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Synthesis and Antimicrobial Activity of Schiff's and Mannich Bases of 1H–Indole–2,3–Dione Derivatives

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Abstract

1H–indole–2,3–dione and its derivatives were reacted with 4–amino–N–(5,6–dimethoxypyrimidin–4–yl)benzenesulfonamide to form Schiff's bases and the Mannich bases of these compounds were synthesized by reacting them with formaldehyde and piperidine. All the compounds were characterized by means of their IR, ^{1}H NMR spectroscopic data and elemental analysis. The antimicrobial activity of these compounds was evaluated by tube dilution method. All compounds showed considerable enhanced antibacterial activity (low MIC) against all bacteria when compared to reference drug sulfadoxine. None of the compounds was active against C. abony. None of the compounds showed antifungal activity.

Key Words: 1H–indole–2,3–dione, sulfadoxine, Schiff's base, Mannich bases, Antimicrobial activity.

INTRODUCTION

Isatin (1H–indole–2,3–dione) is an endogamous compound identified in humans and its effect has been studied in variety of systems.

In recent years, schiffs and Mannich bases of isatins are reported to exhibit broad spectrum chemotherapeutic properties such as antiviral [1–3], anti TB [4,5], antifungal and antibacterial [6,7].

Investigation of the structure activity relationships in isatin derivatives revealed that 5–halogenation [4–8], N. alkylation [8,9], N. Mannich bases [5,7] and thiosemicarbazone formation(2,3,6) were active against various bacteria and virus. 4–amino–N–(5,6–dimethoxypyrimidine–4–yl) benzenesulfonamide (sulfadoxine) is a potent antibacterial.

In view of these facts and continuation of our work on 1H–indole–2,3–dione, we have synthesized new Schiff's bases of isatin derivatives with sulfadoxine. The N–Mannich bases of above Schiff's bases were synthesized by condensing the acidic imino group of isatin with formaldehyde and piperidine. All the synthesized compounds were screened for the antibacterial and anti fungal activities.

RESULTS AND DISCUSSION

All the synthesized compounds were screened for antibacterial activity against three Gram positive and Gram negative bacterial strains. Also included is the activity of reference compound sulfadoxine. It has been observed that all compounds tested showed more activity (Less MIC) than reference drug sulfadoxine.

Compounds, 45, 46, 47, 48, 49 and 50 showed very significant results against *S. aureus.*

Compounds 45, 46, 47, 49 and 55 were most active against *B, pumitis.* Compounds 47 was conspicuously most active against *E. Coli.* Compound 49 was most active against *K. pneumoniae.* None of the compounds was bound to be active against *Salmonella abony.*

The compounds were also screened for antifungal activity using clotrimazole as standard reference drug. None of the synthesized compounds possessed antifungal activity.

Table–2: Antimicrobial activity MIC (μg mL^{-1}) antibacterial activity

Compound Microorganism	1	2	3	4	5	6	7	8	9	10	11	12	Sulfadoxine
S. aureus	125	138	138	138	125	125	163	185	200	200	185	180	250
B. pumulis	125	125	125	190	137	175	137	225	200	125	125	200	350
B. subtilis	125	125	125	125	125	138	190	225	190	185	190	220	250
E. coli	225	240	163	185	175	185	200	250	190	185	210	230	650
S. abony	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1500
K. pneumoniae	300	300	300	300	175	250	300	325	300	325	325	325	500

N.A. not active

Table–3: Antifungal activity MIC (μg mL^{-1})

