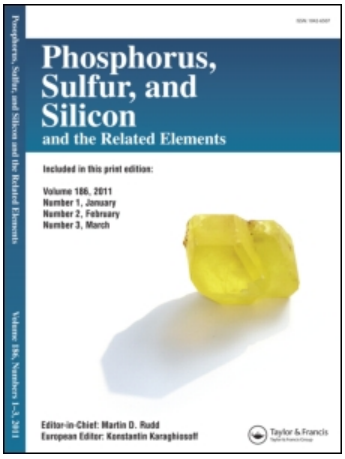

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Synthesis and Biological Activity of Novel 4-/5-/6-/7-Nitro-*N*'-(4-Aryl-1,3-Thiazol-2-yl)1*H*-Indole-2-Carbohydrazide Derivatives

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Synthesis and Biological Activity of Novel 4-/5-/6-/7-Nitro-*N′*-(4-Aryl-1,3-Thiazol-2-yl)-1*H*-Indole-2-Carbohydrazide Derivatives

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*New 4-/5-/6-/7-nitro-*N′*-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazides (**4a–t**) were prepared by treating respective nitroindole thiosemicarbazide with aromatic acylbromides. The newly synthesized compounds were characterized by analytical and spectral data. The compounds were also screened for antifungal and antibacterial activity. Some of the compounds exhibited promising antimicrobial activity.*

Keywords 1*H*-indole; 1,3-thiazole; biological activity; nitro; synthesis

INTRODUCTION

Many medicinally used natural products have been found to possess the indole nucleus as a structural unit.[1] The synthesis and biological evaluation of indole derivatives has been a topic of special interest to organic and medicinal chemists for over 100 years. A number of indole derivatives were reported to exhibit antibacterial, antifungal, antituberculosis, antithrombotic, anticancer, and antiinflammatory activities.[2–12] Indolyl thiazoles were reported for their central nervous system (CNS) depressant, antiinflammatory, and anticancer activities.[13–15] Some of the thiazole derivatives also exclusively were

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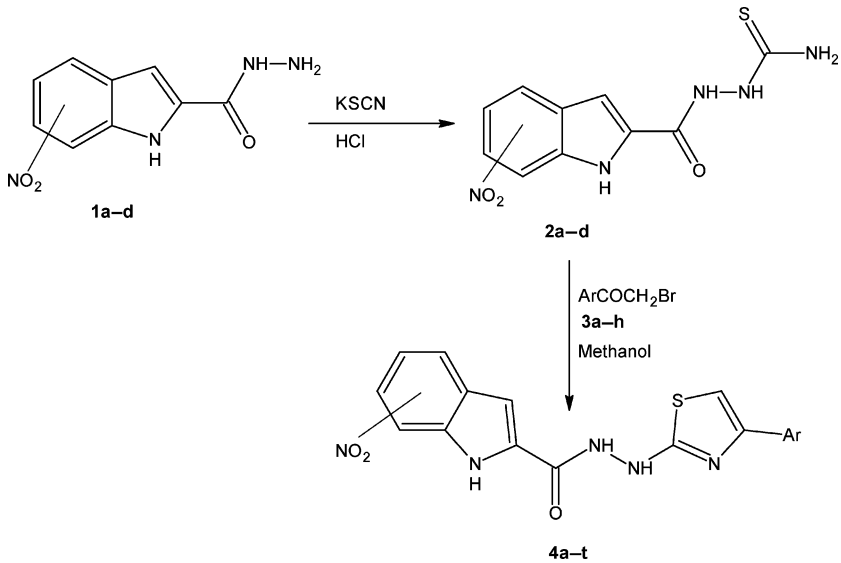


SCHEME 1

studied for their antifungal and antibacterial activities.[16] As a continuation of our research to explore biologically active thiazole-containing molecules[17–19] and also to synthesize new indole derivatives,[20] we aimed at synthesizing new 4-/5-/6-/7-nitro-*N*′-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide derivatives that might possess enhanced antimicrobial activities.

