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Synthesis of Novel Hydrazonoyl Chlorides as Useful Precursor in Synthesis of New Thiadiazoles, Selenadiazoles and Triazolotriazines

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Abstract

The reaction of hydrazino of pyrazolopyrimidine derivatives with *N*-phenyl-*C*-acetylmethanohydrazonoyl chloride afforded the corresponding hydrazonoyl chlorides. The treatment of the obtained hydrazonoyl chlorides with both of potassium thiocyanate or potassium selenocyanate gave the corresponding 1,3,4-thiadiazol-2(3*H*)-imine, or the selenadiazol analog, respectively. Reaction of the hydrazonoyl chloride derivatives with 6-arylmethylene-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4*H*)-one derivatives afforded the corresponding triazolotriazine derivatives. The chemical structures of the isolated compounds were elucidated by their spectral and elemental analyses.

Keywords: Hydrazine derivatives; *N*-phenyl-*C*-acetylmethanohydrazonoyl chloride; potassium thiocyanate; thiadiazoles; selenadiazoles; triazolotriazines.

1. Introduction

Hydrazonoyl halides represent a very interesting skeleton of the organic structures, due to their pharmaceutical properties and their utility in the preparation of novel heterocyclic, nitrogen, oxygen, sulfur and selenium compounds. Plenty of efforts on describing the hydrazonyl chlorides in details of the varied use of these compounds, with different groups on carbon and nitrogen atoms, as reagents and intermediates for the synthesis of fused heterocycle compounds such as pyrazolo[3,4-d]pyrimidine derivatives have been reported by our research group [1-11] or other research groups[12-19].

The involvement of the fused heterocycles such as pyrazolo[3,4-*d*]pyrimidine and its derivatives in organic compounds acting against various ailments is not a mere coincidence. On the chemical structural analysis, the pyrazolo[3,4-*d*]pyrimidine derivatives delivers an insight to the potential therapeutic activities due to their biological activity and crucial role in numerous diseases as purine analogues [20, 21]. The pyrazolopyrimidines have been tailored to show multiple pharmacological activities and to name a few they can act as antitumor agents[22], mammalian target of rapamycin (mTOR) pathway [23], anti-obesity agents [24], antibacterial agents [25], anti-inflammatory agents [24], anti-viral agents [25], dipeptidyl peptidase-4 (DPP-IV) [26], central nervous system (CNS) agents [24], inhibitors of protein kinase [27], and they are known to act as CRF1 antagonist agents [28]. The pyrazolopyrimidine core has been found as a principal skeleton in plenty of drugs which approved for various ailments such as zaleplon, repotrectinib, indiplon, dinaciclib, lorediplon, ocinaplon [27, 29, 30].

In addition, compounds containing 1,2,4-triazolo[1,5-*c*]pyrimidine moiety were reported to exhibit a remarkable adenosine receptor affinity [31]. In the light of these facts and in continuation of our ongoing research work on the chemistry of hydrazonoyl halides, we report herein the syntheses of novel 2-(2-(1,3-diaryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazono)-*N*-phenylpropane-hydrazonoylchlorides using pyrazolo[3,4-*d*]pyrimidine derivatives and their utility in synthesis of new thiadiazoles, selenadiazoles and triazolotriazines.

1. Experimental

Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO–d_6 as solvent

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on Varian Gemini NMR spectrometer at 300 MHz and 75 MHz, respectively, using TMS as internal standard. Chemical shifts were reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro analytical center, Cairo University.

Synthesis of 2-(2-(1,3-disubstituted-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)-N-phenylpropane-hydrazonoyl chlorides (**4** and **5**):

A mixture of hydrazino of pyrazolopyrimidine derivatives **1** or **2** (5.0 mmol) and *N*-phenyl-*C*-acetylmethanohydrazonoyl chloride **3** (1 gm, 5.0 mmol) was refluxed in absolute ethanol (30 mL) for 6 h in the presence of few drops of acetic acid. The reaction mixture was cooled; the precipitate that separated was collected and crystallized from DMF to give the corresponding hydrazonoyl chlorides **4** or **5**.