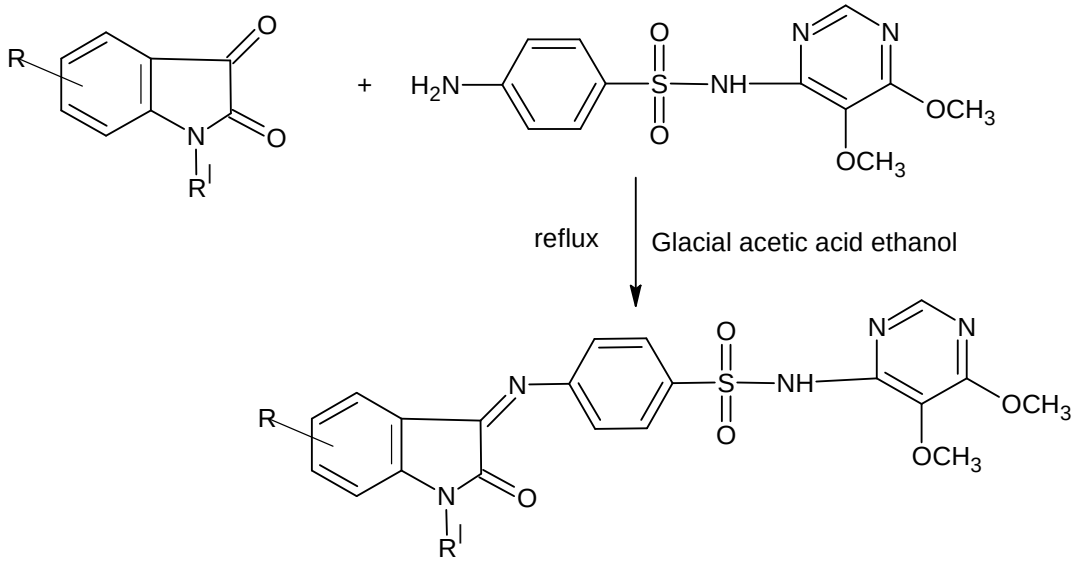
Compound Microorganism	1	2	3	4	5	6	7	8	9	10	11	12	Clotrimazole
S. cerevisiae	NA	NA	250	NA	280	NA	NA	NA	NA	NA	NA	NA	10
C. albicans	NA	NA	600	NA	NA	NA	NA	NA	NA	NS	NA	NA	0.3

NA – not active

MATERIALS AND METHODS

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on 300 MHz Brucker DRX–300 using DMSO with TMS as internal standard IR spectra were recorded in KBr on FTIR 8400S Shimdzu spectrophotometer. The elemental analysis was performed on Carlo Erba 1108 and were within ± 4% of the theoretical values. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) silica-G (Merk) coated glass plates, visualized by iodine vapour.

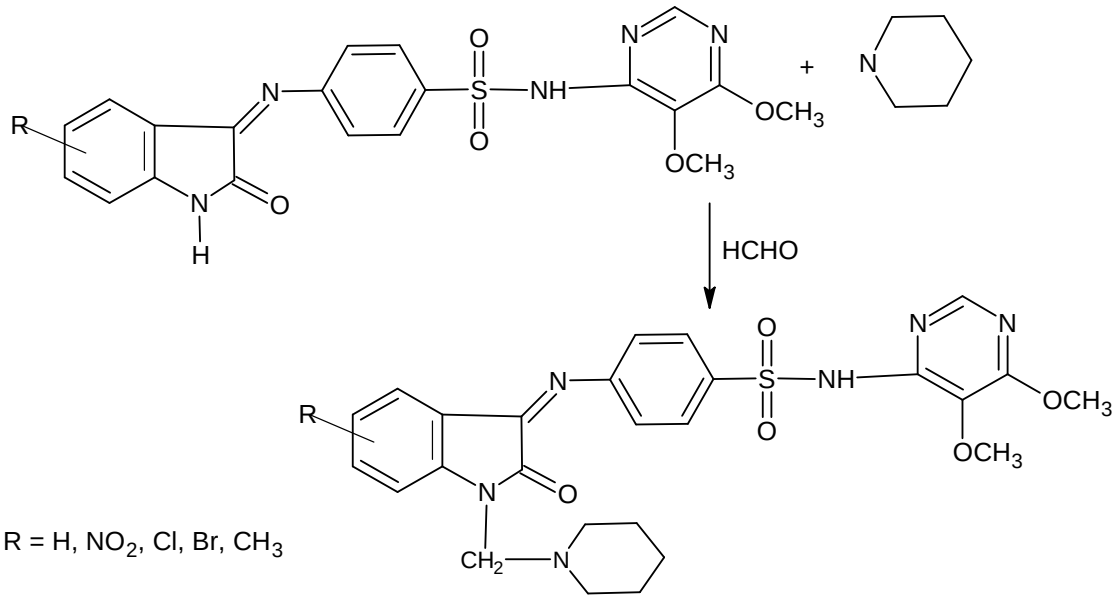
5–Nitroisatin [10], 5–methyl isatin[11], 5–chloroisatin[12], N–methylisatin[13] and N–acetylisatin[14] were synthesized by the methods given in previous literature.



