

Synthesis and antimicrobial activities of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted pyridin-2-yl)thiosemicarbazide

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Abstract

A series of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl)thiosemicarbazide derivatives were synthesized by the reaction of 4-(substituted-pyridin-2-yl)thiosemicarbazide and 5-halogenated isatin derivatives. The newly synthesized compounds were characterized on the basis of spectral (FT-IR, ¹H, ¹³C NMR and mass) analysis. Investigation of *in vitro* anti-bacterial and anti-fungal activity of synthesized compounds was done by disc diffusion method against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *A. niger*. All the compounds exhibited moderate to good anti-bacterial and anti-fungal activity.

Keywords: Isatin, Schiff base, anti-microbial

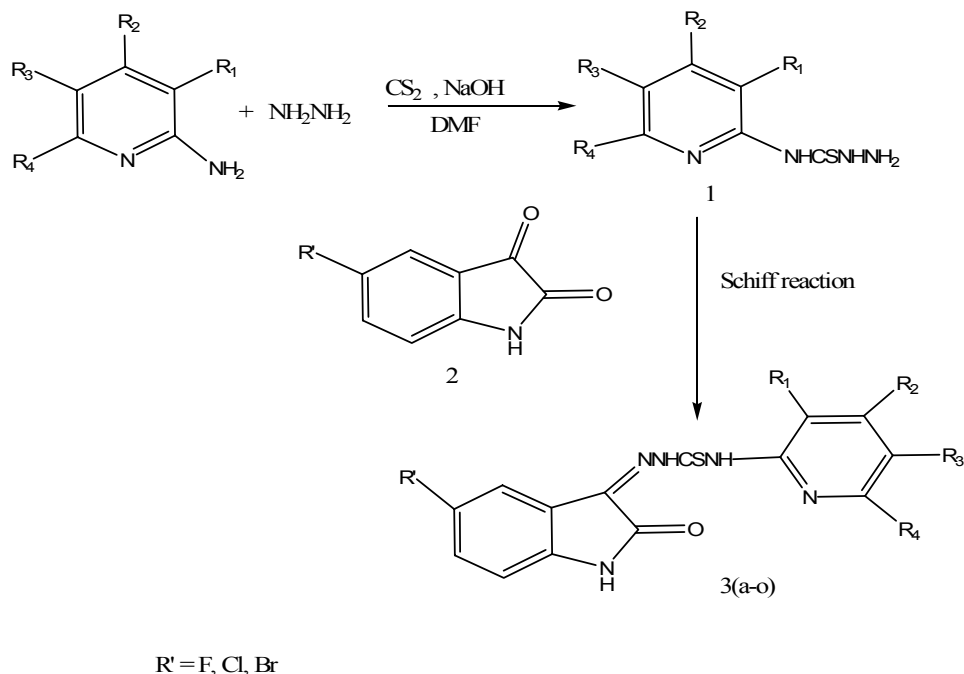
Introduction

Isatin is reported to possess a wide range of central nervous system activities.^{1,2} Schiff bases of isatin (indolin-2,3-dione) derivatives are reported to show variety of biological activities like antibacterial,³⁻⁵ antifungal,⁶⁻⁸ antiviral,⁹⁻¹¹ anti HIV,¹²⁻¹⁴ antiprotozoal^{15,16} and antihelminthic^{17,18} activities. In addition pyridines are associated with diverse biological activities.^{19,20} Previous reports³⁻⁸ revealed that 5-halogenated isatin derivatives show good antimicrobial activity. Prompted by the biological properties of isatin derivatives and their Schiff bases, it was envisaged that a new series of isatin derivatives with 4-(substituted-pyridin-2-yl)thiosemicarbazide would possess high antimicrobial activity.

Results and Discussion

The target compounds were prepared by using the reaction sequence in Scheme 1. The Schiff bases of isatin derivatives were synthesized by condensation of the keto group of isatin with

various thiosemicarbazides. All the compounds gave satisfactory elemental analysis ($\pm 0.4\%$). The chemical structures of the synthesized compounds (in Table 1) were confirmed by means of their IR, ^1H , ^{13}C NMR and mass spectral analysis.