2-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)-N-phenylpropanehydrazonoyl chloride (**4**): Yellow crystals; mp 202-204 ºC; yield (79%); IR (KBr): ν = 3349, 3330 (2NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 7.28-8.42 (m, 16H, ArH), 10.12 (s, 1H, NH) and 11.31 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.8, 101.3, 113.7, 120.6, 122.1, 124.6, 127.0, 127.7, 128.0, 128.6, 128.9, 129.0, 129.1, 131.9, 138.1, 143.6, 147.1, 148.1, 150.6, 154.1. MS, *m/z* (%): 481 (M^+, 11.8), 77 (100). *Anal.* Calcd. for $C_{26}H_{21}ClN_8$ (481.0): C, 64.93; H, 4.40; N, 23.30, found: C, 64.82; H, 4.54; N, 23.26.

2-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)-N-phenyl-propanehydrazonoyl chloride (**5**): Yellow crystals; mp 212-214 ºC; yield (70 %); IR (KBr): ν = 3347, 3329 (2NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.34 (m, 6H, $(CH_3)_2CH$), 2.39 (s, 3H, CH_3), 3.33-3.39 (m, 1H, $CH(CH_3)_2$), 6.89-8.42 (m, 10H, ArH), 10.07 (s, 1H, NH) and 11.40 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.2, 20.6, 28.2, 57.6, 88.5, 102.8, 113.7, 120.2, 120.6, 120.7, 120.9, 124.8, 125.0, 129.1, 143.5, 144.4, 146.0, 148.8, 168.2. MS, *m/z* (%): 492 (M^+, 17.3), 77 (100). *Anal.* Calcd. for $C_{23}H_{22}ClN_9O_2$(491.9): C, 56.16; H, 4.51; N, 25.63, found: C, 56.08; H, 4.47; N, 25.57.

Synthesis of 5-(1-(2-(1,3-disubstituted-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-imine and its selenadiazole analogue (**6** and **7**):

A solution of potassium thiocyanate (0.58 g, 6.0 mmol) or potassium selenocyanate (0.86 g, 6.0 mmol) in water (5 mL) was added to a warm solution of each of appropriate hydrazonoyl chloride **4** or **5** (6.0 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 15 min, and cooled. The crude products were collected and crystallized from DMF. The compounds prepared together with their physical properties are listed below:

5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-imine (**6a**): Yellow crystals; mp 258-260 ºC; yield (68 %); IR (KBr): ν = 3340, 3326 (2NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3), 7.30-8.42 (m, 16H, ArH), 9.89 (s, 1H, imine-NH) and 10.31 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 100.3, 118.7, 120.4, 122.7, 125.6, 127.1, 127.8, 128.5, 128.9, 129.1, 132.7, 138.1, 139.0, 143.5, 144.9, 148.4, 149.2, 151.6, 158.7, 160.1. MS, *m/z* (%): 504 (M^+, 100). *Anal.* Calcd. for $C_{27}H_{21}N_9S$ (503.6): C, 64.40; H, 4.20; N, 25.03, found: C, 64.29; H, 4.08; N, 25.17.

5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selen-adiazol-2(3H)-imine (**6b**): Yellow crystals; mp 232-234 ºC; yield (70 %); IR (KBr): ν = 3349, 3323 (2NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3), 7.29-8.40 (m, 16H, ArH), 9.87 (s, 1H, imine-NH) and 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7, 100.0, 118.7, 121.0, 122.3, 125.8, 127.5, 128.0, 128.3, 128.7, 129.0, 134.2, 138.5, 140.6, 143.1, 144.4, 148.4, 149.8, 153.6, 159.2, 163.5. MS, *m/z* (%): 550 (M^+, 100). *Anal.* Calcd. for $C_{27}H_{21}N_9Se$ (550.5): C, 58.91; H, 3.85; N, 22.90, found: C, 58.82; H, 3.89; N, 22.85.

