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Synthesis, Reactions and Antimicrobial Activity of Some New 3-Substituted Indole Derivatives

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Abstract

Reaction of indole-3-carboxaldehydes 4 with hydrazine derivatives and different substituted acid hydrazides afforded the corresponding hydrazine derivatives 5a-c and acid hydrazide derivatives 7-11 respectively. Condensation of indole-3-carboxaldehydes 4 with phenacyl bromide and thiourea gives 1,3-thiazol-2-amine derivative 18. On the other hand, reaction 4 with 3-acetylchromene-2-one afforded chalcone derivative 19. Compound 4 undergoing Knoevenagel condensation with cyanoacetamide, ethyl cyanoacetate, benzimidazol-2-ylacetonitrile, rhodanine-3-acetic acid, 2,3-dihydropyrimidin-4-one derivative and 2,4-dihydropyrazol-3-one afforded the compounds 20a,b, 22, 23, 27 and 28 respectively. The structure of the newly synthesized compounds has been confirmed by elemental analysis and spectra data. The antimicrobial activities of the some newly synthesized compounds were measured and showed that most of them have high activities.

Keywords

Indole-3-Carboxaldehyde, Acid Hydrazide, 1,3-Thiazole, Pyrimidine, Antimicrobial

1. Introduction

In the recent past, bacterial infections have increased at an alarming rate causing deadly diseases and widespread epidemics in humans. All types of bacterial diseases have taken a high toll on humanity. The resistance of antibiotics to control emerging and pre-emerging bacterial pathogens focused the medicinal chemists to search potential new antimicrobial agents to cure microbial infections effectively [1].

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Heterocyclic compounds containing nitrogen have been described for their biological activity against various micro-organisms. The indole unit is the key building block for a variety of compounds which have crucial roles in the functions of biologically important molecules. Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties [2] [3]. For example, five new indole alkaloids, meridianins A-E have been isolated from the tunicate *Aplidium meridianum*, which showed cytotoxicity toward murine tumor cell lines [4].

Introduction of different groups to the modified indole structure can produce a series of compounds with multiple activities. Various 3-substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals and perfumes. Also 3-substituted indole derivatives possess various types of broad spectrum's biological activities such as antimicrobial, antitumor, hypoglycemic, anti-inflammatory, analgesic and antipyretic activities [5] [6]. Moreover the substitution at the 3-position of the indole ring can take place by connecting an additional heterocyclic ring, such as imidazole (topsentins, nortopsentins) [7] [8], dihydroimidazole (discodermindole) [9], oxazole (pimprinols A-C, almazole C) [10] [11], thiazole (bacillamide A) [12], quinazoline (tremorgens) [13], and pyrimidine [14]. Therefore, 3-substituted indoles still represent a significant synthetic challenge. In view of the important biological properties of the indole ring, we planned to synthesize a new series of 3-substituted indole derivatives bearing side chains with different structures; as such derivatives could possess interesting and useful antimicrobial activity.

2. Materials and Methods

2.1. Experimental

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer (υ_{max} in cm^{-1}). The 1H NMR and ^{13}C NMR spectra were determined in DMSO-d6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 Ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Spectral data of the synthesized compounds were given in **Table 1**.

2.1.1. General Procedure for the Synthesis of 2-Substituted-Indole (3a-d)

Synthesis of 2-substituted-1*H*-indole **3a-d** was carried out by the procedure of Fischer indole synthesis. Phenylhydrazone derivatives **2a-d** were prepared by warming a mixture of compounds **1a-d** (0.04 mol) and phenyl hydrazine (0.072 ml, 0.04 mol) with 60 ml of ethanol and few drops of glacial acetic acid. The resulting reaction mixture was allowed to stirring for about 2 h. The reaction mixture was then poured into ice water (50 ml) where upon the crude compound was precipitated. The residue obtained after filtration was washed with water and used in second step. A mixture of **2a-d** (0.01 mol) and polyphosphoric acid (20 ml) was refluxed for 6 h. After the completion of the reaction, it was filtered and filtrate was poured into ice cooled water. The solid obtained was filtered and recrystallized from the ethanol to give **3a-d.**

2-(4-Methylphenyl)-1*H*-indole 3a

Yellow crystals. Yield: (1.24 g, 60%); m.p.: 220-221˚C. Anal. calcd. for C_{15} H_{13} N(207.27): C, 86.92; H, 6.32; N, 6.76. Found: C, 86.62; H, 6.12; N, 6.56.

4-(1*H*-Indol-2-yl)aniline 3b

White crystals. Yield (1.37 g, 66%); m.p.: 250-252˚C. Anal. calcd. for C_{14} H_{12} N_2 (208.25):C, 80.74; H, 5.81; N,13.45.Found: C, 80.54; H, 5.61; N, 13.35.

2-(4-Bromophenyl)-1*H*-indole 3c

Yellow crystals. Yield (1.63, 60%); m.p.: 220-222˚C. Anal. calcd. for C_{14} H_{10} Br N (272.14): C, 61.79; H, 3.70; Br, 29.36; N, 5.15. Found: C, 61.59; H, 3.50; Br, 29.16; N, 5.00.

3-(1*H*-Indol-2-yl)-2*H*-chromen-2-one 3d

Dark brown crystals. Yield (1. 57, 60%; m.p.: 240-242˚C (DMF). Anal. calcd. for C_{17} H_{11} NO_2 (261.27): C, 78.15; H, 4.24; N, 5.36. Found: C, 78.00; H, 4.04; N, 5.06.

2.1.2. 2-(4-Bromophenyl)-1*H*-indole-3-carboxaldehyde 4

Phosphorous oxychloride (21.47 ml, 0.14 mol) was added drop wise to N,N/-dimethylformamide (DMF) (10.23 ml, 0.14 mol) under cooling with an ice bath and the reaction mixture was stirred for 2 h. to prepare the Vilsmeier reagent. Then compound **3c** (19.59 g, 0.072 mol) in DMF (20 ml) was added drop wise into the Vilsmeier

Table 1. Spectral data of the newly prepared compounds **3-31**.

Compd. No.	Spectral Data
3a	FT-IR (KBr υ_{max} cm^{-1}): 3436 (NH), 3042, 2911, 2856 (CH), 1610 (C=N). 1H NMR (DMSO-d6) δ ppm: 2.50 (s, 3H, CH_3), 6.82 (s, 1H, H-3 indole), 6.97 - 7.07 (m, 4H. Ar-H), 7.25 (d, 1H, indole proton), 7.36 - 7.73 (m, 2H, indole proton), 7.76 (d, 1H, indole proton), 11.45 (s, 1H, NH). MS. *m/z* (%): 207 (M^+, 100), 192 (3.12), 180 (3.18), 116 (1.99), 89 (20.56), 69 (29.66).
3b	FT-IR (KBr υ_{max} cm^{-1}): 3366, 3260, 3180 (NH_2, NH), 2915, 2855 (CH), 1599 (C=N). 1H NMR (DMSO-d6) δ ppm: 6.54 (s, 2H, NH_2), 6.70 - 7.21 (m, 5H, Ar-H and H-3 indole), 7.50 (d, 1H, indole proton), 7.71 - 7.82 (m, 2H, indole proton), 8.19 (d, 1H, indole proton), 9.13 (s, 1H, NH).
3c	FT-IR (KBr υ_{max}, cm^{-1}): 3182 (NH), 3057, 2977, 2867 (CH). 1H NMR (DMSO-d6) δ ppm: 6.46 (s, 1H, H-3 indole), 7.22 - 7.32 (m, 4H, Ar-H), 7.47 (d, 1H, indole proton), 8.21 (d, 1H, indole proton), 12.43 (s, 1H, NH).
3d	FT-IR (KBr υ_{max} cm^{-1}): 3426 (NH), 3037, 2917, 2851 (CH), 1671 (C=O). 1H NMR (DMSO-d6) δ ppm: 5.46 (s, 1H, H-3 indole proton), 7.14 - 7.95 (m, 9H, Ar-H and indole proton), 8.20 (s, 1H, NH). MS. *m/z* (%): 261 (M^+, 18.48), 193 (2.80), 145 (18.01), 116 (13.51), 69 (100).
4	FT-IR (KBr, υ_{max} cm^{-1}): 3181 (NH); 3063, 2978, 2868, 2713 (CH), 1672 (C=O), 1578 (C=N). 1H NMR (DMSO-d6) δ ppm: 7.22 - 7.32 (m, 4H, Ar-H), 7.50 (d, 1H, indole proton), 7.72 -7.82 (m, 2H, indole proton), 8.19 (d, 1H, indole proton), 9.95 (s, 1H, CHO), 12.40 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 300 (M^+, 100, %), 220 (47), 219 (90.8), 190 (53), 165 (19.1), 143 (15.7).
5a	FT-IR (KBr, υ_{max} cm^{-1}): 3421, 3385, 3129 (NH_2, NH), 3048, 2965, 2860 (CH), 1607 (C=N), 1578 (C=C). 1H NMR (DMSO-d6) δ ppm: 7.05 - 7.29 (m, 4H, Ar- H), 7.46 (d, 1H, indole proton), 7.66 - 7.68 (m, 2H, indole proton), 8.42 (d, 1H, indole proton), 8.91 (s, 1H, =CH), 12.06 (s, 1H, NH exchanged by D_2O), 4.34 (s, 2H, NH_2 exchanged by D_2O).
5b	FT-IR (KBr, υ_{max} cm^{-1}): 3249 (NH), 3056, 2921, 2855 (CH), 1592 (C=N), 1532 (C=C). 1H NMR (DMSO-d6) δ ppm: 7.04 - 8.10 (m, 13H, Ar-H), 6.75 (s, 1H, =CH), 8.22 (s, 1H, NH exchanged by D_2O), 4.33 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 391(M^+ +1, 26.6), 389 (M^+ - 1, 30.5), 233 (2.1), 298 (100), 284 (12.3), 271 (46.9), 190 (60.5).
5c	FT-IR (KBr, υ_{max} cm^{-1}): 3181 (NH), 3050, 2921 (CH), 1600 (C=N), 1573 (C=C). 1H NMR (DMSO-d6) δ ppm: 7.06 - 7.24 (m, 4H, Ar-H), 7.26 - 7.31 (m, 2H, benothiazole proton), 7.38 (d, 1H, benothiazole proton), 7.47 (d, 1H, indole proton),7.61-7.64 (m, 2H, indole proton), 7.73 (d, 1H, benothiazole proton), 8.36 (d, 1H, indole proton), 8.42 (s, 1H, =CH), 7.95 (s, 1H, NH exchanged by D_2O), 11.82 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 447 (M^+, 11.24), 313 (13.70), 296 (10.33), 204 (15.63), 150 (100).
7	FT-IR (KBr, υ_{max} cm^{-1}): 3207(NH), 3054, 3008, 2932, 2862 (CH), 1652 (C=O), 1611 (C=N), 1573 (C=C). 1H NMR (DMSO-d6) δ ppm: 7.14 - 8.80 (m, 14H, -Ar-H), 4.89 (s, 2H, CH_2), 8.90 (s, 1H, =CH), 11.92 (s, 1H, NH exchanged by D_2O), 12.05 (s, 1H, NH exchanged by D_2O).
8	FT-IR (KBr, υ_{max} cm^{-1}): 3389, 3165 (NH), 3054, 2962, 2848 (CH), 1654 (C=O), 1604 (C=N). 1H NMR (DMSO-d6) δ ppm: 3.78 (s, 2H,CH_2), 7.16 - 7.28 (m, 5H, Ar-H and H-2 indole), 7.45 (d, 2H, indole proton), 7.56 - 7.89 (m, 4H, indole proton), 8.41 (d, 2H, indole proton), 8.90 (s, 1H, =CH), 4.31 (s, 1H, NH exchanged by D_2O), 12.03 (s, 2H, NH exchanged by D_2O). MS. *m/z* (%): 471 (M^+, 0.94), 211 (4.96), 203 (74.04), 177 (12.11), 159 (13.50), 136 (37.99), 91 (100).
9	FT-IR (KBr, υ_{max} cm^{-1}): 3419, 3379, 3273 (NH), 3051, 2918, 2856 (CH), 1658 (C=O), 1604 (C=N). 1H NMR (DMSO-d6) δ ppm: 1.95 - 2.03 (m, 2H, CH_2), 2.20 (t, 2H,CH_2), 2.71(t, 2H, CH_2), 6.93 - 7.33 (m, 5H, Ar-H and H-2 indole), 7.42 (d, 2H, indole proton), 7.49 - 7.83 (m, 4H, indole proton), 8.12 (d,1H, indole proton), 8.35 (d, 1H, indole proton), 8.27 (s, 1H, =CH), 10.75 (s, 1H, NH exchanged by D_2O), 10.99 (s, 1H, NH exchanged by D_2O), 11.85 (s, 1H, NH exchanged by D_2O).
10	FT-IR (KBr, υ_{max} cm^{-1}): 3426, 3168 (NH), 3098, 3048, 2953, 2849 (CH), 1648 (C=O), 1608 (C=N). 1H NMR (DMSO-d6) δ ppm: 7.17 - 7.29 (m, 5H, Ar-H and H-3 benzofuran), 7.46 (d, 2H, indol and benzofuran),7.65 - 7.85 (m, 4H, indole and benzofuran), 8.42 (d, 2H, indole and benzofuran), 8.90 (s, 1H, =CH), 7.95 (s, 1H, NH exchanged by D_2O),12.04 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 458 (M^+, 0.10), 313 (0.11), 296 (5.76), 52 (66.65), 204 (63.53), 133 (43.88), 91 (100).
11	FT-IR (KBr, υ_{max} cm^{-1}): 3394, 3171 (NH), 3045, 2961, 2918 (CH), 1650 (C=O), 1604 (C=N), 2205 (CN). 1H NMR (DMSO-d6) δ ppm: 4.33 (s, 2H, CH_2), 7.16 - 7.28 (m,4H, Ar-H),7.44 (d, 1H, indole proton), 7.55 - 7.79 (m, 2H, indole proton), 8.11 (d, 1H, indole proton), 8.33 (s, 1H, N=CH), 11.33 (s, 1H, NH exchanged by D_2O), 11.93 (s, 1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ ppm: 24.39 (CH_2), 116.19 (CN), 157.73 (C=N), 163.58 (CO), 107.75, 111.44, 111.66, 120.95, 122.14, 122.27, 123.13, 125.09, 130.07, 130.97, 131.16, 131.73, 131.89, 136.46.

