Synthesis and Antiviral Activity of New Indole-Based Heterocycles

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New 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine and 1,3-thiazole derivatives incorporating indole nucleus were prepared using 3-acetylindole as precursor and evaluated for their antiviral activity against herpes simplex type 1 (HSV-1).

Key words 3-aetylindole; 1,3-thiazole; hydrazonoyl halide; antiviral activity; herpes simplex type 1

Indole, the potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties such as antiviral agents which inhibits of Herpes Simplex Virus replication,[1—3] Fungicidal,[4] anti-inflammatory,[5] anticonvulsant,[6] and antibacterial.[7] Other compounds derived from 3-acetylindoles used in the treatment of gastrointestinal,[8] antiproliferative agent,[9,10] potential antiviral agents,[11] cardiovascular and central nervous system (CNS) disorders,[12] and also used as Herpes simplex type 1 (HIV-1) integrase inhibitors.[13] Encouraged by these observations and in continuation of our previous work in the synthesis of biologically active heterocycles,[14—17] we synthesized newer heterocyclic indole derivatives with the hope to get better antiviral agents.

Results and Discussion

Treatment of 5-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide **1**[18] with tetrachlorophthalic anhydride in refluxing glacial acetic acid afforded imide **2** in excellent yield. While, the reaction of nucleophile **1** with carbon disulfide resulted in the formation of the potassium salt of hydrazinecarbodithioate **3** in moderate yield (Chart 1).

Treatment of the salt **3** with hydrazine hydrate in aqueous ethanol afforded the corresponding 4-amino-1,2,4-triazole-5-thione **4**, subsequent treatment of **4** with phenacyl bromide in dry ethanol and in the presence of a catalytic amount of triethylamine afforded 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivative **5** in good yield. The reaction of potassium salt **3** with phenacyl bromide or hydrazonoyl chlorides **7a**, **b** in aqueous ethanol led to the formation of 1-phenyl-*N*-(4-phenyl-2-thioxothiazol-3(2*H*)-yl)-1*H*-pyrazole-3-carboxamides **6** and **8a**, **b**, respectively (Chart 1). The ^{1}H-NMR spectrum of compound **6** contained a new singlet, not present in the spectrum of the starting material, at δ=7.03 ppm, attributed to C<u>H</u> of the 2-thioxothiazole ring, whereas the ^{1}H-NMR spectrum of compound **5** contained a singlet signal at δ=5.25 ppm corresponding to the two protons of –S–CH_2 in the thiadiazine ring.

The target compounds **11**—**14** were obtained by reaction of equimolar quantities of thiosemicarbazide **9**[19] with 4-methoxyphenacyl bromide **10**, hydrazonoyl chlorides **7a**—**c**, chloroacetic acid or chloroacetic acid and 4-flurobenzaldehyde. The alternative synthesis of 5-(4-fluorobenzylidene)-thiazolidin-4-one derivative **14** has been proceeded *via* reac-

