	77	166	$C_{21}H_{26}N_6OS$
4h		H	CH_3	69	170	$C_{22}H_{28}N_6OS$
4i		H	CH_3	73	168	$C_{19}H_{20}N_6OS$
4j		H	CH_3	80	158	$C_{20}H_{22}N_6OS$

and petroleum ether.

1-(1-((Ethyl(methyl)amino)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (**4a**): The sample was recrystallized using chloroform and petroleum ether. Yield: 68%. mp 160 °C. IR (KBr) cm^{-1}: 3364, 2852, 1694, 1645, 1283, 1105. ^{1}H-NMR (DMSO-d_6) δ: 8.12 (1H, d, J=7.4 Hz), 7.6 (1H, d, J=8.1 Hz), 7.4 (1H, s), 7.1 (1H, d, J=8.1 Hz), 7.0 (1H, s), 6.60 (1H, s), 6.50 (1H, d, J=7.4 Hz), 4.03 (2H, t), 4.0 (1H, s), 2.40 (2H, m), 2.37 (3H, s), 2.36 (3H, s), 2.28 (3H, s), 1.00 (3H, m). ^{13}C-NMR (DMSO-d_6) δ: 12.8, 24.3, 40.8, 49.4, 72.6, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 167.5, 186; MS *m*/*z*: 396.17 (M^+). *Anal.* Calcd for $C_{20}H_{24}N_6OS$: C, 60.58; H, 6.10; N, 21.20. Found: C, 60.55; H, 6.09; N, 21.18.

1-(5-Methyl-1-((methyl(propyl)amino)methyl)-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (**4b**): the sample was recrystallized using chloroform and petroleum ether. Yield: 74%. mp 172 °C. IR (KBr) cm^{-1}: 3360, 2854, 1682, 1640, 1123. ^{1}H-NMR (DMSO-d_6) δ: 8.13 (1H, d, J=7.5 Hz), 7.6 (1H, d, J=8.0 Hz), 7.4 (1H, d), 7.1 (1H, d, J=8.0 Hz), 7.0 (1H, d), 6.60 (1H, s), 6.52 (1H, d, J=7.5 Hz), 4.03 (2H, d), 4.01 (1H, s), 2.40 (2H, d), 2.37(3H, s), 2.36 (2H, d), 2.34 (3H, s), 2.29 (3H, s), 1.43 (2H, d,), 0.96 (3H, d); ^{13}C-NMR (DMSO-d_6) δ: 11.8, 20.09, 24.3, 41.1, 56.5, 72.9, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 410.19 (M^+); *Anal.* Calcd for $C_{21}H_{26}N_6OS$: C, 61.44; H, 6.38; N, 20.47. Found: C, 61.42; H, 6.36; N, 20.45.

1-(1-((Ethyl(propyl)amino)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (**4c**): The sample was recrystallized using chloroform and petroleum ether. Yield: 71%. mp 182 °C. IR (KBr) cm^{-1}: 3369, 2872, 1684, 1642, 1286, 1125. ^{1}H-NMR (DMSO-d_6) δ: 8.14 (1H, d, J=7.6 Hz), 7.61 (1H, d, J=7.2 Hz), 7.4 (1H, d), 7.12 (1H, d, J=7.2 Hz), 7.01 (1H, d), 6.60 (1H, s), 6.52 (1H, d, J=7.6 Hz), 4.03 (2H, s), 4.01 (1H, s), 2.40 (2H, d), 2.37 (3H, s), 2.36 (2H, d,), 2.35 (3H, s), 1.43 (2H, m), 1.0 (3H, m), 0.96 (3H, d). ^{13}C-NMR (DMSO-d_6) δ: 11.8, 13.1, 21.2, 24.3, 47.2, 54.0, 70.4, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 424.2 (M^+); *Anal.* Calcd for $C_{22}H_{28}N_6OS$: C, 62.24; H, 6.65; N, 19.79. Found: C, 62.21; H, 6.62; N, 19.78.

1-(1-(Aziridin-1-ylmethyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (**4d**): The sample was recrystallized using chloroform and petroleum ether. Yield: 78%. mp 164 °C. IR (KBr) cm^{-1}: 3372, 2858, 1684, 1628, 1110. ^{1}H-NMR (DMSO-d_6) δ: 8.11 (1H, d, J=7.5 Hz), 7.64 (1H, d, J=8.3 Hz), 7.4 (1H, d), 7.15 (1H, d, J=8.3 Hz), 7.0 (1H, d), 6.60 (1H, s), 6.53 (1H, d, J=7.5 Hz), 4.03 (2H, s), 4.01 (1H, s), 2.40 (2H, d), 2.37 (3H, s), 2.36 (2H, d, J=4.0 Hz), 2.35 (3H, s), 1.61 (4H, m). ^{13}C-NMR (DMSO-d_6) δ: 24.3, 25.8, 75.1, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 380.14 (M^+); *Anal.* Calcd for $C_{19}H_{20}N_6OS$: C, 59.98; H, 5.30; N, 22.09. Found: C, 59.97; H, 5.28; N, 22.05.