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12	FT-IR (KBr, υ_{max} cm^{-1}): 3391, 3311, 3184 (NH), 3047, 2960, 2918 (CH), 1667 (C=O), 1603 (C=N), 2212 (CN). 1H NMR (DMSO-d6) δ ppm: 2.29 (s, 3H, CH_3), 7.18 - 7.44 (m, 8H, Ar-H), 7.46 (d,1H, indole proton), 7.55 - 7.79 (m, 2H, indole proton), 8.19 (d, 1H, indole proton), 8.38 (s, 1H, = CH), 11.24 (s, 1H, NH exchanged by D_2O), 11.33 (s, 1H, NH exchanged by D_2O), 11.91 (s, 1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ pm: 10.65 (CH_3), 116.19 (CN), 155.22 (C=N), 159 (C=NNH), 111.41, 119.24, 122.18, 129.79, 130.07, 130.85, 131.04, 131.15, 131.24, 131.79, 133.31, 136.46, 136.46, 136.76.
13a	FT-IR (KBr, υ_{max} cm^{-1}): 3335, 3126(NH), 3055, 2921 (CH), 1686 (C=O), 2204 (CN). 1H NMR (DMSO-d6) δ ppm: 7.19-8.57 (m, 19H, Ar-H and H-5 pyrazole ring), 8.96 (s, 1H, =CH), 9.21 (s, 1H, N=CH); 11.73 (s, 1H, NH exchanged by D_2O), 12.04 (s, 1H, NH exchanged by D_2O). MS, *m/z* (%), 611 (M^+, 0.63), 392 (1.05), 379 (0.51), 358 (11.477), 327 (1.42), 217 (33.11), 77.02 (100).
13b	FT-IR (KBr,υ_{max} cm^{-1}): 3233, 3166 (NH), 3091, 2971 (CH), 1682 (C=O), 2208 (CN). 1H NMR (DMSO-d6) δ ppm: 7.22 - 8.39 (m, 12H, Ar-H), 8.68 (s, 1H, =CH), 8.88 (s, 1H, N=CH), 11.93 (s, 1H, NH exchanged by D_2O), 12.42 (s, 1H, NH exchanged by D_2O).
14	FT-IR (KBr, υ_{max} cm^{-1}): 3372, 3155 (NH), 3093, 2930, 2853 (CH), 1712 (C=O). 1H NMR (DMSO-d6) δ ppm: 5.17 (s, 1H, H-4 coumarin ring), 6.56 - 8.22 (m, 12 H, Ar-H), 8.72 (s, 1H, N=CH), 11.44 (s, 1H, NH exchanged by D_2O), 11.56 (s, 1H, NH exchanged by D_2O), 12.14 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 485(M^+, 0.30), 470 (0.4), 457 (0.4), 442 (0.1), 417 (3.00), 271 (100), 191(61.6), 165 (77.9).
15	FT-IR (KBr, υ_{max} cm^{-1}): 3475, 3396, 3369, 3234, 3180 (2NH_2, NH), 3059, 2934, 2838 (CH), 1721, 1670 (2 C=O), 2210 (CN). 1H NMR (DMSO-d6) δ ppm: 1.26 (t, 3H, CH_2-$\underline{CH_3}$), 4.23 (q, 2H, $\underline{CH_2}$-CH_3), 7.22 - 8.225 (m, 12 H, Ar-H and 2 NH_2), 8.25 (s, 1H, N= CH), 12.91 (s, 1H, NH exchanged by D_2O), 12.45 (s, 1H, NH exchanged by D_2O).
16	FT-IR (KBr, υ_{max} cm^{-1}): 3395, 3269, 3164 (NH_2, NH), 3049, 2974, 2866 (CH), 1665 (C=O), 1237 (C=S). 1H NMR (DMSO-d6) δ ppm: 7.16 - 8.48 (m, 15 H, Ar-H and NH_2), 8.90(s, 1H, N=CH), 11.00 (s, 1H, NH exchanged by D_2O), 12.43 (s, 1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ ppm: 147.39 (C=N), 153 (C-NH_2), 161.36 (CO), 183.91 (CS), 112.10, 113.61, 121.01, 122.38, 123.44, 125.7, 126.93, 130.7, 131.14, 131.87, 135.88, 136.51, 136.51, 141.72.
17	FT-IR (KBr, $\upsilon_{max,}$ cm^{-1}): 3129 (NH), 3091, 3052, 2947, 2860 (CH), 1681 (C=O), 1239 (C=S). 1H NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 7.05-7.81(m, 13 H, Ar-H), 8.22(s, 1H, =CH), 12.40 (s, 1H, NH exchanged by D_2O).
18	FT-IR (KBr, υ_{max} cm^{-1}): 3269 (NH), 3090, 2970, 2869 (CH). 1H NMR (DMSO-d6) δ ppm: 6.85 (s, 1H, N=CH), 6.98-7.32 (m, 10 H, Ar-H and H-5 thiazole ring), 7.50 (d, 1H, indole proton), 7.65 - 7.82 (m, 2H, indole proton), 8.20 - 8.22 (d, 1H, indole proton), 12.43 (s, 1H, NH exchanged by D_2O).
19	FT-IR (KBr, υ_{max} cm^{-1}): 3127 (NH), 3084, 2967, 2862 (CH), 1671, 1718 (2C=O). 1H NMR (DMSO-d6) δ ppm: 7.22 - 7.32 (m, 5 H, Ar-H and H-4 chromene), 7.44 (d, 2H, indole and chromene), 7.70 - 7.92 (m, 4H, indole and chromene), 7.93 - 7.97 (m, 2H, CH= CH), 8.00 - 8.22 (d, 2H, indole and chromene), 12.43 (s, 1H, NH exchanged by D_2O).
20a	FT-IR (KBr, υ_{max} cm^{-1}): 3466, 3310, 3149 (NH_2, NH), 3048, 2970, 2865 (CH), 1688 (C=O) and 2203 (CN). 1H NMR (DMSO-d6) δ ppm: 7.22 - 7.32 (m, 6 H, Ar-H and NH_2 proton), 7.47 - 7.83 (m, 3H, indole proton), 7.96 (d, 1H, indole proton), 8.22 (s, 1H, C=CH), 12.43 (s, 1H, NH exchanged by D_2O).
20b	FT-IR (KBr, υ_{max} cm^{-1}): 3269 (NH), 3047, 2973, 2861 (CH), 2208 (CN), 1708 (C=O). 1H NMR (DMSO-d6) δ ppm: 1.03 (t, 3H, CH_2CH_3), 4.23 (q, 2H, $\underline{CH_2}$ CH_3), 7.29 - 7.35 (m, 4H, Ar-H), 7.56 - 7.86 (m, 3H, indole proton), 8.15 - 8.17 (d, 1H, indole proton), 8.25 (s, 1H, =CH); 4.34 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 395 (M^+, 11.8), 321 (44.6), 242 (100), 215 (17.6), 214 (32.8).
21	FT-IR (KBr, υ_{max} cm^{-1}): 3303 (NH), 2203(CN), 3052, 2961, 2921, 2859 (CH), 1672 (C=O). 1H NMR (DMSO-d6) δ ppm: 4.20 (d, 1H, pyrazoline), 6.11 (d, 1H, pyrazoline), 6.97 - 7.00 (m, 4H, Ar-H), 7.02 - 7.87 (m, 3H, indole proton), 7.97 (d, IH, indole proton), 10.18 (s, 1H, NH exchanged by D_2O), 11.41 (s, 1H, NH exchanged by D_2O), 12.22 (s, 1H, NH exchanged by D_2O).
22	FT-IR (KBr, υ_{max} cm^{-1}): 3384 (NH), 2212 (CN), 3054, 2957, 2852 (CH). 1H NMR (DMSO-d6) δ ppm: 7.21 - 7.32 (m, 4H, Ar-H), 7.57 - 7.95 (m, 8H, indole and benzimidazole proton), 8.31 (s, 1H, =CH), 12.57 (s, 1H, NH exchanged by D_2O), 12.88 (s, 1H, NH exchanged by D_2O).
23	FT-IR (KBr, υ_{max} cm^{-1}): 3355 (OH), 3179 (NH), 1623, 1707 (2C=O), 3095, 2974, 2865 (CH), 1242 (C=S). 1H NMR (DMSO-d6) δ ppm: 4.71 (s, 2H, CH_2), 7.32 - 7.33 (m, 4H, Ar-H), 7.50 (d, 1H, indole proton), 7.66 - 7.79 (m, 2H, indole proton), 7.99 (s, 1H, CH=C), 8.19 (d, 1 H, indole proton), 12.43 (s, 1H, NH exchanged by D_2O), 12.60 (s, 1H, OH exchanged by D_2O). MS. *m/z* (%): 473 (M^+, 1.4), 472 (M^+-1, 4.1), 456 (0.2), 382 (0.7), 327 (15.6), 271 (100), 202 (4.9).