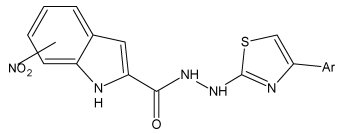
RESULTS AND DISCUSSION

Chemistry

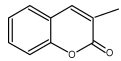
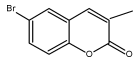
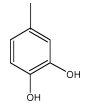
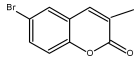
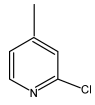
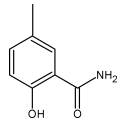
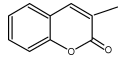
4-/5-/6-/7-Nitroindole carbohydrazides **1a–d** were treated with potassium thiocyanate (KSCN) in an acidic medium to get 1-[(4-/5-/6-/7-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazide **2a–d**. 1-[(4-/5-/6-/7-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazides **2a–d** on treatment with aromatic acyl bromides **3a–h** yielded corresponding 4-/5-/6-/7-nitro-*N*′-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazide derivatives **4a–t** (Scheme 1). The structures of newly synthesized compounds were established through IR, ^{1}H NMR, and ^{13}C NMR methods, in addition to fast atom bombardment mass spectrum (FABMS) and elemental analysis.

The characterization data of each compound are presented in Table I. The spectral data is presented in Table II.

TABLE I The Characterization Data of the Compounds 4a–t

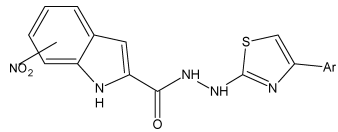


4a–t

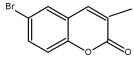
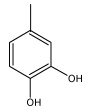
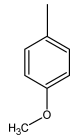
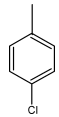
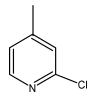
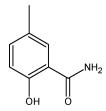
Compound	Position of $-NO_2$ in the indole ring	Ar–	Yield* %	M.P. °C	Nature of crystals	% Nitrogen Found	% Nitrogen Calcd.
4a	4		60	250–252	Off-red microcrystals	20.12	20.26
4b	4		72	>250	Yellow microcrystals	15.32	15.65
4c	4		85	>250	Yellow microcrystals	13.05	13.31
4d	4		65	240–242	Yellow power	18.32	18.46
4e	5		42	212–214	Brown powder	16.89	17.02
4f	5		40	152–154	Brown microcrystals	13.08	13.31
4g	6		81	196–198	Orange powder	20.04	20.26
4h	6		81	200–202	Orange powder	17.89	18.01
4i	6		60	>250	Light-brown microcrystals	15.46	15.65

(Continued on next page)

TABLE I The Characterization Data of the Compounds 4a–t ***(Continued)***

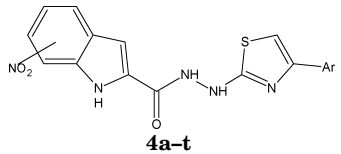


4a–t

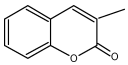
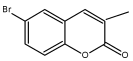
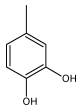
Compound	Position of $-NO_2$ in the indole ring	Ar–	Yield* %	M.P. °C	Nature of crystals	% Nitrogen Found	% Nitrogen Calcd.
4j	6		60	>250	Yellow microcrystals	13.09	13.31
4k	6		40	180–182	Light-brown powder	16.95	17.02
4l	6		62	>250	Light-brown powder	18.40	18.46
4m	6		72	256–258	Yellow powder	17.01	17.11
4n	6		70	200	Reddish-brown powder	16.78	16.92
4o	7		73	242–244	Yellow powder	20.10	20.26
4p	7		83	246–248	Brown powder	19.02	19.17

(Continued)

TABLE I The Characterization Data of the Compounds 4a–t ***(Continued)***



4a–t

Compound	Position of $-NO_2$ in the indole ring	Ar–	Yield* %	M.P. °C	Nature of crystals	% Nitrogen Found	% Nitrogen Calcd.
4q	7		80	214–216	Yellow microcrystals	15.48	15.65
4r	7		88	240–242	Brown microcrystals	13.16	13.31
4s	7		53	244–246	Yellow powder	16.93	17.02
4t	7		65	240–242	Yellow microcrystals	18.28	18.46

*All yields are on an isolated basis.

Biological Activity

Antibacterial Activity

We investigated the antimicrobial activity of newly synthesized1-[(4-/5-/6-/7-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazides **2a–d** and 4-/5-/6-/7-nitro-*N*′-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazides **4a–t** against *Escherichia coli* (ATTC-25922), *Staphyllococcus aureus* (ATTC-25923), *Psuedomonus aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains by the disc diffusion method.[21–23] Nitrofurazone was used as the standard drug. Solvent and growth controls were kept, and the zones of inhibition and minimum inhibitory concentrations (MIC) were noted. The results of such studies are given in Table III.

