Synthesis, Reactions and Antimicrobial Activity of Some New Indolyl-1,3,4-Oxadiazole, Triazole and Pyrazole Derivatives

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Indole-3-carboxylic acid hydrazide **3** was prepared and was treated with aromatic aldehydes in ethanol to give the corresponding hydrazone derivatives **4-7** in good yields. The indole carbohydrazide was incorporated into the 3-indolyloxadiazoles **8-11** and **18**, 3-indolyltriazoles **13-17** and **35**, 3-indolylpyrazole derivatives **19-23** and carbamate derivatives **26-27**. Furthermore, interaction of the carboazide **24** with hydrazine hydrate in refluxing toluene afforded the corresponding semicarbazide derivative **30**. The thiadiazine derivative **34** was also prepared. Some of these compounds were screened *in vitro* for their antibacterial and antifungal activity.

Keywords: Monoamine oxidase; 3-Indolyloxadiazoles; 3-Indolytriazoles and pyrazoles.

INTRODUCTION

Indole derivatives have attracted particular attention due to their various pharmacological activities.[1,2] Several of these derivatives possess potent central nervous system (CNS) as well as anti-inflammatory properties.[3-6] Indole-3-carbohydrazide derivatives have been shown to inhibit monoamine oxidase A activity.[7-9] Some N-methylindol-3-hydrazones have shown antihypertensive activity in spontaneously hypertensive rates.[10] Moreover, it was reported that several 3-substituted indoles were used as materials for alkaloids, agrochemicals, pharmaceuticals and perfumes.[11] Indolyl quinazolones possess potent anti-inflammatory as well as CNS activity.[12,13] Also, it has been reported that the substitution by hetrocyclic moieties, i.e., oxadiazoles or triazoles at positions 1 and 3 of the indole nucleus enhances these activities.[14] All these findings prompted the synthesis of a number of indole-3-carbohydrazide derived systems of anti-microbial activity.

EXPERIMENTAL

All melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer (KBr; υ_{max} in cm^{-1}). ^1H NMR spectra were recorded on a Jeol LA 400 MHz FT-NMR spectrophotometer with TMS as internal standard (δ values in ppm.). Mass spectra were obtained with a Jeol JMS-600 mass spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240 C Microanalyzer, and the results were in an acceptable range. The characterization data of the newly synthesized compounds are listed in Table 1.

Ethyl 1-benzyl-1*H*-indole-3-carboxylate (2)

To a mixture of the compound **1** (0.189 g, 0.001 mol) and K_2CO_3 (0.414 g, 0.003 mol) in dry DMF (10 mL) was added benzyl chloride (0.139 g, 0.0011 mol). The mixture was heated under reflux for 12 h. After cooling, the solvent was removed under reduced pressure and the residue was triturated with water, then the product was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with water (3 × 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a buff solid product, which was recrystallized from ethyl acetate/light petroleum to afford buff needles.

1-Benzyl-1*H*-indole-3-carbohydrazide (3)

A mixture of compound **2** (5 g, 0.019 mol) and hydrazine hydrate (15 mL) was refluxed for 4 h. The excess of hydrazine hydrate was removed *in vacuo* and the residue was triturated with water, filtered off, dried and recrystallized from ethanol to give colorless crystals.

N-Arylmethylene-1-benzyl-1*H*-indole-3-carbohydrazide (4-7)

To a solution of **3** (0.265 g, 0.001 mol) in ethanol (15 mL), an ethanolic solution of appropriate aldehyde (0.001 mol) was added. The resulting mixture was refluxed for 2 h.

