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Synthesis and Screening of Some Novel Substituted Indoles Contained Fused Triazolo[1,5-a]pyridine and Thiazolo[3,2-a]pyridine Derivatives

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A series of heterocyclic derivatives including 1*H*-pyrazol-4-carbonitrile (**3**), 1*H* pyrazol-5(4*H*)-one (**4,5**), 2-thioxopyrimidine-4,6-dione (**6**) 1,2,4-triazole-3(4*H*)-one (**7**), 1,6-diaminopyridine (**9**), triazolo[1,5-a]pyridin (**10**) and thiazolo[3,2-a]pyridine (**11**) moieties conjugated with 1-substituted indole moiety were synthesized on reaction with cyanoacetohydrazide, 3-amino-5-oxo-2-pyrazoline, thiobarbituric acid, thiosemicarbazide, malononitrile followed by cyanoacetohydrazide, different aromatic aldehydes and mercaptoacetic acid, respectively, by using 1-[2-(piperidin-1-yl)ethyl]-1*H*-indole-3-carbaldehyde (**1**) as starting material. The structures of all the newly synthesized products have been established on the basis of analytical and spectral data.The antimicrobial activity of some selected products was examined and some of them showed good activities.

Keywords: N-substituted indole derivatives, Triazolo[1,5-a]pyridine, Thiazolo[3,2-a]pyridine, Antimicrobial activity.

INTRODUCTION

Nitrogen-containing heterocycles always display extensive bioactivities and which are also extremely versatile structural units serving as important intermediates for the construction of active molecules in drug design and agrochemical industry[1-3]. Among these heterocyclic building blocks, indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their varied biodynamic properties as a most promising class of synthons for pharmaceutical drugs and functional materials[4-7]. Up to now, many heterocyclic compounds derived from indole have been identified as potential antibacterial, anticancer, antiviral agents, antiinflammatory, anticonvulsant, antimalarial, protein kinase inhibitors and many other activities[8-18]. In addition, some indole intermediates can also be used as important synthons for further transformation to related fused-heterocycles or various indole alkaloids[19-26]. Due to the structural similarity of indole nuclei with some naturally occurring compounds such as serotonin, tryptamine, hinckdentine A, they can easily interact with biomolecules of the living systems[27]. The introduction of an additional substituent on the indole nuclei has been increasing attention in the expectation that such changes could potentially affect the interaction of the molecules with biological targets. Furthermore, several modifications on the 3-formyl group were carried out in order to overcome the *in vivo* instability of the aldehyde functional group. These modifications included the formation of oximes, methylamine, propane dinitriles, hydrazones and other derivatives that proved to possess high stability and good antimitotic activity[28-30]. Indoles and their cyclic derivatives constitute an important class of compounds for new drug development in order to discover an effective compound against multi-drug-resistant microbial infections.

EXPERIMENTAL

Melting points were determined in opend glass capillary tubes with an "Electro Thermal" Digital melting point apparatus, (model: IA9100) and are uncorrected. Elemental microanalysis for carbon, hydrogen and nitrogen (Microanalytical Unit, NRC) was found within the acceptable limits of the calculated values. Infrared spectra (KBr) were recorded on a Nexus 670 FTIR Nicolet, Fourier Transform infrared spectrometer. Proton nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were run on JöEL 270 MHz or 500 MHz instruments. Mass spectra were run on a MAT Finnigan SSQ 7000 spectrometer, using the electron impact technique (EI). Analytical thin layer

chromatography (TLC) was performed on silica gel oaluminum sheets, 60 F254 (E. Merck).

1-[2-(Piperidin-1-yl)ethyl]-1*H*-indole-3-carbaldehyde (1): To a solution of indole-3-carboxaldehyde (0.005 mol) in anhydrous acetone (50 mL) was added anhydrous K_2CO_3 (0.01 mol) and 1-(2-chloroethyl) piperidine hydrochloride (0.005 mol). The reaction mixture was heated at reflux for 6 h and the resulting solution was filtrated and K_2CO_3 washed with acetone. The filtrate was concentrated *in vacuo*, the residue formed was filtered, dried and crystallized from ethanol to give the title compound **1** in 62 % yield, m.p.: 81-83 °C; IR (KBr, ν_{max}, cm^{-1}): 1705 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.16-2.41 (m, 10H, $5CH_2$), 2.65 (t, 2H, CH_2), 3.98 (t, 2H, CH_2), 6.87-8.32 (m, 5H, Ar-H), 9.91 (s, 1H, CHO); ^{13}C NMR (DMSO-δ_6) δ: 24.14, 25.99, 44.61, 54.83, 57.97, 109.90, 118.14, 122.14, 122.83, 123.85, 125.36, 137.27, 139.12, 184.54; MS *m/z* (%): 256 (M^+). Anal. Calcd. for $C_{16}H_{20}N_2O$ (256.34): C 74.97, H 7.86, N 10.93; found C 74.78, H 7.69, N 10.85.