Among the tested compounds, the compounds **4e** (5-nitro-*N*′-[4-(3,4-dihydroxyphenyl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide) and

TABLE II Spectral Data of Compounds 4a–t

Compound No.	Spectral data
4a	**IR**(KBr, ν in cm^{-1}): 3381.0 (−NH), 1683.7 and 1654.8 (−C═O), 1070.2 (C—Cl); **^{1}H-NMR**: δ 7.46 (t, 1H, ArH), 7.81 (s, 1H, ArH), 7.81 (s, 1H, ArH), 7.85 (s,1H, ArH), 7.93 ($d_{(J=9.0)}$, 1H, ArH), 7.97 (s, 1H, ArH), 8.14 ($d_{(J=9.0)}$, 1H, Ar-H), 8.4 ($d_{(J=6.0)}$, 1H, ArH), 9.99 (s, 1H, NH), 11.31 (s, 1H, NH) and 12.69 (1H, NH); **^{13}C-NMR**: 103.18, 109.64, 118.31, 119.28, 119.82, 120.45, 123.23, 133.00, 138.56, 140.44, 144.65, 146.88, 150.44, 151.11, 160.57, 172.69; DEPT: 103.18, 109.64, 118.31, 119.81, 120.47, 123.25, 150.44; **FABMS**: m/z 444 (I = 75%, M+CH_3OH), 248 (I = 100%, $C_{10}H_9N_5O_3$)
4d	**IR**(KBr, ν in cm^{-1}): 3284.5 (−NH), 1652.9 (−C═O); **^{1}H-NMR**: δ 6.87 (s, 1H, Ar-H), 7.30–7.44 (m, 8H, ArH), 7.82 (t, 1H, ArH), 7.89 ($d_{(J=8.42)}$, 1H, ArH), 8.04 ($d_{(J=1.98)}$, 1H, ArH), 8.14 ($d_{(J=7.62)}$, 1H, ArH), 9.992 (s, 1H, NH), 11.31 (s, 1H, NH) and 12.69 (1H, NH); **FABMS**: m/z 380 (I = 50%, M+1), 379 (I = 25%, M^+), 307 (I = 30%, $C_{17}H_{13}N_3OS$)
4e	**IR**(KBr, ν in cm^{-1}): 3325.0 (−NH), 1701.1 (−C═O), 1066.2 (C—Cl); **FABMS**: m/z 414 (I = 15%, M+2), 444 (I = 20%, M+CH_3OH), 307 (I = 30%, $C_{17}H_{13}N_3OS$)
4h	**IR**(KBr, ν in cm^{-1}): 3458.1 and 3363.6 (−OH) 3234.4 (−NH), 1668.3 and 1624.0 (−C═O); **^{1}H-NMR**: δ 6.88 ($d_{(J=8.7)}$,1H, ArH), 6.96 (s, 1H, ArH), 7.36 (bs, 1H, OH), 7.41 (s, 1H, ArH), 7.76 ($d_{(J=8.8)}$, 1H, ArH), 7.82 (s, 1H, Ar-H), 7.85 ($d_{(J=8.5)}$, 1H, ArH), 7.93 ($dd_{(J=2.0,8.8)}$, 1H, ArH), 8.31 ($d_{(J=1.8)}$, 2H, $-NH_2$), 8.44 (s, 1H, ArH), 10.99 (s, 1H, NH, exchangeable with D_2O), 12.27 (s, 1H, NH exchangeable with D_2O); **FABMS**: m/z 439 (I = 5%, M^+), 444 (I = 80%, M+4), 279 (I = 15%, M-salicylamide), 248 (I = 100%, $C_{10}H_9N_4O_2S$)
4j	**IR**(KBr, ν in cm^{-1}): 3288.4 and 3182.3 (−NH), 1691.5 and 1649.0 (−C═O), 783.1 and 732.9 (C—Br); **^{1}H-NMR**: δ 7.39 ($d_{(J=8.7)}$, 1H, ArH), 7.45 (s, 1H, ArH), 7.73 ($d_{(J=8.7)}$, 2H, ArH), 7.92 (s, 2H, ArH), 8.16 (s, 1H, ArH), 8.34 (s, 1H, Ar-H), 8.51 (s, 1H, ArH), 9.92 (s, 1H, NH), 11.26 (s, 1H, NH) and 12.60 (1H, NH); **^{13}C-NMR**: δ 103.95, 109.03, 111.01, 114.76, 116.35, 118.08, 121.17, 121.32, 122.7, 130.78, 131.63, 133.89, 134.53, 135.01, 137.10, 142.87, 151.29, 158.28, 160.55, 171.77; DEPT: 103.95, 109.05, 111.02, 114.79, 118.1, 122.7 130.8, 133.91, 137.10; **FABMS**: m/z 526 (I = 40%, M^+), 528 (I = 35%, M+2), 307 (I = 30%, $C_{17}H_{13}N_3OS$)
41	**IR**(KBr, ν in cm^{-1}): 3184.3 (−NH), 1679.9 and 1629.7 (−C═O); **^{1}H-NMR**: δ 7.04 (s, 1H, ArH), 7.40–7.48 (m, 3H, ArH), 7.52 (s, 1H, ArH), 7.69 (s, 1H, ArH), 7.71 ($dd_{(J=2.0,8.0)}$, 1H, ArH), 7.78 ($d_{(J=8.9)}$, 1H, Ar-H), 7.95 ($dd_{(J=2.0,9.0)}$, 1H, ArH), 8.47 (s, 1H, ArH), 11.49 (s, 1H, NH, exchangeable with D_2O) and 12.32 (1H, NH, exchangeable with D_2O); **FABMS**: m/z 379 (I = 50%, M^+), 381 (I = 55%, M+2)
4p	**IR**(KBr, ν in cm^{-1}): 3460.0 and 3363.8 (−OH) 3250.0 (−NH), 1650.0 and 1622.0 (−C═O); **^{1}H-NMR**: δ 6.87 ($d_{(J=8.5)}$, 1H, ArH), 6.96 (s, 1H, ArH), 7.30 ($t_{(J=7.9)}$, 1H, ArH), 7.37 (bs, 1H, OH), 7.54 ($d_{(J=,1.8)}$, 1H, ArH), 7.85 (s, 1H, Ar-H), 8.15 ($d_{(J=7.7)}$, 1H, ArH), 8.26 ($d_{(J=8.0)}$, 1H, ArH), 8.31($d_{(J=1.7)}$, 2H, $-NH_2$), 9.4 (bs, 1H, NH), 11.19 (s, 1H, NH), 12.82 (bs, 1H, NH)