Scheme 1. Synthesis of title compounds.

Table 1. Substituents used for title compounds

Compound	R'	R ₁	R ₂	R ₃	R ₄	Yield in %
3a	F	H	H	H	H	78
3b	F	H	H	Cl	H	72
3c	F	CH ₃	H	H	H	75
3d	F	H	CH ₃	H	H	68
3e	F	H	H	H	CH ₃	81
3f	Cl	H	H	H	H	71
3g	Cl	H	H	Cl	H	79
3h	Cl	CH ₃	H	H	H	67
3i	Cl	H	CH ₃	H	H	66
3j	Cl	H	H	H	CH ₃	76
3k	Br	H	H	H	H	79
3l	Br	H	H	Cl	H	76
3m	Br	CH ₃	H	H	H	75
3n	Br	H	CH ₃	H	H	80
3o	Br	H	H	H	CH ₃	74

All the synthesized compounds were evaluated for their antimicrobial activities. The zones of inhibition formed for the compounds against gram-positive, gram-negative bacteria and fungi are presented in Table 2. All the compounds have shown moderate activity. In general, the order of antibacterial activity of the substituents at the 5th position of isatin is Br > Cl > F. The antimicrobial activity of title compounds revealed that 4-(5-chloropyridin-2-yl)-1-(5-fluoro-2-oxoindolin-3-ylidene)-thiosemicarbazide (**3b**), 1-(5-Chloro-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl) thiosemicarbazide (**3j**) and 1-(5-Bromo-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl) thiosemicarbazide (**3n**) exhibited highest activity against *B. subtilis* NCIM2063, *S. aureus* NCIM2079, *E. coli* NCIM2065, *P. aeruginosa* NCIM2200, *C. albicans* NCIM3102 and *A. niger*. However, these compounds showed lesser antimicrobial activity as compared to their respective standards.

Table 2. Antimicrobial data of synthesized compounds

Compd No.	Antibacterial activity*				Antifungal activity*	
	<i>B.subtilis</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>P.aeruginosa</i>	<i>C.albicans</i>	<i>A.niger</i>
3a	12	15	14	13	10	09
3b	19	17	20	18	17	16
3c	09	10	11	12	08	07
3d	13	08	09	10	11	10
3e	18	20	16	19	14	13
3f	12	13	13	12	12	14
3g	14	16	13	15	11	13
3h	18	16	19	17	14	12
3i	17	15	18	19	12	11
3j	19	17	20	18	15	19
3k	13	15	16	14	14	13
3l	18	17	21	19	11	08
3m	12	14	15	11	14	15
3n	20	19	21	18	15	17
3o	18	17	20	19	14	16
Ciprofloxacin	29	30	28	30	-	-
Ketoconazole	-	-	-	-	27	26

*Zone of inhibition in mm.

Experimental Section

General Procedures. Melting points were determined in open capillary tubes and are uncorrected. ^1H 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, N were performed in a Heraeus CHN Rapid Analyser.

Synthesis of 4(substituted pyridine-2-yl) thiosemicarbazide (1). To a solution of 2-amino pyridine (0.001 mol) in DMF (10 mL) was added sodium hydroxide (0.001 mol) and carbon disulphide (0.75 mL). The mixture was stirred for 1 h at 15-20°C, to the stirred mixture was added hydrazine hydrate (0.01mol) and stirring continued at 45 °C for 1 h. On adding water a pale yellow solid separated out which was recrystallized from DMF-ethanol (1:1). The yield of product was 88-90%. Similarly other compounds were prepared.

Synthesis of 5-substituted isatin (2). To 55 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 rt and poured upon cracked ice. After 90 min, the 5-substituted isatin was filtered, washed several times with cold water to remove sulphuric acid and then dried in air. The yield of product was 80-82.5%.

