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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and bioevaluation of Schiff and Mannich bases of isatin derivatives with 4-amino-5-benzyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

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Abstract Isatin (2,3-dioxindole) and its derivatives show a wide range of biological activities. In the present study, a series of Schiff and Mannich bases of isatin derivatives were prepared using 4-amino-5-benzyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione. The structures of these derivatives were characterized by IR, ^{1}H NMR and elemental analysis. In vitro antimicrobial activities were evaluated by agar dilution method and the zone of inhibition values of these derivatives were compared with ciprofloxacin and fluconazole. Chloro and Bromo groups at fifth position of isatin broaden the spectrum of antibacterial activity against *S. aures*, *P. aeruginoa*, and *E. coli*, respectively. For the antifungal activity, the compound **6h** showed equipotent activity against *A. niger*. The remaining majority of the compounds were found active in the biological screening. The efforts were also made to establish structure activity relationships among synthesized compounds.

Keywords Isatin · 1,2,4-Triazole · Schiff bases · *N*-Mannich bases · Antimicrobial activity

Introduction

Schiff and Mannich bases of isatin derivatives play an important role in the medicinal chemistry because of their potential biological properties. They are reported to show a variety of pharmaceutical properties such as antibacterial (Pandeya and Sriram, 1998), antifungal (Jarrahpour *et al.*, 2007; Varma and Nobels, 1975), antiviral (Jarrahpour *et al.*, 2007 and Varma and Nobels, 1975), anti HIV (Bal *et al.*, 2005; Pandeya *et al.*, 1999), antitubercular (Hussein *et al.*, 2005), anticancer (Vine *et al.*, 2007), and anticonvulsant (Varma *et al.*, 2004; Sridhar *et al.*, 2002). Literature survey reveals that 1,2,4-trizole ring containing compounds exhibit potential chemotherapeutic properties such as antimicrobial (Hacer *et al.*, 2009), anti-inflammatory (Asif and Arif 2009; Knysh *et al.*, 1983), analeptic (Knysh *et al.*, 1983), neuroleptic (Parmar *et al.*, 1972), analgesic (George *et al.*, 1971), and antiviral (Khim, 1976). Currently the substituted 1,2,4-triazole ring consist chemotherapeutics viz., vorozole, letrozole, and anastrozole (Fig. 1), are being used for the treatment of breast cancer (Clemons *et al.*, 2004). Schiff and Mannich bases containing 1,2,4-trizole derivatives were reported to possess some biological activities like anti tumor (Demirbas *et al.*, 2004) and antimicrobial (Ashok *et al.*, 2007). Hetrocycles containing mercapto and amino groups are an attractive synthones for the construction of condensed hetrocyclic rings. The amino and mercapto groups are the convenient nucleophiles to react with electrophiles (Hacer *et al.*, 2009). For example, some alkylation and Mannich reactions can take place at S- or N- atoms were reported (Bijev and Prodanova, 2007; Krasovskii *et al.*, 2000; Mekuskiene *et al.*, 2003). Prompted by these observations, it was contemplated to synthesize some isatin containing congeners of 1,2,4-triazole Schiff and Mannich bases with a view to explore their potency as better chemotherapeutic agents. All newly synthesized compounds were screened for the antibacterial antifungal activity.

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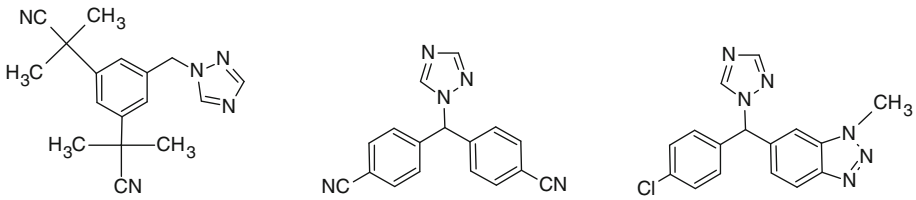
Fig. 1 Substituted 1,2,4-triazole ring drug moieties



