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Synthesis of Some New 5-fluoro/chloro/bromo-*N*'-(4-aryl-1, 3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide Derivatives as Possible Antifungal and Antibacterial Agents

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Abstract: Novel 5-fluoro/chloro/bromo-*N*'-(4-aryl-1, 3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide derivatives (4a-l) were prepared by treating corresponding 5-fluoro/chloro/bromo thiosemicarbazide with aromatic acylbromides. The newly synthesized compounds were characterized by analytical and spectral data. All the compounds were screened for antifungal and antibacterial activities. Most of the compounds exhibited promising antimicrobial activity.

Key words: Synthesis, thiazolyl indoles, antifungal and antibacterial

Introduction

The indole nucleus is an important element in many pharmacologically active compounds. A number of indole derivatives are reported to exhibit antibacterial, antifungal, antituberculosis, antithrombotic, anticancer and antiinflammatory activities (Forbes *et al*., 1993; Murphy *et al*., 1997; Young *et al*., 2001; Mackman *et al*., 2002; Narayana *et al*., 2005). Various indolyl thiazoles were synthesized and reported for their CNS depressant, anti-inflammatory and anticancer activities (Arya *et al*., 1977; Gu *et al*., 1999). Antimicrobial activity of thiazole derivatives is extensively studied by many researchers (Demirayak *et al*., 1997; Katsura *et al*., 1999; Vingkar *et al*., 2001; Holla *et al*., 2003). As a continuation of the present study to explore potent biologically active thiazole containing molecules (Narayana *et al*., 2004, 2006a, 2006b), we synthesized some new 5-fluoro/chloro/bromo-*N*'-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide derivatives and screened for their antifungal and antibacterial activities.

Materials and Methods

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates. IR spectra were recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (300 MHZ) spectrometer using TMS as internal standard and ^{13}C NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (75 MHZ) spectrometer. FABMS spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas.

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Synthesis of 1-[(5-fluoro/chloro/bromo-1H-indol-2-yl) carbonyl] thiosemicarbazide (2a-c)

5-Fluoro/chloro/bromo indole-2-carbohydrazide (0.01 mole) was refluxed with 10 mL 10% HCl and potassium thiocyanate (0.012 mole) for 2-3 h. The solid separated was filtered and washed with sufficient quantity of water and then dried. All the compounds were taken for next step without further purification

2a. 1-[(5-Fluoro-1H-indol-2-yl) carbonyl] thiosemicarbazide

This compound was isolated as yellowish orange powder with a yield of 78%, m.p 223-225°C; IR (KBr, ν in cm^{-1}): 3417.6 and 3244.0 (-$NHNH_2$), 3124.5 and 2970.2 (-CH), 1670.2 (-C = O), 1542.9 (-C = N), 1240.1 (-C = S).

2b. 1-[(5-Chloro-1H-indol-2-yl) carbonyl] thiosemicarbazide

This compound was isolated as brown crystals with a yield of 80%, m.p 229-230°C; IR (Kbr, ν in cm^{-1}): 3484.8 (-$NHNH_2$), 3163.0 (-CH), 1676.0 (-C = O), 1560.3 (-C = N), 1234.4 (-C = S).

2c. 1-[(5-Bromo-1H-indol-2-yl) carbonyl] thiosemicarbazide

This compound was isolated as yellow crystals with a yield of 82%, m.p 222-223°C; IR (KBr, ν in cm^{-1}): 3516.0 and 3421.5 (-$NHNH_2$), 3139.9 (-CH), 1658.7 (-C = O), 1541.90 (-C = N), 1244.0 (-C = S).

Synthesis of 5-fluoro/chloro/bromo-N'-(4-aryl-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide (4a-l)

1-[(5-Fluoro/chloro/bromo-1*H*-indol-2-yl) carbonyl] thiosemicarbazide (0.001 mole) and appropriate aromatic acyl bromide (0.0012 mole) was refluxed in methanol for 6-8 h. The reaction mixture was then kept overnight. The solid separated was filtered and then recrystallized in ethanol, dimethylformamide mixture.