Synthesis of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl) thiosemicarbazide (3a-o)

Equimolar quantities of 5-substituted isatin and 4-(substituted pyridin-2-yl) thiosemicarbazide were dissolved in warm ethanol (50mL) containing 1mL 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-chloroform (1:1).

1-(5-Fluoro-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl)thiosemicarbazide (3a). The sample was recrystallized using ethanol and chloroform mixture. Yield: 78%. m.p. 163- 165 °C. IR(KBr): 3358 (NH), 1695 (C=O), 1620 (C=N), 1045 (C=S), 1102 (C—F) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.60-8.11(m, 4H, 2-pyridine), 7.0-7.7(m, 3H, Ar-H), 7.0 (s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H); ^{13}C NMR (DMSO d_6): δ 109.9, 113.3, 114.3, 118.0, 119.4, 123.3, 132.8, 138.3, 142.4, 148.2, 158.6, 167.5, 186; MS (relative intensity): m/z value 315.06 (11%); Calcd. for $\text{C}_{14}\text{H}_{10}\text{FN}_5\text{OS}$ % C 53.33, H 3.20, N 22.21; found C 53.31, H 3.18, N 22.19.

4-(5-Chloropyridin-2-yl)-1-(5-fluoro-2-oxoindolin-3-ylidene)thiosemicarbazide (3b). The sample was recrystallized using ethanol and chloroform mixture. Yield: 72%. m.p. 160-162 °C. IR(KBr): 3300 (NH), 1680 (C=O), 1640 (C=N), 1040 (C=S), 1122 (C—F) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.89-8.31(m, 3H, 2-pyridine), 7.0-7.7(m, 3H, Ar—H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H); ^{13}C NMR (DMSO d_6): δ 110.6, 114.3, 118.0, 119.4, 123.3, 123.5, 132.8, 137.1, 142.4, 150.6, 157.2, 158.6, 167.5, 186;

MS (relative intensity): m/z value 349.02 (13%); Calcd. for $C_{14}H_9ClFN_5OS$ % C 48.07, H 2.59, N 20.02; found C 48.05, H 2.57, N 20.01

1-(5-Fluoro-2-oxoindolin-3-ylidene)-4-(3-methylpyridin-2-yl)thiosemicarbazide (3c). The sample was recrystallized using ethanol and chloroform mixture. Yield: 75%. m.p. 158-160 °C. IR(KBr): 3365 (NH), 1737 (C=O), 1615 (C=N), 1122 (C=S), 1131 (C—F) cm^{-1} ; 1H NMR (DMSO d_6): δ 6.51-8.09 (m, 3H, 2-pyridine), 7.0-7.7(m, 3H, Ar-H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H), 2.32 (s, 3H, CH₃); ^{13}C NMR (DMSO d_6): δ 15.8, 112.5, 114.3, 117.0, 118.0, 119.4, 123.3, 132.8, 137.5, 142.4, 145.9, 154.6, 158.6, 167.5, 186; MS (relative intensity): m/z value 329.07 (17%); Calcd. for $C_{15}H_{12}FN_5OS$ % C 54.70, H 3.67, N 21.26; found C 54.68, H 3.65, N 21.24

1-(5-Fluoro-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (3d). The sample was recrystallized using ethanol and chloroform mixture. Yield: 68%. m.p. 174-176 °C. IR(KBr): 3370 (NH), 1712 (C=O), 1619 (C=N), 1140 (C=S), 1078 (C—F) cm^{-1} ; 1H NMR (DMSO d_6): δ 6.50-8.12 (m, 3H, 2-pyridine), 7.0-7.7(m, 3H, Ar-H), 7.0 (s, H, N—H), 8.0 (s, H, N—H), 4.0(s, H, N—H), 2.37(s, 3H, CH₃); ^{13}C NMR(DMSO d_6): δ 24.3, 112.7, 114.3, 117.7, 118.0, 119.4, 123.3, 132.8, 137.5, 142.4, 148.7, 149.6, 158.6, 159.1, 167.5, 186; MS (relative intensity): m/z value 329.07 (24%); Calcd. for $C_{15}H_{12}FN_5OS$ % C 54.70, H 3.67, N 21.26; found C 54.67, H 3.64, N 21.25