5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-imine (**7a**): Yellow crystals; mp 260-262 ºC; yield (73 %); IR (KBr): ν = 3343, 3322 (2NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (d, 6H, $CH(\underline{CH_3})_2$), 2.10 (s, 3H, CH_3), 3.02-3.11 (m, 1H, $\underline{CH}(CH_3)_2$), 7.30-8.49 (m, 10H, ArH), 9.60 (s, 1H, imine-NH) and 10.39 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.0, 21.6, 31.9, 105.3, 117.2, 121.7, 122.1, 123.0, 124.9, 129.8, 136.9, 144.5, 145.6, 145.9, 148.0, 150.7, 153.0, 159.1, 166.6. MS, m/z (%): 514 (M^+, 10.0), 91 (100). Anal. Calcd. for $C_{24}H_{22}N_{10}O_2S$ (514.6): C, 56.02; H, 4.31; N, 27.22, found: C, 55.93; H, 4.36; N, 27.09.

5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-imine (**7b**): Yellow crystals; mp 224-226 ºC; yield (70 %); IR (KBr): ν = 3340, 3320 (2NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30 (d, 6H, $CH(\underline{CH_3})_2$), 2.12 (s, 3H, CH_3), 3.00-3.93 (m, 1H, $\underline{CH}(CH_3)_2$), 7.26-8.41 (m, 10H, ArH), 9.58 (s, 1H, imine-NH) and 10.42 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.1, 21.5, 31.9, 104.9, 117.0, 120.9, 122.3, 122.8, 124.8, 129.9, 137.0, 144.6, 145.6, 145.7, 148.1, 150.5, 152.8, 159.1, 166.6. MS, m/z (%): 561 (M^+, 7.5), 77 (100).

Anal. Calcd. for $C_{24}H_{22}N_{10}O_2Se$ (561.5): C, 51.34; H, 3.95; N, 24.95, found: C, 51.29; H, 3.90; N, 24.88.

Synthesis of N-(5-(1-(2-(1,3-disubstituted-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)benzamide and its selenadiazole analogue (**8** and **9**):

The appropriate imine compound **6** or **7** (6.0 mmol) and benzoyl chloride (0.8 g, 6.0 mmol) were refluxed in pyridine (20 mL) for 30 min. The reaction mixture was left to cool and treated with dilute hydrochloric acid (30 mL). The crude products were collected and crystallized from DMF to give compounds **8** and **9**. The compounds prepared with their physical properties are listed below:

N-(5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)benzamide (**8a**): Orange crystals; mp 270-272 °C; yield (65 %); IR (KBr): ν = 3315 (NH), 1640 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 2.10 (s, 3H, CH_3), 6.88-8.33 (m, 21H, ArH) and 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): *δ* 13.8, 100.9, 113.2, 118.7, 119.5, 120.3, 122.0, 124.5, 125.7, 126.0, 127.3, 128.2, 129.0, 129.4, 129.7, 132.5, 138.6, 143.7, 145.6, 146.0, 149.6, 152.6, 154.3, 163.7, 164.2, 168.9. MS, *m/z* (%): 607 (M^+, 7.0), 105 (100). *Anal.* Calcd. for $C_{34}H_{25}N_9OS$ (607.7): C, 67.20; H, 4.15; N, 20.74, found: C, 67.09; H, 4.06; N, 20.68.