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26	FT-IR (KBr, υ_{max} cm^{-1}): 3249, 3154 (2 NH), 3026, 2814 (CH), 1689 (C=O), 1283 (C=S). 1H NMR (DMSO-d6) δ ppm: 3.21 (s, 2H, CH_2), 6.79 - 7.79 (m, 6H, Ar-H and H-5 thiazole), 8.31 (s, 1H, NH exchanged by D_2O), 9.34 (s, 1H, NH exchanged by D_2O).
27	FT-IR (KBr, υ_{max} cm^{-1}): 3232, 3260, 3176 (NH), 1668 (C=O), 3053, 2990, 2873 (CH), 1242(C=S). 1H NMR (DMSO-d6) δ ppm: 6.95 - 7.31 (m, 10 H, Ar-H and H-5 thiazole), 7.50 - 7.90 (m, 4H, indole proton), 9.96 (s, 1H, =CH), 12.18 (s, 1H, NH exchanged by D_2O), 12.22 (s, 1H, NH exchanged by D_2O), 12.40 (s, 1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ ppm: 185.37 (CS), 168 (CO), 155.46 (C=C), 166 (C-NH), 108.01, 112.01, 112.01, 113.74, 121.01, 123.44, 125.70, 127.62, 128.93, 129.01, 130.21, 130.8, 134.46, 135.88, 144.51, 146.01, 148.01.
28	FT-IR (KBr, υ_{max} cm^{-1}): 3275 (NH), 1706 (C=O), 3037, 2988, 2817(CH). 1H NMR (DMSO-d6) δ ppm: 2.38 (s, 3H, CH_3), 7.31 - 7.35(m, 9H, Ar-H), 7.36 - 7.53 (m, 4H, indole proton and =CH), 7.82 (d, 1H, indole proton), 12.40 (s, 1H, NH exchanged by D_2O). ^{13}C NMR (DMSO-d6) δ ppm: 12.58 (CH_3), 153(C=C), 160 (C=O), 108.82, 120.62, 120.74, 126.43, 126.63, 128.87, 129.07, 137.15, 140.16, 140.34. MS. *m/z* (%): 456 (M^+, 1.9), 441 (0.3), 413 (0.4), 336 (3.4), 359 (48.1), 358 (100), 341 (62.3), 266 (20.3), 77 (92.7).
29a	FT-IR (KBr, υ_{max}, cm^{-1}): 3428, 3198 (NH), 3039, 2865(CH). 1H NMR (DMSO-d6) δ ppm: 2.26 (s, 3H, CH_3), 6.93 - 7.18 (m, 9H, Ar-H), 7.29 - 7.82 (m, 4H, indole proton), 8.04 (s, 1H, NH exchanged by D_2O), 11.56 (s, 1H, NH exchanged by D_2O).
29b	FT-IR (KBr, υ_{max} cm^{-1}): 3209 (NH), 3048, 2917, 2863 (CH). 1H NMR (DMSO-d6) δ ppm: 2.21 (s, 3H, CH_3), 6.93 - 7.32 (m, 14H, Ar-H), 7.37 - 7.82 (m, 4H, indole proton), 11.56 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 544 (M^+, 3.3), 529 (2.3), 467 (22.9), 375 (15.41), 295 (6.2), 298 (100), 273 (71.8), 271 (17.2).
30	FT-IR (KBr,υ_{max} cm^{-1}): 3323, 3174 (NH), 3055, 2969, 2864 (CH), 1242 (C= S). 1H NMR (DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 7.11 - 7.35 (m, 13H, Ar-H), 7.37 - 7.86 (m, 4H, indole proton), 11.48 (s, 1H, NH exchanged by D_2 O), 12.00 (s, 1H, NH exchanged by D_2O). MS. *m/z* (%): 617 (M^+, 0.46), 587 (0.54), 522 (0.46), 467 (0.63), 414 (1.35), 330 (2.73), 252 (57.01), 125 (100).
31	FT-IR (KBr, υ_{max}, cm^{-1}): 3436 (NH), 3050, 2972, 2865 (CH), 1277 (C=S). 1H NMR (DMSO-d6) δ ppm: 2.28 (s, 3H, CH_3), 7.93 - 8.31 (m, 17H, Ar-H), 11.54 (s, 1H, NH exchanged by D_2O).

reagent and continuous stirring and kept at room temperature for 2 h. The reaction mixture was allowed to stand overnight and was then refluxed for 2 h. under vigorous stirring. The mixture was then poured onto ice cold water and neutralized with dilute ammonia solution till the precipitation occurs. The formed precipitate was collected by filtration and recrystallized from ethanol to give **4** as yellow crystals. Yield (15.13 g, 70%, m.p.: 270-272˚C. Anal. calcd. for C_{15} H_{10} Br NO (300.15): C, 60.02; H, 3.36; Br, 26.62; N, 4.67. Found: C, 59.89; H, 3.16; Br, 26.42; N, 4.37.

2.1.3. General Procedure for the Synthesis of 5a-c

An equimolecular mixture of **4** (3 g, 0.01 mol) and the hydrazine derivatives (0.5 ml, 0.01 mol) were refluxed in absolute ethanol (20 ml) in the presence of 2 - 3 drops of glacial acetic acid for the appropriate time. The reaction mixture was cooled to room temperature and poured into ice-cold water. The separated product was filtered, washed with cold water, dried and recrystallized from the appropriate solvent to give **5a-c.**

1-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]hydrazine 5a

Compound **5a** was prepared from hydrazine hydrate for 1 h. Orange crystals. Yield (2.48 g, 79%); m.p.: 338-340˚C (xylene). Anal. calcd. for $C_{15}H_{12}Br$ N_3 (314.18): C, 57.34; H, 3.85; Br, 25.43; N, 13.37. Found: C, 57.24; H, 3.65; Br, 25.33; N, 13.17.

1-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-2-phenyl-hydrazine 5b

Compound **5b** was prepared from phenyl hydrazine for 4 h. Pale brown powder. Yield (2.5 g, 64%); m.p.: 115-117˚C (hexane). Anal.calcd. for $C_{21}H_{16}BrN_3$ (390.28): C, 64.63; H, 4.13; Br, 20.47; N, 10.77. Found: C, 64.43; H, 4.00; Br, 20.27; N, 10.57.

2-{2-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]hydrazine}-1,3-benzothiazole 5c

Compound **5c** was prepared from 2-hydrazinyl-1,3-benzothiazole for 4 h. Pale yellow crystal. Yield (2.46 g, 55%); m.p.: 280-282˚C (ethanol/DMF). Anal. calcd. for $C_{22}H_{15}BrN_4S$ (447.35): C, 59.07; H, 3.38; Br, 17.86; N, 12.52; S, 7.17. Found: C, 58.98; H, 3.18; Br, 17.66; N, 12.40; S, 7.00.

2.1.4. General Procedure for the Synthesis of 7-10

An equimolecular mixture of **4** (3 g,0.01 mol) and the acid hydrazide derivatives **6a-d** (0.01 mol) was refluxed for 2 h. in absolute ethanol (20 ml) in the presence of 2 - 3 drops of glacial acetic acid. The reaction mixture was cooled to room temperature and poured into ice-cold water. The separated product was filtered, washed with cold water, dried and recrystallized from the appropriate solvent.

***N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-2-(quinolin-8-yloxy)acetohydrazide 7**

Yellow crystals. Yield (3 g, 60%); m.p.: 290-292˚C (ethanol/DMF). Anal. calcd for $C_{26}H_{19}BrN_4O_2$ (499.35): C, 62.54; H, 3.84; Br, 16.00; N, 11.22. Found: C, 62.24; H, 3.62; Br, 15.88; N, 11.02.

***N*'-(2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene)-2-(1*H*-indol-3-yl)acetohydrazide 8**

Red crystals. Yield (2.83 g, 60%); m.p.: 330-332˚C (ethanol). Anal. calcd for $C_{25}H_{19}BrN_4O$ (471.35): C, 63.70; H, 4.06; Br, 16.95; N, 11.89. Found: C, 63.40; H, 4.00; Br, 16.65; N, 11.59.

***N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-4-(1*H*-indol-3-yl)-butanehydrazide 9**

Dark yellow powder. Yield (3.75 g, 75%); m.p.: 170-172˚C (xylene). Anal.calcd for $C_{27}H_{23}BrN_4O$ (499.40): C, 64.94; H, 4.64; Br, 16.00; N, 11.22. Found: C, 64.74; H, 4.34; Br, 15.88; N, 11.00.

***N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-benzofuran-2-carbohydrazide 10**

Yellow crystals. Yield (2.75 g, 60%); m.p.: 320-322˚C (ethanol/DMF). Anal. calcd for $C_{24}H_{16}BrN_3O_2$ (458.30): C, 62.90; H, 3.52; Br, 17.43; N, 9.17. Found: C, 62.70; H, 3.32; Br, 17.23; N, 9.00.

2.1.5. *N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-2-cyanoacetohydrazide 11

An equimolecular mixture of **4** (3 g, 0.01 mol) and cyanoacetohydrazide (1.98 g, 0.02 mol) in absolute ethanol (30 ml) was heated under reflux for 2 h. The precipitate formed after cooling was filtered off, washed with cold ethanol, dried and recrystallized from DMF to give **11** as pale brown powder. Yield (3.24 g, 85%); m.p.: 290-292˚C. Anal. calcd for $C_{18}H_{13}BrN_4O$ (381.22): C, 56.71; H, 3.44; Br, 20.96; N, 14.70. Found: C, 56.41; H, 3.24; Br, 20.86; N, 14.50.

2.1.6. *N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-2-cyano-2-[(4-methylphenyl)hydrazono]-acetohydrazide 12

To a cold solution of **11** (3.81 g, 0.01 mol) in ethanol (20 ml) containing sodium acetate (3.0 g) was added with continuous stirring 4-methylbenzene diazonium salt (0.01 mol) [prepared by adding sodium nitrite (1.38 g, 0.02 mol) in water (8 ml) to a cold solution of *p*-toluidine (1.07 g, 0.01 mol) in the appropriate amount of hydrochloric acid]. The reaction mixture was stirred for 2 h. and the formed solid was collected by filtration and recrystallized from ethanol to give **12** as orange crystals. Yield (3.5 g, 70%); m.p.: 240-242˚C. Anal. calcd for $C_{25}H_{19}BrN_6O$ (499.36): C, 60.13; H, 3.84; Br, 16.00; N, 16.83. Found: C, 60.00; H, 3.54; Br, 15.98; N, 16.75.

2.1.7 General Procedure for the Synthesis of 13a,b and 14

Equimolecular mixture of **11** (3.81 g, 0.01 mol) and the selected aldehydes such as 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde, *p*-nitrobenzaldehyde and salicyaldehyde (0.01 mol) in 1,4-dioxane (20 ml) containing piperidine (0.5 ml) was heated under reflux for 3 h. The reaction mixture was left to cool then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration and recrystallized from the appropriate solvent.

***N*'-[2-(4-Bromophenyl-1*H*-indol-3-ylmethylene]-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl) acrylohydrazide 13a**

Yellow crystal. Yield (3.6 g, 55%); m.p.: 255-257˚C (ethanol/DMF). Anal. calcd for $C_{34}H_{23}BrN_6O$ (611.49): C, 66.78; H, 3.79; Br, 13.07; N, 13.74. Found: C, 66.48; H, 3.59; Br, 13.00; N, 13.55.

***N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-3-(4-nitrophenyl)-2-cyanoacrylohydrazide 13b**

Yellow crystals. Yield (2.31 g, 45%); m.p.: 230-232˚C (ethanol). Anal.calcd for $C_{25}H_{16}BrN_5O_3$ (514.33): C, 58.38; H, 3.14; Br, 15.54; N, 13.62. Found: C, 58.18; H, 3.00; Br, 15.34; N, 13.32.