R = H, NO_2, Cl, Br, CH_3

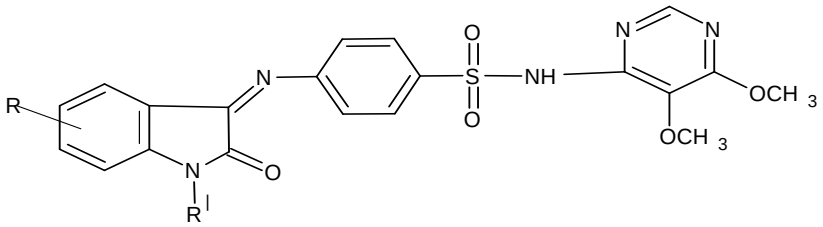
R^I = H, CH_3, $COCH_3$

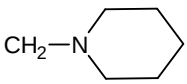
Scheme - 1: Synthesis of Schiff's bases

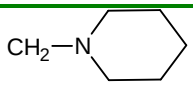
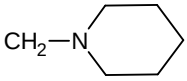
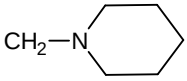
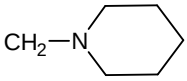


Scheme – 2: Synthesis of N–Mannich base

Table 1: Physical Constants



Code	R	R'	M.P. (°C)	Mol. Formula	Yield (%)	Rf
AS1	H	H	165	$C_{20}H_{17}N_5O_2S$	69	0.47
AS2	NO_2	H	175	$C_{20}H_{16}N_6O_7S$	61.8	0.45
AS3	Br	H	170	$C_{20}H_{16}BrN_5O_5S$	69.76	0.8
AS4	CH_3	H	168	$C_{21}H_{19}N_5O_5S$	61.0	0.48
AS5	Cl	H	160	$C_{20}H_{16}ClN_5O_5S$	65.0	0.50
AS6	H	CH_3	200	$C_{21}H_{19}N_5O_5S$	51.54	0.48
AS7	H	$COCH_3$	180	$C_{22}H_{19}N_5O_6S$	43.32	0.66
AS8	H		130	$C_{26}H_{28}N_6O_5S$	87	0.53

AS9	NO_2		115	$C_{26}H_{27}N_7O_7S$	93	0.54
AS10	Br		120	$C_{26}H_{27}BrN_6O_5S$	97	0.70
AS11	CH3		90	$C_{27}H_{30}N_6O_5S$	97	0.75
AS12	Cl		135	$C_{26}H_{27}ClN_6O_5S$	97	0.53

Synthesis of Schiff's base (AS1–AS7) general Method:

Equimolar quantities of (0.01) mol of isatin/substituted isatins and 4–amino–N–(5,6–dimethoxy pyrimidin–4–yl) benzene sulfonamide were dissolved in 40 mL of ethanol. Glacial acetic acid (2 mL) was added and refluxed for about 8–12 hours. The content was poured on crushed ice. The crystalline product was collected by filtration, dried and recrystallised.

(Z)−N−(5,6−dimethoxypyrimidin−4−yl)−4(2−oxoindolin)–3–ylidineamino)benzenesulfonamide
IR (KBr) 3380 (NH), 1720 (C=O), 1640 (C=N), 1330 anti 1170 syn (O=S=O); ^{1}HNMR (DMSO) ppm: 2.48 (6H, s, OCH_3), 6–8.09 (9H, m, ArH), 10.58 (1H, s, NH) 11.2 (1H, s, SO_2NH cm^{-1}).

