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Synthesis And Antimicrobial Activity Of Some Novel Mannich Bases Of Isatin

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ABSTRACT

A series of novel Mannich bases have been synthesized by treating 1(5 bromo-2-oxoindolin-3-ylidene)-4-(pyridine-2-yl)thiosemicarbazide with formaldehyde and different secondary amines. The structures of compounds were established on the basis of the elemental analysis. IR, ^{1}H-NMR and mass spectral data. The compounds were investigated for antimicrobial activity against *B.subtilis, S.aureus, S.epidermidis,E.coli, P.aeruginosa, Salmonella typhi, Candida albicans, Cryptococcus neoformas and A.niger.*

KEYWORDS

Isatin;
Mannich base;
Antimicrobial activity.

INTRODUCTION

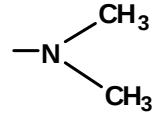
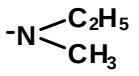
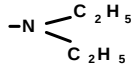
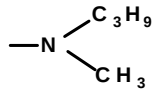
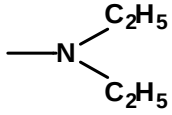
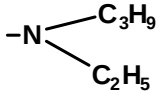
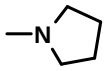
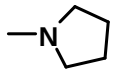
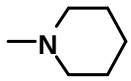
Isatin is an endogenous compound isolated in 1988[1] and reported to possess a wide range of central nervous system activities[2-3]. Isatin is the biologically active chemical produced by an alteromones sp. Strain inhabiting the surface of embryos of the cardiean shrimp palaemon macrodectyius, which protects them from the pathogenic fungus langenidum callinecus[4]. Mannich bases and isatin derivatives were reported to possess antibacterial[5-7], antifungal[8-10], antiviral[11-13], anti-HIV[14-16], antiprotozoal[17-18] and antihelminthic[19-20] activities. The N-mannich bases of the above isatin derivatives were synthesized by condensing the isatin derivative with formaldehyde and secondary amines (SCHEME 1). All compounds (TABLE 1) gave satisfactory elemental analysis. IR, ^{1}H-NMR and mass spectra were consistent with the assigned structures. All the synthesized compounds were screened for antibacterial, antifungal activity by the disc diffusion method.

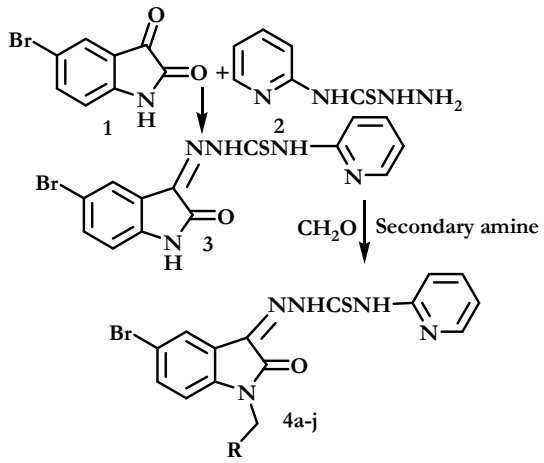
EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was routinely checked by TLC on silica gel G. ^{1}H-NMR spectra were recoded on JEOL GSX 400 spectrometer using TMS as internal standard(chemical shifts in δppm); IR spectra on a Shimadzu FT 8300 infrared spectrophotometer(ν_{max} cm^{-1}) and mass spectra on a JEOL MSMATE spectrometer.