N-(5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-ylidene)benzamide (**8b**): Orange crystals; mp 283-285 °C; yield (69 %); IR (KBr): ν = 3319 (NH), 1645 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 6.82-8.30 (m, 21H, ArH) and 10.27 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.3, 100.7, 112.8, 118.5, 119.9, 120.5, 121.7, 124.5, 125.7, 126.3, 126.9, 128.0, 129.2, 129.4, 130.0, 132.5, 137.9, 142.9, 144.9, 145.7, 149.6, 152.6, 154.1, 163.7, 164.0, 167.6. MS, m/z (%): 666 (M^+, 10.5), 64 (100). Anal. Calcd. for $C_{34}H_{25}N_9OSe$ (654.6): C, 62.39; H, 3.85; N, 19.26, found: C, 62.28; H, 3.78; N, 19.19.

N-(5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-ylidene)benzamide (**9b**): Orange crystals; mp 290-292 °C; yield (69 %); IR (KBr): ν = 3310 (NH), 1643 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33 (d, 6H, CH($\underline{CH_3}$)$_2$), 2.18 (s, 3H, CH_3), 3.03-3.83 (m, 1H, $\underline{CH}(CH_3)_2$), 6.83-8.38 (m, 15H, ArH) and 10.42 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8, 21.6, 31.7, 105.9, 119.5, 120.3, 122.5, 124.5, 126.4, 127.3, 128.2, 129.4, 129.7, 132.5, 138.6, 143.7, 145.6, 146.0, 149.6, 152.6, 154.3, 163.7, 164.2, 168.9. MS, m/z (%): 666 (M^+, 10.5), 64 (100). Anal. Calcd. for $C_{31}H_{26}N_{10}O_3Se$ (665.6): C, 55.94; H, 3.94; N, 21.04, found: C, 55.86; H, 3.88; N, 21.12.

Synthesis of N-(5-(1-(2-(1,3-disubstituted-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)acetamide and its selenadiazole analogue (**10** and **11**):

The appropriate imine compound **6** or **7** (3.0 mmol) was refluxed in acetic anhydride (20 mL) for 30 min and the mixture was cooled, diluted with water and the crude products were collected and crystallized from dimethylformamide to give compounds **10** and **11**. The compounds prepared with their physical constant are listed below:

N-(5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)acetamide (**10a**): Yellow crystals; mp 280-282 °C; yield (73 %); IR (KBr): ν = 3317 (NH), 1673 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 2.19 (s, 3H, C$\underline{H_3}$), 2.43 (s, 3H, C$\underline{H_3}$CO), 7.43-8.38 (m, 16H, ArH) and 11.80 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): *δ* 13.7, 24.1, 100.5, 117.7, 119.0, 121.9, 126.0, 127.3, 128.0, 129.4, 129.7, 130.5, 132.5, 138.0, 143.6, 145.6, 146.1, 149.6, 152.5, 154.3, 163.7, 164.2, 168.9. *Anal.* Calcd. for $C_{29}H_{23}N_9OS$ (545.6): C, 63.84; H, 4.25; N, 23.10, found: C, 63.77; H, 4.29; N, 23.18.

N-(5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-ylidene)acetamide (**10b**): Yellow crystals; mp 258-260 °C; yield (65 %); IR (KBr): ν = 3320 (NH), 1670 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 3H, C$\underline{H_3}$), 2.40 (s, 3H, C$\underline{H_3}$CO), 7.40-8.40 (m, 16H, ArH) and 11.76 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8, 24.0, 100.9, 118.7, 119.5, 122.0, 126.0, 127.3, 128.2, 129.0, 129.4, 129.7, 132.5, 138.6, 143.7, 145.6, 146.0, 149.6, 152.6, 154.3, 163.7, 164.2, 168.9. Anal. Calcd. for $C_{29}H_{23}N_9OSe$ (592.5): C, 58.79; H, 3.91; N, 21.28, found: C, 58.66; H, 3.83; N, 21.22.