Table 1. Characterization Data of the Synthesized Compounds

Compd	M.P. (°C)/ (Yield: %)	Formula (M.W.)	Spectral data and elemental analysis
2	66-68 (95)	$C_{18}H_{17}NO_2$ (279.3)	IR: 2950 (CH aliphatic); 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ 8.35-8.30 (m, 1H, H-4); 7.79 (s, 1H, H-2); 7.50-7.31 (m, 3H, H-5, H-6, H-7 and Ph-H); 5.43 (s, 2H, CH_2); 3.98 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.28; H, 5.98; N, 4.89.
3	150-52 (90)	$C_{16}H_{15}N_3O$ (265.3)	IR: 3330-3200 ($NHNH_2$); 1640 (C=O). ^{1}H NMR (DMSO-d_6): δ 9.26 (s, 1H, NH); 8.19 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.13 (s, 1H, H-2); 7.50 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.32-7.12 (m, 7H, H-5, H-6 and Ph-H); 5.43 (s, 2H, CH_2); 4.39 (s, 2H, NH_2). Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.38; H, 5.58; N, 15.75.
4	183-85 (87).	$C_{23}H_{19}N_3O$ (353.4)	IR: 3200 (NH); 1650 (C=O). ^{1}H NMR (DMSO-d_6): δ 9.18 (s, 1H, NH); 8.17 (s, 1H, N=CH); 8.12-6.93 (m, 15H, Ar-H and H-2); 5.35 (s, 2H, CH_2). Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.28; H, 5.58; N, 11.78.
5	227-29 (90)	$C_{23}H_{18}N_3Ocl$ (387.9)	IR: 3210 (NH0; 1630 (C=O). ^{1}H NMR (DMSO-d_6): δ 9.18 (s, 1H, NH); 8.20 (s, 1H, N=CH); 8.13-6.83 (m, 14H, Ar-H and H-2); 5.35 (s, 2H, CH_2). Anal. Calcd. for $C_{23}H_{18}ClN_3O$: C, 71.22; H, 4.68; N, 10.83; Cl, 9.14. Found: C, 71.28; H, 4.58; N, 10.76; Cl, 8.89.
6	223-25 (83)	$C_{24}H_{21}N_3O_2$ (383.5)	IR: 3200 (NH); 1630 (C=O). ^{1}H NMR (DMSO-d_6): δ 9.18 (s, 1H, NH); 8.20 (s, 1H, N=CH); 8.15-6.84 (m, 14H, Ar-H and H-2); 5.38 (s, 2H, CH_2); 3.78 (s, 3H, OCH_3). Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 78.23; H, 5.54; N, 10.87.
7	257-59 (81)	$C_{25}H_{24}N_4O$ (396.5)	IR: 3200 (NH); 1630 (C=O). ^{1}H NMR (DMSO-d_6): δ 9.19 (s, 1H, NH); 8.20 (s, 1H, N=CH); 8.13-6.73 (m, 14H, Ar-H and H-2); 5.38 (s, 2H, CH_2); 2.96 (s, 6H, N $(CH_3)_2$). Anal. Calcd. for $C_{25}H_{24}N_4O$: C, 75.73; H, 6.10; N, 14.13. Found: C, 75.68; H, 6.28; N, 14.29.
8	93-95 (61)	$C_{25}H_{21}N_3O_2$ (395.5)	IR: 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.19-7.10 (m, 15 H, Ar-H and H-2); 5.28 (s, 2H, CH_2); 2.30 (s, 3H, CH_3); 2.10 (s, 1H, CH oxadiazole). Anal. Calcd. for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.33; N, 10.63. Found: C, 75.88; H, 5.28; N, 10.45.
9	113-115 (48)	$C_{17}H_{13}N_3O$ (275.3)	IR: 3030 (CH aromatic). ^{1}H NMR (DMSO-d_6): δ 8.18 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.12 (s, 1H, H-2); 7.50 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.34-7.14 (m, 7H, H-5, H-6 and Ph-H); 5.43 (s, 2H, CH_2); 2.13 (s, 1H, CH oxadiazole). Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.10; H, 4.60; N, 15.17.
10	203-205 (87)	$C_{17}H_{13}N_3OS$ (307.4)	IR: 3200 (NH). ^{1}H NMR (DMSO-d_6): δ 13.4 (s, 1H, NH); 8.19 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.13 (s, 1H, H-2); 7.50 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.32-7.12 (m, 7H, H-5, H-6 and Ph-H); 5.43 (s, 2H, CH_2). Anal. Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.30; H, 4.18; N, 13.48.
11	202-204 (93)	$C_{16}H_{13}N_3O_2$ (291.3)	IR: 3200 (NH); 1780 (C=O). ^{1}H NMR (DMSO-d_6): δ 13.4 (s, 1H, NH); 8.18 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.12 (s, 1H, H-2); 7.49 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.34-7.14 (m, 7H, H-5, H-6 and Ph-H); 5.43 (s, 2H, CH_2). Ms: 290 (M^{-1}, 100%). Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42; S,10.98. Found: C, 70.20; H, 4.38; N, 14.35; S, 10.88.
12	175-77 (97)	$C_{23}H_{20}N_4OS$ (401.5)	IR: 3400, 3250, 3150 (NH); 1640 (C=O). ^{1}H NMR (DMSO-d_6): δ 10.05 (s, 1H, NH); 9.72 (s, 1H, NH); 8.26 (s, 1H, NH); 8.20 (d, J_{4-5} = 6.8 Hz, 1H, H-4); 7.57 (s, 1H, H-2); 7.47 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.34-7.12 (m, 12H, H-5, H-6 and Ph-H); 5.49 (s, 2H, CH_2). Anal. Calcd. for $C_{23}H_{20}N_4OS$: C, 68.98; H, 5.03; N, 13.99; S,8.01. Found: C, 68.87; H, 4.98; N, 13.79; S, 7.97.
13	126-28 (98)	$C_{17}H_{15}N_5S$ (321.4)	IR: 3280, 3180 (NH_2); 3100 (NH). ^{1}H NMR (DMSO-d_6): δ 13.3 (s, 1H, NH); 8.19 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.13 (s, 1H, H-2); 7.50 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.32-7.12 (m, 7H, H-5, H-6 and Ph-H); 5.20 (s, 2H, NH_2); 5.35 (s, 2H, CH_2). Ms: 321 (M^+, 4%). Anal. Calcd. for $C_{17}H_{15}N_5S$: C, 63.53; H, 4.70; N, 21.79; S,9.98. Found: C, 63.48; H, 4.86; N, 21.69; S, 9.87.
14	110-112 (78)	$C_{23}H_{18}N_4S$ (382.5)	IR: 3200 (NH). ^{1}H NMR (DMSO-d_6): δ 13.7 (s, 1H, NH); 8.25-7.10 (m, 15H, Ph-H and H-2); 5.40 (s, 2H, CH_2). Anal. Calcd. for $C_{23}H_{18}N_4S$: C, 72.23; H, 4.74; N, 14.65; S, 8.38. Found: C, 72.08; H, 4.67; N, 14.69; S, 8.47.
15	125-27 (66)	$C_{17}H_{15}N_5O$ (305.3)	IR: 3280, 3170 (NH_2); 3100 (NH). ^{1}H NMR (DMSO-d_6): δ 13.10 (s, 1H, NH); 8.23 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.13 (s, 1H, H-2); 7.40 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.22-7.12 (m, 7H, H-5, H-6 and Ph-H); 5.20 (s, 2H, NH_2); 5.35 (s, 2H, CH_2). Anal. Calcd. for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.94; S, 5.24. Found: C, 66.78; H, 4.87; N, 5.19; S, 8.47.
16	168-70 (52)	$C_{29}H_{31}N_5S$ (481.7)	IR: 2950 (CH aliphatic). ^{1}H NMR ($CDCl_3$): δ 8.24-8.21 (m, 1H, H-4); 7.68 (s, 1H, H-2); 7.32-6.92 (m, 13 H, H-5, H-6, H-7 and Ph-H); 5.30 (s, 2H, CH_2); 3.54 (t, J = 7.4 Hz, 2H, SCH_2); 3.01 (t, J = 7.4 Hz, 2H, $SCH_2C\underline{H}_2$ NEt_2); 2.66 (q, J = 7.2 Hz, 4H, SCH_2CH_2 $N(C\underline{H}_2CH_3)_2$); 1.06 (t, J = 7.2 Hz, 6H, SCH_2CH_2 $N(CH_2C\underline{H}_3)_2$). Ms: 486 ($M^{+2}$, 12%). Anal. Calcd. for $C_{29}H_{31}N_5S$: C, 72.32; H, 6.49; N, 14.54; S, 6.66. Found: C, 72.22; H, 6.33; N, 14.43; S, 6.50.

