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Synthesis and Antimicrobial Activity of Schiff's and N-Mannich Bases of Isatin and Its Derivatives with 4-Amino-N-Carbamimidoyl Benzene Sulfonamide

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ABSTRACT
Isatin and substituted Isatin were reacted with 4-amino-N-carbamimidoyl benzene sulfonamide to form a series of Schiff's bases. The Mannich bases of these compounds were synthesized by reacting them with formaldehyde and secondary amine (piperidine). All the compounds were characterized by means of their IR, ^{1}H NMR spectroscopic data and elemental analysis. The antimicrobial activity of the synthesized compounds was evaluated by tube dilution method. The synthesized compounds showed better antibacterial activity than the reference drugs.

Keywords: Isatin, Schiff's bases, Mannich bases, Antimicrobial activity.

INTRODUCTION

Isatin (2, 3–dioxindole) has been recently found to exhibit endogamous activity in mammals. [1] In recent years schiff's and Mannich bases of isatins are reported to exhibit broad spectrum chemotherapeutic properties such as antibacterial [2–15], antifungal [2-15], anti HIV [6-10, 16-17], antiviral [18-19], anticonvulsant [20-23], antitubercular [24-26] and anticancer. [27-29]

In continuation of our work on Isatin, we have synthesized new Schiff's bases of Isatin with 4-amino-N-carbamimidoyl benzenesulfonamide. The N–Mannich bases of above Schiff's bases were synthesized by condensing the acidic imino group of Isatin with formaldehyde and piperidine.

MATERIALS AND METHODS

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR were recorded on 300 MHz Brucker DRX–300 using DMSO with TMS as internal standard. IR spectra were recorded in KBr on FTIR 8400S Shimadzu IR Spectrophotometer. The elemental analysis was performed on Carlo Erba 1108 and was within ± 4 % of the theoretical values. The turbidity was recorded on UV-Visible spectrophotometer (UV-1601, Shimadzu). The homogeneity of the compounds was monitored by thin layer chromatography (TLC) Silica-G (Merck) coated glass plates, visualized by iodine vapour.

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Synthesis of Schiff's base (PS1–PS7), General Method

Equimolar quantities of 0.01 mol of Isatin/substituted Isatin and 4-amino-N-carbamimidoyl 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-Carbamimidoyl-3 (2-oxoindolin-3-ylideneamino) benzenesulfonamide

IR (KBr) 3468 (NH str), 1733 (C=O str), 1640 (C=N str), 1330 anti, 1127 Syn (O=S=O str) cm^{-1}. ^{1}H NMR (DMSO) ppm. 5.63 (3H, s, NH=C–NH_2), 6.51–7.57 (8H, m, ArH), 10.0 (1H, s, NH), 10.96 (1H, s, SO_2NH).

(Z)-4-(5-bromo-2-oxoindolin-3-ylideneamino)-N-carbamimidoyl benzene sulfonamide

IR (KBr) 3408 (NH str), 1733 (C=O str), 1640 (C=N str), 1330 anti, 1127 Syn (O=S=O str), 620 (CBr str) cm^{-1}. ^{1}H NMR (DMSO) ppm. 5.64 (3H, s, NH=C–NH_2), 6.51–7.73 (7H, m, ArH), 10.0 (1H, s, N–H), 11.02 (1H, s, SO_2NH).

(Z)-N-carbamimidoyl-4-(5-nitro-2-oxoindolin-3-ylidene amino) benzene-sulfonamide

IR (KBr) 3460 (NH str), 1730 (C=O str), 1640 (C=N str), 1519 (N–O str), 1330 anti, 1127 Syn (O=S=O str) cm^{-1}. ^{1}H

NMR (DMSO) ppm. 5.68 (3H, s, NH=C–NH_2), 6.5–9.4 (7H, m, ArH), 11.50 (1H, s, NH), 11.69 (1H, s, SO_2NH).