1-(5-Fluoro-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (3e). The sample was recrystallized using ethanol and chloroform mixture. Yield: 81%. m.p. 166-168 °C. IR(KBr): 3360 (NH), 1730(C=O), 1589 (C=N), 1114 (C=S), 1038 (C—F) cm^{-1} ; 1H NMR (DMSO d_6): δ 6.49-7.43 (m, 3H, 2-pyridine), 7.0-7.7 (m, 3H, Ar-H), 7.0 (s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H), 2.55 (s, 3H, CH₃); ^{13}C NMR(DMSO d_6): δ 24.8, 106.9, 113.5, 114.3, 118.0, 119.4, 123.3, 132.8, 138.5, 142.4, 157.2, 158.2, 158.6, 167.5, 186; MS (relative intensity): m/z value 329.07 (43%); Calcd. for $C_{15}H_{12}FN_5OS$ % C 54.70, H 3.67, N 21.26; found C 54.67, H 3.64, N 21.25

1-(5-Chloro-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl)thiosemicarbazide (3f). The sample was recrystallized using ethanol and chloroform mixture. Yield: 71%. m.p. 182-184 °C. IR(KBr): 3347 (NH), 1668 (C=O), 1618 (C=N), 1038 (C=S), 660 (C—Cl) cm^{-1} ; 1H NMR (DMSO d_6): δ 6.60-8.11(m, 4H, 2-pyridine), 7.3-7.6(m, 3H, Ar-H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H); ^{13}C NMR(DMSO d_6): δ 109.9, 113.3, 119.2, 123.1, 129.5, 130.0, 131.4, 132.8, 138.3, 144.9, 148.2, 158.6, 167.5, 186; MS (relative intensity): m/z value 331.03 (27%); Calcd. for $C_{14}H_{10}ClN_5OS$ % C 50.68, H 3.04, N 21.11; found C 50.66, H 3.02, N 21.09

1-(5-Chloro-2-oxoindolin-3-ylidene)-4-(5-chloropyridin-2-yl)thiosemicarbazide (3g). The sample was recrystallized using ethanol and chloroform mixture. Yield: 79%. m.p. 146-148°C. IR(KBr): 3309 (NH), 1681 (C=O), 1641 (C=N), 1045 (C=S), 618 (C—Cl) cm^{-1} ; 1H NMR (DMSO d_6): δ 6.89-8.31(m, 3H, 2-pyridine), 7.3-7.6(m, 3H, Ar—H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0(s, H, N—H); ^{13}C NMR (DMSO d_6): δ 110.6, 119.2, 123.1, 123.5, 129.5, 130.0, 131.4, 132.8, 137.1, 144.9, 150.6, 157.2, 167.5, 186; MS (relative intensity): m/z value 364.99 (19%); Calcd. for $C_{14}H_9Cl_2N_5OS$ % C 45.91, H 2.48, N 19.12; found C 45.89, H 2.46, N 19.10

1-(5-Chloro-2-oxoindolin-3-ylidene)-4-(3-methylpyridin-2-yl)thiosemicarbazide (3h). The sample was recrystallized using ethanol and chloroform mixture. Yield: 67%. m.p. 154-156°C. IR(KBr): 3369 (NH), 1721 (C=O), 1613 (C=N), 1120 (C=S), 657 (C—Cl) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.51-8.09(m, 3H, 2-pyridine), 7.3-7.6 (m, 3H, Ar-H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0(s, H, N—H), 2.32 (s, 3H, CH₃); ^{13}C NMR(DMSO d_6): δ 15.8, 112.5, 117.0, 119.2, 123.1, 129.5, 130.0, 131.4, 132.8, 137.5, 144.9, 145.9, 154.6, 167.5, 186; MS (relative intensity): m/z value 345.05 (32%); Calcd. for C₁₅H₁₂ClN₅OS % C 52.10, H 3.50, N 20.25; found C 52.08, H 3.49, N 20.23