(Z)−N−(5,6−dimethoxypyrimidin−4−yl)−4−(5−nitro−2−oxoindolin−3−ylideneamino) benzenesulfonamide
IR (KBr) 3377 (NH), 1752 (C=O), 1651 (C=N), 1508 (NO) anti 1318 anti 1157 syn (O=S=O) cm^{-1}; ^{1}HNMR (DMSO) ppm: 2.06 (6H, s, OCH_3), 6.02–8.1 (8H, m, ArH), 10.50 (1H, s, NH) 11.9 (1H, s, SO_2NH).

(Z)−N−(5−bromo−2−oxoindolin−3−ylideneamino)−N−(5,6−dimethoxypyrimidin−4−yl) benzenesulfonamide
IR (KBr) 3377 (NH), 1746 (C=O), 1640 (C=N), 1388 anti 1158 syn (O=S=O), 620 (C–Br) cm^{-1}; ^{1}HNMR (DMSO) ppm: 1.19 (6H, s, OCH_3), 6.54–6.09 (8H, m, ArH), 10.16 (1H, s, NH) 11.11 (1H, s, SO_2NH).

(Z)−N−(5,6−(5,6−dimethoxypyrimidin−4−yl)−4−(5−methyl−2−oxoindolin−3−ylideneamino) benzenesulfonamide
IR (KBr) 3380 (NH), 2918 (C–H), 1730 (C=O), 1640 (C=N), 1340 anti 1170 syn (O=S=O) cm^{-1}; ^{1}HNMR (DMSO) ppm: 1.052 (6H, s, OCH_3), 7.0–8.0 (8H, m, ArH), 10.5 (1H, s, NH) 11.9 (1H, s, SO_2NH).

(Z)−4−(5−Chloro−2−oxoindolin−3−ylideneamino)−N−(5,6− dimethoxypyrimidin−4−yl) benzenesulfonamide
IR (KBr) 3480 (N–H), 1750 (C=O), 1640 (C=N), 1350 anti 1470 syn (O=S=O), 720 (C–Cl) cm^{-1}; ^{1}HNMR (DMSO) ppm: 1.03 (6H, s, OCH_3), 6.03–7.6 (8H, m, ArH), 10.1 (1H, s, NH) 11.13 (1H, s, SO_2NH).

(Z)−N−(5,6−dimethoxypyrimidin−4−yl)−4−(1−methyl−2− oxoindolin−3−ylidineamino) benzenesulfonamide
IR (KBr) 2950 (C–H), 1741 (C=O), 1651 (C=N), 1363 anti 1180 syn (O=S=O) cm^{-1}, ^{1}HNMR (DMSO) ppm: 1.03 (3H, s, CH_3), 2.0 (6H, s, OCH_3), 6.05–8.0 (9H, m, ArH) 10.9 (1H, s, SO_2NH).

(Z)−4−(1−acetyl−2−oxoindolin−3−ylidineamino)−N−(5,6− dimethoxypyrimidine−4−yl) benzenesulfonamide
IR (KBr) 2900 (C–H), 1680 (C=O), 1640 (C=N), 1350 anti 1140 syn (O=S=O) cm^{-1}, ^{1}HNMR (DMSO) ppm: 1.03 (3H, s, $COCH_3$), 1.95 (6H, s, OCH_3), 6.54–8.11 (9H, m, ArH) 10.63 (1H, s, SO_2NH).

Synthesis of Mannich bases (AS8–AS12) General Method:

A slurry consisting of 0.005 mol of Schiff base containing the acidic imino group of isatin, 5 mL of tetrahydrofuran and 2 mL of 37% formalin was made. To this piperidine (0.005 mol) was added dropwise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 hour with occasional shaking after which it was warmed on a steam bath for 15 minutes. At the end of the period the contents were cooled and the product obtained was recrystallised from petroleum ether.