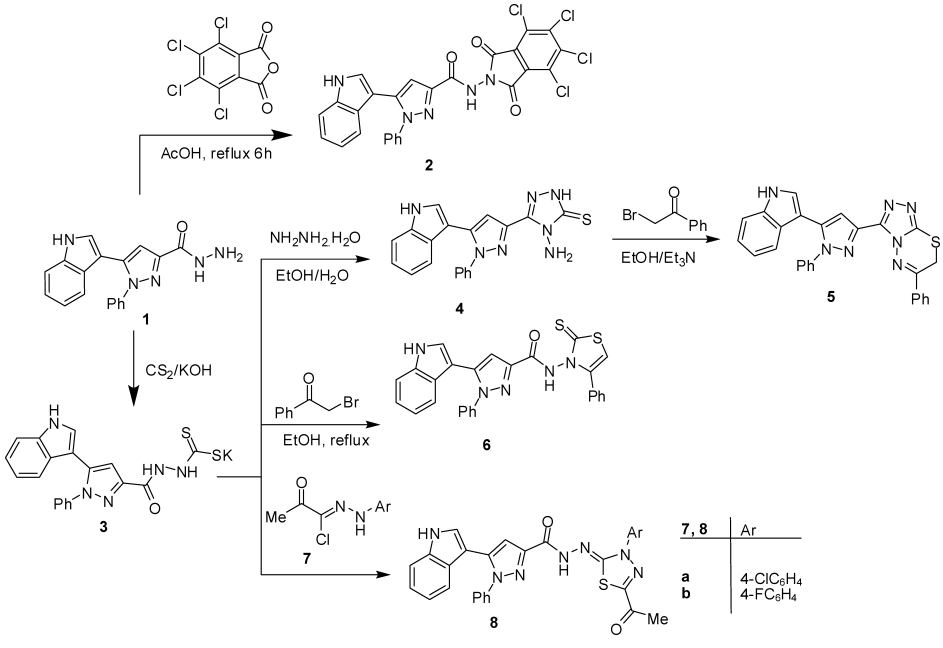

Chart 1

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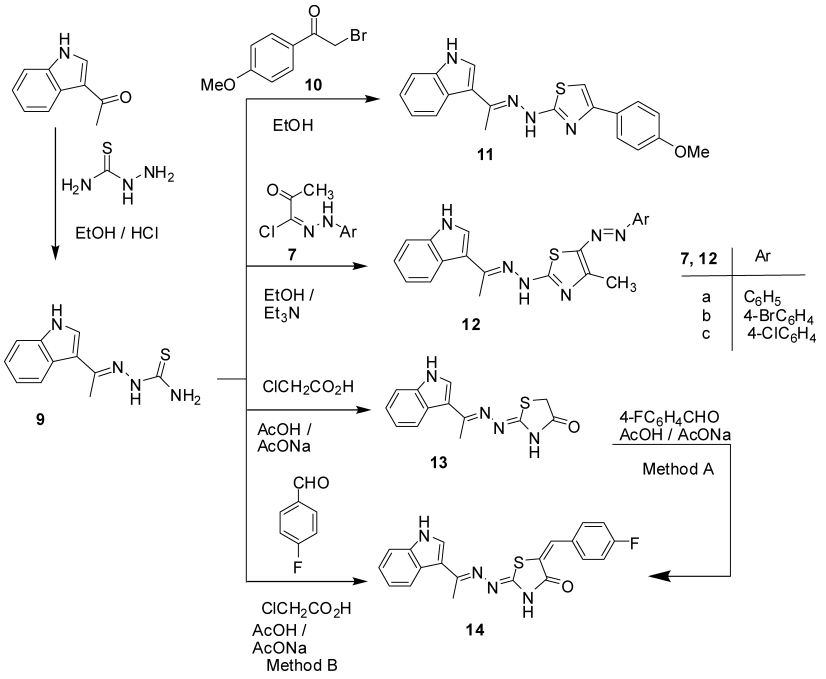

Chart 2

Table 1. Results of *in Vitro* Anti-herpes Simplex-1 Virus (HSV-1) and Cytotoxicity

Compound	% Reduction[a)]	MAC[b)]	CD_{50}[c)]
2	45	0.1	0.05
4	None	0.1	0.02
5	35	0.1	0.01
6	None	0.1	0.03
8a	None	0.1	0.03
8b	None	0.1	0.03
11	28	0.1	0.04
12a	17	0.1	0.03
12b	27	0.1	0.04
12c	62	0.1	0.18
13	None	0.1	0.03
14	37	0.1	0.05
Aphidicolin[d)]	100	0.005	0.2

a) Percent (%) reduction in the number of viral plaques. *b*) Minimum antiviral concentration (in mg/ml). *c*) Cytotoxicity (compound concentration caused 50% loss of the monolayer present around the viral plaques) (in mg/ml). *d*) Positive antiviral control.

tion of thiazolidin-4-one **13** with 4-flurobenzaldehyde in glacial acetic acid and presence of excess anhydrous sodium acetate (Chart 2).

The ^{1}H-NMR spectra data were also consistent with the assigned structures; thiazole CH proton of **11** was observed as a broad singlet at about δ 6.99 ppm, thiazolidinone CH_2 protons of **13** appeared at δ 3.93 ppm and all the other aromatic and aliphatic protons were observed at the expected regions.