(E)-2-Cyano-3-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl]acrylohydrazide (2): A mixture of compound **1** (0.001 mol) and cyanoacetohydrazide (0.001 mol) in ethanol (15 mL) containing few drops of triethylamine was stirred vigorously for 3 h at room temperature then left overnight. The precipitate formed was filtered, washed with cold ethanol, air dried and crystallized from methanol to give compound **2** in 72 % yield; m.p.: 160-162 °C; IR (KBr, ν_{max}, cm^{-1}): 3486, 3219 (NH_2, NH), 2226 (CN), 1697 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.15-2.40 (m, 10H, $5CH_2$), 2.64 (t, 2H, CH_2), 3.94 (s, 2H, CH_2), 6.83-8.36 (m, 6H, Ar-H + =CH), 8.95 (br. s, 2H, NH_2) exchangeable with D_2O), 9.37 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.26, 25.78, 27.35, 45.46, 54.38, 57.82, 107.23, 110.69, 113.21, 116.29, 121.32, 122.86, 123.82, 126.43, 136.04, 139.15, 154.26, 167.01; MS *m/z* (%): 337 (M^+). Anal. Calcd. for $C_{19}H_{23}N_5O$ (337.42): C 67.63, H 6.87, N 20.76; found C 67.48, H 6.58, N 20.67.

4,5-Dihydro-5-oxo-3-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl]-1*H*-pyrazole-4-carbonitrile (3): Method A: Compound **2** (0.001 mol) was heated under reflux in acetic acid (85 %, 10 mL) for 0.5 h. The reaction mixture was then partially evaporated under vacuum to half of its volume and left to cool. The product obtained was filtered, washed with water, air dried and crystallized from ethanol; yield 67 %.

Method B: A mixture of compound **1** (0.001 mol) and cyanoacetohydrazide (0.001 mol) in ethanol (20 mL) containing few drops of glacial acetic acid was refluxed for 3 h and left to cool. The solid formed was filtered, washed with cold ethanol, air dried and crystallized from ethanol to give compound **3** in 78 % yield, m.p. 206-208 °C; IR (KBr, ν_{max}, cm^{-1}): 3265 (NH), 2217 (CN), 1682 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.12-2.42 (m, 10H, $5CH_2$), 2.70 (t, 2H, CH_2), 4.01 (t, 2H, CH_2), 6.95-8.31 (m, 5H, Ar-H), 11.26 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.29, 25.95, 45.26, 54.13, 57.94, 80.56, 108.72, 110.81, 116.14, 121.36, 122.43, 123.65, 126.44, 136.02, 139.17, 156.17, 174.15; MS *m/z* (%): 335 (M^+). Anal. calcd. for $C_{19}H_{21}N_5O$ (335.40): C 68.04, H 6.31, N 20.88; found C 67.85, H 6.17, N 20.68.

(4E)-3-Amino-4-[{1-(2-(piperidin-1-yl)ethyl)-1*H*-indol-3-yl}methylene]-1*H*-pyrazol-5(4*H*)-one (4): A mixture of compound **1** (0.001 mol) and 3-amino-5-oxopyrazoline (0.001 mol) in absolute ethanol (15 mL) containing few drops of triethylamine was refluxed for 1 h. After cooling, the solid formed was filtered, washed with cold ethanol, air dried and crystallized from ethanol to give the title compound **4** in 78 % yield, m.p. 221-223 °C; IR (KBr, ν_{max}, cm^{-1}): 3465, 3186 (NH_2, NH), 1690 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.10-2.46 (m, 10H, $5CH_2$), 2.76 (t, 2H, CH_2), 3.98 (t, 2H, CH_2), 5.80 (s, 2H, NH_2), 6.90-8.32 (m, 6H, Ar-H + =CH), 9.72 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.15, 25.49, 45.22, 54.12, 57.91, 109.34, 110.85, 118.91, 119.47, 122.19, 126.42, 131.68, 136.06, 139.11, 143.55, 151.79, 169.54; MS *m/z* (%): 337 (M^+). Anal. calcd. for $C_{19}H_{23}N_5O$ (337.42): C 67.63, H 6.87, N 20.76; found C 67.49, H 6.70, N 20.57.