1-(5-Chloro-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (3i). The sample was recrystallized using ethanol and chloroform mixture. Yield: 66%. m.p. 192-194 °C. IR(KBr): 3343 (NH), 1732 (C=O), 1623 (C=N), 1131 (C=S), 654 (C—Cl) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.50-8.12(m, 3H, 2-pyridine), 7.3-7.6(m, 3H, Ar-H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0(s, H, N—H), 2.37(d, 3H, CH₃); ^{13}C NMR (DMSO d_6): δ 24.3, 112.7, 117.7, 119.2, 123.1, 129.5, 130.0, 131.4, 132.8, 144.9, 148.7, 149.6, 159.1, 167.5, 186; MS (relative intensity): m/z value 345.05 (21%); Calcd. for C₁₅H₁₂ClN₅OS % C 52.10, H 3.50, N 20.25; found C 52.08, H 3.49, N 20.23

1-(5-Chloro-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (3j). The sample was recrystallized using ethanol and chloroform mixture. Yield: 76%. m.p. 186-188 °C. IR(KBr): 3339 (NH), 1680(C=O), 1556 (C=N), 1105 (C=S), 643 (C—Cl) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.49-7.43 (m, 3H, 2-pyridine), 7.3-7.8(m, 3H, Ar-H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0(s, H, N—H), 2.55 (s, 3H, CH₃); ^{13}C NMR (DMSO d_6): δ 24.8, 106.9, 113.5, 119.2, 123.1, 129.5, 130.0, 131.4, 132.8, 138.5, 144.9, 157.2, 158.2, 167.5, 186; MS (relative intensity): m/z value 345.05 (29%); Calcd. for C₁₅H₁₂ClN₅OS % C 52.10, H 3.50, N 20.25; found C 52.08, H 3.49, N 20.23

1-(5-Bromo-2-oxoindolin-3-ylidene)-4-(pyridin-2-yl) thiosemicarbazide (3k). The sample was recrystallized using ethanol and chloroform mixture. Yield: 79%. m.p. 148-150°C. IR(KBr): 3345 (NH), 1683 (C=O), 1604 (C=N), 1087 (C=S), 532 (C—Br) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.60-8.11(m, 4H, 2-pyridine), 7.4-7.8 (m, 3H, Ar-H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H); ^{13}C NMR(DMSO d_6): δ 109.9, 113.3, 118.8, 120.0, 123.9, 132.8, 132.9, 134.2, 138.3, 145.8, 148.2, 158.6, 167.5, 186; MS (relative intensity): m/z value 376.98 (28%); Calcd. for C₁₄H₁₀BrN₅OS % C 44.69, H 2.68, N 18.61; found C 44.67, H 2.65, N 18.59

1-(5-Bromo-2-oxoindolin-3-ylidene)-4-(5-chloropyridin-2-yl)thiosemicarbazide (3l). The sample was recrystallized using ethanol and chloroform mixture. Yield: 76%. m.p. 170-172°C. IR(KBr): 3308 (NH), 1682 (C=O), 1648 (C=N), 1042 (C=S), 542 (C—Br) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.89-8.31(m, 3H, 2-pyridine), 7.4-7.8(m, 3H, Ar—H), 7.0(s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H); ^{13}C NMR (DMSO d_6): δ 110.6, 118.8, 120.0, 123.5, 123.9, 132.8, 132.9, 134.2, 137.1, 145.8, 150.6, 157.2, 167.5, 186; MS (relative intensity): m/z value 408.94 (20%); Calcd. for C₁₄H₉BrClN₅OS % C 40.94, H 2.21, N 17.05; found C 40.92, H 2.20, N 17.03

1-(5-Bromo-2-oxoindolin-3-ylidene)-4-(3-methylpyridin-2-yl) thiosemicarbazide (3m). The sample was recrystallized using ethanol and chloroform mixture. Yield: 75%. m.p. 152-154°C.