(Continued on next page)

TABLE II Spectral Data of Compounds 4a–t (*Continued*)

Compound	Spectral data
4q	**IR**(KBr, ν in cm^{-1}): 3282.6 (−NH), 1720.4 and 1685.7 (−C═O); ^{1}**H-NMR**: δ 7.26–7.35 (m, 3H, ArH), 7.51–7.61 (m, 4H, ArH), 7.73 ($d_{(J=8.7)}$, 1H, ArH), 8.09 ($d_{(J=7.89)}$, 1H, ArH), 8.16 ($d_{(7.98)}$, 1H, ArH), 8.59 (s, 1H, Ar-H), 11.12 (s, 1H, NH), 11.21 (s, 1H, NH), 12.82 (s, 1H, NH); **FABMS**: m/z 447 (I = 50%, M^+), 448 (I = 90%, M+1), 391(I = 90%, $C_{20}H_{17}N_5O_2S$), 307 (I = 30%, $C_{17}H_{13}N_3OS$)

4f (5-nitro-*N*′-[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide) exhibited maximum antibacterial activity. Compound **2c** (1-[(6-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazide) exhibited moderate activity. We observed in our earlier work[18] that thiazoles containing the 3,4-dihydroxyphenyl moiety have exhibited excellent antibacterial activity. Thus the greater activity of compound **4e** (5-nitro-*N*′-[4-(3,4-dihydroxyphenyl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide) may be due to the presence of the 3,4-dihydroxyphenyl

TABLE III The Antibacterial Activity of Newly Synthesized Compounds at the Conc. 10 μg/mL–100 μg/mL

Compound	*E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*
4a	—	—	—	10
4b	—	—	—	—
4c	—	—	—	6.25
4d	—	—	—	6.25
4e	10	10	10	10
4f	10	10	10	10
4g	—	—	—	10
4h	—	10	—	10
4i	—	—	—	—
4j	—	—	—	—
4k	—	—	—	12.5
4l	—	—	—	12.5
4m	—	—	—	12.5
4n	—	—	—	—
4o	—	—	—	—
4p	—	—	—	—
2a	—	—	—	—
2b	—	10	—	10
2c	10	10	—	12.5
2d	—	12.5	—	—
Nitrofurazone	6	12.5	>100	—

moiety. Warfarin, a rodenticide drug,[24] contains 2-oxo-2*H*-chromen-4-yl as the main moiety. Compound **4f** (5-nitro-*N*′-[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide) also contains the 2-oxo-2*H*-chromen-3-yl moiety that may be the reason for its greater activity. The moderate activity of 1-[(6-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazide could not be explained.