(3E)-3-[{1-(2-(Piperidin-1-yl)ethyl)-1*H*-indol-3-yl}methyleneamino]-1*H*-pyrazol-5(4*H*)-one (5): A mixture of compound **1** (0.001 mol) and 3-amino-5-oxopyrazoline (0.001 mol) in absolute ethanol (15 mL) containing few drops of glacial acetic acid was refluxed for 2 h. After cooling, the solid formed was filtered, washed with cold ethanol, air dried and crystallized from ethanol to give the title compound **5** in 69 % yield, m.p. 185-187 °C; IR (KBr, ν_{max}, cm^{-1}): 3219 (NH), 1679 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.14-2.42 (m, 10H, $5CH_2$), 2.74 (t, 2H, CH_2), 3.96 (t, 2H, CH_2), 4.12 (s, 2H, CH_2), 6.87-8.35 (m, 6H, Ar-H + =CH), 11.28 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.01, 25.43, 37.24, 45.27, 54.10, 57.88, 108.67, 110.81, 118.97, 122.15, 122.89, 126.45, 137.29, 139.15, 157.14, 164.36, 172.49; MS *m/z* (%): 337 (M^+). Anal. Calcd. for $C_{19}H_{23}N_5O$ (337.42): C 67.63, H 6.87, N 20.76; found C 67.52, H 6.69, N 20.48.

Dihydro-5-[{1-(2-(piperidin-1-yl)ethyl)-1*H*-indol-3-yl}methylene]-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (6): A mixture of compound **1** (0.001 mol), thiobarbituric acid (0.001 mol) and anhydrous sodium acetate (0.001 mol) in acetic acid (10 mL) were refluxed for 1 h. After completion (TLC), the reaction mixture was allowed to cool to room temperature and poured into crushed ice with constant stirring. Crude product was isolated and recrystallized from DMF/H_2O to yield the title compound **6** in75 % yield, m.p.: > 300 °C; IR (KBr, ν_{max}, cm^{-1}): 3325, 3201 (2 NH), 1663 (C=O), 1203 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.13-2.40 (m, 10H, $5CH_2$), 2.65 (t, 2H, CH_2), 4.09 (t, 2H, CH_2), 6.79-8.38 (m, 6H, Ar-H+ =CH), 9.98, 11.34 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.21, 25.86, 45.34, 54.25, 57.89, 110.69, 118.92, 121.18, 122.29, 122.91, 124.58, 126.47, 137.31, 139.12, 148.61, 169.23, 181.22; MS *m/z* (%): 382 (M^+). Anal. calcd. for $C_{20}H_{22}N_4O_2S$ (382.48): C 62.80, H 5.80, N 14.65; found C 62.68, H 5.72, N 14.47.

5-[1-{2-(Piperidin-1-yl)ethyl}-1*H*-indol-3-yl]-2*H*-1,2,4-triazole-3(4*H*)-thione (7): A mixture of compound **1** (0.001 mol) and thiosemicarbazide (0.001 mol) in absolute ethanol (15 mL) containing few drops of glacial acetic acid was refluxed for 2 h. After cooling and dilution with water, the solid formed was filtered, washed with water, air dried and crystallized from absolute ethanol to give compound **7** in 70 % yield, m.p.: 167-169 °C; IR (KBr, ν_{max}, cm^{-1}): 3329, 3166 (2 NH), 1205 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.10-2.43 (m, 10H, $5CH_2$), 2.75 (t, 2H, CH_2), 3.99 (t, 2H, CH_2), 6.89-8.41 (m, 6H, Ar-H), 9.56,

11.28 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.18, 25.79, 45.31, 54.26, 57.90, 107.38, 110.43, 121.15, 122.23, 122.86, 126.45, 134.77, 137.32, 157.16, 183.02; MS *m/z* (%): 327 (M^+). Anal. Calcd. for $C_{17}H_{21}N_5S$ (327.45): C 62.36, H 6.46, N 21.39; found C 62.19, H 6.31, N 21.23.