***In-Vitro* Anti-herpes Simplex-1 Virus (HSV-1) and Cytotoxicity Assays** All new compounds were tested for their possible antiviral activity against herpes simplex type 1 (HSV-1) grown on Vero African green monkey kidney cells.[20—22)] Aphidicolin was used as a positive control.

From the results obtained in Table 1, we can conclude that, compounds 1,2,4-triazole-5(4*H*)-thione **4**, 2-thioxothiazole **6**, thiazoles **8a**, **b** and thiazolidin-4-one **13** showed no antiviral activity. But 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine **5**; thiazoles **11**; **12a**, **b** and 5-(4-fluorobenzylidene)thiazolidin-4-one **14** showed a weak to moderate activity in reducing the number of plaques at the same concentration (0.1 mg/ml). Compounds **12c** and **2** were the best among the tested compounds; they reduced the number of viral plaques of herpes simplex type-1 (HSV-1) by 62% and 45% respectively with respect to Aphidicolin.

Experimental

Chemistry All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accord with the calculated values) were obtained from the microanalytical unit, National Research Centre, Dokki, Giza, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H-NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift (δ) values are given in parts per million. The mass spectra were determined using a Varian MAT CH-5 spectrometer (70 eV). 5-(1*H*-Indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide **1**[18]; 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazinecarbothioamide **9**[19] and hydrazonoyl chlorides **7**[23] were prepared according to the reported procedures.

5-(1*H*-Indol-3-yl)-1-phenyl-*N*-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)-1*H*-pyrazole-3-carboxamide (2)[24] Yield 87%; mp >300 °C; IR (KBr) ν_{max}/cm^{-1} 3403, 3138 (2NH), 1781, 1736, 1656 (3C=O); ^{1}H-NMR (DMSO-d_6) δ: 5.85 (s, 1H, CH-pyrazole), 7.45—8.61 (m, 9H, Ar-H), 12.31, 13.67 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 585 (M^+, 2), 59 (100).

Potassium 2-[5-(1*H*-Indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbonyl]hydrazinecarbodithioate (3)[25] Yield 76%; IR (KBr) ν'=3380—3028 (3NH), 1653 (C=O) cm^{-1}.

3-[5-(1*H*-Indol-3-yl)-1-phenyl-1*H*-pyrazol-3-yl]-4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione (4)[25] Yield 38%; mp 216—218 °C; IR (KBr) ν_{max}/cm^{-1}: 3393—3291 (NH_2, 2NH), 1496 (C=S); ^{1}H-NMR (DMSO-d_6) δ: 6.02 (s, 2H, NH_2, D_2O-exchangeable), 7.03 (s, 1H, CH-pyrazole), 7.21—7.48 (m, 9H, Ar-H), 11.57, 14.00 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 373 (M^+, 9), 359 (100).

3-[5-(1*H*-Indol-3-yl)-1-phenyl-1*H*-pyrazol-3-yl]-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (5)[25] Yield 59%; mp 196—198 °C; ^{1}H-NMR (DMSO-d_6) δ: 6.02 (s, 2H, NH_2, D_2O-exchangeable), 5.25(s, 2H, S-C<u>H</u>$_2$), 7.03 (s, 1H, CH-pyrazole), 7.23—8.15 (m, 14H, Ar-H), 11.57, (s, H,

NH, D_2O-exchangeable); MS *m*/*z* (%): 493 (M^+, 1.7), 105 (100).

5-(1*H*-Indol-3-yl)-1-phenyl-*N*-(4-phenyl-2-thioxothiazol-3(2*H*)-yl)-1*H*-pyrazole-3-carboxamide (6)[25] Yield 48%; mp 194—195 °C; ^{1}H-NMR (DMSO-d_6) δ: 5.25 (s, H, pyrazole-CH), 7.03 (s, H, CH, thiazole-CH), 7.24—8.14 (m, 14H, Ar-H), 11.56 (s, H, NH, D_2O-exchangeable); MS *m*/*z* (%): 473 (M^+, 21), 359 (100).