Anastrozole Letrozole Vorozole

Results and discussion

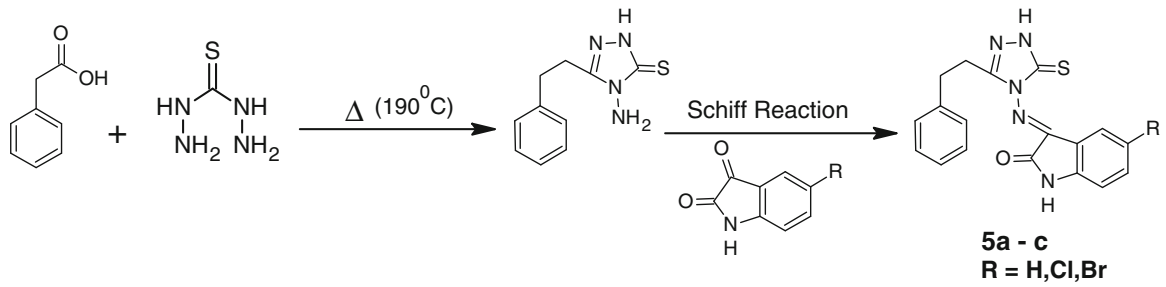
Compound **3** was synthesized first time by direct heating an equimolar mixture of phenyl acetic acid **1** and thiocarbohydrazide **2** and all the synthesized compounds from Scheme 1 viz., **3**, **5a–c**, and **6a–i** were characterized by the IR, ^{1}H-NMR, and elemental analysis. IR-spectra (cm^{-1}) of compound **3** showed absorption bands at 3309 (NH_2), 3153, 3097 (NH), 1625 (C=N), 1296 (C–N), 1045 (C=S). Compounds **5** and **6** showed additional peak belonging to isatin C=O functional group in the region 1,688–1,698 (cm^{-1}). The other peaks observed were same as compound **3**. In the ^{1}H NMR spectra for **5a–c**, the characteristic NH_2 protons of compound **3** were observed at δ 5.6 ppm. The compounds **5a–c** were not shown characteristic signal of NH_2 protons, it concludes that, the formation of –N=C< bond between triazole moiety and isatin ring. The Schiff bases **5a–c** displayed the NH protons of indole ring around δ 11.45–11.30 ppm. The ^{1}H NMR spectra of Mannich bases **6a–i** were not shown signal corresponding to NH protons of indole ring and showed additionally the characteristic signal of >N–CH_2–N< bond around δ 4.81–4.51 ppm, it confirms that, the NH protons of indole ring participate to the formation of >N-CH_2-N< bond with secondary amines in the presence of formaldehyde. The physical constants of synthesized compounds **5a–c** and **6a–i** were shown in the Table 1.

The synthesized compounds **5a–c** and **6a–i** were tested for in vitro antimicrobial activity. The activity was reported by measuring the diameter of inhibition zone in mm, against gram-positive and gram-negative bacteria and fungi and is presented in Table 2. The tested compounds have shown moderate activity against tested bacteria and fungi. However, the compound **5b**, **5c**, **6b**, **6c** showed good activity (nearly equal to the inhibition zone value of ciprofloxacin) against to the *E. coli* bacteria. In general the antimicrobial activity of the Schiff bases of isatin has shown less activity than Mannich bases of isatin. It is because of the presence of >N-CH_2–N< bond. Among the Schiff and Mannich bases of isatin, the 5th position substituted isatin containing compounds showed more activity than unsubstituted isatin containing compounds. It concludes that, the 5-Cl and 5-Br substituent's of isatin increases the activity against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa.* For the antifungal activity, the compound **6h** showed equipotent activity against *A. niger*. Compounds with piperidine and morpholine showed better activity than the diethyl amine, against almost all the organisms used. Thus, from the above discussion it may be conjectured that Mannich bases are playing their role in enhancing the antibacterial activity.