2-[{1-(2-(Piperidin-1-yl)ethyl)-1*H*-indol-3-yl}methylene]-malononitrile (8): To a solution of compound **1** (0.01 mol) in absolute ethanol (20 mL) was added malononitrile (0.01 mol) and piperidine (0.5 mL). The reaction mixture was stirred vigorously for 10 min at room temperature. The solid obtained was filtered off, dried and crystallized from methanol to give compound **8** in 68 % yield, m.p.: 162-164 °C; IR (KBr, ν_{max}, cm^{-1}): 2225 (CN); ^1H NMR (DMSO-d_6) δ: 1.14-2.40 (m, 10H, $5CH_2$), 2.68 (t, 2H, CH_2), 4.32 (t, 2H, CH_2), 6.79-8.37 (m, 6H, Ar-H + =CH); ^{13}C NMR (DMSO-d_6) δ: 24.31, 25.95, 45.27, 54.04, 58.34, 76.32, 110.96, 116.01, 118.29, 121.36, 122.14, 122.85, 126.43, 137.11, 139.28, 157.90; MS *m/z* (%): 304 (M^+). Anal. Calcd. for $C_{19}H_{20}N_4$ (304.39): C 74.97, H 6.62, N 18.41; found C 74.78, H 6.49, N 18.26.

1,2-Dihydro-1,6-diamino-2-oxo-4-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl]pyridine-3,5-dicarbonitrile (9): A mixture of compounds **8** (0.001 mol) and 2-cyanoacetohydrazide (0.001 mol) in absolute ethanol (30 mL) containing few drops of piperidine was stirred at room temperature overnight. The precipitate that formed was filtered off, washed with cold ethanol and crystallized from methanol to give the title compound **9** in 71 % yield, m.p.: 210-212 °C; IR (KBr, ν_{max}, cm^{-1}): 3495, 3418 ($2NH_2$), 2221 (CN), 1671 (C=O); ^1H NMR (DMSO-d_6) δ: 1.14-2.43 (m, 10H, $5CH_2$), 2.65 (t, 2H, CH_2), 4.31 (t, 2H, CH_2), 5.64 (s, 2H, NH_2 exchangeable with D_2O), 6.86-8.26 (m, 5H, Ar-H), 8.27 (broad s, 2H, NH_2 exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.36, 25.97, 45.30, 54.01, 58.33, 76.64, 107.92, 110.95, 117.01, 118.28, 121.13, 122.15, 122.87, 126.38, 137.10, 139.25, 159.66, 161.21, 170.12; MS *m/z* (%): 401 (M^+). Anal. Calcd. for $C_{22}H_{23}N_7O$ (401.46): C 65.82, H 5.77, N 24.42; found C 65.71, H 5.59, N 24.28.

1,5-Dihydro-5-oxo-2-substituted phenyl-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl][1,2,4]-triazolo[1,5-a]pyridine-6,8-dicarbonitriles (10a-g): General procedure: A mixture of compound **9** (0.005 mol) and aromatic aldehydes, (0.005 mol) in absolute ethanol (30 mL) was refluxed for 3-5 h. The solid obtained after cooling was filtered off, dried and crystallized from DMF/H_2O to give the title compounds **10a-g**.

1,5-Dihydro-5-oxo-2-phenyl-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl][1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (10a): Yield 59 %, m.p.: 174-176 °C; (KBr, ν_{max}, cm^{-1}): 3219 (NH), 2227 (CN), 1697 (C=O); ^1H NMR (DMSO-d_6) δ: 1.14-2.45 (m, 10 H, $5CH_2$), 2.63 (t, 2H, CH_2), 4.23 (t, 2H, CH_2), 6.85-8.43 (m, 10H, Ar-H), 9.32 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.26, 25.84, 45.25, 54.11, 58.44, 76.51, 107.90, 110.95, 116.51, 118.22, 121.04, 122.17, 122.79, 126.12, 126.41, 128.79, 129.05, 130.65, 137.15, 139.21, 157.12, 159.60, 162.41, 170.15; MS *m/z* (%): 487 (M^+). Anal. Calcd. for $C_{29}H_{25}N_7O$ (487.56): C 71.44, H 5.17, N 20.11; found C 71.27, H 5.01, N 19.87.

1,5-Dihydro-2-(4-nitrophenyl)-5-oxo-7-[1-{2-(piperidin-1-yl}ethyl)-1*H*-indol-3-yl][1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (10b): Yield 52 %, m.p.: 192-194 °C; IR (KBr, ν_{max}, cm^{-1}): 3265 (NH), 2220 (CN), 1689 (C=O); ^1H NMR (DMSO-d_6) δ: 1.12-2.44 (m, 5H, $5CH_2$), 2.78 (t, 2H, CH_2), 4.26 (t, 2H, CH_2), 6.87-8.46 (m, 9H, Ar-H), 9.28 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.20, 25.79, 45.23, 54.08, 58.42, 76.55, 107.89, 110.94, 117.11, 118.25, 121.07, 121.55, 122.14, 122.51, 126.09, 127.13, 128.95, 134.77, 137.11, 139.26, 150.28, 153.67, 159.53, 161.99, 170.05; MS *m/z* (%): 532 (M^+). Anal. Calcd. for $C_{29}H_{24}N_8O_3$ (532.55): C 65.40, H 4.54, N 21.04; found C 65.24, H 4.35, N 20.85.