(Z)−N−(5,6−dimethoxypyrimidin−4−yl)−4−(2−oxo−1−(piperidine−1−ylmethyl)indolin−3−yli dineamino) benzenesulfonamide
IR (KBr) 2942 (C–H), 1714 (C=O), 1640 (C=N), 1315 anti 1180 syn (O=S=O) cm^{-1}, ^{1}HNMR (DMSO) ppm: 2.01 (6H, s, OCH_3), 3.84–4.12 (10H, d, piperidine), 5.9 (2H, s, N–CH_2) 6.53–8.04 (9H, m, ArH), 10.6 (1H, s, SO_2NH).

(Z)−N−(5,6−dimethoxypyrimidin−4−yl)−4−(5−nitro−1−oxo−1−(piperidine−1−ylmethyl)indol in−3−ylidineamino) benzene-sulfonamide
IR (KBr) 2945 (CH), 1738 (C=O), 1650 (C=N), 1530 (NO), 1315 anti, 1160 syn (O=S=O) cm^{-1}, ^{1}HNMR (DMSO) ppm: 1.18 (6H, s, OCH_3), 4.67–4.8 (10H, d, piperidine), 5.5 (2H, s, N–CH_2) 6.2–8.56 (8H, m, ArH), 9.90 (1H, s, SO_2NH).

(Z)−N−(5−bromo−2−oxo−1−(piperidine−1−ylmethyl)indolin−ylidineamino)−N−(5,6−dimeth oxypyrimidin−4−yl) benzene-sulfonamide
IR (KBr) 2880 (C–H), 1720 (C=O), 1640 (C=N), 1315 anti 1168 syn (O=S=O) cm^{-1}, ^{1}HNMR (DMSO) ppm: 1.98 (6H, s, OCH_3), 4.63–4.94 (10H, d, piperidine), 5.96 (2H, s, N–CH_2) 6.53–8.60 (8H, m, ArH), 9.97 (1H, s, SO_2NH).

(Z)−4−(5−methyl−2−oxo−1−(piperidine−1−ylmethyl)indolin−3−ylidineamino)−N−(5,6−dime thoxypyrimidin−4−yl) benzene-sulfonamide
IR (KBr) 2900 (CH), 1730 (C=O), 1640 (C=N), 1315 anti, 1165 syn (O=S=O) cm^{-1}, ^{1}HNMR (DMSO) ppm: 1.02 (3H, s, CH_3), 2.01 (6H, s, OCH_3), 4.2–4.8 (10H, d, piperidine), 6.2–8.9 (8H, m, ArH), 10.2 (1H, s, SO_2NH).

(Z)−4−(5−chloro−2−oxo−1−(piperidine−1−ylmethyl)indolin−3−ylidineamino)−N−(5,6−dimethoxypyrimidin−4−yl) benzene-sulfonamide
IR (KBr) 2945 (CH), 1720 (C=O), 1640 (C=N), 1315 anti, 1168 syn (O=S=O), 720 (C–Cl) cm^{-1}, ^{1}HNMR (DMSO) ppm: 1.8 (6H, s, OCH_3), 4.59–4.9 (10H, d, piperidine), 5.52 (1H, s, N–CH_2), 6.02–7.9 (8H, m, ArH) , 9.98 (1H, s, SO_2NH).

Antimicrobial Screening
A series of glass tubes[14] containing different concentrations of the synthesized compounds (in DMF) with Muellor–Hinton broth was inoculated with the required amount of the inoculum to obtain a suspension of microorganism which contains 10^5 colony forming units per milliliter. One growth control tube was prepared with the addition of the compound and one blank tube was prepared without the addition of microorganism. The tubes was inoculated at 37°C for 24 hours. The turbidity produced was recorded by using a UV−visible spectrometer. The minimum inhibitory concentration (MIC– μgL^{-1}) was considered to be the lowest concentration which exhibited the same turbidity as the blank tube. The observed MIC_3 ($\mu g\ mL^{-1}$) are presented in table 2 and 3.

CONCLUSION

Both schiff's and Mannich bases were active but Schiff bases showed better antibacterial activity than Mannich bases. Substitution by $-CH_3$ and −Cl at 5 position produced maximum activity against Gram negative strains *E. Coli* and *K. Pneumoniae*.

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