N-(5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)acetamide (**11a**): Orange crystals; mp 320-322 °C; yield (63 %); IR (KBr): ν = 3313 (NH), 1678 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (d, 6H, CH($\underline{CH_3}$)$_2$), 2.10 (s, 3H, CH_3), 2.45 (s, 3H, C$\underline{H_3}$CO), 3.06-3.88 (m, 1H, $\underline{CH}(CH_3)_2$), 6.89-8.30 (m, 10H, ArH) and 11.76 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.6, 22.0, 24.1, 32.0, 101.0, 118.0, 119.9, 126.0, 127.3, 128.8, 129.5, 130.5, 132.5, 139.2, 144.2, 145.6, 146.1, 148.3, 153.0, 163.9, 167.5. MS, m/z (%): 556 (M^+, 41.6), 338 (100). Anal. Calcd. for $C_{26}H_{24}N_{10}O_3S$ (556.6): C, 56.11; H, 4.35; N, 25.17, found: C, 56.00; H, 4.26; N, 25.08.

N-(5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-ylidene)acetamide (**11b**): Orange crystals; mp 336-338 °C; yield (70 %); IR (KBr): ν = 3310 (NH), 1676 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.31 (d, 6H, CH($\underline{CH_3}$)$_2$), 2.11

(s, 3H, CH_3), 2.47 (s, 3H, $C\underline{H}_3CO$), 3.03-3.86 (m, 1H, $\underline{CH}(CH_3)_2$), 6.92-8.32 (m, 10H, ArH) and 11.77 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7, 22.2, 23.8, 32.2, 100.5, 118.2, 119.5, 126.1, 127.5, 128.4, 129.3, 130.6, 132.4, 139.0, 144.0, 145.4, 146.0, 148.2, 153.4, 163.9, 167.5. MS, m/z (%): 603 (M^+, 9.2), 64 (100). Anal. Calcd. for $C_{26}H_{24}N_{10}O_3Se$ (603.5): C, 51.75; H, 4.01; N, 23.21, found: C, 51.66; H, 4.12; N, 23.15.

Synthesis of N-(5-(1-(2-(1,3-disubstituted-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)nitrous and its selenadiazole analogue (**12** and **13**):

To a suspension of the appropriate imine compound **6** or **7** (3.0 mmol) in acetic acid (15 mL), a saturated solution of sodium nitrite was added dropwise while stirring in an ice bath. The crude products were collected and crystallized rapidly from acetonitrile to give compounds **12** or **13**. The compounds prepared with their analytical data are listed below:

N-(5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)nitrous amide (**12a**): Red crystals; mp 266-268 °C, yield (78%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3), 7.31-8.40 (m, 16H, ArH) and 10.28 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.5, 100.2, 118.3, 120.1, 122.5, 125.3, 127.0, 127.4, 128.5, 128.6, 129.0, 132.8, 138.6, 139.0, 143.8, 144.4, 148.3, 149.0, 151.8, 158.7, 160.3. Anal. Calcd. for $C_{27}H_{20}N_{10}OS$ (532.6): C, 60.89; H, 3.79; N, 26.30, found: C, 60.72; H, 3.70; N, 26.22.

N-(5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-ylidene)nitrous amide (**12b**): Red crystals; mp 248-250 °C, yield (73%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 3H, CH_3), 7.32-8.43 (m, 16H, ArH) and 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.4, 100.1, 118.4, 120.0, 122.4, 125.6, 126.8, 127.8, 128.2, 128.6, 129.0, 131.5, 138.0, 138.7, 142.8, 143.9, 147.2, 149.1, 151.4, 158.3, 160.0. Anal. Calcd. for $C_{27}H_{20}N_{10}OSe$ (579.5): C, 55.96; H, 3.48; N, 24.17, found: C, 55.88; H, 3.41; N, 24.03.