17	78-80 (57)	$C_{29}H_{29}N_5OS$ (495.7)	IR: 2950 (CH aliphatic). ^{1}H NMR ($CDCl_3$): δ 8.23-8.20 (m, 1H, H-4); 7.70 (s, 1H, H-2); 7.32-6.92 (m, 13 H, H-5, H-6, H-7 and Ph-H); 5.30 (s, 2H, CH_2); 3.68 (t, J = 4.5 Hz, 4H, OCH_2); 3.43 (t, J = 8 Hz, 2H, SCH_2); 2.82 (t, J = 8 Hz, 2H, $SCH_2C\underline{H}_2$ N); 2.53 (t, J = 4.5 Hz, 4H, NCH_2). Anal. Calcd. for $C_{29}H_{29}N_5OS$: C, 70.28; H, 5.90; N, 14.13; S, 6.47. Found: C, 70.14; H, 5.79; N, 14.04; S, 6.39.
18	105-107 (71)	$C_{23}H_{24}N_4O_2S$ (420.5)	IR: 2950 (CH aliphatic). ^{1}H NMR ($CDCl_3$): δ 8.23-8.20 (m, 1H, H-4); 7.69 (s, 1H, H-2); 7.32-6.92 (m, 8H, H-5, H-6, H-7 and Ph-H); 5.30 (s, 2H, CH_2); 3.68 (t, J = 4.5 Hz, 4H, OCH_2); 3.43 (t, J = 8 Hz, 2H, SCH_2); 2.82 (t, J = 8 Hz, 2H, $SCH_2C\underline{H}_2$ N); 2.53 (t, J = 4.5 Hz, 4H, NCH_2). Ms: 418 (M^{-2}, 10%). Anal. Calcd. for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32; S, 7.62. Found: C, 65.58; H, 5.66; N, 13.22; S, 7.56.
19	238-40 (60)	$C_{20}H_{17}N_3O_2$ (331.4)	IR: 3150 (NH); 1660 (C=O). ^{1}H NMR (DMSO-d_6): δ 8.98 (s, 1H, NH); 8.27 (d, J_{4-5} = 8 Hz, 1H, H-4); 7.58 (s, 1H, H-2); 7.33-7.29 (m, 8H, H-5, H-6, H-7 and Ph-H); 6.03 (s, 1H, CH pyrazolone); 5.61 (s, 2H, CH_2); 2.42 (s, 3H, CH_3). Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.33; H, 7.11; N, 12.54.
21	107-109 (85)	$C_{21}H_{19}N_3O$ (329.4)	IR: 2900 (CH aliphatic); 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H, H-2); 8.50 (d, J_{4-5} = 7.8 Hz, 1H, H-4); 7.30-7.14 (m, 8H, H-5, H-6, H-7 and Ph-H); 5.99 (s, 1H, CH pyrazole); 5.37 (s, 2H, CH_2); 2.66, 2.27 (2s, 6H, $2CH_3$). Anal. Calcd. for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.44; H, 5.76; N, 12.68.
22	228-30 (91)	$C_{20}H_{15}N_5O$ (341.4)	IR: 3400, 3300 (NH_2); 2210 (C=N); 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.89 (s, 1H, H-2); 8.47 (d, J_{4-5} = 8 Hz, 1H, H-4); 7.70 (s, 1H, CH pyrazole); 7.33-7.23 (m, 9H, H-5, H-6, NH_2 and Ph-H); 7.13 (d, J_{6-7} = 8 Hz, 1H, H-7); 5.37 (s, 2H, CH_2). Anal. Calcd. for $C_{20}H_{15}N_5O$: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.25; H, 4.33; N, 20.45.
23	143-45 (85)	$C_{22}H_{20}N_4O_3$ (388.4)	IR: 3450, 3350 (NH_2); 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.91 (s, 1H, H-2); 8.48 (d, J_{4-5} = 8 Hz, 1H, H-4); 7.72 (s, 1H, CH pyrazole); 7.33-7.23 (m, 9H, H-5, H-6, NH_2 and Ph-H); 7.13 (d, J_{6-7} = 8 Hz, 1H, H-7); 5.36 (s, 2H, CH_2); 4.29 (q, J = 7.07 Hz, 2H, $C\underline{H}_2CH_3$); 1.35 (t, J = 7 Hz, 3H, $CH_2C\underline{H}_3$). Anal. Calcd. for $C_{22}H_{20}N_4O$: C, 68.03; H, 5.19; N, 14.42. Found: C, 67.97; H, 5.05; N, 14.34.
24	112-14 (90)	$C_{16}H_{12}N_4O$ (276.1)	IR: 2150 (N_3); 1650 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.91 (s, 1H, H-2); 8.48 (d, J_{4-5} = 8 Hz, 1H, H-4); 7.33-7.23 (m, 7H, H-5, H-6, and Ph-H); 7.13 (d, J_{6-7} = 8 Hz, 1H, H-7); 5.35 (s, 2H, CH_2). Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.48; H, 4.24; N, 20.151.
26	141-43 (72)	$C_{18}H_{18}N_2O_2$ (294.3)	IR: 3300 (NH); 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.50 (d, J_{4-5} = 8 Hz, 1H, H-4); 7.27 (s, 1H, H-2); 7.30-7.13 (m, 7H, H-5, H-6, and Ph-H); 7.10 (d, J_{6-7} = 8 Hz, 1H, H-7); 6.66 (s, 1H, NH); 5.26 (s, 2H, CH_2); 4.26 (q, J = 7.16 Hz, 2H, $C\underline{H}_2CH_3$); 1.34 (t, J = 6.96 Hz, 3H, $CH_2C\underline{H}_3$).
27	128-30 (72)	$C_{19}H_{20}N_2O_2$ (308.2)	IR: 3300 (NH); 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.49 (d, J_{4-5} = 8 Hz, 1H, H-4); 7.26 (s, 1H, H-2); 7.29-7.12 (m, 7H, H-5, H-6, and Ph-H); 7.10 (d, J_{6-7} = 8 Hz, 1H, H-7); 6.58 (s, 1H, NH); 5.24 (s, 2H, CH_2); 4.03 (quant, J = 6.10 Hz, 1H, $C\underline{H}(CH_3)_2$); 1.33, 1.31 (2s, 6H, $2CH_3$).
29	233-35 (35)	$C_{31}H_{26}N_4O$ (470.2)	IR: 3300 (NH); 1635 (C=O). ^{1}H NMR (DMSO-d_6): δ 8.54 (s, 1H, NH); 7.68 (s, 1H, H-2); 7.56 (d, J_{4-5} = 7.50 Hz, 1H, H-4); 7.45 (d, J_{6-7} = 8.08 Hz, 1H, H-7); 7.29-7.03 (m, 7H, H-5, H-6 and Ph-H); 5.35 (s, 2H, CH_2).
30	198-200 (71)	$C_{16}H_{16}N_4O$ (280.1)	IR: 3400-3200 (NH and NH_2); 1680 (C=O). ^{1}H NMR (DMSO-d_6): δ 8.65 (s, 1H, NH); 8.37 (s, 1H, NH); 7.57 (s, 1H, H-2); 7.52 (d, J_{4-5} = 7.50 Hz, 1H, H-4); 7.41 (d, J_{6-7} = 8.08 Hz, 1H, H-7); 7.28-6.97 (m, 7H, H-5, H-6 and Ph-H); 5.34 (s, 2H, CH_2); 4.35 (s, 2H, NH_2).
31	78-80 (65)	$C_{21}H_{23}N_3O$ (333.2)	IR: 3400 (NH); 1580 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, J_{4-5} = 7.50 Hz, 1H, H-4); 7.39 (s, 1H, H-2); 7.26-7.10 (m, 9H, H-5, H-6, H-7, NH and Ph-H); 5.26 (s, 2H, CH_2); 3.60 (t, unresolved, 4H, $N(CH_2)_2$); 1.62-1.57 (m, 6H, $3CH_2$).
32	98-100 (50)	$C_{20}H_{21}N_3O_2$ (335.2)	IR: 3400 (NH); 1600 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, J_{4-5} = 7.50 Hz, 1H, H-4); 7.39 (s, 1H, H-2); 7.26-7.10 (m, 9H, H-5, H-6, H-7, NH and Ph-H); 5.26 (s, 2H, CH_2); 3.68 (t, unresolved, 4H, $OC\underline{H}_2$); 2.53 (t, 4H, $NC\underline{H}_2$).
33	107-109 (58)	$C_{18}H_{19}N_3O_2$ (309.2)	IR: 3300 (NH); 1660 (C=O). ^{1}H NMR (DMSO-d_6): δ 8.65 (s, 1H, NH); 8.37 (s, 1H, NH); 8.19 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.13 (s, 1H, H-2); 7.50 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.32-7.12 (m, 7H, H-5, H-6 and Ph-H); 5.43 (s, 2H, CH_2); 3.79-3.35 (m, 5H, $2CH_2$ and OH).
34	115-17 (61)	$C_{25}H_{19}N_5S$ (421.53)	IR: 3040 (CH aromatic). ^{1}H NMR (DMSO-d6): δ 8.19 (d, J_{4-5} = 8 Hz, 1H, H-4); 8.13 (s, 1H, H-2); 7.50 (d, J_{6-7} = 8 Hz, 1H, H-7); 7.87-7.17 (m, 12H, H-5, H-6 and 2Ph-H); 5.35 (s, 2H, CH_2); 4.30 (s, 2H, CH_2 thidiazine).
35	100-104 (51)	$C_{20}H_{19}N_5OS$ (377.5)	IR: 3400, 3300 (NH_2); 1700 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.71 (s, 1H, H-2); 8.50 (d, J_{4-5} = 7.8 Hz, 1H, H-4); 7.30-7.23 (m, 7H, H-5, H-6 and Ph-H); 7.15 (d, J_{6-7} = 8 Hz, 1H, H-7); 5.70 (s, 2H, N-NH_2); 5.30 (s, 2H, NCH_2); 3.30 (s, 2H, SCH_2); 2.13 (s, 3H, CH_3).