1,5-Dihydro-2-(4-isopropylphenyl)-5-oxo-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3yl][1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (10c): Yield 61 %, m.p 147-149 °C; IR (KBr, ν_{max}, cm^{-1}): 3241 (NH), 2204 (CN), 1689 (C=O); ^1H NMR (DMSO-d_6) δ: 1.12-2.40 (m, 16H, $5CH_2$ + $2CH_3$), 2.68 (t, 2H, CH_2), 2.87 (m, 1H, CH), 4.17 (t, 2H, CH_2), 6.89-8.37 (m, 9H, Ar-H), 9.41 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 23.56, 24.25, 25.80, 37.12, 45.29, 54.16, 58.41, 76.57, 107.83, 110.89, 116.21, 118.26, 1221.08, 122.14, 122.86, 125.79, 126.01, 126.28, 126.87, 128.65, 137.27, 139.26, 153.67, 159.72, 162.49, 170.24; MS *m/z* (%): 529 (M^+). Anal. Calcd. for $C_{32}H_{31}N_7O$ (529.63): C 72.57, H 5.90, N 18.51; found C 72.41, H 5.73, N 18.38.

1,5-Dihydro-2-(4-chlorophenyl)-5-oxo-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl][1,2, 4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (10d): Yield 55 %, m.p.: 119-121 °C; IR (KBr, ν_{max}, cm^{-1}): 3219 (NH), 2216 (CN), 1690 (C=O); ^1H NMR (DMSO-d_6) δ: 1.12-2.43 (m, 10H, $5CH_2$), 2.73 (t, 2H, CH_2), 4.12 (t, 2H, CH_2), 6.94-8.45 (m, 9H, Ar-H), 9.56 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.19, 25.76, 45.28, 54.06, 58.40, 76.47, 107.95, 110.91, 116.23, 118.19, 121.18, 122.15, 122.83, 126.14, 126.68, 128.82, 129.01, 135.81, 137.11, 139.28, 153.49, 159.62, 162.78, 170.12; MS *m/z* (%): 522 (M^+). Anal. Calcd. for $C_{29}H_{24}N_7OCl$ (522): C 66.73, H 4.63, N 18.78; found C 66.58, H 4.49, N 18.61.

1,5-Dihydro-2-(4-methoxyphenyl)-5-oxo-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl][1,2,4]triazolo [1,5-a]pyridine-6,8-dicarbonitrile (10e): Yield 63 %, m.p.: 136-138 °C; IR (KBr, ν_{max}, cm^{-1}): 3226 (NH), 2223 (CN), 1685 (C=O); ^1H NMR (DMSO-d_6) δ: 1.14-2.45 (m, 10H, $5CH_2$), 2.71 (t, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.26 (t, 2H, CH_2), 6.98-8.46 (m, 9H, Ar-H), 9.11 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.21, 25.79, 45.28, 54.09, 56.22, 58.43, 76.49, 108.14, 110.98, 114.32, 117.02, 118.27, 121.15, 121.50, 122.18, 122.45, 126.43, 127.33, 137.19, 139.28, 153.46, 159.65, 162.01, 163.12, 170.12; MS *m/z* (%): 517 (M^+). Anal. Calcd. for $C_{30}H_{27}N_7O_2$ (517.58): C 69.62, H 5.26, N 18.94; found C 69.49, H 5.07, N 18.83.

1,5-Dihydro-2-(4-hydroxyphenyl)-5-oxo-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl][1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (10f): Yield 51 %, m.p.: 187-189 °C; IR (KBr, ν_{max}, cm^{-1}): 3210 (NH), 2217 (CN), 1698 (C=O); ^1H NMR (DMSO-d_6) δ: 1.12-2.45 (m, 10H, $5CH_2$), 2.67 (t, 2H, CH_2), 4.19 (t, 2H, CH_2), 4.95 (broad s, 1H, OH exchangeable with D_2O), 6.90-8.39 (m, 9H, Ar-H), 9.51 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.31, 25.82, 45.30, 54.02, 58.43, 76.46, 107.89, 110.94,

117.01, 118.22, 121.35, 122.18, 122.48, 126.19, 126.62, 128.78, 129.11, 135.87, 137.10, 139.32, 153.54, 159.68, 162.73, 170.21; MS *m/z* (%): 503 (M^+). Anal. Calcd. for $C_{29}H_{25}N_7O_2$ (503.55): C 69.17, H 5, N 19.47; found C 69.01, H 4.86, N 19.31.