(Z)-N-carbamimidoyl-4-(5-methyl-2-oxoindolin-ylidene amino) benzene sulfonamide

IR (KBr) 3460 (NH str), 2900 (CH str), 1730 (C=O str), 1640 (C=N str), 1330 anti, 1127 Syn (O=S=O str) cm^{-1}. ^1H NMR (DMSO) ppm. 1.6 (3H, s, CH_3), 5.68 (3H, s, NH=C–NH_2), 6.5–8.4 (7H, m, ArH), 11.50 (1H, s, NH), 11.6 (1H, s, SO_2NH).

(Z)-N-carbamimidoyl-4-(5-chloro-2-oxoindolin-3-ylidene amino) benzene sulfonamide

IR (KBr) 3468 (NH str), 1730 (C=O str), 1640 (C=N str), 1330 anti, 1127 Syn (O=S=O str), 730 (C–Cl str) cm^{-1}. ^1H NMR (DMSO) ppm. 5.6 (3H, s, NH=C–NH_2), 6.48–7.60 (7H, a, ArH), 10.9 (1H, s, NH), 11.10 (1H, s, SO_2NH).

(Z)-4-(1-acetyl-2-oxoindolin-3-ylideneamino)-N-carbamimidoyl benzene-sulfonamide

IR (KBr) 3430 (NH str), 2900 (CH str), 1728 (C=O str), 1640 (C=N str), 1346 anti, 1127 Syn (O=S=O str), cm^{-1}. ^1H NMR (DMSO) ppm. 1.89 (3H, s, $NHCOCH_3$), 5.67 (3H, s, NH=C–NH_2), 6.5–7.9 (8H, m, ArH), 10.14 (1H, s, SO_2NH).

(Z)-N-carbamimidoyl-4-(1-methyl-2-oxoindolin-3-ylideneamino) benzene-sulfonamide

IR (KBr) 3468 (NH str), 2930 (CH str), 1730 (C=O str), 1640 (C=N str), 1346 anti, 1127 Syn (O=S=O str), cm^{-1}. ^1H NMR (DMSO) ppm. 1.88 (3H, s, CH_3), 5.6 (3H, s, NH=C–NH_2), 6.50–7.96 (8H, m, ArH), 10.9 (1H, s, SO_2NH).

Synthesis of N-Mannich bases (PS8-PS12) General Method

A slurry consisting of 0.005 mol of Schiff's base containing the acidic imino group of Isatin, 5 ml of tetrahydrofuran and 2 ml of 37 % formula was made. To this piperidine (0.005 mol) was added drop wise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 hour with occasional shaking then 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-Carbamimidoyl-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidine-amino) benzenesulfonamide

IR (KBr) 3438 (NH str), 2920 (CH str), 1733 (C=O str), 1612 (C=N str), 1346 anti, 1127 Syn (O=S=O str), cm^{-1}. 4.50 (10H, s, piperidine), 4.8 (2H, s, N–CH_2), 5.08 (3H, s, NH=C–NH_2), 6.24–7.93 (8H, m, ArH), 9.9 (1H, s, SO_2NH).

(Z)-4-(5-bromo-2-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino)-N-carbamimidoyl benzenesulfonamide

IR (KBr) 3432 (NH str), 2930 (CH str), 1730 (C=O str), 1630 (C=N str), 1320 anti, 1127 Syn (O=S=O str), 620 (CBr str) cm^{-1}. ^1H NMR (DMSO) ppm, 4.52 (10H, s, piperidine), 4.72 (2H, s, C–CH_2), 5.08 (3H, s, NH=C–NH_2), 6.24–7.93 (7H, m, ArH), 9.9 (1H, s, SO_2NH).