After cooling, the solid precipitate was collected by filtration and recrystallized from ethanol to afford the title compounds as white crystals of **4-7**.

4-Acetyl-4,5-dihydro-2-(1-benzyl-1*H*-indol-3-yl)-5-phenyl-1,3,4-oxadiazole (8)

Compound **3** (0.353 g, 0.001 mol) and redistilled acetic anhydride (10 mL) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto water and allowed to stand at room temperature for 3 h. The solid product formed was collected and recrystallized from petroleum ether/ethyl acetate mixture as white crystals.

2-(1-Benzyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (9)

A mixture of **3** (0.265 g, 0.001 mol) and triethylorthformate (5 mL) was refluxed for 8 h. The solvent was evaporated and the residue was triturated with ethanol. The solid product obtained was filtered off and recrystallized from ethanol to give buff crystals.

2-(1-Benzyl-1*H*-indol-3-yl)-1,3,4-oxadiazole-5(4*H*)-thione (10)

A mixture of **3** (0.265 g, 0.001 mol) and carbon disulfide (3 mL) in pyridine was refluxed on a water bath for 7 h, then cooled and poured onto ice-cold water. The precipitate formed was filtered off and recrystallized from ethanol to give yellow crystals.

2-(1-Benzyl-1*H*-indol-3-yl)-1,3,4-oxadiazol-5(4*H*)-one (11)

A mixture of the hydrazide compound **3** (0.265 g, 0.001 mol) and 1,1′-carbonyldiimidazole (0.162 g, 0.001 mol) in dry dioxane (10 mL) was heated under reflux for 6 h. After cooling, the solvent was removed under reduced pressure and the residue was triturated with cold water (20 mL). The solid product was filtered off, dried and recrystallized from ethanol to afford colorless crystals.

N^1-(1-Benzyl-1*H*-indol-3-oyl)-N^4-phenylthiosemicarbazide (12)

A mixture of compound **3** (0.265 g, 0.001 mol) and phenyl isothiocyanate (0.13 mL, 0.001 mol) in ethanol (10 mL) was refluxed for 5 h. The reaction mixture was left to cool and the white solid product formed was filtered off and recrystallized from ethanol to give colorless crystals.

4-Amino-3-(1-benzyl-1*H*-indol-3-yl)-1,2,4-triazole-5(1*H*)-thione (13)

A suspension of **10** (0.307 g, 0.001 mol) and hydrazine hydrate 99% (2 mL, 0.04 mol) in ethanol (10 mL) was refluxed for 6 h. After cooling, the precipitate formed was collected and recrystallized from ethanol to afford white crystals.

3-(1-Benzyl-1*H*-indol-3-yl)-4-phenyl-1,2,4-triazole-2-thione (14)

Compound **12** (0.4 g, 0.001 mol), in an ethanolic potassium hydroxide solution 4% (10 mL), was heated under reflux for about 4 h. The solvent was concentrated, diluted with water and neutralized with diluted HCl at 0-5 °C. The crude product was filtered off, washed with water and recrystallized from ethanol to give white crystals.