Spectral Data

4a. *5-Fluoro-N'-(4-(2-chloropyridin-4-yl)-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide*

IR (KBr, ν in cm^{-1}): 3285.0 (-NH), 1708.9 (-C = O); ^{1}H-NMR (300MHz, DMSO-d_6): δ 6.99 (m, 1H, ArH), 7.26 (s, 1H, ArH), 7.42 (m, 2H, ArH), 7.72 (m, 2H, ArH), 7.83 (m, 1H, ArH), 8.35 (s, 1H, ArH), 9.82 (bs, 1H, NH), 10.80 (s,1H, NH) and 11.56 (1H, NH); FABMS: m/z 388 (I = 50%, M^+), 389 (I = 50%, M+1).

4b. *5-Fluoro-N'-(4-(6-bromocoumarin-3-yl)-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide*

IR (KBr, ν in cm^{-1}): 3286.5 (-NH), 1718.5 and 1650.0 (-C = O); ^{1}H-NMR (300MHz, DMSO-d_6): δ 7.09 ($dt_{(J = 9.0,2.7)}$, 1H, ArH), 7.27 (s,1H, ArH), 7.43 (m, 3H, ArH), 7.74 (m, 2H, ArH), 8.17 ($d_{(J=2.1)}$, 1H, ArH), 8.52 (s, 1H, ArH), 9.8(bs, 1H, NH), 10.99 (s, 1H, NH) and 11.90 (1H, NH); FABMS: m/z 499 (I = 45%, M^+), 501 (I = 50%, M+1).

4c. *5-Chloro-N'-(4-(6-bromocoumarin-3-yl)-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide*

IR(KBr, ν in cm^{-1}): 3390.6 and 3313.5 (-NH), 1722.3 and1629.7(-C = O); ^{1}H-NMR (300MHz, DMSO-d_6): δ 7.15 ($d_{(J = 8.7)}$, 1H, Ar-H), 7.26 (s, 1H, ArH), 7.32 ($d_{(J = 9.0)}$, 1H, ArH), 7.45 ($d_{(J = 8.70)}$, 1H, ArH), 7.66 ($dd_{(J = 9.3)}$, 2H, ArH), 7.75 (s,1H, ArH), 7.99 (s,1H, ArH), 8.09 (s,1H, ArH), 8.53 (s, 1H, ArH), 9.72 (bs, 1H, NH),10.92 (s,1H, NH) and 11.84 (1H, NH); FABMS: m/z 516 (I = 48%, M+1), 517 (I = 75%, M+1).

4e. *5-Chloro-N'-(4-(3,4-dihydroxyphenyl)-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide*

IR(KBr, ν in cm^{-1}): 3390.0(-NH), 1720.0 and 1629.9(-C = O); ^{1}H-NMR (300MHz, DMSO-d_6): δ 6.84 ($d_{(J=6.9)}$, 2H, Ar-H), 7.02 ($dd_{(J=1.8,8.1)}$, 1H, ArH), 7.32 ($dd_{(J=1.8,8.7)}$,2H, ArH), 7.30 (s, 1H, ArH), 7.46 ($d_{(J=8.7)}$, 1H, ArH), 7.63 ($d_{(J=1.5)}$ 1H, ArH), 7.93 (s, 1H, ArH), 8.09 (s, 1H, ArH), 8.53 (s, 1H, ArH), 11.34 (s, 1H, NH),11.87 (1H, NH); FABMS: m/z 400 (I = 30%, M^+), 401 (I = 60%, M+1).

4g. *5-Bromo-N'-(4-(coumarin-3-yl)-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide*