(Z)-N-Carbamimidoyl-4-(5-nitro-2-oxo-1(piperidin-1-ylmethyl) indolin-3-ylideneamino) benzenesulfonamide

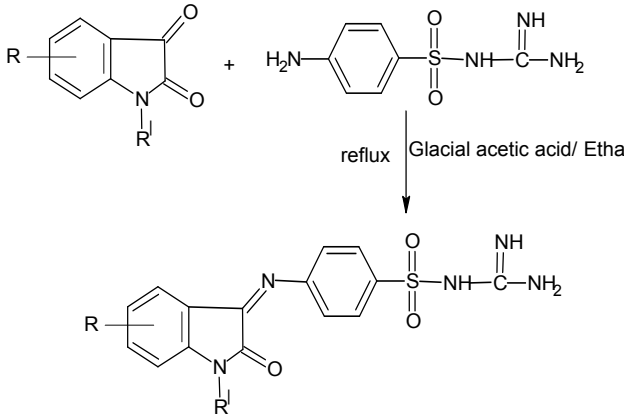
IR (KBr) 3230 (NH str), 2900 (CH str), 1740 (C=O str), 1614 (C=N str), 1530 (NO str), 1320 anti, 1127 Syn (O=S=O str) cm^{-1}. ^1H NMR (DMSO) ppm, 4.36 (10H, s, piperidine), 4.48 (2H, s, C–CH_2), 4.67 (3H, s, NH=C–NH_2), 6.31–8.30 (7H, m, ArH), 9.67 (1H, s, SO_2NH).

(Z)-N-Carbamimidoyl-4-(5-methyl-2-oxo-1(piperidin-1-ylmethyl) indolin-3-ylideneamino) benzenesulfonamide

IR (KBr) 3438 (NH str), 2935 (CH str), 1740 (C=O str), 1614 (C=N str), 1530 (NO str), 1330 anti, 1127 Syn (O=S=O str) cm^{-1}. ^1H NMR (DMSO) ppm, 4.43 (10H, s, piperidine), 4.73 (2H, s, N–CH_2), 4.67 (3H, s, NH=C–NH_2), 6.31–8.30 (7H, m, ArH), 9.67 (1H, s, SO_2NH).

(Z)-N-Carbamimidoyl-4-(5-chloro-2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylideneamino) benzenesulfonamide

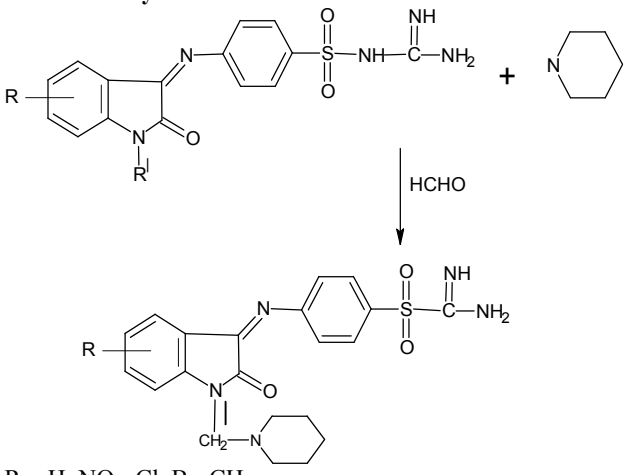
IR (KBr) 3440 (NH str), 2935 (CH str), 1740 (C=O str), 1640 (C=N str), 1330 anti, 1127 Syn (O=S=O str) 720 (CCl str) cm^{-1}. ^1H NMR (DMSO) ppm, 4.48 (10H, s, piperidine), 4.74 (2H, s, N–CH_2), 4.9 (3H, s, NH=C-NH_2), 6.78–7.71 (7H, m, ArH), 10.0 (1H, s, SO_2NH).



R = H, NO_2, Cl, Br, CH_3

R^1 = CH_3, $COCH_3$

Scheme–1: Synthesis of Schiff's base



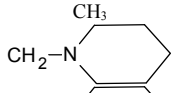
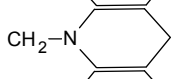
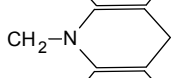
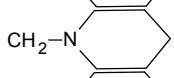
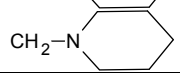
R = H, NO_2, Cl, Br, CH_3

Scheme–2: Synthesis of N-Mannich base

Antimicrobial Screening

A series of glass tubes [29-30] containing different concentrations of the synthesized compounds (in DMF) with Muller–Hinton broth was inoculated with the required amount of inoculum to obtain a suspension of microorganism which contains 10^5 colony forming units per milliliter. One growth control tube was prepared without the addition of compound and one blank tube was prepared without the addition of microorganism. The tube was inoculated at 37°C for 24 hours. The turbidity produced was recorded by using a UV –visible spectrometer. The minimum inhibitory concentration (MIC–mg L^{-1}) was considered to be the lowest concentration which exhibited the same turbidity as the blank tube. The observed MIC (mg L^{-1}) is presented in Table 2 and 3.