4-Amino-3-(1-benzyl-1*H*-indol-3-yl)-1,2,4-triazol-5(1*H*)-one (15)

A mixture of **11** (0.29 g, 0.001 mol) and hydrazine hydrate 99% (2 mL, 0.04 mol) in ethanol (10 mL) was refluxed for 6 h. After cooling, the precipitate formed was collected and recrystallized from ethanol to afford rosy pink crystals.

5-(2′-Diethylaminoethylthio)-3-(1-benzyl-1*H*-indol-3-yl)-4-phenyl-1,2,4-triazole (16)

To a mixture of the thione **14** (0.382 g, 0.001 mol) and sodium acetate (0.4 g, 0.005 mol) in ethanol (10 mL) was added 2-diethylaminoethyl chloride hydrochloride (0.172 g, 0.001 mol). The mixture was refluxed for 7 h. and the reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue was dissolved in water. The product formed was collected and recrystallized from ethanol as greenish white crystals.

5-(2′-Morpholinoethylthio)-3-(1-benzyl-1*H*-indol-3-yl)-4-phenyl-1,2,4-triazole (17)

A mixture of the thione **14** (0.382 g, 0.001 mol), sodium acetate (0.4 g, 0.005 mol) in ethanol (10 mL) and 4-(2-chloroethyl) morpholine hydrochloride (0.188 g, 0.001 mol) was refluxed for 6 h. The solvent was removed under reduced pressure, the residue washed with water and the precipitate obtained was filtered off and recrystallized from petroleum ether/ethyl acetate mixture to give greenish white crystals.

5-(2′-Morpholinoethylthio)-2-(1-Benzyl-1*H*-indol-3-yl)-1,3,4-oxadizole (18)

To a solution of the oxadiazolethione **10** (0.307 g, 0.001 mol), sodium acetate (0.4 g, 0.005 mol) and 4-(2-chloroethyl) morpholine hydrochloride (0.188 g, 0.001 mol) in ethanol (10 mL) was refluxed for 5 h. The solvent was evaporated and

the residue was diluted with water and the solid product formed was collected and recrystallized from petroleum ether/ether mixture to afford white crystals.

1-(1-Benzyl-1*H*-indole-3-yl) carbonyl-1,2-dihydro-5-methyl pyrazol-3-one (19)

A mixture of hydrazide derivative **3** (0.265 g, 0.001 mol) and ethyl acetoacetate (5 mL) was heated under reflux for about 8 h. The excess of the solvent was removed *in vacuo* and the residue was collected and recrystallized from ethanol as buff crystals.

(1-Benzyl-1*H*-indol-3-yl)-(3,5-dimethyl pyrazol-1-yl) methanone (21)

A suspension of **3** (0.265 g, 0.001 mol) and acetylacetone (2 mL, 0.02 mol) was gently refluxed for 2 h. After cooling, the reaction mixture was triturated with ethanol and the resulting product was collected and recrystallized from methanol/ethyl acetate mixture as white crystals.

5-Amino-1-(1-benzyl-1*H*-indol-3-yl) carbonyl-1*H*-pyrazole-4-carbonitrile (22)

A mixture of **3** (0.265 g, 0.001 mol) and ethoxymethylene malononitrile (0.122 g, 1 mol) in absolute ethanol (10 mL) was heated under reflux for 6 h. After cooling, the solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol to give white crystals.

Ethyl 5-amino-1-(1-benzyl-1*H*-indol-3-yl) carbonyl)-1*H*-pyrazole-4-carboxylate (23)

A mixture of the hydrazide **3** (0.265 g, 0.001 mol) and ethyl ethoxymethylene cyanoacetate (0.169 g, 0.001 mol) in absolute ethanol (10 mL) was refluxed for 6 h. After cooling, the solvent was removed under reduced pressure and the solid residue was recrystallized from ethanol/light petroleum (1:2) to afford colorless crystals.

1-Benzyl-1*H*-indole-3-carbonylazide (24)

To a cold solution of **3** (2.65 g, 0.01 mol) in glacial acetic acid (10 mL), sodium nitrite solution 10% (7 mL, 0.01 mol) was added. The reaction mixture was stirred at room temperature over 15 min. The buff solid product formed was filtered off, air dried and used in the next reaction without purification.

Ethyl N-(1-benzyl-1*H*-indol-3-yl) carbamate (26)

Compound **24** (0.265 g, 0.001 mol) was heated under reflux in ethanol (10 mL) for 5 h. The solvent was removed under vacuum and the residue was recrystallized from ethanol as brownish yellow crystals.

Isopropyl N-(1-benzyl-1*H*-indol-3-yl) carbamate (27)

This compound was obtained via the above procedure using isopropyl alcohol (10 mL) instead of ethanol. The product resulted was recrystallized from the same alcohol to afford the title compound as buff crystals.

1,3-Bis-(1-benzyl-1*H*-indol-3-yl) urea (29)

A mixture of **24** (0.265 g, 0.001mol) and tertiary butyl alcohol (10 mL) was refluxed for 4 h. After cooling, the solvent was removed under reduced pressure and the solid product obtained was recrystallized from tertiary butyl alcohol to give white crystals.

N^4-(1-Benzyl-1*H*-indol-3-yl) semicarbazide (30)

A mixture of **24** (0.276 g, 0.001 mol) in dry toluene was refluxed for 2 h. After cooling, hydrazine hydrate (2 mL, 0.04 mol) was added and the resulting mixture was heated under reflux for 2 h. The solid precipitate formed was collected and recrystallized from ethanol as brown crystals.

Reaction of acid azide 24 with amines: Formation of the derivatives 31-33

General procedure

A mixture of **24** (0.276 g, 0.001 mol) and an excess (0.02 mol) of the respective amine (Piperdine, morpholine and ethanol amine) was gently heated at 100-110 °C for 2 h. The reaction mixture then was triturated with ethanol and left to cool. The crystalline solid precipitate was collected and recrystallized.

1-Benzyl-3-piperidinocarbonylamino-1*H*-indole (31)

This compound was yielded employing the above procedure as buff crystals from petroleum ether/ethyl acetate (1:1).

1-Benzyl-3-morpholinocarbonylamino-1*H*-indole (32)

This compound was yielded employing the above procedure as buff crystals from petroleum ether/ethyl acetate (2:1).