IR(KBr): 3365 (NH), 1737 (C=O), 1615 (C=N), 1122 (C=S), 524 (C—Br) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.51-8.09 (m, 3H, 2-pyridine), 7.4-7.8(m, 3H, Ar-H), 7.0 (s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H), 2.32 (s, 3H, CH₃); ^{13}C NMR (DMSO d_6): δ 15.8, 112.5, 117.0, 118.8, 120.0, 123.9, 132.8, 132.9, 134.2, 137.5, 145.8, 145.9, 154.6, 167.5, 186; MS (relative intensity): m/z value 388.99 (31%); Calcd. for C₁₅H₁₂BrN₅OS % C 46.16, H 3.10, N 17.95; found C 46.14, H 3.08, N 17.93

1-(5-Bromo-2-oxoindolin-3-ylidene)-4-(4-methylpyridin-2-yl)thiosemicarbazide (3n). The sample was recrystallized using ethanol and chloroform mixture. Yield: 80%. m.p. 188-190 °C. IR(KBr): 3338 (NH), 1706 (C=O), 1630 (C=N), 1102 (C=S), 512 (C—Br) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.50-8.12 (m, 3H, 2-pyridine), 7.4-7.8 (m, 3H, Ar-H), 7.0 (s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H), 2.37 (s, 3H, CH₃); ^{13}C NMR (DMSO d_6): δ 24.3, 112.7, 117.7, 118.8, 120.0, 123.9, 132.8, 132.9, 134.2, 145.8, 148.7, 149.6, 159.1, 167.5, 186; MS (relative intensity): m/z value 388.99 (37%); Calcd. for C₁₅H₁₂BrN₅OS % C 46.16, H 3.10, N 17.95; found C 54.67, H 3.64, N 21.25.

1-(5-Bromo-2-oxoindolin-3-ylidene)-4-(6-methylpyridin-2-yl)thiosemicarbazide (3o). The sample was recrystallized using ethanol and chloroform mixture. Yield: 74%. m.p. 156-158 °C. IR(KBr): 3344 (NH), 1736 (C=O), 1581 (C=N), 1131 (C=S), 517 (C—Br) cm^{-1} ; ^1H NMR (DMSO d_6): δ 6.49-7.43 (m, 3H, 2-pyridine), 7.4-7.8 (m, 3H, Ar-H), 7.0 (s, H, N—H), 8.0 (s, H, N—H), 4.0 (s, H, N—H), 2.55 (s, 3H, CH₃); ^{13}C NMR (DMSO d_6): δ 24.8, 106.9, 113.5, 118.8, 120.0, 123.9, 132.8, 132.9, 134.2, 138.5, 145.8, 157.2, 158.2, 167.5, 186; MS (relative intensity): m/z value 388.99 (41%); Calcd. for C₁₅H₁₂BrN₅OS % C 46.16, H 3.10, N 17.95; found C 54.67, H 3.64, N 21.25.

Antibacterial activity

The compounds 3a-o were screened *in vitro* for their antibacterial activity against pathogenic organisms *B. subtilis* NCIM2063, *S. aureus* NCIM2079, *E. coli* NCIM206 and *P. aeruginosa* NCIM2200 using ciprofloxacin as standard and DMSO as solvent control. The disc diffusion method was performed using Muller- Hinton agar (Hi- Media) medium. After 24h of incubation at 37°C the zones of inhibition formed were measured in mm and are shown in Table 2.

Antifungal activity

The synthesized compounds were screened for their antifungal activity against *Candida albicans* NCIM3102 and *Aspergillus niger* using ketoconazole as standard. The plates were incubated at 26°C for 72 h and zones of inhibition formed were measured. The activity data are given in Table 2.

Acknowledgements

The authors are thankful to Vel's College of Pharmacy and its management for providing research facilities and encouragement and to our friends those who helped us to complete this research.

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