General procedure for the synthesis of 5-bromo isatin (1)

55ml of concentrated sulphuric acid was warmed and to this, 15g of dry isonitrosoacetanilide derivative was added. After the addition of the isonitroso

Compounds	R	Compounds	R
4a		4f	
4b		4g	
4c		4h	
4d		4i	
4e		4j	



SCHEME 1

TABLE 1

Characterization data of compounds 4a-4j

Comp.	Mol.formula	m.p °C (±2°C)	Yield %	Elemental analysis of compounds (%)found		
				C	H	N
4a	$C_{17}H_{17}BrN_6OS$	158	81	47.05	3.78	19.25
4b	$C_{19}H_{21}BrN_6OS$	168	79	49.45	4.42	18.16
4c	$C_{27}H_{21}BrN_6OS$	179	80	58.08	3.66	14.98
4d	$C_{19}H_{19}BrN_6OS$	163	80	49.58	4.15	18.11
4e	$C_{20}H_{21}BrN_6OS$	148	78	50.25	4.34	17.58
4f	$C_{18}H_{19}BrN_6OS$	162	85	48.32	4.15	18.67
4g	$C_{19}H_{21}BrN_6OS$	152	79	49.40	4.39	18.12
4h	$C_{20}H_{23}BrN_6OS$	167	83	50.15	4.67	17.56
4i	$C_{17}H_{15}BrN_6OS$	152	78	47.18	3.48	19.42
4j	$C_{18}H_{17}BrN_6OS$	167	71	48.32	3.76	18.57

acetanilide derivative was finished, the solution was heated to 80^{0}C and was kept at this temperature for about 10 minutes to complete the reaction. Then the reaction mixture was cooled to room temperature and poured upon ten to twelve times its volume of cracked ice. After standing for about 90 minutes, the 5- bromo isatin was filtered with suction, washed several times with cold water to remove sulphuric acid and then dried in the air[21].

General procedure for the synthesis of 4(pyridine-2-yl)thio semicarbazide (2)

To a solution of 2-amino pyridine(0.001mol) in DMF was added sodium hydroxide(0.001mol) and carbon disulphide(0.75ml). The mixture was stirred for 1 hour, to the stirred mixture was added hydrazine hydrate(0.01mol) and stirring continued at 45^{0}C for 1 hour. On adding water a pale yellow solid separated out which is recrystallized from DMF-ethanol.

General procedure for the synthesis of 1(5 bromo -2-oxoindolin-3-ylidene)-4-(pyridine-2-yl) thiosemicarbazide (3)

Equimolar quantities of 5-bromo isatin and (pyridine -2-yl)thio semicarbazide were dissolved in warm ethanol containing 1ml of glacial acetic acid. The reaction mixture was refluxed for 5 hours and set aside. The resultant solid was washed with dilute ethanol dried and recrystallized from ethanol and chloroform mixture.

General procedure for synthesis of (4a-4j)

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

Antimicrobial activity

The compounds**(4a-j)** were screened for their antibacterial activity against pathogenic organisms *B.subtilis, S.aureus, S.epidermidis, E.coli, P.aeruginosa, S.almonella typhi,* using ciprofloxacin as standard and antifungal activity against *Candida albicans, Cryptococcus neoformas and A.niger* using ketoconazole as standard. DMSO was used as solvent control, nutrient

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TABLE 2(a)

Comp. no	Antibacterial activity Zone of inhibition (mm)					
	B.subtilis	*S.aureus*	*S.epidermidis*	*E.coli*	*P.aeruginosa*	*S.typhi*
4a	19	17	21	20	18	19
4b	24	23	19	24	22	18
4c	12	06	14	12	13	14
4d	09	11	10	09	09	13
4e	20	18	19	18	20	19
4f	14	18	09	14	14	15
4g	18	14	19	20	18	21
4h	21	20	24	13	21	19
4i	08	13	11	08	11	14
4j	17	12	16	17	16	19
Ciprofloxacin	35	36	32	35	32	36

TABLE 2(b)

Comp.no.	Antifungal activity Zone of inhibition (mm)		
	C.albicans	*A.niger*	*Cryptococcus neoformas*
4a	09	10	09
4b	15	17	16
4c	09	08	10
4d	09	11	08
4e	10	12	11
4f	12	11	11
4g	08	14	12
4h	18	16	17
4i	12	09	15
4j	10	11	12
Ketoconazole	25	28	27

agar was used as culture medium and the method employed was disc diffusion method. The zones of inhibition formed were measured in mm and are shown in TABLE 2(a and b).