N^1-(1-Benzyl-1*H*-indol-3-yl)-N^3-(2-hydroxyethyl) urea (33)

This compound was yielded employing the above procedure as buff crystals from methanol/ethyl acetate (1:1).

3-(1-Benzyl-1*H*-indol-3-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (34)

A mixture of compound **13** (0.321 g, 0.001 mol), phenacyl bromide (0.198 g, 0.001 mol) and sodium acetate (0.4 g, 0.005 mol) in ethanol (10 mL) was refluxed for 7 h. The solvent was evaporated, the residue was poured onto water and the white solid product formed was filtered off and recrystallized from ethanol to give yellow crystals.

4-Amino-3-(1-benzyl-1*H*-indol-3-yl)-5-acetonylthio-1,3,4-triazole (35)

A mixture of compound **13** (0.321 g, 0.001mol), chloro acetone (0.93 g, 0.001 mol) and sodium acetate (0.4 g, 0.005 mol) in ethanol (10 mL) was refluxed for 7 h. The solvent was evaporated, the residue was poured onto water and the white solid product formed was filtered off and recrystallized from benzene to give brown crystals.

Biological Screening

The filter paper disc method was performed in nutrient agar for bacteria and Czapek's Dox agar for fungi. These agar media were inculcated with 0.5 mL of the 24 h liquid cultures. Filter paper discs (5 mm diameter) saturated with each compound solution (10 mg/1 mL of *N,N*-dimethylformamide, DMF) were placed on the indicated agar media. The incubation time was 48 h (at 37 C for bacteria and 28 C for fungi). Discs saturated with DMF were used as control. The diameters of inhibition zones (mm) were measured and recorded.

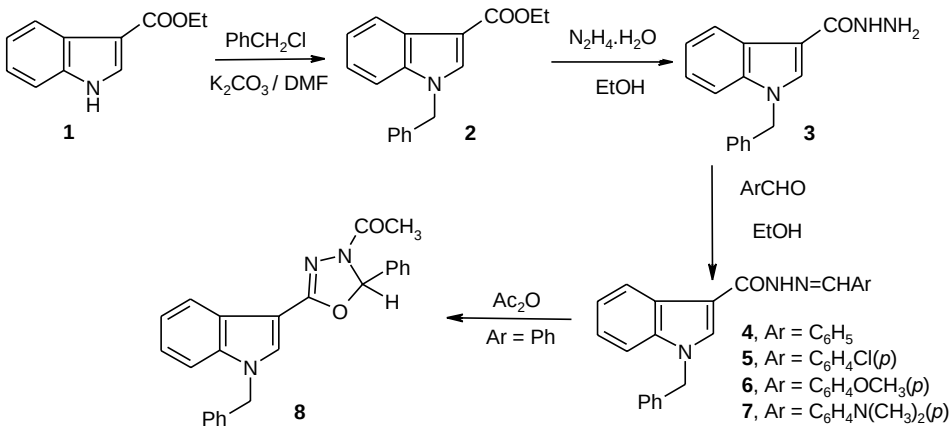
RESULTS AND DISCUSSION

With all the above facts in mind and in continuation of our previous work directed to the synthesis of new pyridazino[4,5-*b*]indole derivatives of pharmaceutical interest,[15] the author reports herein the synthesis of oxadiazolo, triazolo and pyrazolo compounds derived from indole. The starting material **2**[9] was prepared by the reaction of ethyl 1*H*-indol-3-carboxylate with benzyl chloride in presence of anhydrous potassium carbonate. Treatment of the ethyl 1-benzylindol-2-carboxylate with hydrazine hydrate afforded the carbohydrazide derivative **3**. Compound **3** proved to be a versatile compound for the synthesis of a variety of oxdiazole and s-triazole derivatives **8-18**. The vast pharmaceutical activity of the indole hydrazones[10] encouraged us to synthesis a number of new arylidene derivatives of potential biological interest. Thus, condensation of the hydrazide **3** with aromatic aldehydes gave the corresponding arylidene derivatives **4-7**. Cyclization of the benzylidene compound **4** by its boiling with acetic anhydride afforded the oxadizole derivative **8** (Scheme I).

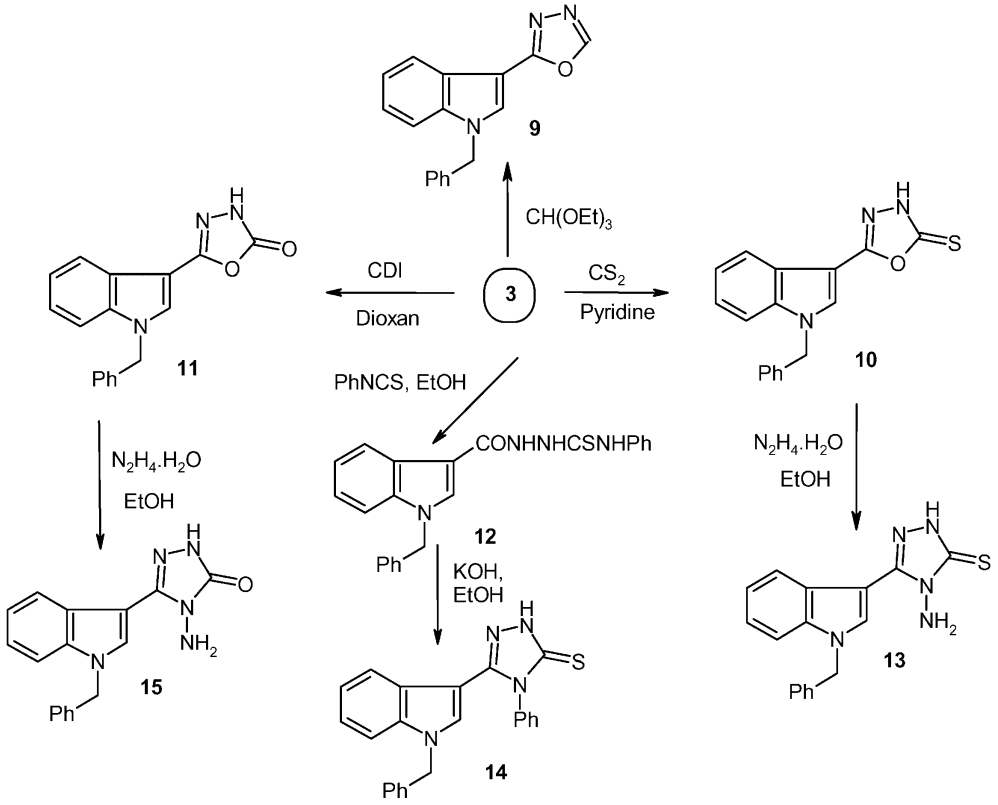
The interaction of hydrazide **3** with triethylorthoformate yielded the oxadiazole derivative **9**, whereas its reaction with carbon disulfide in boiling pyridine gave the corresponding oxadiazolthione **10** in 87% yield. A convenient synthesis for its oxygen analogue was done. Thus the oxadiazolone **11** was accomplished by treatment of the hydrazide **3** with 1,1′-carbonyldiimidazolyl (CDI) in refluxing dioxane (93% yield).