N-(5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-ylidene)nitrous amide (**13b**): Red crystals; mp 264-266 °C, yield (66%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30 (d, 6H, $CH(\underline{CH_3})_2$), 2.13 (s, 3H, CH_3), 3.10-3.15 (m, 1H, $\underline{CH}(CH_3)_2$), 7.32-8.45 (m, 10H, ArH) and 10.41 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.1, 21.3, 31.6, 100.3, 105.0, 117.1, 121.7, 123.2, 124.7, 129.9, 136.7, 144.3, 145.4, 145.6, 148.1, 150.5, 153.2, 159.0, 166.8. Anal. Calcd. for $C_{24}H_{21}N_{11}O_3Se$ (590.5): C, 48.82; H, 3.58; N, 26.09, found: C, 48.70; H, 3.47; N, 26.00.

Synthesis of 5-(1-(2-(1,3-disubstituted-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-one and its selenadiazole analogue (**14** and **15**):

The appropriate nitrous amide **12** or **13** (1.0 mmol) was boiled in xylene (20 mL) till all bubbles of nitrogen ceased to evolve. The excess solvent was then evaporated, and the solid was crystallized from dimethylformamide to give the products **14** or **15**. The products prepared with their analytical data are listed below:

5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-thia-diazol-2(3H)-one (**14a**): Biege crystals; mp 310-312 °C, yield (78%); IR (KBr): ν = 3318 (NH), 1628 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3), 7.30-8.42 (m, 16H, ArH) and 10.31 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 100.3, 118.7, 120.4, 122.7, 125.6, 127.1, 127.8, 128.5, 128.9, 129.1, 132.7, 138.1, 139.0, 143.5, 144.9, 148.4, 149.2, 151.6, 158.7, 160.1. MS, *m/z* (%): 504 (M^+, 12.9), 327 (100). MS, *m/z* (%): 505 (M^+, 100). Anal. Calcd. for $C_{27}H_{20}N_8OS$ (504.6): C, 64.27; H, 4.00; N, 22.21, found: C, 64.15; H, 4.09; N, 22.11.

5-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selen-adiazol-2(3H)-one (**14b**): Biege crystals; mp 268-270 °C, yield (72%); IR (KBr): ν = 3316 (NH), 1625 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3), 7.29-8.40 (m, 16H, ArH) and 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7, 100.0, 118.7, 121.0, 122.3, 125.8, 127.5, 128.0, 128.3, 128.7, 129.0, 134.2, 138.5, 140.6, 143.1, 144.4, 148.4, 149.8, 153.6, 159.2, 163.5. MS, *m/z* (%): 552 (M^+, 100). *Anal.* Calcd. for $C_{27}H_{20}N_8OSe$ (551.5): C, 58.81; H, 3.66; N, 20.32, found: C, 58.70; H, 3.53; N, 20.39.

5-(1-(2-(3-Isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-3-phenyl-1,3,4-selenadiazol-2(3H)-one (**15b**): Biege crystals; mp 280-282 °C, yield (74%); IR (KBr): ν = 3313 (NH), 1622 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (d, 6H, $CH(\underline{CH_3})_2$), 2.10 (s, 3H, CH_3), 3.02-3.11 (m, 1H, $\underline{CH}(CH_3)_2$), 7.30-8.49 (m, 10H, ArH) and 10.39 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.0, 21.6, 31.9, 100.4, 105.3, 117.2, 121.7, 123.0, 124.9, 129.8, 136.9, 144.5, 145.6, 145.9, 148.0, 150.7, 153.0, 159.1, 166.6. MS, m/z (%): 563 (M^+, 100). Anal. Calcd. for $C_{24}H_{21}N_9O_3Se$ (562.5): C, 51.25; H, 3.76; N, 22.41, found: C, 51.13; H, 3.68; N, 22.35.