***N*'-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-2-imino-2*H*-chromene-3-carbohydrazide 14**

Brown crystals. Yield (2.9 g, 60%); m.p.: 130-132˚C (hexane). Anal. calcd for $C_{25}H_{17}BrN_4O_2$ (485.33): C, 61.87; H, 3.53; Br, 16.46; N, 11.54. Found: C, 61.57; H, 3.33; Br, 16.26; N, 11.34.

2.1.8. General Procedure for the Synthesis of 15 and 16

To a solution of compound **11** (3.81 g, 0.01 mol) in absolute ethanol (50 ml) containing triethylamine (1 ml) either ethyl cyanoacetate (1.13 g, 0.01 mol) or phenylisothiocyanate (1.39 g, 0.01 mol) together with elemental

sulfur (0.32 g, 0.01 mol) were added. Reaction mixture was heated under reflux for 8 h. then poured onto ice/water mixture and the formed solid product, in each case, was collected by filtration recrystallized from ethanol.

Ethyl 2,4-diamino-5-{[2-(2-(4-bromophenyl)-1*H*-indol-3-ylmethylene)hydrazino]-carbonyl}thiophene-3-carboxylate 15

Dark brown crystals. Yield (2.63 g, 50%); m.p.: 190-192˚C. Anal. calcd for $C_{23}H_{20}$ BrN_5O_3S (526.40): C, 52.48; H, 3.83; Br,15.18; N, 13.30; S, 6.09. Found: C, 52.28; H, 3.53; Br, 15.00; N, 13.00; S, 6.00.

4-Amino-*N*'-[2-(4-bromophenyl)-1*H*-indol-3-ylmethylene]-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazole-5-carbohydrazide 16

Brown crystals. Yield (3.35 g, 61%); m.p.: 245-247˚C. Anal. calcd for $C_{25}H_{18}Br$ N_5OS_2 (548.47): C, 54.75; H, 3.31; Br, 14.57; N,12.77; S, 11.69. Found C, 54.55; H, 3.11; Br, 14.37; N, 12.57; S, 11.49.

2.1.9. 6-[(2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene)amino]-5-methyl-2-thioxo-3-phenyl-2,3-dihydro-1,3-thiazolo[4,5-d]pyrimidin-7(6H)-one 17

A solution of compound **16** (5.48 g, 0.01 mol) in a mixture of acetic acid (5 ml) and acetic anhydride (10 ml) was heated under reflux for 8 h. and then allowed to cool. The precipitate that formed was collected by filtration, dried and recrystallized from acetic acid to give compound **17** as yellow crystals; Yield (3.4 g, 60%); m.p.: 316-318˚C. Anal. Calcd. C_{27} H_{18} Br N_5 O S_2 (572.50): C, 56.64; H, 3.17; Br, 13.96; N, 12.23; S, 11.2. Found: C, 56.44; H, 3.07; Br, 13.66; N, 12.03; S, 11.00.

2.1.10. *N*-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-4-phenyl-1,3-thiazol-2-amine 18

A mixture of compound **4** (3 g, 0.01 mol), phenacyl bromide (0.01 mol) and thiourea (0.78 g, 0.01 mol) in absolute ethanol (30 ml) containing acetic acid (1 ml) were heated under reflux for 8 h. Reaction mixture poured in an ice cold water, the solid obtained was filtered, dried and recrystallized from ethanol to give **18** as brown powder. Yield (3.21 g, 70%); m.p.: 230-232˚C. Anal. calcd. for $C_{24}H_{16}Br$ N_3S (458.37): C, 62.89; H, 3.52; Br, 17.43; N, 9.17; S, 7.00. Found: C, 62.59; H, 3.22; Br, 17.23; N, 9.00; S, 6.81.

2.1.11. 3-[3-(2-(4-Bromophenyl)-1*H*-indol-3-yl)prop-2-enoyl]-2*H*-chromen-2-on 19

A mixture of **4** (3 g, 0.01 mol), 3-acetyl-2*H*-chromen-2-one (1.88 g, 0.01 mol) in 20 ml absolute ethanol and 0.5 ml piperdine was refluxed for 30 min. The reaction mixture was left overnight at room temperature, the obtained solid was filtered off and recrystallized from ethanol to give **19** as yellow crystals. Yield (4.01 g, 64%); m.p.: 280-282˚C. Anal. calcd. for $C_{26}H_{16}BrNO_3$ (470.31): C, 66.40; H, 3.43; Br, 16.99; N, 2.98. Found: C, 66.30; H, 3.23; Br, 16.79; N, 2.78.

2.1.12. General Procedure for the Synthesis of 20a,b and 22

To a solution of compound **4** (3 g, 0.01 mol) in 20 ml ethanol, the appropriate active methylene compounds such as cyanoacetamide, ethyl cyanoacetate and 1*H*-benzimidazol-2-ylacetonitrile (0.01 mol) and few drops of triethylamine was added. The reaction mixture was refluxed for 5 h. and then allowed to cool. The formed solid product was collected by filtration, washed with ethanol and recrystallized from the appropriate solvent.

3-[2-(4-Bromophenyl)-1*H*-indol-3-yl]-2-cyanoprop-2-enamide 20a

Yellow powder. Yield (2.38 g, 65%); m.p.: 210-212˚C (ethanol).Anal. calcd for $C_{18}H_{12}BrN_3O$ (366.21): C, 59.03; H, 3.30; Br, 21.82; N, 11.47. Found: C, 58.89; H, 3.00; Br, 21.52; N, 11.17.

Ethyl 3-[2-(4-bromophenyl)-1*H*-indol-3-yl]-2-cyanoprop-2-enoate 20b

Yellow powder. Yield (2.37 g, 60%); m.p.: 245-247˚C (ethanol\DMF). Anal. calcd. for $C_{20}H_{15}BrN_2O_2$ (395.24): C, 60.78; H, 3.83; Br, 20.22; N, 7.09. Found: C, 60.48; H, 3.53; Br, 20.02; N, 7.00**.**

2-(1*H*-Benzimidazol-2-yl)-3-[2-(4-bromophenyl)-1*H*-indol-3-yl]acrylonitrile 22

Brown powder. Yield (2.64 g, 60%); m.p. 250-253˚C (ethanol\DMF). Anal. calcd. for $C_{24}H_{15}BrN_4$ (439.30): C, 65.62; H, 3.44; Br, 18.19; N, 12.75. Found: C, 65.42; H, 3.24; Br, 18.09; N, 12.65.

2.1.13. 3-[2-(4-Bromophenyl)-1*H*-indol-3-yl]-5-oxopyrazolidine-4-carbonitrile 21

A mixture of compound **20b** (3.95 g, 0.01 mole) and hydrazine hydrate (0.75 ml, 0.015 mole) in ethanol (20 ml) was refluxed for 3 h, then poured into water. The resulting solid was collected and recrystallized from ethanol to give **21** as yellowish white crystals. Yield (1.91 g, 50%); m.p.: 198-200˚C. Anal. calcd for $C_{18}H_{13}BrN_4O$

(381.23): C, 56.71; H, 3.44; Br, 20.96; N, 14.70. Found: C, 56.51; H, 3.24; Br, 20.76; N, 14.50.

2.1.14. {5-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}acetic acid 23

To a solution of rhodanine-3-acetic acid (1.91 g, 0.01 mol) and anhydrous sodium acetate (0.5 g) in glacial acetic acid was added the 1*H*-indole-3-carboxaldehyde **4** (3 g, 0.01 mol). The mixture was stirred under reflux for 6 h and then poured into ice-cold water. The precipitate was filtered, washed with water, dried and recrystallized from xylene to gives **23** as orange powder. Yield (3.08 g, 65%); m.p.: 223-225˚C. Anal. calcd. For $C_{20}H_{13}BrN_2O_3S_2$ (473.36): C, 50.75; H, 2.77; Br, 16.88; N, 5.92; S, 13.55. Found: C, 50.45; H, 2.57; Br, 16.58; N, 5.62; S, 13.25.

2.1.15. Ethyl 3-Oxo-3-[(4-phenyl-1,3-thiazol-2-yl)amino]propanoate 25

A mixture of an equimolar amount of 4-phenyl-2-aminothiazole **24** (1.76 g, 0.01 mol) and diethylmalonate 1.6 g, 0.01 mol) was heated in an oil bath at 180˚C for 2 hours then left to cool. The product was collected and used in second step.

2.1.16. 6-[(4-Phenyl-1,3-thiazol-2-yl)amino]-2-thioxo-2,3-dihydro-pyrimidin-4(5*H*)-one 26

A mixture of ester **25** (2.9 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in ethanol (30 ml) containing sodium ethoxide was heated under reflux for 6 h. The reaction mixture was poured into cold water and the formed solid product was collected by filtration, washed, dried and recrystallized from ethanol to gives **26** as yellow crystals. Yield (3.8 g, 60%); m.p.:200-202˚C. Anal. calcd. for C_{13} H_{10} N_4 O S_2 (302.37): C, 51.64; H, 3.33; N, 18.53; S, 21.21. Found: C, 51.44; H, 3.13; N, 18.33; S, 21.01.

2.1.17. 5-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-6-[(4-phenyl-1,3-thiazol-2-yl)amino]-2-thioxo-2,5-dihydropyrimidin-4(3*H*)-one 27

A mixture of pyrimidine derivative **26** (3 g, 0.01 mol) and 1*H*- indole-3-carboxaldehyde **4** (3 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for 6 h., then left to cool. The solid product was collected by filtration and recrystallized from xylene to give **27** as green powder. Yield (2.34 g, 40%. m.p.: 208-210˚C. Anal. calcd. for $C_{28}H_{18}BrN_5OS_2$ (584.50): C, 57.54; H, 3.10; Br, 13.67; N,11.98; S,10.97. Found: C, 57.34; H, 3.00; Br, 13.47; N, 11.68; S, 10.67.

2.1.18. 4-[2-(4-Bromophenyl)-1*H*-indol-3-ylmethylene]-3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one 28

A mixture of 1*H*-pyrazol-5(4*H*)-one (1.74 g, 0.01 mol) and 1*H*- indole-3-carboxaldehyde **4** (3 g, 0.01 mol) in acetic acid in the presence of anhydrous sodium acetate was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into ice cold water. The solid separated out was filtered washed with water and recrystallized from (ethanol/DMF) to give **28** as orange crystals. Yield (3.01g, 66%); m.p.: 190-192˚C. Anal. calcd. for $C_{25}H_{18}BrN_3O$ (456.33): C, 65.80; H, 3.98; Br,17.51; N, 9.21. Found: C, 65.56; H, 3.68; Br, 17.31; N, 9.00.

2.1.19. 2-(4-Bromophenyl)-3-(4-methyl-6-phenyl-2,6-dihydropyrazolo[3,4-*c*]pyrazol-3-yl)-1*H*-indole 29a

A mixture of compound **28** (4.56 g, 0.01 ml) and hydrazine hydrate (0.5 ml, 0.01 ml) in ethanol in present of few drops of acetic acid was refluxed for 7 h. Reaction mixture was cooled at room temperature and poured in ice cold water. The solid separated was filtered, washed with water and recrystallized from ethanol to give **29a** as yellow crystals. Yield (2.81 g, 60%); m.p.: 180-182˚C. Anal.calcd. for $C_{25}H_{18}BrN_5$ (468.34): C, 64.11; H, 3.87; Br, 17.06; N, 14.95. Found: C, 64.00; H, 3.57; Br, 16.89; N, 14.65.

2.1.20. 2-(4-Bromophenyl)-3-(4-methyl-2,6-diphenyl-2,6-dihydropyrazolo[3,4-*c*]pyrazol-3-yl)-1*H*-indole 29b

A mixture of compound **28** (4.56 g, 0.01 ml), phenyl hydrazine (1.08 ml, 0.01 mol), anhydrous sodium acetate (0.5 g) and acetic acid (20 ml) was refluxed for 7 h. Reaction mixture was cooled to room temperature and poured in ice cold water. The solid separated out was filtered, washed with water and recrystallized from ethanol

to give **29b** as yellow crystals. Yield (3.54 g, 65%); m.p.: 105-106˚C. Anal. calcd. for $C_{31}H_{22}BrN_5$ (544.44): C, 68.39; H, 4.07; Br, 14.68; N, 12.86. Found: C, 68.09; H, 4.00; Br, 14.48; N, 12.66.