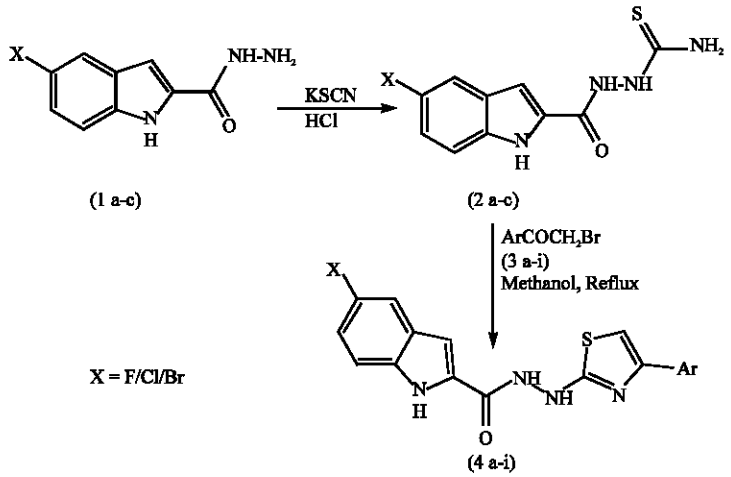
IR(KBr, ν in cm^{-1}): 3408.0 and 3155.3(-NH), 1725.0 and 1678.0(-C = O); ^{1}H-NMR (300MHz, DMSO-d_6): δ 7.28 ($d_{(J=6.6)}$, 2H, Ar-H), 7.35 ($d_{(J=9.6)}$, 1H, ArH), 7.32 ($d_{(J=8.4)}$,2H, ArH), 7.57 ($t_{(J=7.5)}$,1H, ArH), 7.70 ($dd_{(J=7.2)}$, 1H, ArH), 7.73 (s, 1H, ArH), 7.79 (s,1H, ArH), 7.98 (s, 1H, ArH), 8.58 (s, 1H, ArH), 10.92 (s, 1H, NH),11.79 (1H, NH); FABMS: m/z 481 (I = 45%, M^+),482 (I = 30%, M+1). 483 (I = 52%, M+2).

4h. *5-Bromo-N'-(4-(6-bromocoumarin-3-yl)-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide*

IR(KBr, ν in cm^{-1}): 3301.9 (-NH), 1732.0 and 1641.3 (-C = O); ^{1}H-NMR (300MHz, DMSO-d_6): δ 7.27 ($d_{(J=8.7)}$,2H, ArH), 7.42 ($d_{(J=9.0)}$, 1H, ArH), 7.62 ($dd_{(J=2.4,9.0)}$, 1H, ArH), 7.76 (s, 1H, ArH), 7.85 ($d_{(J=11.1)}$, 2H, ArH), 8.50 (s, 1H, Ar-H), 9.8 (bs, 1H, NH), 10.84(s, 1H, NH) and 11.68 (1H, NH);FABMS: m/z 560 (I = 75%, M-2), 561(I = 100%, M-1), 562 (I = 70%, M^+), 307 (I = 30%, $C_{17}H_{13}N_3OS$).

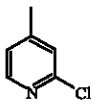
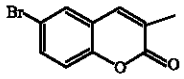
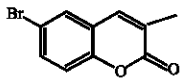
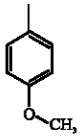
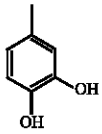
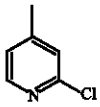
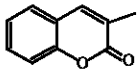
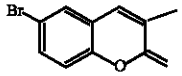
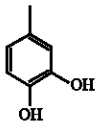
Results and Discussion

5-Fluoro/chloro/bromo indole-2-carbohydrazides (1a-c) on treatment with KSCN in acidic medium yielded 1-[(5-fluoro/chloro/bromo-1*H*-indol-2-yl) carbonyl]thiosemicarbazide (2a-c). The compounds (2a-c) on treatment with aromatic acyl bromides (3a-I) to give corresponding 5-fluoro/chloro/bromo-*N*'-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide derivatives (4a-I); (Scheme-1). The structures of newly synthesized compounds were confirmed by recording IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analysis. All the compounds were isolated in good yields after recrystallisation from methanol-DMF mixture. Few selected compounds were characterized by IR, ^{1}H-NMR and mass spectral analysis. Characterization data are given in Table 1 and the spectral data are given in the experimental section.