1-(5-bromo-1-((dimethylamino)methyl)-2-oxoindolin-3-ylidene)-4-(pyridine-2-yl) thiosemi carbazide(4a)

The sample was recrystallized using Chloroform and petroleum ether IR(KBr): 3392, 3345, 1790, 1462, 1155 and 532cm^{-1};^{1}H-NMR(DMSO d$_6$): δ, 8.15(d, H), 7.75(s, H), 7.58(m, 3H), 7.05(s, H), 6.50 (m, 2H), 4.44(s, 2H), 4.11(s, H), 2.15(s, 6H). MS (relative intensity): m/z value 435(MH$^+$, 50), 433 (50), 434(15), 256(100), 211(12), 160(48), 128(43), 84(24), 64 (63)

1-(5-bromo-1-((diethylamino)methyl)-2-oxoindolin-3-ylidene)-4-(pyridine-2-yl)thiosemicarbazide(4b)

The sample was recrystallized using Chloroform and petroleum ether IR(KBr): 3651, 2944, 1720, 1437, 1341 and 539cm^{-1}; ^{1}H-NMR(DMSO d$_6$):δ8.05 (d, H), 7.85(s, H), 7.39(m, 3H), 7.10(s, H), 6.32(m, 2H), 4.44(s, 2H), 4.11(s, H), 2.40(m, 4H), 1.20(m, 6H). MS(relative intensity): m/z value 463 (MH$^+$,52), 461(48), 445(18), 256(100), 205(10), 165(49), 135(46), 64(63).

1-(5-bromo-1-((diphenylamino)methyl)-2-oxoindolin-3-ylidene)-4-(pyridine-2-yl)thiosemi carbazide (4c)

The sample was recrystallized using chloroform and petroleum ether IR(KBr): 3752, 3652, 3444, 1697, 1600, 1493, 1305 and 620cm^{-1}; ^{1}H-NMR(DMSO d$_6$): δ 8.08(d, H), 7.9(s, H), 7.45(m, 3H), 7.10(t, 5H), 6.60 (m, 8H), 4.55(s, 2H), 3.9(s, H). MS (relative intensity): m/z value 559(MH$^+$, 51), 557(49), 500(16), 446(18), 256(100), 210(12), 167(52), 132(43), 65(62).

1-(5-bromo-2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene)-4-(pyridine-2-yl) thiosemicar bazide(4d)

The sample was recrystallized using chloroform and petroleum ether IR(KBr): 3693, 3433, 3246, 1697, 1308, 1052 and 539cm^{-1}; ^{1}H-NMR(DMSO d$_6$): δ8.30 (d, H), 7.5(s, H), 7.38 (m, 3H), 6.90(t, 5H), 6.44 (m, 2H), 4.38(s, 2H), 4.2(s, H), 2.40(t, 4H), 1.40(t, 4H). MS(relative intensity): m/z value 461(MH$^+$, 50.5), 459(49.5), 452(20), 442(16), 256(100), 225 (16), 158(58), 132(43), 128(37), 68(63).

1-(5-bromo-2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene)-4-(pyridine-2-yl) thiosemicar bazide(4e)

The sample was recrystallized using chloroform and petroleum ether IR(KBr): 3693, 3654, 3435, 1698, 1309, 1072 and 550cm^{-1}; ^{1}H-NMR(DMSO d$_6$): δ8.00(d, H), 7.7(s, H), 7.45(m, 3H), 6.85(s, H), 6.55 (m, 2H), 4.66(s, 2H), 4.1(s, H), 2.40(m, 4H), 1.7(s, 6H). MS(relative intensity): m/z value 475(MH$^+$, 53), 473(47), 452(22), 420(15), 256(100), 230(20), 150 (55), 128(37), 73(66).