1,5-Dihydro-2-(4-fluorophenyl)-5-oxo-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl][1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (10g): Yield 51 %, m.p.: 154-156 °C; IR (KBr, ν_{max}, cm^{-1}): 3205 (NH), 2227 (CN), 1689 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.14-2.41 (m, 10H, $5CH_2$), 2.69 (t, 2H, CH_2), 4.21 (t, 2H, CH_2), 6.93-8.42 (m, 9H, Ar-H), 9.56 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 24.15, 25.72, 45.26, 54.12, 58.37, 76.51, 107.74, 110.79, 116.13, 118.22, 121.10, 122.19, 122.89, 126.02, 126.72, 128.86, 129.11, 135.76, 137.10, 139.23, 153.41, 159.48, 165.14, 170.34; MS *m/z* (%): 505 (M^+). Anal. Calcd. for $C_{29}H_{24}FN_7O$ (505.55): C 68.90, H 4.79, N 19.39; found C 68.78, H 4.56, N 19.21.

5-Amino-3,7-dihydro-3-oxo-7-[1-{2-(piperidin-1-yl)ethyl}-1*H*-indol-3-yl]-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (11): A solution of compound **8** (0.01 mol) and thioglycollic acid (0.01 mol) in ethanol (50 mL) and a catalytic amount of piperidine was refluxed for 5 h. The solvent was evaporated and the solid product was collected by filtration and recrystallized from AcOH to give the title compound **11** in 71 % yield, m.p. 221-223 °C; IR (KBr, ν_{max}, cm^{-1}): 3462 (NH_2), 2197 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6) δ: 1.14-2.45 (m, 10H, $5CH_2$), 2.73 (t, 2H, CH_2), 3.66 (s, 2H, CH_2), 4.27 (t, 2H, CH_2), 5.90 (s, 2H, NH_2 exchangeable with D_2O), 6.85-8.33 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 24.27, 25.71, 33.93, 41.07, 45.23, 54.15, 57.33, 58.37, 61.57, 107.21, 110.95, 117.43, 118.77, 122.15, 122.49, 126.41, 135.67, 137.11, 159.47, 161.51, 163.33; MS *m/z* (%): 444 (M^+). Anal. Calcd. for $C_{24}H_{24}N_6OS$ (444.55): C 64.84, H 5.44, N 18.90; found C 64.73, H 5.29, N 18.77.

RESULTS AND DISCUSSION

The key building block N-substituted indole **1** were obtained *via* reaction of indole-3-carbaldehyde with 1-(2-chloroethyl)piperidinein the presence of K_2CO_3 and then the reactant **1** was conveniently transferred to the corresponding hydrazone **2** *via* condensation with cyanoacetohydrazide in ethanol containing a few drops of triethanolamine at room temperature and upon refluxing in ethanol containing a few drops of acetic acid was cyclized and gave the corresponding pyrazolinone derivative **3**.

The key intermediate **1** was reacted with 3-amino-5-oxo-2-pyrazoline in refluxing ethanol containing few drops of triethanolamine. The formyl function condensed with the active methylene in the ring forming the respective arylidene derivative **4**. However, when the reaction takes place in refluxing ethanol containing few drops of acetic acid, the formyl function condensed with the 3-amino group forming Schiff's base **5**. Compound **1** undergo knoevenagel condensation with thiobarbituric acid in presence of acetic acid and anhydrous sodium acetate to produce knoevenagel product **6**. The desired 1,2,4-triazole-3(4*H*)-thione derivative **7** was obtained on reaction of compound **1** with thiosemicarbazide in presence of acetic acid (**Scheme-I**). The base catalyzed reaction of compound **1** with malononitrile in ethanol yielded the corresponding 3-indolylidene malononitrile derivative **8**. Treating compound **8** with 2-cyanoacetohydrazide in presence of organic base yielded the corresponding 3-[1,6-diamino-2-oxo-3,5-dicarbonitrile-pyridin-4-yl]indole (**9**). Moreover, compound **9** was used as intermediate for preparation of a series of fused triazolo[1,5-a]pyridine system **10a-g** through the reaction with various aromatic aldehydes namely, benzaldehyde, *p*-nitro benzaldehyde, *p*-isopropyl benzaldehyde, *p*-chloro benzaldehyde, *p*-methoxy benzaldehyde, *p*-hydroxy benzaldehyde and *p*-fluoro benzaldehyde in refluxing ethanol. Also, fused thiazolo-[3,2-a]pyridine derivative **11** could be obtained through reaction of 3-indolylidene malononitrile derivative **8** with thioglycollic acid in presence of catalytic amount of piperidine in ethanol (**Scheme-II**).