2.1.21. 3-(2-(4-Bromophenyl)-1*H*-indol-3-yl)-4-methyl-*N*-(4-methylphenyl)-6-phenyl-pyrazolo [3,4-c]-pyrazole-2(6*H*)-carbothioamide 30

A mixture of compound **28** (4.56 g, 0.01 mol) and *N*-(4-methylphenyl)thiosemicarbazide (1.81 g, 0.01 mol) was refluxed in ethanol in the presence of $NaOH/H_2O$ (10%, 5 ml) for 8 h. Reaction mixture was cooled to room temperature and poured in ice-cold water. The solid separated out was filtered, washed with water and recrystallized from ethanol to give **30** as yellow crystals, Yield (3.89 g, 63%); m.p.: 240-242˚C (ethanol). Anal. Calcd. for $C_{33}H_{25}BrN_6S$ (617.56): C, 64.18; H,4.08; Br,12.94; N, 13.61; S, 5.19. Found: C, 64.00; H, 4.00; Br, 12.70; N, 13.36; S, 5.09.

2.1.22. 4-(2-(4-Bromophenyl)-1*H*-indol-3-yl)-3-methyl-5-(4-nitrophenyl)-1-phenyl-1,5-dihydro-6*H*-pyrazolo[3,4-*d*]pyrimidine-6-thione 31

A mixture of compound **28** (4.56 g, 0.01 mol), *N*-(4-nitrophenyl)thiourea (1.97 g, 0.01 mol) and potassium hydroxide (0.5 g) in ethanol (20 ml) was refluxed with stirring for 4 h. The reaction mixture was left overnight and then concentrated under reduced pressure. The solid residue was collected, washed with water and recrystallized from ethanol to gives **31** as orange powder, Yield (3.48 g, 55%); m.p.: 150-152˚C. Anal. calcd. for $C_{32}H_{21}BrN_6O_2S$ (633.52): C, 60.67; H, 3.34; Br, 12.61; N, 13.27; S, 5.06. Found: 60.47; H, 3.14; Br, 12.41; N, 13.07; S, 4.89.

2.2. Antimicrobial Assays

Synthesized compounds **5c**, **7**, **9**, **11**, **13a**, **27**, **30** and **31** were screened for their antimicrobial activities*in vitro* against two species of Gram-positive bacteria, namely *Staphylococcus saureus* RCMB 0100010 (SA), *Bacillus subtilis RCMB* 010067 (BS) and two negative bacteria, namely *Pseudomonas aeuroginosa* RCMB 010043 (PA), *Escherichia coli* CMB 010052 (EC). Two fungal strains *Aspergillus fumigatus* RCMB 02568 *(*AF) and *Candida albicans* RCMB 05036 (CA) are used for antifungal activity. The antibacterial and antifungal activities were determined by means of inhibition% ± standard deviation at a concentration of 100 µg/ml of tested samples [15] [16]. Optical densities of antimicrobial were measured after 24 hours at 37˚C to bacteria and measured after 48 hours at 28˚C to fungal using a multidetection microplate reader at the Regional Center for Mycology and Biotechnology (Sun Rise-Tecan, USA at 600 nm) Al-Azhar University. Ampicillin, gentamicin were used as bacterial standards and amphotericin B was used as fungal standards for references to evaluate the efficacy of the tested compounds under the same conditions. The MICs of the compounds assays were determined by using microbroth kinetic system [17].

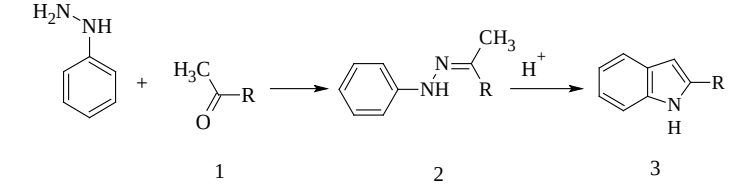
3. Results and Discussion

3.1. Chemistry

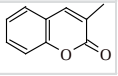
The synthesis of the new compounds is outlined in **Schemes 1-6**. 2-Substituted-indole reported to be obtained via Fischer indole synthesis using phenyl hydrazine and acetophenone derivatives **1a-d** in present of polyphosphoric acid as catalysis [18]. Synthesis of 1*H*-indole-3-carboxaldehyde derivative **4** from the 2-(4-bromophenyl)-1*H*-indole **3c** via Vilsmeir Haack's formylation using phosphorus oxychloride ($POCl_3$) and N,N/-dimethylformamide (DMF) [19] (**Scheme 1**). The IR spectrum of **4** revealed C=O stretching band of formyl group at 1672 cm^{-1}. 1H NMR spectrum showed an D_2O-exchangeable signal at 12.40 ppm assigned to the NH proton and a non exchangeable signal at δ 9.95 ppm corresponding to the formyl proton. The mass spectrum showed the molecular ion peak at *m/z* 300 corresponding to the molecular formula $C_{15}H_{10}BrNO$.

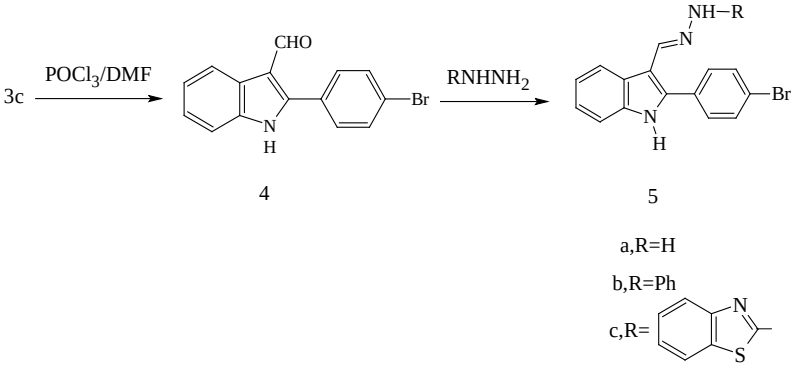
The hydrazine derivatives **5a-c** were obtained by the reaction of 1*H*-indole-3-carboxaldehyde derivative **4** with different substituted hydrazines [20] namely, hydrazine hydrate, phenyl hydrazine and 2-hydrazinyl-1,3-benzothiazole (**Scheme 1**). The molecular structure of the synthesis compounds were established based on analytical and spectral data. For example, 1H NMR spectrum of compound **5c** showed an D_2O -exchangeable signal at 7.95 and 11.82 assigned to the two NH protons and a non exchangeable signal at 8.42 ppm corresponding =CH proton. On other hand mass spectrum of **5c** showed a molecular ion peak *m/z* at 447 corresponding to the molecular formula $C_{22}H_{15}BrN_4S$.

Reaction of 1*H*-indole-3-carboxaldehyde derivative **4** with different substituted acid hydrazides [21] such as 2-(quinolin-8-yloxy)acetohydrazide **6a**, 2-(1*H*-indol-3-yl)acetohydrazide **6b**, 4-(1*H*-indol-3-yl)butanehydrazide **6c** and 1-benzofuran-2-carbohydrazide **6d** in presence of catalytic amount of acetic acid in absolute ethanol



1 2 3

1,2,3	R
a	4-$CH_3C_6H_4$
b	4-$NH_2C_6H_4$
c	4-BrC_6H_4
d	



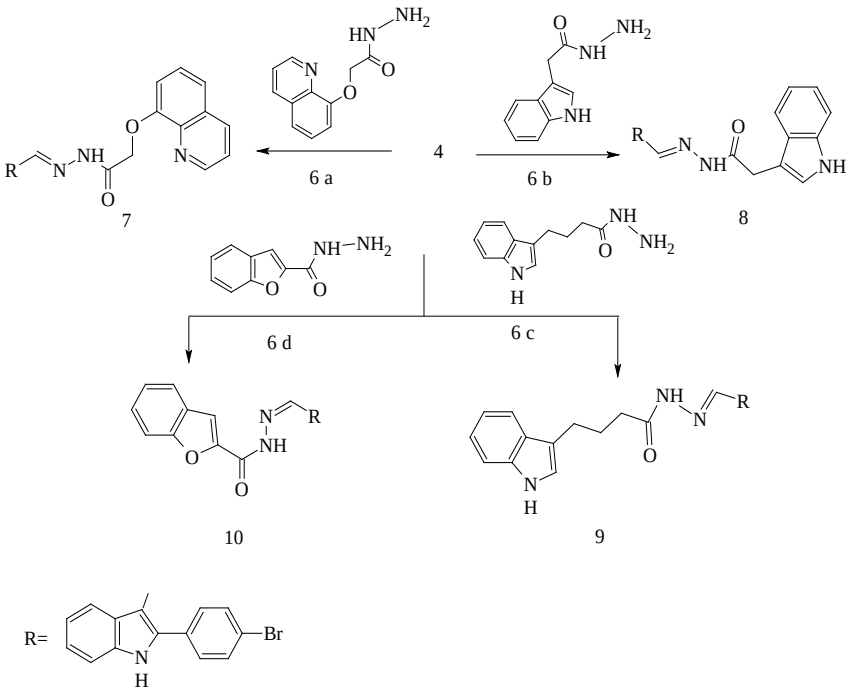
4 5

a,R=H

b,R=Ph

c,R=

Scheme 1. Synthesis of compounds **3-5**.