Experimental

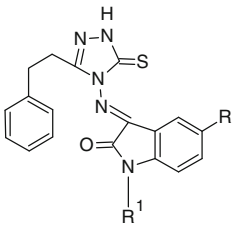
Methods and materials

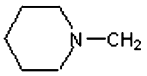
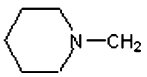
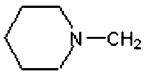
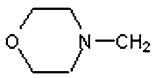
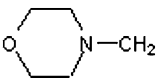
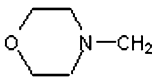
All the chemicals used in the present study are of analytical grade and were obtained from local suppliers. Melting points (m.p) were recorded on Kumar capillary melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded from KBr disks on Thermo Nicolet (Model: 6700) spectrophotometer. The nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz Fourier transform-nuclear magnetic resonance (Bruker Model: Avance-II) spectrophotometer using trimethoxysilane as an internal



Scheme 1 Synthesis of Schiff bases **5a–c**

Table 1 Physical constant of the synthesized compounds



Compound	*R*	R_1	Yield (%)	m.p (°C)[a]	Molecular formula	Molecular weight
5a	H	H	72	247–249	$C_{17}H_{13}N_5OS$	335.38
5b	Cl	H	67	274–278	$C_{17}H_{12}$ ClN_5OS	369.82
5c	Br	H	69	278–280	$C_{17}H_{12}BrN_5OS$	414.27
6a	H	$CH_2N(C_2H_5)_2$	74	258–260	$C_{22}H_{24}N_6OS$	420.53
6b	Cl	$CH_2N(C_2H_5)_2$	66	265–268	$C_{22}H_{23}ClN_6OS$	454.97
6c	Br	$CH_2N(C_2H_5)_2$	71	262–265	$C_{22}H_{23}BrN_6OS$	499.42
6d	H		74	225–228	$C_{23}H_{24}N_6OS$	432.54
6e	Cl		72	238–241	$C_{23}H_{23}ClN_6OS$	466.98
6f	Br		70	266–268	$C_{23}H_{23}BrN_6OS$	511.43
6g	H		73	252–256	$C_{22}H_{22}N_6O_2S$	434.51
6h	Cl		68	263–266	$C_{22}H_{21}ClN_6O_2S$	468.95
6i	Br		63	255–257	$C_{22}H_{21}BrN_6O_2S$	513.41

[a] Melting points are based on decomposition temperatures

standard. Elemental analyses were performed on an Elementar Vario EL elemental analyzer. The determination of the products purity and reaction monitoring were accomplished by TLC on silica gel plates.

General procedure for the synthesis of compounds

*Synthesis of 4-amino-5-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (**3**)*

An equimolar mixture of phenyl acetic acid **1** and thiocarbohydrazide **2** were heated at 190°C for 5 min. The mixture was cooled to room temperature and then treated with dilute sodium bicarbonate to remove unreacted phenyl acetic acid. The crude was washed with water and dried. The synthesized compound **3** was recrystalized from methanol.

Yield 79%; m.p 142–143°C; IR KBr (cm^{-1}): 3309 (NH_2), 3153, 3097 (NH), 1625 (C=N), 1296 (C–N), 1045 (C=S); ^1H NMR 90 MHz (DMSO-d_6) ppm: 13.02 (s, 1H, NH), 7.20–7.59 (br, s, 5H Ar–H), 5.65 (s, 2H, NH_2), 4.15 (s, 2H benzyl CH_2); Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.39; H, 4.87; N, 27.18.

*Synthesis of Schiff bases **5a–c***

An equimolar mixture of compound **3** was condensed with isatin or substituted isatin (5-Cl and 5-Br) in the presence of few drops of 50% H_2SO_4 in methanol. The reaction mixture was refluxed for 4 h and then kept at room temperature overnight. The solid product was washed with dilute ethyl alcohol and dried. The synthesized compounds **5a–c** were recrystalized from ethanol–water (1:2) mixture (Scheme 2).