1-(5-bromo-1-((ethyl(methyl)amino)methyl)-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl)thiosemi carbazide(4f)

Tthe sample was recrystallized using chloroform and petroleum ether IR(KBr): 3745, 3432, 1659, 1560, 1310, 605 and 535cm^{-1}; ^{1}H-NMR(DMSO d$_6$): δ8.05(d, H), 7.65(s, H), 7.25(m, 3H), 6.75(s, H), 6.35(m, 2H), 4.54(s, 2H), 4.23(s, H), 2.54(m, 3H),

2.20(s, 2H), 1.15(m, 3H). MS(relative intensity): m/z value 447(MH^+, 55), 475(45), 426(23), 419(13), 256(100), 243(26), 149(54), 123(34), 72(64).

1-(5-bromo-1-((methyl(propyl)amino)methyl)-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl)thiosemicarbazide(4g)

The sample was recrystallized using Chloroform and petroleum ether IR(KBr): 3687, 3343, 1659, 1507, 1051 and 542cm^{-1}; ^{1}H-NMR(DMSO d_6): δ 8.05(d, H), 7.78(s, H), 7.34(m, 3H), 6.90(s, H), 6.40(m, 2H), 4.8(s, 2H), 4.40(s, H), 2.5(m, 2H), 2.10(s, 3H), 1.40(m, 5H). MS(relative intensity): m/z value 463(MH^+, 53), 461(47), 435(23), 425(16), 256(100), 239(22), 155 (58), 121(33), 69(61)

1-(5-bromo-1-((ethyl(propyl)amino)methyl)-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl)thiosemicarbazide(4h)

The sample was recrystallized using Chloroform and petroleum ether IR(KBr): 3655, 3380, 3220, 1612, 1475, 1200 and 552cm^{-1}; ^{1}H-NMR (DMSO d_6): δ8.24(d, H), 7.9(s, H), 7.55 (m, 3H), 7.05(s, H), 6.40 (m, 2H), 4.40(s, 2H), 4.2(s, H), 2.65(m, 4H), 1.171(m, 2H), 1.10(m, 6H). MS(relative intensity): m/z value 477(MH^+, 50), 475(50), 427(42), 402(33), 256 (100), 245(25), 153(17), 169(26), 82(23)

1-(1-(aziridin-1-ylmethyl)-5-bromo-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl) thiosemicarbazide(4i)

The sample was recrystallized using chloroform and petroleum ether IR(KBr): 3649, 3415, 3280, 1695, 1482, 1181, 1325 and 556cm^{-1}; ^{1}H NMR (DMSO d_6): δ 8(d, H), 7.5(s, H), 7.35(m, 3H), 7.10(s, H), 6.38(m, 2H), 4.30(s, 2H), 4.1(s, H), 1.85(s, 4H). MS(relative intensity): m/z value 433(MH^+, 53), 432(47), 422(23), 412(56), 367 (25), 256(100), 236(12), 136(17), 82 (23)

1-(1-(azetidin-1-ylmethyl)-5-bromo-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl)thiosemicarbazide(4j)

The sample was recrystallized using chloroform and petroleum ether IR(KBr): 3625, 2945, 1710, 1421 and 525cm^{-1}; ^{1}H-NMR (DMSO d_6): δ8.05(d, H), 7.48(s, 4H), 7.10(s, H), 6.25(m, 2H), 4.28(s, 2H), 4.22(s, H), 3.23(m, 4H), 2.49(m, 2H). MS(relative intensity): m/z value 445(MH^+, 56), 443(44), 432 (68), 385(12), 256(100), 226(34), 126(14), 84(22).

RESULTS AND DISCUSSION

All the synthesized compounds were tested for in vitro antibacterial activity by the disc diffusion method. The MIC values of the synthesized compounds against pathogenic bacteria are presented in TABLE 2a. Ciprofloxacin was used as the reference for inhibitory activity against bacteria. All the compounds showed significant antibacterial activity. Antifungal activity of the compounds was studied for the pathogenic fungi. The results are summarized in TABLE 2b. Ketoconazole was used as the reference for inhibitory activity against fungi. All the compounds showed significant antifungal activity.

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