Antifungal Activity

Newly synthesized compounds 1-[(4-/5-/6-/7-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazides **2a–d** and 4-/5-/6-/7-nitro-*N*′-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazides **4a–t** 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 the serial plate dilution method[21–23]. Antifungal activity was determined by measuring the diameter of the inhibition zone. The results of such studies are given in Table IV. The activity of each compound was compared with Itraconozole as the

TABLE IV The Antifungal Activity of Newly Synthesized Compounds at the Conc. 10 μg/mL–100 μg/mL

Compound	*P. marneffei*	*A. flavus*	*A. fumigatus*	*T. mentagrophytes*
4a	—	60	60	—
4b	—	60	60	10
4c	—	60	60	—
4d	—	60	60	10
4e	60	60	60	10
4f	60	60	60	10
4g	60	60	60	10
4h	60	60	60	10
4i	60	60	60	10
4j	60	60	60	10
4k	60	60	60	10
4l	60	60	60	10
4o	60	60	10	10
4p	60	60	60	10
4q	60	60	60	10
4r	60	60	60	10
4t	60	60	60	10
2a	60	60	60	60
2b	10	60	60	60
2c	10	10	10	10
2d	60	60	60	60
Itraconazole	<16	<16	<16	<16

standard drug. The MIC for the Itraconazole in DMSO is 0.03–16 μg/mL against the tested species.[21]

Among the tested compounds, compound **4o** (7-nitro-*N*′-[4-(2-chloropyridin-4-yl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide) and the compound **2c** (1-[(6-nitro-1*H*-indol-2-yl) carbonyl] thiosemicarbazide) exhibited maximum antifungal activity. All other compounds exhibited moderate activity. The higher activity of **4o** may be due to the presence of the 2-chloropyridin-4-yl moiety, which is an active moiety found in some pyridine based therapeutically useful compounds.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by TLC 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}). ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as an internal standard, and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian (75 MHz) spectrometer. FABMS was recorded on a JEOL SX 102/DA-6000 mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas.

The Synthesis of 1-[(4-/5-/6-/7-nitro-1*H*-indol-2-yl)-carbonyl]thiosemicarbazides 2a–d

Nitroindole-2-carbohydrazide (0.01 mole) was refluxed with 10 mL of 10% HCl and potassium thiocyanate (0.012 mole) for 2–3 h. The solid separated was filtered and washed with water and then dried. All compounds were taken for preparation of thiazolyl derivatives without further purification.

*2a: 1-[(4-Nitro-1*H*-indol-2-yl)carbonyl]thiosemicarbazide*

This compound was isolated as a yellowish orange powder with a yield of 78%, m.p. 223–225°C; **IR** (KBr, ν in cm^{-1}): 3400.0 and 3224.8 (–$NHNH_2$), 2968.2 and 2821.7 (–CH), 1678.4 (–C=O), 1542.9 (–C=S), 1155.3 (–C=S).

*2b: 1-[(5-Nitro-1*H*-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}): 3406.1 and 3301.9 (–$NHNH_2$), 2925.8 and 2856.0 (–CH), 1666.4 (–C=O), 1533.3 (–C=S), 1072.0 (–C=S).

*2c: 1-[(6-Nitro-1*H*-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}): 3435.0 and 3323.1 (—$NHNH_2$), 3163.0 and 2962.5 (—CH), 1681.8 (—C=O), 1542.9 (—C=S), 1068.5 (—C=S).

*2d: 1-[(7-Nitro-1*H*-indol-2-yl)carbonyl]thiosemicarbazide*

This compound was isolated as a buff powder with a yield of 80%, m.p. 224–226°C; **IR**(KBr, ν in cm^{-1}): 3450.0 and 3310.0 (—$NHNH_2$), 3163.0 and 2964.4 (—CH), 1668.3 (—C=O), 1533.3 (—C=S), 1166.9 (—C=S).

The Synthesis of 4-/5-/6-/7-nitro-*N*′-(4-aryl-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazides 4a–t

1-[(4-Nitro-1*H*-indol-2-yl)carbonyl]thiosemicarbazide (0.001 mole) and the 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 from a mixture of ethanol and dimethylformamide (90:10).

Other nitro-*N*′-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazides were also prepared in a similar way.

CONCLUSION

Some new 4-/5-/6-/7-nitro-*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-nitro-*N*′-[4-(3,4-dihydroxyphenyl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide, and the compound **4f**, 5-nitro-*N*′-[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]-1*H*-indole-2-carbohydrazide, exhibited maximum antibacterial activity. The compound **2c**, 1-[(6-nitro-1*H*-indol-2-yl)-carbonyl]thiosemicarbazide, exhibited maximum antifungal activity.

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