Table 2 Antibacterial and antifungal in vitro activity expressed as diameter of growth inhibitory zone (GIZ, mm) for tested compounds (applied 400 μg per disk)

Compound	Conc. of compound	Bacteria				Fungi	
		E .coli	*P. aeruginosa*	*S .aureus*	*B. subtilis*	*C. albicans*	*A. niger*
Ciprofloxacin	A	30	28	26	25	–	–
Fluconazole	A	–	–	–	–	20	18
Compound **5a**	A	23	24	22	20	15	14
	B	19	16	16	15	9	9
	C	12	13	10	9	–	–
Compound **5b**	A	27	25	23	20	16	12
	B	18	13	11	14	9	9
	C	11	9	–	9	–	–
Compound **5c**	A	27	25	20	22	17	14
	B	17	15	12	15	11	10
	C	11	10	9	9	–	–
Compound **6a**	A	22	20	23	20	17	13
	B	15	13	16	13	10	9
	C	9	9	11	9	–	–
Compound **6b**	A	27	22	21	20	15	12
	B	17	16	12	14	9	9
	C	11	9	9	9	–	–
Compound **6c**	A	26	23	20	20	16	13
	B	16	14	14	13	10	9
	C	10	9	9	9	–	–
Compound **6d**	A	23	20	20	20	16	13
	B	18	16	14	12	10	9
	C	11	10	9	9	–	–
Compound **6e**	A	25	21	20	22	16	15
	B	16	15	12	13	11	9
	C	10	10	9	9	9	–
Compound **6f**	A	25	22	21	20	16	15
	B	16	15	14	15	10	9
	C	10	10	9	10	–	–
Compound **6g**	A	23	22	19	20	15	12
	B	15	12	15	13	10	9
	C	9	9	10	9	–	–
Compound **6h**	A	25	25	20	22	17	17
	B	16	15	14	13	10	9
	C	11	9	9	9	–	–
Compound **6i**	A	24	24	20	21	15	12
	B	16	15	13	12	10	9
	C	9	10	9	9	–	–

A 200 μg/ml, *B* 100 μg/ml, *C* 50 μg/ml

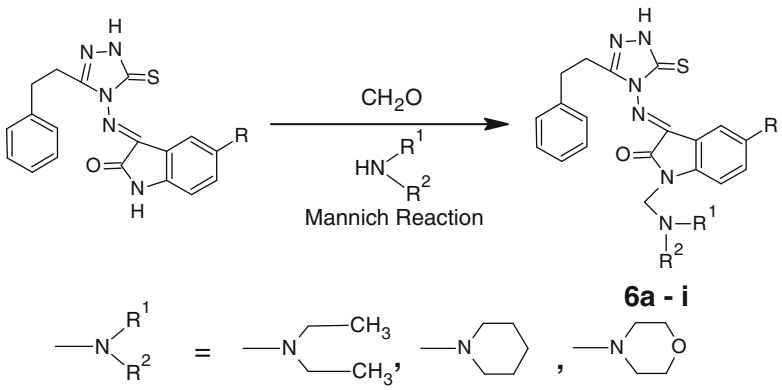
*Synthesis of Mannich bases **6a–i***

A mixture of various secondary amines (diethyl amine, piperidine, and morpholine) (1 mmol) was added drop wise to 0.5 ml of 37% formaldehyde solution under vigorous stirring. The resulting solution was mixed with corresponding Schiff bases **5a–c** (1 mmol) dissolved in 100 ml methanol. The reaction mixture was refluxed for 10 h. After the completion of reaction, the solid product was washed with petroleum ether. The synthesized compounds **6a–i** were recrystalized from methanol–chlorofrom (1:2) mixture.

Characterization of synthesized compounds

*Compound **5a** 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3196, 3059 (NH), 1699 (C=O), 1621 (C=N), 1266 (C–N),

Scheme 2 Synthesis of Mannich bases **6a–i**



1123 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.00 (s, 1H, trizole NH), 11.33 (s, 1H, isatin NH), 8.31–7.59 (m, 5H), 7.44–6.97 (m, 4H), 4.52 (s, 2H, benzyl CH_2); Anal. Calcd. for $C_{17}H_{13}N_5OS$: C, 60.88; H, 3.91; N, 20.88. Found: C, 60.90; H, 3.90; N, 20.86.

Compound ***5b*** *3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-5-chloro-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3215, 3071 (NH), 1705 (C=O), 1620 (C=N), 1286 (C–N), 1130 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 12.90 (s, 1H, trizole NH), 11.45 (s, 1H, isatin NH), 7.65–7.57 (m, 5H), 6.94–6.92 (m, 3H), 4.16 (s, 2H benzyl CH_2); Anal. Calcd. for $C_{17}H_{12}ClN_5OS$: C, 55.21; H, 3.27; N, 18.94. Found: C, 55.20; H, 3.27; N, 18.95.