***N*′-[5-Acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3*H*)-ylidene]-5-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (8a)**[25] Yield 50%; mp 257—258 °C; IR (KBr) ν_{max}/cm^{-1} 3284 (NH), 1666, 1602 (2C=O); ^{1}H-NMR (DMSO-d_6) δ: 2.56 (s, 3H, CH_3), 7.03 (s, 1H, CH-pyrazole), 7.16—8.08 (m, 13H, Ar-H), 11.30, 11.49 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 554 (M^+, 0.17), 91 (100).

***N*′-[5-Acetyl-3-(4-fluorophenyl)-1,3,4-thiadiazol-2(3*H*)-ylidene]-5-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (8b)**[25] Yield 43%; mp 273—274 °C; IR (KBr) ν_{max}/cm^{-1} 3387 (NH), 1679, 1605 (2C=O); ^{1}H-NMR (DMSO-d_6) δ: 2.54 (s, 3H, CH_3), 7.01 (s, 1H, CH-pyrazole), 7.17—8.01 (m, 13H, Ar-H), 11.29, 11.56 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 573 (M^+, 1.2), 91 (100).

2-{2-[1-(1*H*-Indol-3-yl)ethylidene]hydrazinyl}-4-(4-methoxyphenyl)thiazole (11)[26] Yield 62%; mp 241—242 °C; IR (KBr) ν_{max}/cm^{-1} 3388, 3343 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 4.44 (s, 3H, OCH_3), 6.99 (s, 1H, CH-thiazole), 7.17—8.12 (m, 8H, Ar-H), 8.46, 11.52 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 362 (M^+, 100).

2-{2-[1-(1*H*-Indol-3-yl)ethylidene]hydrazinyl}-4-methyl-5-(phenyldiazenyl)thiazole (12a)[27] Yield 44%; mp 240—242 °C; IR (KBr) ν_{max}/cm^{-1} 3424, 3239 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.50 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.59—8.52 (m, 9H, Ar-H), 10.54, 11.79 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 374 (M^+, 100).

2-{2-[1-(1*H*-Indol-3-yl)ethylidene]hydrazinyl}-5-[(4-bromophenyl)diazenyl]-4-methylthiazole (12b)[27] Yield 53%; mp 260—261 °C; IR (KBr) ν_{max}/cm^{-1} 3426, 3236 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.50 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.89—8.32 (m, 8H, Ar-H), 10.54, 11.79 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 454, 453 (M^+, 42, 41).

2-{2-[1-(1*H*-Indol-3-yl)ethylidene]hydrazinyl}-5-((4-chlorophenyl)diazenyl)-4-methylthiazole (12c)[27] Yield 56%; mp 258—259 °C; IR (KBr) ν_{max}/cm^{-1} 3417, 3230 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.87—8.30 (m, 8H, Ar-H), 10.35, 11.71 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 408 (M^+, 62), 91(100).

2-{[1-(1*H*-Indol-3-yl)ethylidene]hydrazono}thiazolidin-4-one (13)[16] Yield 67%; mp 280—282 °C; IR (KBr) ν_{max}/cm^{-1} 3377, 3315 (2NH), 1751 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 2.54 (s, 3H, CH_3), 3.93 (s, 2H, thiazilidinone-CH_2), 7.20—8.49 (m, 4H, Ar-H), 11.57, 11.93 (2s, 2H, 2NH, D_2O-exchangeable); MS *m*/*z* (%): 272 (M^+, 27), 98 (100).

2-{[1-(1*H*-Indol-3-yl)ethylidene]hydrazono}-5-(4-fluorobenzylidene)thiazolidin-4-one (14). Method A; Method B[16] Yield A: 57%; B: 63%; mp 298—299 °C; IR (KBr) ν_{max}/cm^{-1} 3415, 3040 (2NH), 1713 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 3.90 (s, 1H, NH, D_2O-exchangeable), 7.20—7.85 (m, 8H, Ar-H), 8.42 (s, 1H, CH=N–), 12.00 (s, H, NH, D_2O-exchangeable); MS *m*/*z* (%): 378 (M^+, 0.7), 236 (100).

Antiviral and Cytotoxicity Assays The antiviral activity was determined applying our reported method.[28]

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