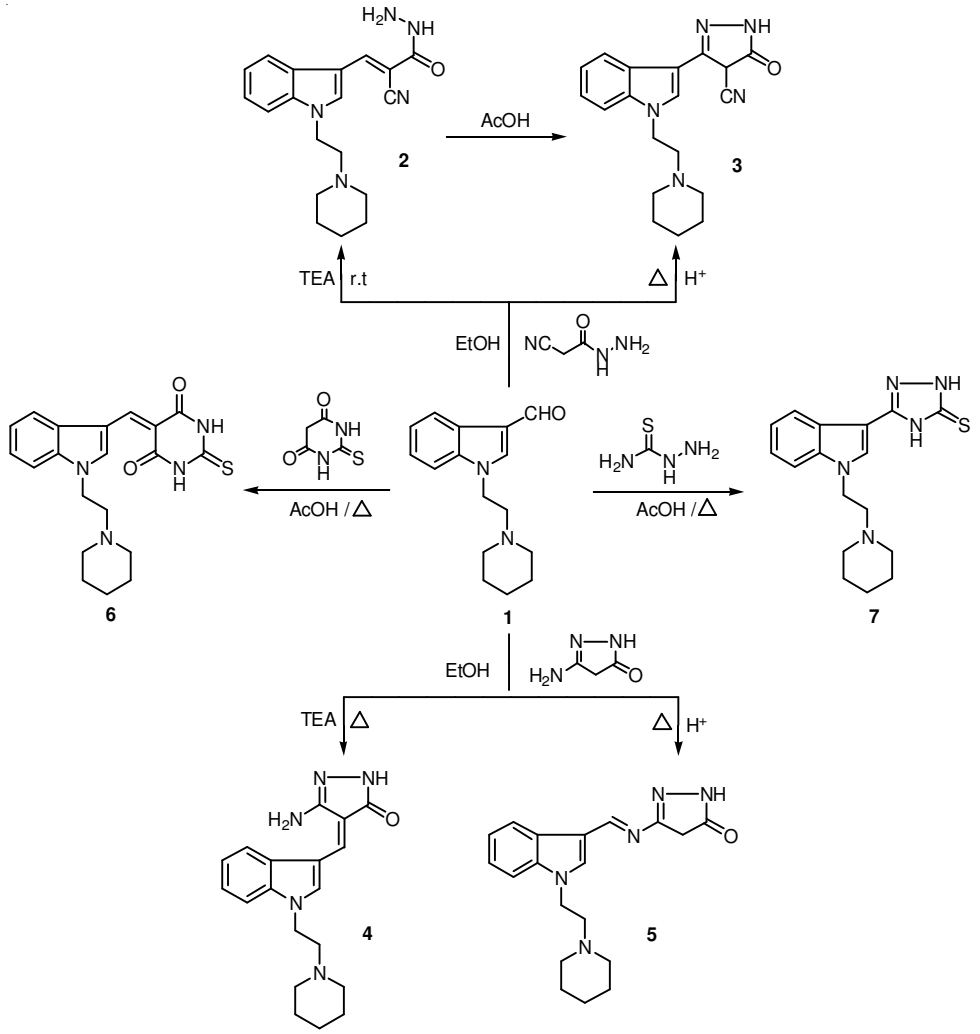
Antimicrobial evaluation: The antibacterial activity of some synthesized compounds was tested against 3 different bacterial strains: two Gram-negative bacteria (*S. typhimurium* and *Ps. aeruginosa*) and one Gram-positive bacteria (*S. aureus*) which were isolated from food of animal origin. The strains were streaked onto Muller Hinton agar plates (oxoid). Also, the synthesized compounds were tested for their antimycotic activities against two yeast (*C. albicans* and *A. flavus*) using Sabaroud Dextrose agar plates (Difco). The obtained results were summarized in Table-1.