1-(1-(Azetidin-1-ylmethyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (**4e**): The sample was recrystallized using chloroform and petroleum ether. Yield: 81%. mp 150 °C. IR (KBr) cm^{-1}: 3363, 2872, 1658, 1638, 1115. ^{1}H-NMR (DMSO-d_6) δ: 8.10 (1H, d, J=7.7 Hz), 7.65 (1H, d, J=8.5 Hz), 7.4 (1H, d), 7.12 (1H, d, J=8.5 Hz), 7.0 (1H, d), 6.60 (1H, s), 6.50 (1H, d, J=7.7 Hz), 4.03 (2H, s), 4.02 (1H, s), 3.29 (4H, m), 2.37 (3H, s), 2.34

(3H, s), 1.24 (2H, m). ^{13}C-NMR (DMSO-d_6) δ: 16.5, 24.3, 46.4, 72.6, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 394.16 (M^+); *Anal.* Calcd for $C_{20}H_{22}N_6OS$: C, 60.89; H, 5.62; N, 21.30. Found: C, 60.86; H, 5.60; N, 21.31.

1-(1-((Ethyl(methyl)amino)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (**4f**): The sample was recrystallized using chloroform and petroleum ether. Yield: 71%. mp 162 °C. IR (KBr) cm^{-1}: 3370, 2868, 1682, 1641, 1140. ^{1}H-NMR (DMSO-d_6) δ: 7.61 (1H, d, *J*=8.2 Hz), 7.44 (1H, m), 7.4 (1H, s), 7.1 (1H, d, *J*=8.2 Hz), 7.0 (1H, s), 6.54 (1H, m), 6.50 (1H, m), 4.03 (2H, s), 4.0 (1H, s), 2.57 (3H, s), 2.40 (2H, d), 2.33 (3H, s), 2.27 (3H, s), 1.00 (3H, m). ^{13}C-NMR (DMSO-d_6) δ: 12.8, 24.3 (d), 40.8, 49.4, 72.6, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 167.5, 186; MS *m*/*z*: 396.17(M^+); *Anal.* Calcd for $C_{20}H_{24}N_6OS$: C, 60.58; H, 6.10; N, 21.20. Found: C, 60.57; H, 6.09; N, 21.17.

1-(5-Methyl-1-((methyl(propyl)amino)methyl)-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (**4g**): The sample was recrystallized using chloroform and petroleum ether. Yield: 77%. mp 166 °C. IR (KBr) cm^{-1}: 3362, 2862, 1678, 1633, 1134. ^{1}H-NMR (DMSO-d_6): δ 7.62 (1H, d, *J*=8.3 Hz), 7.44 (1H, m), 7.4 (1H, s), 7.1 (1H, d, *J*=8.3 Hz), 7.0 (1H, s), 6.54 (1H, m), 6.50 (1H, m), 4.03 (2H, s), 4.0 (1H, s), 2.55 (3H, s), 2.36 (2H, d), 2.35 (3H, s), 2.27 (3H, s), 1.43 (2H, m), 0.96 (3H, t); ^{13}C-NMR (DMSO-d_6) δ: 11.8, 20.09, 24.3, 41.1, 56.5, 72.9, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 410.19 (M^+); *Anal.* Calcd for $C_{21}H_{26}N_6OS$: C, 61.44; H, 6.38; N, 20.47. Found: C, 61.41; H, 6.35; N, 20.4.

1-(1-((Ethyl(propyl)amino)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (**4h**): The sample was recrystallized using chloroform and petroleum ether. Yield: 69%. mp 170 °C. IR (KBr) cm^{-1}: 3368, 2812, 1662, 1626, 1126. ^{1}H-NMR (DMSO-d_6) δ: 7.6 (1H, d, *J*=8.1 Hz), 7.44 (1H, m), 7.4 (1H, s), 7.11 (1H, d, *J*=8.1 Hz), 7.01 (1H, s), 6.54 (1H, m), 6.50 (1H, m), 4.04 (2H, s), 4.01 (1H, s), 2.56 (3H, s), 2.40 (2H, d), 2.36 (2H, d), 2.35 (3H, s), 1.43 (2H, m), 1.01 (3H, d), 0.96 (3H, t); ^{13}C-NMR (DMSO-d_6) δ: 11.8, 13.1, 21.2, 24.3, 47.2, 54.0, 70.4, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 424.2 (M^+); *Anal.* Calcd for $C_{22}H_{28}N_6OS$: C, 62.24; H, 6.65; N, 19.79. Found: C, 62.20; H, 6.63; N, 19.77.