Scheme 1:

Table 1: Characterization data of the compound (4a-I)

Comp.	X	Ar-	Yield* (%)	MP°C	Nature of crystals	Nitrogen (%) found	Calc'd
4a	F		60	195-197	Off red	17.95	18.06
4b	F		92	>250	Brown	11.15	11.22
4c	Cl		87	247-249	Light brown	10.65	10.86
4d	Cl		65	182	Dark brown	13.84	14.05
4e	Cl		42	245-247	Off yellow	13.85	13.98
4f	Cl		52	186-88	Off yellow	17.28	17.32
4g	Br		81	>250	Brown	11.54	11.64
4h	Br		88	256-258	Brown	9.86	10.00
4i	Br		60	238-240	Off yellow	12.62	12.58

*All the yields are on isolated basis

Antibacterial Activity

We investigated the newly synthesized 5-fluoro/chloro/bromo-*N*'-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide (4a-I) for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphyllococcus aureus* (ATTC-25923), *Psuedomonus aeruginosa* (ATTC-27853) and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method (Cruickshank *et al*., 1975; Arthington *et al*., 2000). Streptomycin was used as standard drug. Solvent and growth controls were kept and the zone of inhibition in mm was noted. The results of such studies are given in Table 2. It can be seen that most of the compounds are active against all the bacterial strains. The compound

Table 2: Antibacterial activity of newly synthesized compounds at the conc. 10-100 g mL^{-1} (Disc diffusion method)

Compound	*Escherichia coli*	*Staphyllococcus aureus*	*Psuedomonus aeruginosa*	*Klebsiella pneumoniae*
4a	12	12	13	10
4b	8	13	8	9
4c	13	14	12	14
4d	-	28	30	-
4e	8	10	8	9
4f	18	20	14	19
4g	23	-	30	30
4h	13	14	12	14
4i	23	24	-	-
Standard (Streptomycin)	20	21	24	24

Zone of inhibition in mm

Table 3: Antifungal activity of newly synthesized compounds at the conc. 10-100 g mL^{-1} (Serial plate dilution method)

Compound	*Penicillium marneffei*	*Aspergilus flavus*	*Aspergilus fumigatus*	*Trichophyton mentagrophytes*
4a	22	14	16	14
4b	24	18	21	14
4c	21	-	21	16
4d	-	-	-	21
4e	22	-	25	20
4f	19	14	16	-
4g	-	-	-	-
4h	30	-	-	-
4i	-	-	-	-
Standard (Fluconozole)	21	18	21	19

Zone of inhibition in mm

4e, 5-chloro-*N*'-(4-(3,4-dihydroxyphenyl)-1, 3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide exhibited the highest inhibition and the compound 4d, 5-chloro-*N*'-(4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide exhibited the least inhibition. Compounds 4a-c and h also exhibited promising antibacterial activity. It can be seen from the studies that the compounds with fluoro and chloro substitution exhibited more inhibition than the compounds with bromo substitution. A correlation between antibacterial activity and substitution at C-4 could not be made from our studies. The higher activity of 4e may be due to the presence of catechol moiety, which is the main moiety present in adrenaline.

Antifungal Activity

Newly synthesized compounds 5-fluoro/chloro/bromo-*N*'-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide (4a-I) were screened for their antifungal activity against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Candida albicans* (NCIM No. 3100), *Penicillium marneffei* (Recultured) and *Trichophyton mentagrophytes* (Recultured) in DMSO by serial plate dilution method (Cruickshank *et al*., 1975; Arthington *et al*., 2000). Antifungal activity was determined by measuring the diameter of the inhibition zone. The results of such studies are given in Table 3. Activity of each compound was compared with Fluconozole as standard drug. The study reveals that most of the compounds possess less inhibition against the fungal strains. The compound 4a, 5-fluoro-*N*'-(4-(2-chloropyridin-4-yl)-1, 3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide exhibited highest inhibition and the compound 4g, 5-bromo-*N*'-(4-(3-coumarinyl)-1, 3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide exhibited least inhibition. The compound 4b and 4f also exhibited moderate activity in comparison with other compounds. It can be seen that compounds with fluoro substitution exhibited more activity than bromo and chloro substitution. A correlation between antibacterial activity and substitution at C-4 could not be made from our studies.

Conclusion

Novel 5-fluoro/chloro/bromo-*N'*-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide derivatives were prepared and screened for their antifungal and antibacterial activities. The compound 4e, 5-chloro-*N'*-[4-(3,4-dihydroxyphenyl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide exhibited maximum antibacterial activity and the compound 4a, 5-fluoro-*N'*-[4-(2-chloropyridinyl)-1, 3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide exhibited maximum antifungal activity. The compounds 4a and 4e can be recommended for further studies.

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