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SOME NOVEL SYNTHESIZED INDOL DERIVATIVES

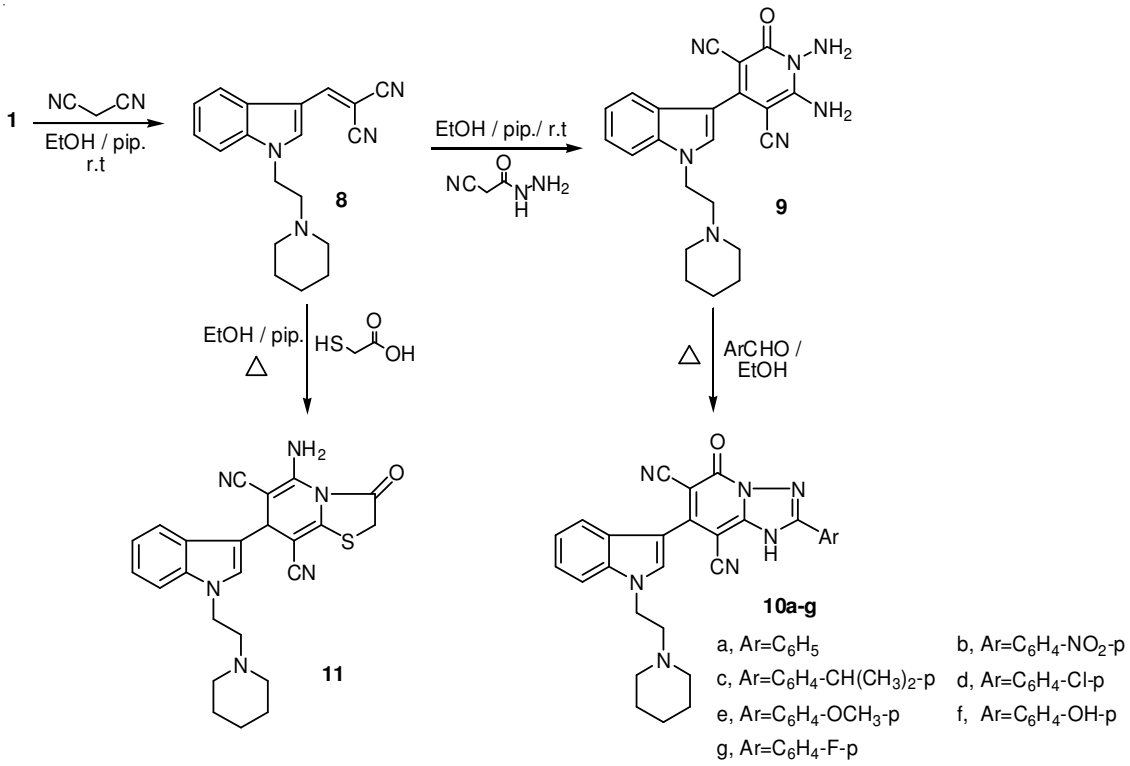
Compound No.	Gram-negative bacteria		Gram-positive bacteria	Yeast	
	ST	PA	SA	CA	AF
3	-ve	-ve	8	9	7
4	8	9	7	8	9
6	7	6	6	7	6
7	11	11	8	10	12
9	10	14	7	10	13
10a	-ve	8	9	7	7
10b	13	12	11	13	11
10c	14	11	14	11	12
11	8	9	7	8	9
Fluconazole (100 µg/L)	-	-	-	15	14
Ciprofloxacin (100 µg/L)	28	25	28	-	-

ST = *S. typhimurium*; PA = *Ps. aeruginosa*; SA = *S. aureus*; CA = *C. albicans*; AF = *A. flavus*

Methode: Six wells were formed in each plate using sterile Pasteur pipette. The strains were prepared in dilution equivalent to 0.5 Mc-Farland and agar well diffusion test[31]. The sterilized media (autoclaved at 120 °C for 0.5 h) were allowed to cool, then agar was poured in plates, after solidification wells were done using sterile Pasteur pipette then 50 mL of the prepared chemicals (100 mg/mL DMSO) were added in wells after streaking the agar surface with the bacterial strains or mycotic strains then plates were allowed to sterile and incubated at 37 °C for 24 h to allow bacterial growth and at 28 °C for 24-72 h for mycotic growth. After incubation the zone of inhibition was measured and tabulated in mm.



Scheme-I: Synthetic route to compounds **1-7**



Scheme-II: Synthetic route to compounds **8-11**

The results for antimicrobial activities depicted in Table-1 revealed that compounds **7**, **9**, **10b** and **10c** exhibited good antibacterial and antifungal activity at a concentration of 100 mg/mL as compared with standard antibiotics ciprofloxacin and fluconazole, while rest of the tested compounds showed moderate antibacterial activity.

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