1-(1-(Aziridin-1-ylmethyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (**4i**) The sample was recrystallized using chloroform and petroleum ether. Yield: 73%. mp 168 °C. IR (KBr) cm^{-1}: 3361, 2867, 1668, 1632, 1120. ^{1}H-NMR (DMSO-d_6) δ: 7.63 (1H, d, *J*=8.0 Hz), 7.44 (1H, m), 7.4 (1H, s), 7.11 (1H, d, *J*=8.0 Hz), 7.01 (1H, s), 6.54 (1H, m), 6.50 (1H, m), 4.04 (2H, s), 4.01 (1H, s), 2.56 (3H, s), 2.36 (3H, s), 1.61 (4H, m); ^{13}C-NMR (DMSO-d_6) δ: 24.3, 25.8, 75.1, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 380.14 (M^+); *Anal.* Calcd for $C_{19}H_{20}N_6OS$: C, 59.98; H, 5.30; N, 22.09. Found: C, 59.96; H, 5.27; N, 22.06.

1-(1-(Azetidin-1-ylmethyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (**4j**): The sample was recrystallized using chloroform and petroleum ether. Yield: 80%. mp 158 °C IR (KBr) cm^{-1}: 3367, 2856, 1656, 1630, 1283, 1122. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (1H, d, *J*=8.5 Hz), 7.43 (1H, m), 7.41 (1H, s), 7.12 (1H, d, *J*=8.5 Hz), 7.0 (1H, s), 6.56 (1H, m), 6.51 (1H, m), 4.04 (2H, s), 4.01 (1H, s), 3.29 (4H, m), 2.56 (3H, s), 2.36 (3H, s), 2.23 (2H, m); ^{13}C-NMR (DMSO-d_6) δ: 16.5, 24.3, 46.4, 72.6, 112.7, 117.7, 121.6, 129.7, 131.6, 132.8, 134.1, 144.4, 148.7, 149.6, 159.1, 163.5, 186; MS *m*/*z*: 394.16 (M^+); *Anal.* Calcd for $C_{20}H_{22}N_6OS$: C, 60.89; H, 5.62; N, 21.30. Found: C, 60.87; H, 5.59; N, 21.28.

Pharmacology. Anti-inflammatory Activity All protocols of animal experiments have been approved by the Institutional Animal Ethics Committee (IAEC). Albino rats of either sex, weighing between 120—150 g were used. They were kept on standardized diet and water *ad libitum*. The 2,3-indoline-dione derivatives **4a**—**j** were dissolved in suitable solvent (Tween-80) and used. The animals were divided into seven groups. Acute inflammation was produced by subplantar injection of 0.1 ml of 1% suspension of carrageenan in normal saline in the right hind paw of the rats. Paw volume was measured plethysmometrically at '0' to '2' h after carrageenan injection. The animals were treated with **4a**—**j** orally using oral feeding needle. Saline (3 ml/kg, orally) treated animals served as control and diclofenac sodium (45 mg/kg, orally) was administered as standard drug to a group of animals. The drugs were administered simultaneously with carrageenan injection. Mean increase in paw volume was measured and percentage of inhibition was calculated (Table 2).

Analgesic Activity The analgesic activiy of isatin derivatives **4a**—**j** were assessed by acetic acid induced writhing in mice. Groups of 6 mice of either sex with body weight of 22 to 41 g were used. Appropriate volume of acetic acid solution was administered to the first group (which serves as control), placed them individually under glass jar for observation.

Onset on wriths were noted, the number of abdominal contractions were recorded, trunk twist response and extension of hind limbs as well as the number of animals showing such response during a period of 10 min were also recorded.

To the second group of animals diclofenac sodium 45 mg/kg were administered. Fifteen minutes later, to these animals acetic acid solution were administered. The onset and severity of writhing response were noted. The mean writhing scores in control and diclofenac sodium treated

Table 2. Effect of **4a**—**j** on Carrageenan Induced Paw Oedema

Treatment	Dose (mg/kg)	Mean increase in paw volume (ml)	Percentage inhibition of oedema
Control	Saline	0.34±0.02	—
Diclofenac sodium	45 mg/kg	0.12±0.01**	64.70
4a	100 mg/kg	0.24±0.02*	29.41
4b	100 mg/kg	0.26±0.01	23.52
4c	100 mg/kg	0.22±0.007*	35.29
4d	100 mg/kg	0.23±0.006*	32.35
4e	100 mg/kg	0.245±0.007	27.94
4f	100 mg/kg	0.20±0.02**	41.17
4g	100 mg/kg	0.19±0.03**	44.11
4h	100 mg/kg	0.246±0.008	27.64
4i	100 mg/kg	0.28±0.02	17.64
4j	100 mg/kg	0.235±0.007*	30.88

*$p<0.05$ was considered as significant. **$p<0.01$ by Dunnet's '*t*' test (multiple comparison test) compared with control. Values are expressed in mean±S.E.M. (n=6).