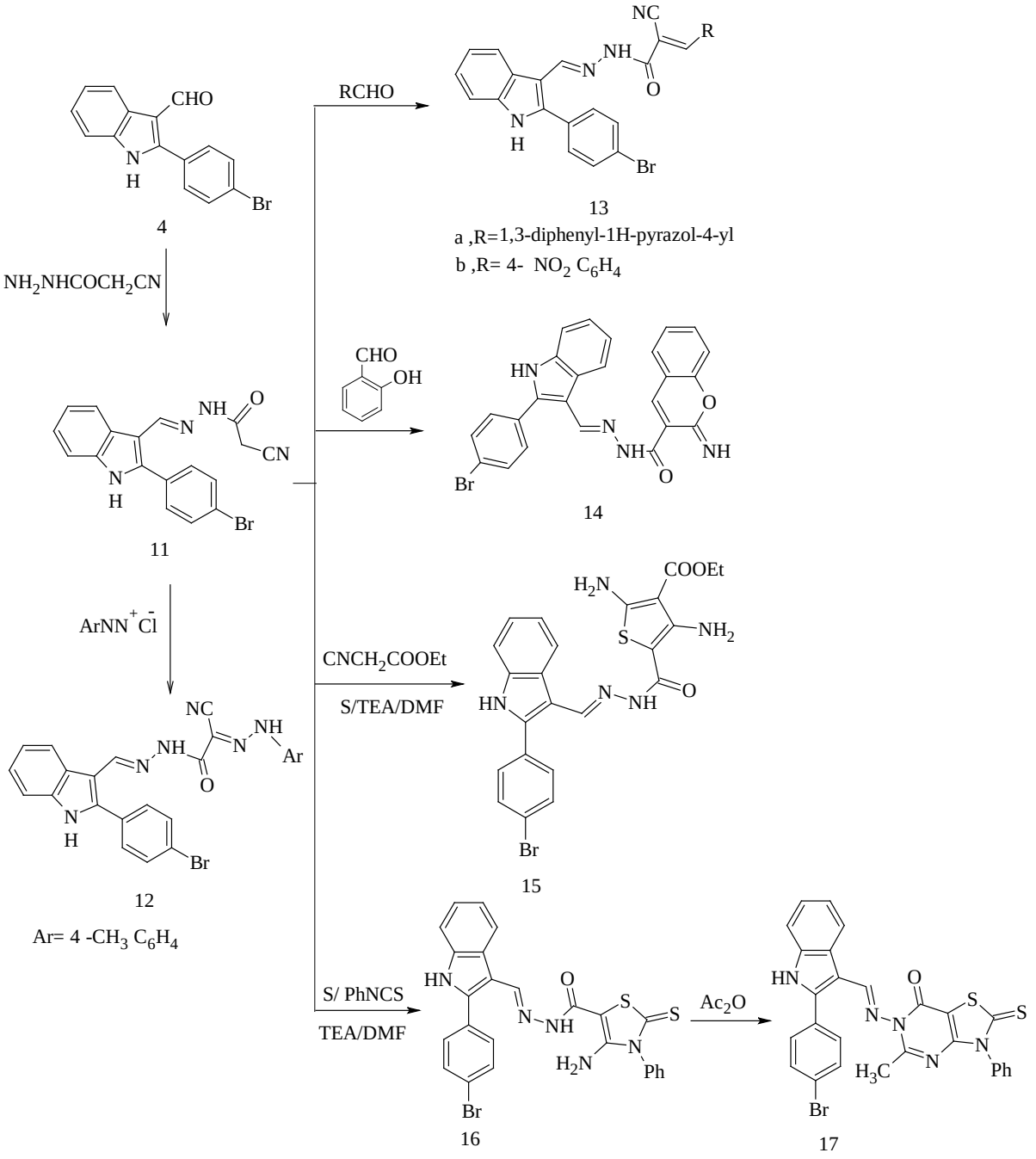
7 6 a 4 6 b 8

6 d 6 c

10 9

R=

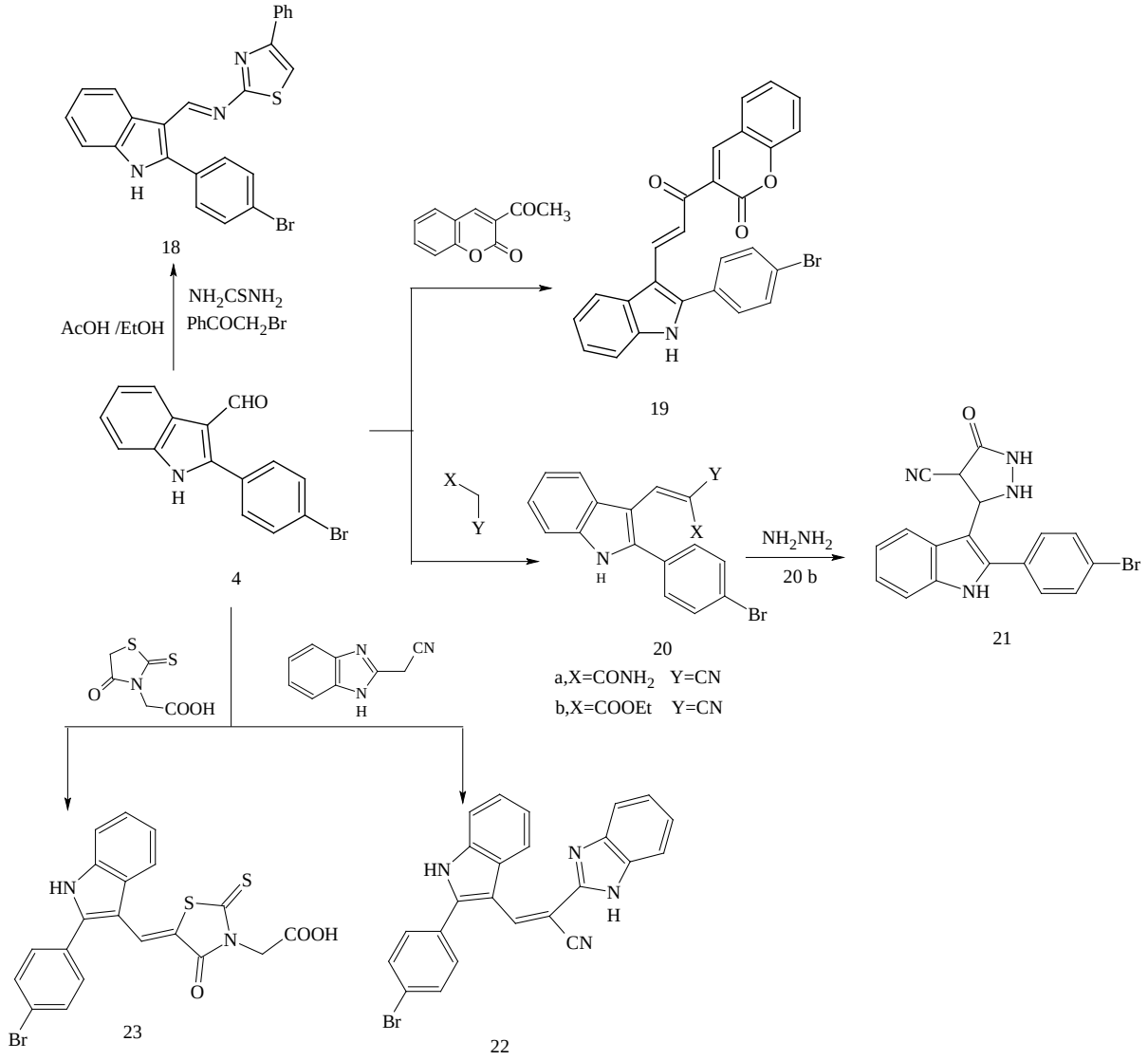
Scheme 2. Synthesis of compounds **7-10**.



Scheme 3. Synthesis of compounds **11-17**.

afforded the corresponding the acid hydrazide derivatives **7-10** respectively (**Scheme 2**). The assignment of the structure of the synthesis compounds were based on analytical and spectroscopic data. For example IR spectrum of **8** exhibit absorption band at 1604 cm^{-1} and 1654 cm^{-1} due to -C=N and CO groups. 1H NMR of **8** exhibits signal at δ 8.90 ppm for =CH proton and D_2O-exchangeable signal at δ 4.31 and 12.03 ppm assigned to the 2NH protons. The mass spectrum of compound **8** showed the molecular ion peak at *m/z* 471 corresponding to the molecular formula $C_{25}H_{19}BrN_4O$.

Reaction 1*H*-indole-3-carboxaldehyde **4** with cyanoacetohydrazide in absolute ethanol [22] to form the *N*'-[1*H*-indol-3-ylmethylene]-2-cyanoacetohydrazide derivative **11**. The assignment of the structure of compound

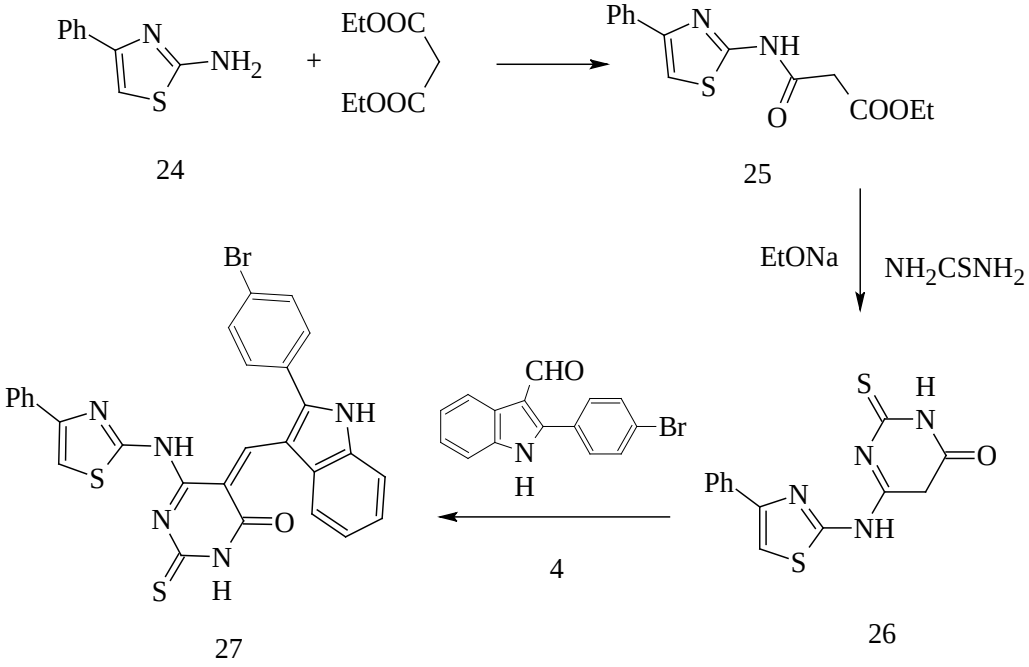


Scheme 4. Synthesis of compounds **18-23**.

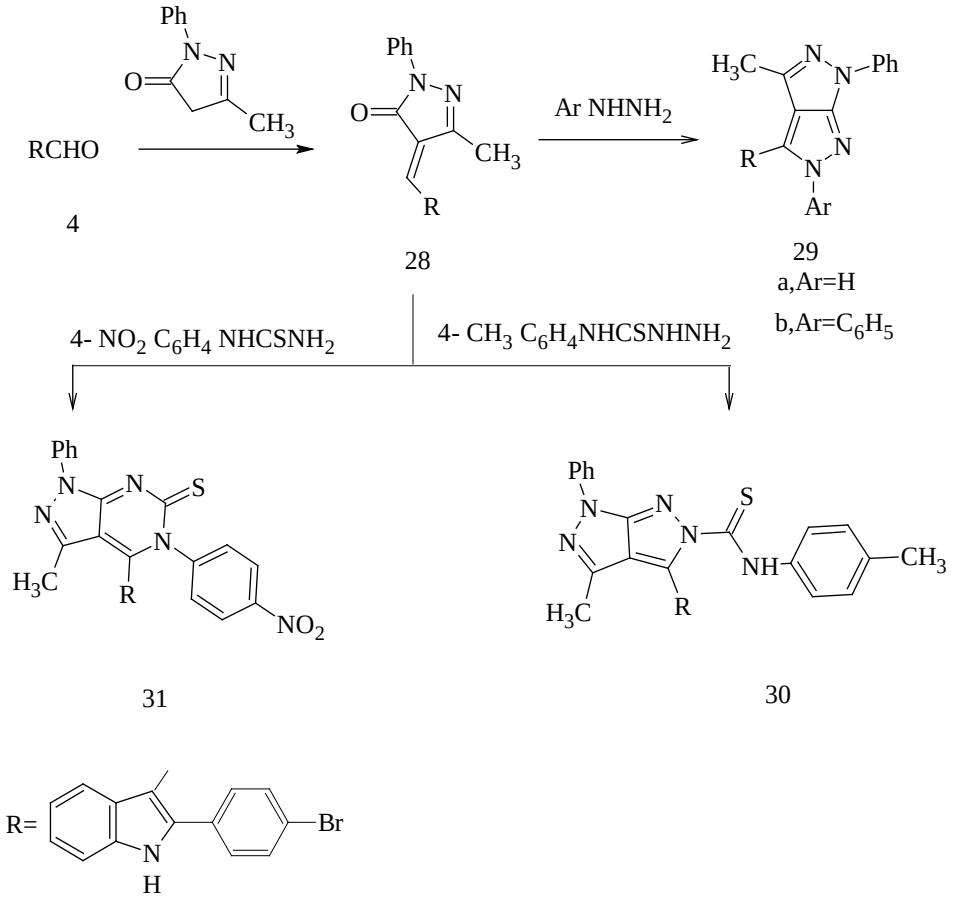
11 was based on analytical and spectroscopic data. Thus, the 1H NMR showed a singlet at δ 4.33 for the CH_2 group, a singlet at δ 8.33ppm for the =CH proton and D_2O-exchangeable single at δ 11.33, 11.93 ppm for the two NH protons. ^{13}C NMR spectrum of **11** displayed signals at δ 24.39, 116.19, 157.73 and 163.58 ppm for CH_2, CN, C=N and CO respectively. Further structure elucidation of compound **11** was obtained through the study of its reactivity towards chemical reagents. Thus, the reaction of **11** with 4-methylbenzene diazonium chloride [23] gave the hydrazone derivatives **12** (**Scheme 3**). The structures of the compound **12** were determined from spectroscopic and elemental analytical data (see Experimental section).