Furthermore, when compound **3** was allowed to react with phenyl isothiocyanate, the product was identified as N^1-(1-Benzyl-1*H*-indol-3-oyl)-N^4-phenylthiosemicarbazide **12**. The latter compound was subjected to a cyclization reaction by refluxing with an ethanolic potassium hydroxide solution to give the s-triazolthione **14**. The amino triazolo derivatives **13** and **15** were obtained by treatment of the precursors

Scheme I



Scheme II



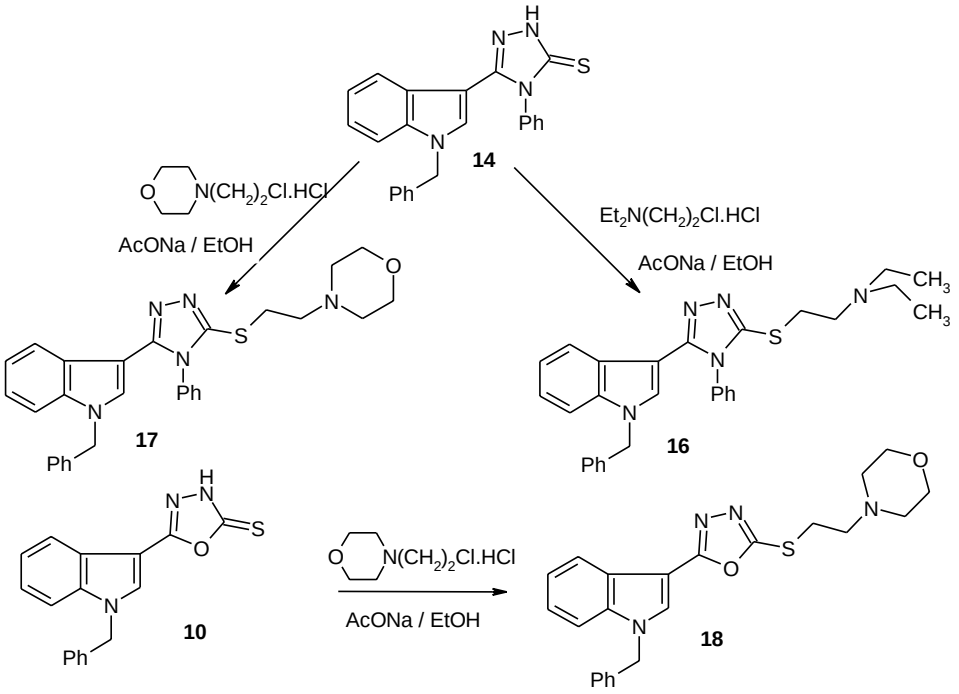
oxadiazolo derivatives **10** and **11** with hydrazine hydrate via ring opening reaction (Scheme II). The ring opening of **10** and **11** was substantiated by spectroscopic data. The IR spectrum of compound **13** or **15** showed bands at 3280, 3180 cm^{-1} (NH_2) and 3100 cm^{-1} (NH).

Interestingly, the thione function in compound **14** should offer the possibility for further elaboration by alkylation reaction, e.g. the introduction of the basic side chains as potentially pharmacophoric substructures. Thus **14** was treated with diethylaminoethyl chloride hydrochloride and with 4-(2-chloroethyl) morpholine hydrochloride in refluxing ethanol in the presence of anhydrous sodium acetate to give the corresponding s-alkylated products **16** and **17**, respectively. Similarly, interaction of **10** with 4-(2-chloroethyl) morpholine hydrochloride under the same reaction conditions gave the s-alkylated product **18** in good yield (Scheme III).

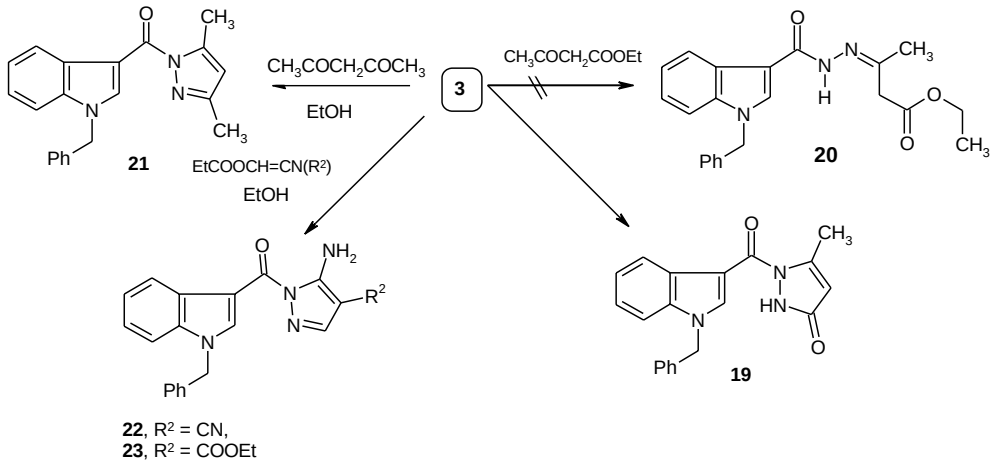
Treatment of **3** with ethyl acetoacetate without solvent did not afford the ester derivative **20** but gave the cyclized product, pyrazolone derivative **19**. On the other hand, condensation of the hydrazide with acetyl acetone in refluxing ethanol gave the corresponding pyrazolyl derivative **21** in 85% yield. Interestingly, the hydrazide **3** was used as a derivative of hydrazine hydrate to prepare new pyrazole derivatives **22** and **23**. Thus, interaction of the **3** with ethoxymethylene malononitrile and ethyl ethoxymethylenecyanoacetate furnished the corresponding pyrazolyl derivatives **22** and **23**, respectively.