*Synthesis of pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one derivatives (**17** and **18**):*

To a mixture of hydrazonoyl chlorides **4** or **5** (6.0 mmol) and 6-aryl-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4H)-ones 16 (6.0 mmol) in chloroform (20 mL),

triethylamine (0.6 mL, 6.0 mmol) was added at room temperature. The reaction mixture was refluxed for 6 h and then cooled, the excess chloroform was removed under reduced pressure and the residue was treated with ethanol (10 mL). The solid that precipitated was collected and crystallized from DMF to give compounds **17** or **18**. The compounds prepared together with their physical properties are listed below:

6-Benzyl-3-(1-(2-(1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one (**17a**): Orange crystals; mp 248-250 ºC; yield (65 %); IR (KBr): ν = 3323 (NH), 1680 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.11 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 7.22-8.24 (m, 21H, ArH) and 10.36 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.2, 25.0, 100.8, 119.6, 122.3, 124.3, 125.1, 125.8, 126.3, 127.0, 128.2, 128.7, 128.9, 129.2, 129.5, 129.7, 132.0, 133.5, 134.6, 139.4, 140.5, 142.9, 145.6, 145.8, 149.6, 150.3, 152.7, 166.2. MS, m/z (%): 629 (M^+, 3.1), 77 (100). Anal. Calcd. for $C_{36}H_{27}N_{11}O$ (629.7): C, 68.67; H, 4.32; N, 24.47, found: C, 68.55; H, 4.25; N, 24.36.

3-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-6-(4-methylbenzyl)-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one (**17b**): Yellow crystals; mp 254-256 ºC; yield (72 %); IR (KBr): ν = 3325 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 2.20 (s, 3H, $\underline{CH_3}C_6H_4$), 3.76 (s, 2H, CH_2), 7.20-8.20 (m, 20H, ArH) and 10.33 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.1, 21.6, 25.2, 100.6, 118.2, 121.6, 124.1, 124.5, 124.6, 125.3, 127.2, 127.9, 128.9, 129.1, 129.4, 129.7, 130.3, 132.0, 133.2, 134.7, 139.3, 140.1, 142.6, 145.5, 145.9, 149.3, 150.4, 152.8, 166.4. MS, m/z (%): 643 (M^+, 1.3), 77 (100). Anal. Calcd. for $C_{37}H_{29}N_{11}O$ (643.7): C, 69.04; H, 4.54; N, 23.94, found: C, 68.92; H, 4.48; N, 23.99.

3-(1-(2-(1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-6-(4-methoxy-benzyl)-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one (**17c**): Yellow crystals; mp 242-244 ºC; yield (73 %); IR (KBr): ν = 3324 (NH), 1677 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.11 (s, 3H, CH_3), 3.30 (s, 3H, $O\underline{CH_3}$), 3.73 (s, 2H, CH_2), 7.20-8.18 (m, 20H, ArH) and 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.0, 25.6, 55.6, 101.0, 118.6, 120.3, 123.8, 124.2, 124.6, 125.1, 127.3, 127.5, 128.4, 129.2, 129.5, 129.9, 130.8, 132.6, 133.8, 134.6, 139.7, 140.3, 142.2, 145.8, 146.0, 149.0, 150.3, 152.5, 166.3. MS, m/z (%): 659 (M^+, 2.3), 77 (100). Anal. Calcd. for $C_{37}H_{29}N_{11}O_2$ (659.7): C, 67.36; H, 4.43; N, 23.36, found: C, 67.44; H, 4.49; N, 23.27.

6-(4-Chlorobenzyl)-3-(1-(2-(1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)ethyl)-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one (**17d**): Yellow crystals; mp 232-234 ºC; yield (68 %); IR (KBr): ν = 3322 (NH), 1679 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 7.25-8.05 (m, 20H, ArH) and 10.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.2, 25.0, 100.8, 119.6, 122.3, 124.2, 125.1, 125.8, 126.3, 127.0, 128.2, 128.7, 128.9, 129.2, 129.5, 129.7, 132.0, 133.5, 134.6, 139.4, 140.5, 142.9, 145.6, 145.8, 149.6, 150.3, 152.7, 166.2. MS, m/z (%): 664 (M^+, 3.0), 77 (100). Anal. Calcd. for $C_{36}H_{26}ClN_{11}O$ (664.1): C, 65.11; H, 3.95; Cl, 5.34; N, 23.20, found: C, 65.03; H, 3.88; Cl, 5.39; N, 23.12.