Table 3. Analgesic Effect of Synthesized Compound by Writhing Reflex Method

Treatment	Dose (mg/kg)	Mean writhing ±S.E.M.	Percentage protection
Control	Saline	32±0.7303	—
Diclofenac sodium	45 mg/kg	8.3±0.33**	74.06
4a	100 mg/kg	23.0±0.4773	28.12
4b	100 mg/kg	26.5±0.4282	17.18
4c	100 mg/kg	21.0±0.730*	34.37
4d	100 mg/kg	27.3±0.494	14.68
4e	100 mg/kg	20.0±0.4216*	37.5
4f	100 mg/kg	15.0±0.6708**	53.12
4g	100 mg/kg	26.8±0.307	16.25
4h	100 mg/kg	22±0.3651*	31.25
4i	100 mg/kg	18.9±0.3073**	40.93
4j	100 mg/kg	25.0±0.3073	21.87

$*p<0.05$ was considered as significant. $**p<0.01$ by Dunnet's 't' test (multiple comparison test) compared with control. Values are expressed in mean±S.E.M. ($n=6$).

groups were calculated (Table 3).

Statistical Analysis The statistical significance between the groups was analysed by means of analysis of variance (ANOVA) followed by Dunnet's multiple comparison test (INSTAT-3 computer program). All values were expressed as mean±S.E.M. Differences below the probability level of 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The target compounds were prepared by using the reaction sequence in Chart 1. The Schiff bases of isatin derivatives were synthesized by condensation of the keto group of isatin with various thiosemicarbazides. The N-Mannich base isatin derivatives were synthesized by condensing 1-(5-methyl-2-oxoindolin-3-ylidene)-4-(substitutedpyridine-2-yl)thiosemicarbazide with formaldehyde and various secondary amines like ethyl methyl amine, methyl propyl amine, ethyl propyl amine, aziridine and azetidine. All the compounds gave satisfactory elemental analysis (±0.4%). The chemical structures of the synthesized compounds were confirmed by means of their IR, ^{1}H-, ^{13}C-NMR and mass spectral analysis.

All the synthesized compounds were tested for anti-inflammatory activity. The synthesized compounds show significant anti-inflammatory activity when compared to standard diclofenac sodium (45 mg/kg). The results of the present investigation suggests that **4g**, **4f** and **4c** followed by **4d** and **4j** have low paw volume when compared with that of control, so these compounds has significant anti-inflammatory effect against carrageenan induced paw oedema in rats. In the present investigation, as the test drugs are effective in this model of inflammation, there is a possibility that these drugs may be effective in acute inflammation.

The synthesized compounds shows significant analgesic activity, but generally, the synthesized compounds 1-(1-((ethyl(methyl)amino)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (**4f**) and 1-(1-(aziridin-1-ylmethyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl) thiosemicarbazide (**4i**) ($p<0.01$) followed by **4c** and **4h** possess remarkable analgesic activity. The exhibited analgesic and anti-inflammatory activity of the compounds may be due to its structural similarity with indomethacin.

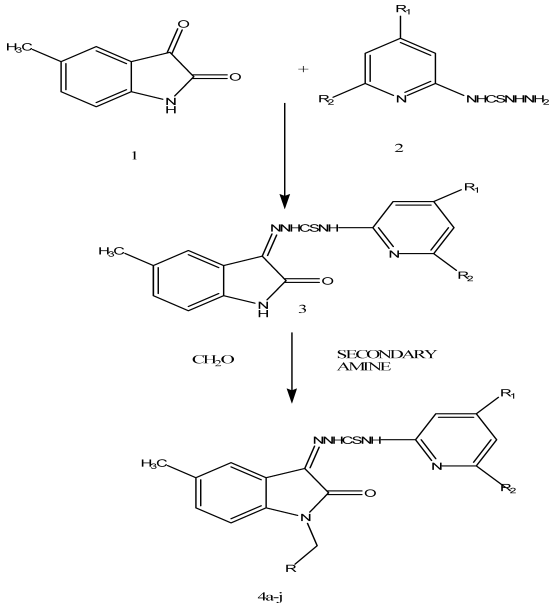


Chart 1

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