Diazotization of **3** with an equimolar quantity of sodium nitrite in glacial acetic acid produced the carboazide compound **24**. On refluxing **24** in ethanol or isopropyl alcohol, it underwent *Curtius* rearrangement where the isocyanate derivative **25** was formed as intermediate (Scheme V). The latter intermediate reacted concomitantly with ethanol and isopropyl alcohol, used as a solvent to give the corresponding ethyl and isopropyl carbamate **26** and **27**, respectively. Interestingly, refluxing of the carboazide **24** with tertiary butyl alcohol did not give the tertiary butyl carbamate **28** but afforded the urea derivative **29**, which was prepared independently by boiling **24** with water. When the alcohols was replaced by amines, the corresponding urea derivatives **31-33** were obtained. It is noteworthy that when the acid azide **24** was heated in an excess of hydrazine hydrate, *Curtius* rearrangement did not occur and the product was

Scheme III



Scheme IV



identified as acid hydrazide **3**. However, when **24** was boiled first in dry toluene to insure the *Curtius* rearrangement of **24** into the isocyanate **25** followed by addition of an excess of hydrazine hydrate, the expected semicarbazide **30** was obtained in 71% yield.

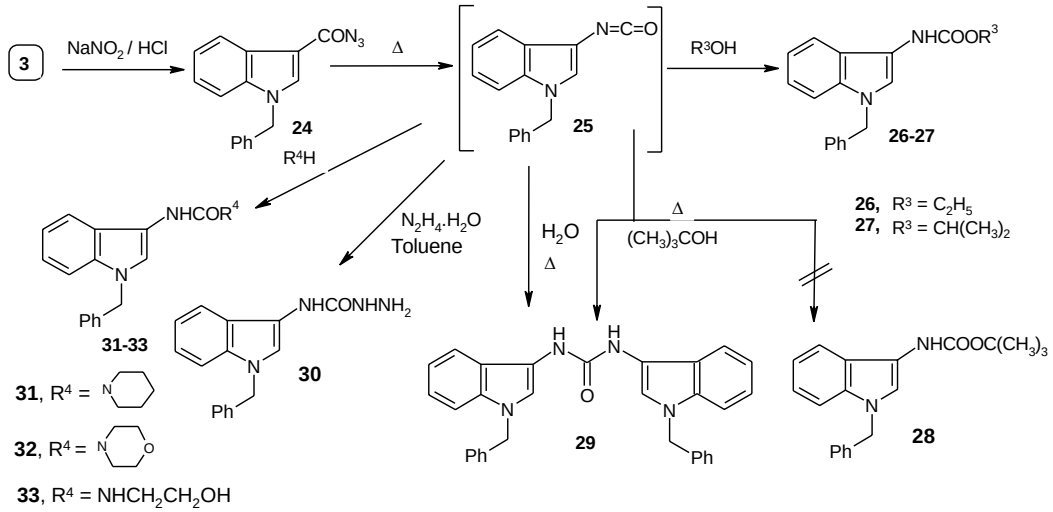
Finally, refluxing the triazolthione **13** with phenacyl bromide in ethanol produced the corresponding 3-(1-Benzyl-1*H*-indol-3-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-b][1,3,4] thiadiazine **34**. Whereas, its reaction with chloro acetone did not give the thiadiazine **36** but gave the corresponding acetonylthio derivative **35**.

Antimicrobial activity

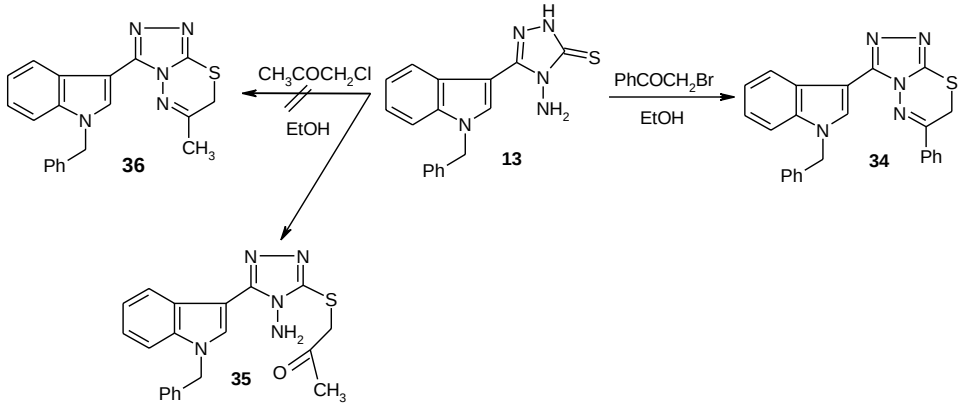
Some selected representatives of the newly synthesized compounds were screened *in vitro* for their antimicrobial activities against four strains of bacteria* (*Staphylococcus*

*All bacteria are from Assiut University, not purchased from ATCC

Scheme V



Scheme VI



aureus, Serratia marcescens, Streptococcus, Pseudomonas aeruginosa) and two species of fungi (*Aspergillus parasitcus, Penicillium oxalicum*) using the filter paper disc method.[16] The screening results given in Table 2 indicated that most of the compounds tested exhibit considerable activities against two bacterial species, *Serratia marcescens* and *Streptococcus*. Compound **33** exhibits a moderate activity against *Staphylococcus aureus*. All the screened compounds were inactive against *Pseudomonas aeruginosa.* As far as the anti-fungal activity is concerned, only compound **7** showed a

Table 2. The Antibacterial and Antifungal Activities of Some Compounds Synthesized (Diameter of inhibition zone in mm)

Compd	*Pseudo. aeruginosa*	*Staph. aureus*	*Streptoc.*	*Serratia marcescns*	*Penicill. oxalicum*	*Asperg. parasitcus*
3	-	-	7	-	-	-
7	-	-	13	9	7	-
10	-	-	-	13	-	-
30	-	-	-	14	-	-
33	-	9	-	-	-	-

-: No inhibition

moderate activity against *Penicillium oxalicum*. The other compounds tested showed no activity against the two fungal species.

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