Table 1: Physical Constants of Synthesized compounds

Compound Code	*R*	*R*[1]	*M.P. (°C)*	*Molecular Formula*	*Yield (%)*	*Rf*
PS–1	H	H	100	$C_{15}H_{13}N_5O_2S$	72	0.65
PS–2	Br	H	300	$C_{15}H_{12}BrN_5O_3S$	56	0.60
PS–3	NO_2	H	240	$C_{15}H_{12}N_6O_6S$	60	0.68
PS–4	CH_3	H	130	$C_{16}H_{15}N_5O_2S$	71	0.53
PS–5	Cl	H	120	$C_{15}H_{12}ClN_2O_3S$	78	0.58
PS–6	H	$COCH_3$	200	$C_{17}H_{15}N_5O_4S$	46	0.54
PS–7	H	CH_3	150	$C_{16}H_{15}N_5O_3S$	70	0.62
PS–8	H		110	$C_{21}H_{24}N_6O_3S$	97	0.70
PS–9	Br		100	$C_{21}H_{23}BrN_6O_3S$	78	0.69
PS–10	NO_2		130	$C_{21}H_{23}N_7O_5S$	89	0.79
PS–11	CH_3		115	$C_{22}H_{26}N_6O_3S$	90	0.73
PS–12	Cl		135	$C_{21}H_{23}ClN_6O_3S$	90	0.67

Solvent system: Benzene: Methanol (8:2 v/v).

Elemental analysis (CHN) was undertaken for all compounds and was within ± 4% of calculated values.

Table 2: Antimicrobial activity MIC (mg L^{-1})

Compound Microorganism	*PS1*	*PS2*	*PS3*	*PS4*	*PS5*	*PS7*	*PS8*	*PS9*	*PS10*	*PS11*	*PS12*	*Sulfaguanidine*
S. aureus	300	225	275	250	50	275	350	375	375	325	375	1200
B. pumulis	275	225	225	250	200	225	275	300	300	275	325	1400
B. subtilis	225	200	225	225	125	225	275	300	275	275	275	1200
E. coli	200	200	225	225	100	225	275	275	300	250	250	1500
S. abony	200	200	225	225	250	225	325	325	350	325	350	>1500
K. pneumoniae	250	250	250	250	225	250	300	325	250	275	275	1700

Table 3: Antifungal activity MIC (mg L^{-1})

Compound Microorganism	*PS1*	*PS2*	*PS3*	*PS4*	*PS5*	*PS7*	*PS8*	*PS9*	*PS10*	*PS11*	*PS12*	*Clotrimazole*
S. cerevisiae	NA	NA	250	NA	280	NA	NA	NA	NA	NA	NA	10
C. albicans	NA	NA	600	NA	NA	NA	NA	NA	NA	NA	NA	0.3

NA – not active

RESULTS AND DISCUSSION

The synthesized compounds were screened for antibacterial activity against three gram positive and three gram negative bacterial strains. 4-amino-N-carbamimidoyl benzene sulfonamide was used as reference compound. It has been observed that all compounds exhibited very significant and better antibacterial activity in comparison to the standard drug against both gram positive and gram negative bacterial strains. The most active compound with lowest MIC against all gram positive and gram negative bacterial strains was found to be compound PS5. Substitution by Cl atom at 5–position produced most active antibacterial compound of the series.

None of the compounds exhibited significant antifungal activity comparable to standard antifungal drug Clotrimazole against *S. cerevisiae* and *C. albicans*.

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