Knoevengel condensation of the 2-cyanoacetohydrazide derivatives **11** with aromatic aldehydes namely 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde and *p*-nitrobenzaldehyde [24] afforded benzylidene derivatives **13a**, **b** (**Scheme 3**). The IR spectrum of compound **13a**, taken as a typical example of the series prepared, revealed absorption bands at 1686 cm^{-1}, 2204 cm^{-1}, 3335 cm^{-1} and 3126 cm^{-1} corresponding to carbonyl, nitrile and 2 NH groups, respectively. Where the 1H NMR spectra showed the absence of the active methylene proton and showed signals at δ 9.21 ppm for N=CH proton and D_2O-exchangeable signal at δ 11.73 and 12.04 assigned to the 2NH protons. Its mass spectrum showed a molecular ion peak at *m/z* 611 corresponding to the molecular formula $C_{34}H_{23}BrN_6O$.

Cyclocondensation of 2-cyanoacetohydrazide derivatives **11** with salicyaldehyde in dioxane in the presence of



Scheme 5. Synthesis of compounds **25-27**.



Scheme 6. Synthesis of compounds **28-31**.

a catalytic amount of piperidine afforded 2-imino-2*H*-chromene-3-carbohydrazide **14**. The plausible mechanism for the formation of compound **14** may be attributed to the initial Knoevenagel condensation of the active methylene nitrile of **11** with carbonyl group of salicyaldehyde followed by an intramolecular 1,6-dipolar cyclization via the addition of the phenolic OH group to the cyano function to afford the target compounds [25] (**Figure 1**). 1H NMR spectrum of **14** showed three D_2O-exchangeable signal at δ 11.44, δ 11.56 and δ 12.14 ppm due to three NH protons. Its mass spectrum showed a molecular ion peak at *m/z* 485 corresponding to the molecular formula $C_{25}H_{17}BrN_4O_2$.

The reaction of **11** with ethyl cyanoacetate and elemental sulfur in the presence of triethylamine gave the thiophene derivatives [26] **15**. The structure of compound **15** was confirmed by its infrared spectrum which indicated the absence of CN absorption band and contain the characteristic absorption bands for NH and CO functional groups. On the other hand the reaction of **11** with elemental sulfur and phenylisothiocyanate [27] gave the thiazole derivative **16**. Compounds **15** and **16** were obtained according to the proposed following mechanism (**Figure 2**). The structure of compounds **15** and **16** were elucidated on the basis of elemental analysis and spectral data. The IR spectrum of thiazoline **16** revealed the absence of CN absorption band and the presence of new absorption bands at 3395, 3269 cm^{-1} assignable to NH_2 group and band at 1237 cm^{-1} due to C=S group. The ^{13}C NMR data showed signals at δ 183.91, δ 161.36, δ 153 and δ 147.39 ppm to CS, CO, C-NH_2 and C=N. Cyclization of thiazoline **16** with acetic anhydride afforded 1,3-thiazolo[4,5-d]pyrimidin-7(6H)-one derivative **17** (**Scheme 3**).

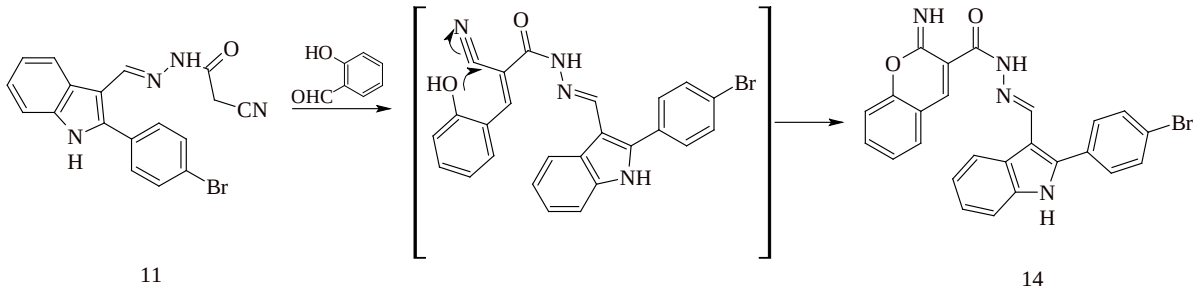


Figure 1. Proposed mechanism of formation of compound **14**.

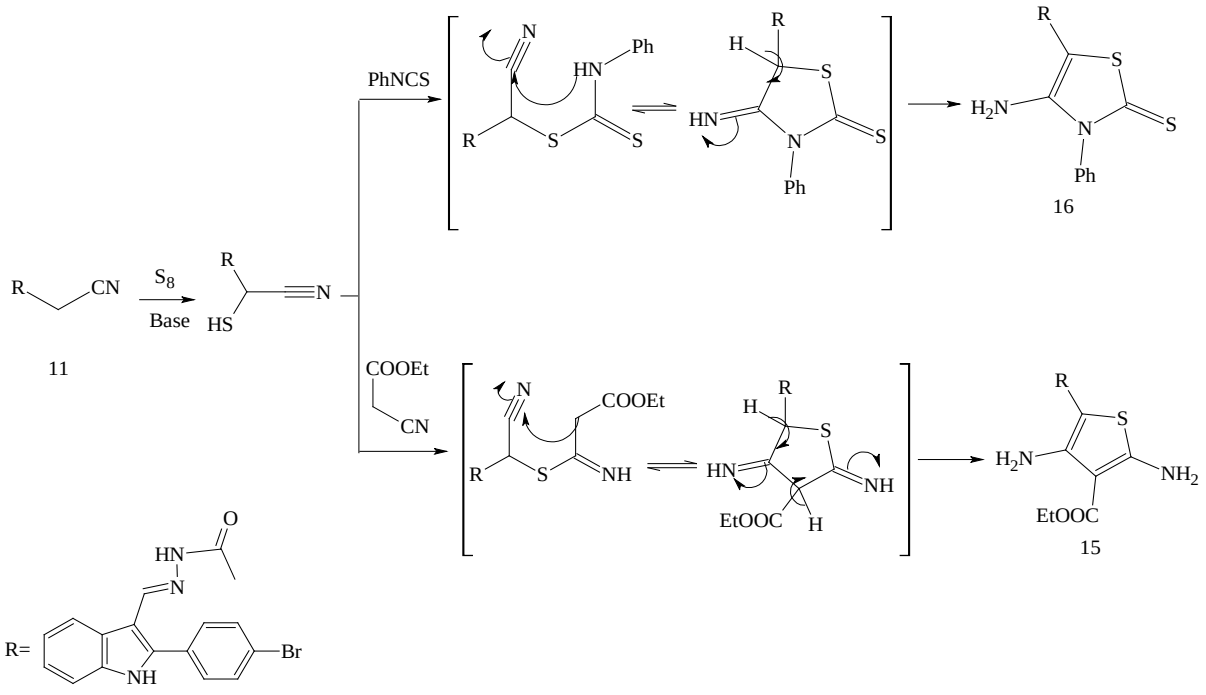


Figure 2. Proposed mechanism of formation of compounds **15** and **16**.

N-[1H-indol-3-ylmethylene]-1,3-thiazol-2-amine **18** was synthesized by the one-pot three compounds. Thus, condensation of phenacyl bromide, 1*H*-indole-3-carboxaldehyde **4** and thiourea [28] under conventional heating in absolute ethanol using catalytic amount of acetic acid. The 1H NMR spectra of compound **18** showed the absence of the aldehyde proton, moreover D_2O-exchangeable signal at δ 12.43 ppm due to the NH proton and signal at δ 6.85 ppm for =CH proton. Condensation of 1*H*-indole-3-carboxaldehyde **4** with 3-acetyl-2*H*-chromen-2-one [29] afforded 3-[3-(1*H*-indol-3-yl)prop-2-enoyl]-2*H*-chromen-2-one **19** (**Scheme 4**).

Condensation of **4** with cyanoacetamide, ethyl cyanoacetate and 1*H*-benzimidazol-2-yl-acetonitrile [30] afforded 3-(1*H*-indol-3-yl)-2-cyanoprop-2-enamide, ethyl 3-(1*H*-indol-3-yl)-2-cyanoprop-2-enoate **20a**,**b** and 2-(1*H*-benzimidazol-2-yl)-3-(1*H*-indol-3-yl)crylonitrile **22** respectively (**Scheme 4**). The structure of the reaction product **20a**,**b** and **22** were ascertained on the basis of its elemental analysis and spectral data. The IR spectrum of compound **20a** exhibited characteristic absorption bands at 3466 cm^{-1}, 3310 cm^{-1}, 2203 cm^{-1} and 1688 cm^{-1} corresponding to NH_2, CN and CO groups respectively. The 1H NMR spectrum of **20a** indicated the presence of one singlet peak at δ 8.22 ppm of the =CH proton and the disappearance of a singlet at δ 9.95 ppm of CHO proton. Cyclization of **20b** by hydrazine hydrate to 5-oxopyrazolidine-4-carbonitrile derivative **21** was achieved by refluxing in ethanol. The 1H NMR spectrum of compound **21** indicated the presence of D_2O-ex- changeable singlet at δ 10.18, δ 11.41 and δ 12.22 ppm which correspond to three NH groups.

On the other hand, the reaction of 1*H*-indole-3-carboxaldehyde **4** with rhodanine-3-acetic acid [31] afforded **[**5-(1*H*-indol-3-ylmethylene)-1,3-thiazolidin-3-yl]acetic acid derivative **23.** The 1H-NMR spectrum of compound **23** indicated the presence of singlet at δ 4.71 ppm of the CH_2 and D_2O-exchangeable singlet at δ 12.60 ppm of the OH proton. Mass spectrum of **23** showed a molecular ion peak *m/z* at 473 corresponding to the molecular formula $C_{20}H_{13}BrN_2O_3S_2$ (**Scheme 4**).

The key substrate ester **25** was synthesized from the reaction of 4-phenyl-2-amino-thiazole **24** and diethyl malonate. Reaction of ester **25** with thiourea in ethanolic sodium ethoxide solution afforded 6-[1,3-thiazol-2-ylamino]-2-thioxo-2,3-dihydropyrimidin-4(5*H*)-one derivative [32] **26**. Treatment of pyrimidinone derivative **26** with 1*H*-indole-3-carboxaldehyde **4** afforded 5-[1*H*-indol-3-ylmethylene]-2-thioxo-2,5-dihydropyrimidin-4(3*H*)-one **27** (**Scheme 5**). The structure of **27** was identified as the reaction product on the basis of its elemental analysis and spectroscopic data. The 1H NMR spectrum of compound **27** indicated the presence of singlet signal at δ 9.96 ppm of the =CH proton and D_2O-exchangeable singlet at δ 12.18, δ 12.22 and δ 12.40 ppm corresponding to the three NH protons.^{13}C NMR spectrum showed signal at δ 185.37 (C=S) and 168.01 (C=O).