Compound ***5c*** *3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-5-bromo-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3245, 3096 (NH), 1700 (C=O), 1619 (C=N), 1290 (C–N), 1122 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 12.90 (s, 1H, triazole NH), 11.45 (s, 1H, isatin NH), 7.65–7.42 (m, 3H), 7.25–6.9 (m, 5H), 4.34 (s, 2H benzyl CH_2); Anal. Calcd. for $C_{17}H_{12}BrN_5OS$: C, 49.29; H, 2.92; N, 16.90. Found: C, 49.30; H, 2.93; N, 16.89.

Compound ***6a****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-1-diethylamino methyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3240, 3061(NH), 1693 (C=O), 1609 (C=N), 1265 (C–N), 1183 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.58 (s, 1H, triazole NH), 7.64–7.28 (m, 4H), 7.25–6.51 (m, 5H), 4.74 (s, 2H, N–CH_2–N), 4.58 (s, 2H, benzyl CH_2), 2.08 (br, s, $2CH_2$), 1.21 (br, s, 6H, $2CH_3$); Anal. Calcd. for $C_{22}H_{23}N_6OS$: C, 62.83; H, 5.75; N, 19.98. Found: C, 62.82; H, 5.74; N, 19.99.

Compound ***6b****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-5-chloro-1-diethylaminomethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3241, 3105 (NH), 1700 (C=O), 1621 (C=N), 1285 (C–N), 1134 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.09 (s, 1H, triazole NH), 7.69–7.39 (m, 3H), 7.23–6.93 (m, 5H), 4.81 (s, 2H, N–CH_2–N), 4.45 (s, 2H benzyl CH_2), 2.64 (br, s, 4H, $2CH_2$), 1.32 (br, s, 6H, $2CH_3$); Anal. Calcd. for $C_{22}H_{23}ClN_6OS$: C, 58.08; H, 5.10; N, 18.47. Found: C, 58.05; H, 5.12; N, 18.47.

Compound ***6c****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-5-bromo-1-diethylaminomethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3231, 3086(NH), 1700 (C=O), 1657 (C=N), 1256 (C–N), 1112 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.04 (s, 1H, triazole NH), 7.63–7.39 (m, 3H), 7.06–6.82 (m, 5H), 4.79 (s, 1H, N–CH_2–N), 4.41 (s, 2H benzyl CH_2), 2.34 (br, s, 4H, $2CH_2$), 1.22 (br, s, 6H, $2CH_3$); Anal. Calcd. for $C_{22}H_{23}BrN_6OS$: C, 52.91; H, 4.64; N, 16.83. Found: C, 52.90; H, 4.64; N, 16.82.

Compound ***6d****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-1-piperidin-1-ylmethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3210, 3054 (NH), 1691 (C=O), 1608 (C=N), 1270 (C–N), 1177 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.08 (s, 1H, triazole NH), 7.63–7.44 (m, 4H), 7.33–7.16 (m, 5H), 4.74 (s, 1H, N–CH_2–N), 4.44 (s, 2H benzyl CH_2), 2.08 (br, s, 4H, piperidine N–$(CH_2)_2$), 1.48 (br, s, 4H, piperidine $2CH_2$), 1.35(br, s, 1H, piperidine CH); Anal. Calcd. for $C_{23}H_{24}N_6OS$: C, 63.87; H, 5.59; N, 19.43. Found: C, 63.86; H, 5.59; N, 19.45.

Compound ***6e****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1, 2,4) triazol-4-ylimino]-5-chloro-1-piperidin-1-ylmethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3223, 3098 (NH), 1699 (C=O), 1618 (C=N), 1253 (C–N), 1137 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.10 (s, 1H, triazole NH), 7.79–7.34 (m, 3H), 7.18–6.82 (m, 5H), 4.71 (s, 1H, N–CH_2–N), 4.46 (s, 2H benzyl CH_2), 2.39 (br, s, 4H, piperidine –N–$(CH_2)_2$), 1.34 (br, s, 4H, piperidine $2CH_2$), 1.26 (br, s, 1H, piperidine CH); Anal. Calcd. for $C_{22}H_{23}ClN_6OS$: C, 59.16; H, 4.96; N, 18.00. Found: C, 59.15; H, 4.97; N, 17.99.