Condensation of 1*H*-indole-3-carboxaldehyde **4** with 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one afforded 4-[1*H*-indol-3-ylmethylene]-1*H*-pyrazol-5(4*H*)one **28** (**Scheme 6**). The IR spectrum of **28** exhibited characteristic absorption bands at 3275 cm^{-1} and 1706 cm^{-1} corresponding to NH and CO groups, respectively.^{13}C NMR spectrum showed signal at δ 12.58 (CH_3), δ 153 (C=C) and δ 160 (C=O). Mass spectrum of **28** showed a molecular ion peak *m/z* at 456 corresponding to the molecular formula $C_{25}H_{18}BrN_3O$.

Compound **28** was used as key intermediates in the synthesis of novel pyrazolo[3,4-***c***]pyrazolone and pyrazole[3.4-d] pyrimidine derivatives via their interaction with different reagents. Thus, the reaction of **28** with hydrazine hydrate, phenyl hydrazine and *N*-(4-methylphenyl)thiosemicarbazide by cyclocondensation reaction [33] afforded 3-(4-methyl-pyrazolo[3,4-*c*]pyrazol-3-yl)-1*H*-indole derivatives **29a**,**b** and pyrazolo[3,4-*c*]-pyrazole-2(6*H*)-carbothioamide **30** respectively (**Scheme 6**). The structure of the newly synthesis compounds were based on their correct elemental analysis and spectral data. 1H NMR spectrum of **30** exhibited a singlet signal at δ 2.28 ppm due to CH_3 protons of tolyl moiety. Its mass spectrum, the compound displayed the molecular ion peak at *m/z* 617 corresponding to the molecular formula $C_{33}H_{25}BrN_6S$. Alternatively, treatment of the compound **28** with *N*-(4-nitrophenyl)thiourea [34] afforded pyrazolo[3,4-*d*]pyrimidine-6-thione derivatives **31**. The structures of the compound **31** were determined from spectroscopic and elemental analytical data (see Experimental section).

3.2. Antimicrobial Activity

The newly synthesized compounds **5c**, **7**, **9**, **11**, **13a**, **27**, **30** and **31** were evaluated for their in vitro antibacterial activity against Gram-positive namely *Staphylococcus aureus* RCMB 0100010 (SA) and *Bacillus subtilis* RCMB 010067 (BS) and Gram-negative *Pseudomonas aeuroginosa* RCMB 010043 (PA) and *Escherichia coli* RCMB 010052 (EC). They were also evaluated for their in vitro antifungal activity against *Aspergillus fumigatus* RCMB 02568 *(*AF) and *Candida albicans* RCMB 05036 (CA). Ampicillin was the standard used for the evaluation of antibacterial activity against gram positive bacteria and Gentamicin was used as a standard in assessing the activity of the tested compounds against gram negative bacteria, while Amphotericin B was taken as

a reference for the antifungal effect. The inhibitory effects of the synthetic compounds against these organisms are given in **Table 2**, **Figure 3** and **Figure 4**.

In general, most of the tested compounds revealed better activity against the Gram-positive rather than the Gram-negative bacteria. All test compounds were found to be inactive against *Pseudomonas aeuroginosa* RCMB 010043 (PA). It was shown (**Figure 3**) that the majority of the compounds studied possessed significant antibacterial activity towards *Staphylococcus aureus* RCMB 0100010 (SA), *Bacillus subtilis* RCMB 010067 (BS) and *Escherichia coli* RCMB 010052 (EC). The highest activities were observed for compounds **9** and **30**, followed by **11**, **13a** and **31**.Compounds **5c**, **7** and **27** showed the least antibacterial activity.

It was shown (**Figure 4**) that the compounds **5c**, **11**, **31** strong antifunger activity against *Aspergillus fumigates* RCMB 02568 (AF) and *Candida albicans* RCMB 05036 (CA) comparable to *Amphotericin B*. The com-

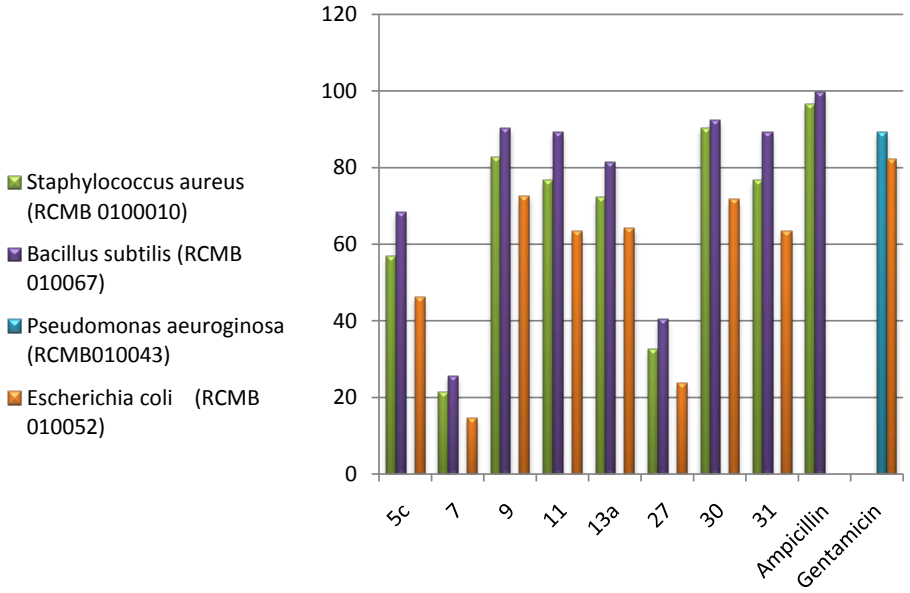


Figure 3. Graphical representation of the antibacterial activity of tested compounds compared to Ampicillin and Gentamicin.

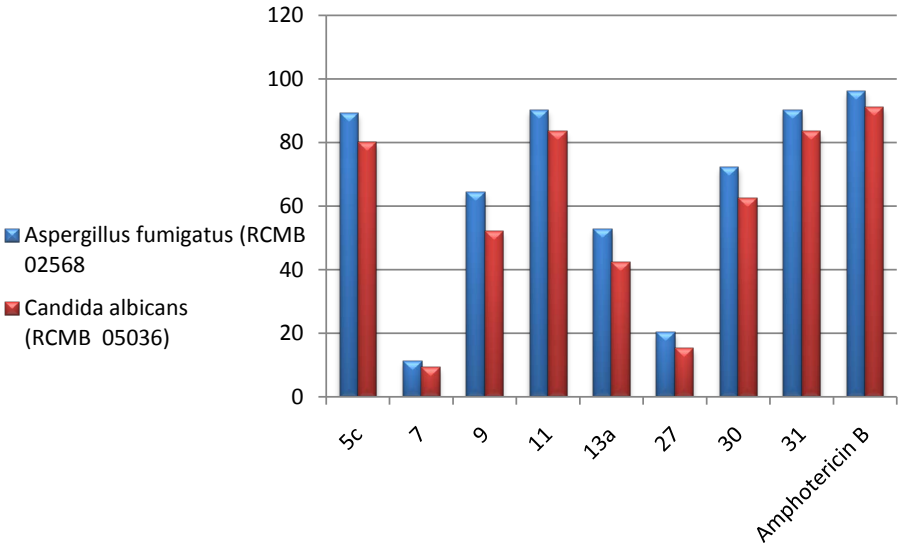


Figure 4. Graphical representation of the antifungal activity of tested compounds compared to Amphotericin B.

pounds **9**, **13a** and **30** showed moderate activities against *Aspergillus fumigates* RCMB 02568 (AF) and *Candida albicans* RCMB 05036 (CA) comparable to *Amphotericin B*. While the compounds **7** and **27** weak antifungal activity against *Aspergillus fumigates* RCMB 02568 (AF) and *Candida albicans* RCMB 05036 (CA) comparable to A*mphotericin B*.

The minimum inhibitory concentration (MIC) was considered to be the lowest concentration of the tested compound which inhibits growth of the microorganisms. The initial screening of the tested compounds showed promising activity of the compounds **5c**, **9**, **30** and **31** which encouraged the determination of their minimum inhibitory concentration (MIC) (**Table 3**).

The best results were demonstrated by compounds **9**, **30** and **31** as antibacteria, it possessed double the activity of the standard, Ampicillin against *Bacillus subtilis* RCMB 010067 (BS) 1.95 and 3.9 µg/ml respectively. Moderate activity against *Staphylococcus aureus* RCMB 0100010 (SA) and *Escherichia coli* RCMB 010052 (EC) were also demonstrated by compounds **9** and **30**. On other hand moderate activity against *Aspergillus fumigatus* RCMB 02568 *(*AF) and *Candida albicans* RCMB 05036 (CA) were also demonstrated by compounds **5c** and **31**.

Table 2. Antimicrobial evaluation of the some synthesized compounds.

Comp. No.	Inhibition % ± standard deviation					
	Gram positive bacteria		Ggram negative e bacteria		Fungal	
	SA	BS	PA	ES	AF	CA
5c	56.85 ± 0.58	68.32 ± 1.2	NA	46.32 ± 0.58	89.25 ± 0.72	80.23 ± 1.2
7	21.25 ± 0.58	25.63 ± 0.28	NA	14.63 ± 0.2	11.22 ± 0.28	9.32 ± 0.72
9	82.63 ± 0.75	90.42 ± 0.28	NA	72.46 ± 0.28	64.35 ± 0.58	52.14 ± 0.63
11	76.8 ± 0.58	89.4 ± 0.63	NA	63.5 ± 0.72	90.3 ± 0.58	83.6 ± 0.28
13a	72.14 ± 0.58	81.32 ± 0.63	NA	64.21 ± 0.63	52.63 ± 0.58	42.18 ± 1.2
27	32.6 ± 0.63	40.4 ± 0.85	NA	23.6 ± 1.2	20.3 ± 1.2	15.4 ± 0.58
30	90.3 ± 1.2	92.4 ± 0.72	NA	71.6 ± 0.93	72.4 ± 0.58	62.5 ± 0.28
31	76.8 ± 0.58	89.4 ± 0.63	NA	63.5 ± 0.72	90.3 ± 0.58	83.6 ± 0.28
Ampicillin	96.52 ± 0.2	99.65 ± 0.3				
Gentamicin			89.23 ± 0.1	82.14 ± 0.3		
Amphotericin B					96.25 ± 0.1	91.29 ± 0.1

(SA): *Staphylococcus aureus* RCMB 0100010, (BS): *Bacillus subtilis* RCMB 010 067 (BS), (PA): *Pseudomonas aeuroginosa* RCMB 010043, (EC): *Escherichia coli* RCMB 010052, (AF): *Aspergillus fumigatus* RCMB02568 and (CA): *Candida albicans* RCMB 05036.

Table 3. Minimum inhibitory concentration of compounds **5c**, **9**, **29** and **31**.

Comp. No.	Minimum inhibitory concentration (µg/ml)					
	Gram positive bacteria		Gram negative e bacteria		Fungi	
	SA	BS	PA	EC	AF	CA
5c	31.25	15.63	NA	62.5	3.9	3.9
9	3.9	1.95	NA	7.81	15.63	31.25
30	1.95	1.95	NA	7.81	7.81	15.63
31	7.81	1.95	NA	15.63	1.95	3.9
Ampicillin	0.98	3.9				
Gentamicin			1.95	3.9		
Amphotericin B					0.98	1.95

4. Conclusion

In the present work, we synthesized novel series of 3-substituted indole by reaction of indole-3-carboxaldehyde derivative with different reagents. Screening for some selected compounds was carried for their potential antibacterial, antifungal activity. Most of the tested compounds revealed better activity against the Gram-positive rather than the Gram negative bacteria. All test compounds were found to be inactive against *Pseudomonas aeuroginosa*. Compounds **9**, **30** and **31** exhibited excellent activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* compared with the standards drugs, while compounds **5c**, **11** and **31** have strong antifunger activity against *Aspergillus fumigatus* and *Candida albicans* comparable to *Amphotericin B*.

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