Compound ***6f****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-5-bromo-1-piperidin-1-ylmethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3253, 3100 (NH),

1696 (C=O), 1607 (C=N), 1240 (C–N), 1168 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.11 (s, 1H, triazole NH), 7.74–7.42 (m, 3H), 7.21–6.95 (m, 5H),4.74 (s, 1H, N–CH_2–N), 4.46 (s, 2H benzyl CH_2), 2.39 (br, s, 4H, piperidine –N–$(CH_2)_2$), 1.34 (br, s, 4H, piperidine $2CH_2$), 1.26 (br, s, 1H, piperidine CH); Anal. Calcd. for $C_{23}H_{23}BrN_6OS$: C, 54.01; H, 4.53; N, 16.43. Found: C, 54.00; H, 4.54; N, 16.45.

Compound ***6g****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-1-morpholin-4-ylmethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3220, 3159 (NH), 1692 (C=O), 1612 (C=N), 1203 (C–N), 1153 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 12.99 (s, 1H, triazole NH), 8.58–7.63 (m, 4H), 7.52–7.31 (m, 5H), 4.54 (s, 1H, N–CH_2–N), 4.14 (s, 2H benzyl CH_2), 3.57 (br, s, 4H, morpholine O–$(CH_2)_2$), 2.60 (br, s, 4H, morpholine –N–$(CH_2)_2$); Anal. Calcd. for $C_{22}H_{22}N_6O_2S$: C, 60.81; H, 5.10; N, 19.34. Found: C, 63.82; H, 5.09; N, 19.35.

Compound ***6h****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4) triazol-4-ylimino]-5-chloro-1-morpholin-4-ylmethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3226, 3159(NH), 1700 (C=O), 1653 (C=N), 1261 (C–N), 1153(C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.04 (s, 1H, triazole NH), 7.83–7.56 (m,3H), 7.33–6.98 (m, 5H), 4.61 (s, 1H, N–CH_2–N), 4.48 (s, 2H benzyl CH_2), 3.75 (br, s, 4H, morpholine O–$(CH_2)_2$), 2.61 (br, s, 4H, morpholine N–$(CH_2)_2$); Anal. Calcd. for $C_{22}H_{21}ClN_6O_2S$: C, 56.35; H, 4.51; N, 17.92. Found: C, 56.34; H, 4.50; N, 17.93.

Compound ***6i****: 3-[(3-benzyl-5-thioxo-1,5-dihydro-(1,2,4)triazol-4-ylimino]-5-bromo-1-morpholin-4-ylmethyl-1,3-dihydro-indol-2-one* IR KBr (cm^{-1}): 3247, 3111(NH), 1688 (C=O), 1613 (C=N), 1256 (C–N), 1143 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 13.04 (s, 1H, triazole NH),7.79–7.47 (m, 3H), 7.34–7.08 (m, 5H), 4.69 (s, 1H, N–CH_2–N), 4.56 (s, 2H benzyl CH_2), 3.70 (br, s,4H, morpholine O–$(CH_2)_2$), 2.52 (br, s, 4H, morpholine N–$(CH_2)_2$); Anal. Calcd. for $C_{22}H_{21}BrN_6O_2S$: C, 51.47; H, 4.12; N, 16.37. Found: C, 51.48; H, 4.10; N, 16.37.

Conclusion

In conclusion, 12 new derivatives of isatin were synthesized and exhibited a range of significant antimicrobial activities, whereas compounds **5b**, **5c**, **6b**, and **6c** exhibited good (nearly equal to the zone of ciprofloxacin) antibacterial activity against *E. coli*. For the antifungal activity, the compound **6h** showed equipotent activity against *A. niger*. The remaining derivatives displayed moderate activity to the tested cell cultures. Therefore, these derivatives may possible to use as lead compounds for other biological activities. The mechanism of antimicrobial activity is unknown and requires further investigation.

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