6-Benzyl-3-(1-(2-(3-isopropyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazono)-ethyl)-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one (**18a**): Orange crystals; mp 212-214 ºC; yield (70 %); IR (KBr): ν = 3320 (NH), 1675 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.35 (d, 6H, $CH(\underline{CH_3})_2$), 2.16 (s, 3H, CH_3), 3.04-3.17 (m, 1H, $\underline{CH}(CH_3)_2$), 3.67 (s, 2H, CH_2), 6.99-8.12 (m, 15H, ArH) and 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.0, 21.6, 25.0, 31.2, 100.0, 121.3, 124.6, 125.2, 126.3, 127.4, 128.0, 128.4, 129.2, 129.5, 129.7, 132.0, 134.6, 139.4, 140.5, 142.9, 145.6, 145.8, 149.6, 150.3, 152.7, 166.2. MS, m/z (%): 640 (M^+, 1.6), 91 (100). Anal. Calcd. for $C_{33}H_{28}N_{12}O_3$ (640.7): C, 61.87; H, 4.41; N, 26.24, found: C, 61.75; H, 4.33; N, 26.29.

Synthesis of 3-acetyl-6-benzyl-1-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-one (**19a**)

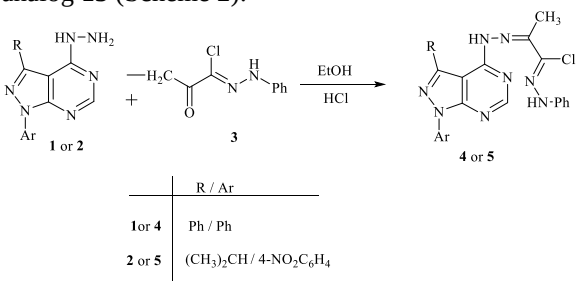
To a mixture of *N*-phenyl-*C*-acetylmethanohydrazonoyl chloride **3** (1 gm, 5.0 mmol) and 6-benzyl-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4*H*)-one **16** (1.1 gm, 5.0 mmol) in chloroform (20 mL), triethylamine (0.5 mL, 5.0 mmol) was added at room temperature. The reaction mixture was refluxed for 6 h and then cooled, the excess chloroform was removed under reduced pressure and the residue was treated with ethanol (10 mL). The solid that precipitated was collected and crystallized from ethanol to give 3-acetyl-6-benzyl-1-phenyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7(1*H*)-one (19a):Yellow crystals; mp 148-150 ºC; yield (70 %);^{1}H NMR (300 MHz, DMSO-d_6): *δ* 2.14 (s, 3H, CH_3), 3.67 (s, 2H, CH_2) and 7.01-8.03 (m, 10H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): *δ* 22.3, 25.6, 109.1, 114.7, 125.3, 127.6, 128.2, 132.3, 136.4, 142.0, 145.4, 146.4, 148.2, 150.3, 152.6. *Anal.* Calcd. For $C_{19}H_{15}N_5O_2$ (345.4): C, 66.08; H, 4.38; N, 20.28, found: C, 65.93; H, 4.19; N, 20.35

2. Results and Discussion

The hydrazino of pyrazolopyrimidine derivatives **1** and **2** were prepared following the literature procedure *via* the reaction of the appropriate imino-amino derivative with hydrazine hydrate in refluxing ethanol [32]. The reaction of hydrazine derivatives **1** and **2** with *N*-phenyl-*C*-acetylmethanhydrazonoyl chloride (**3**) in the presence of few drops of acetic acid in refluxing ethanol afforded the corresponding hydrazonoyl chlorides **4** and **5** (Scheme 1). The structures of the isolated products were identified by

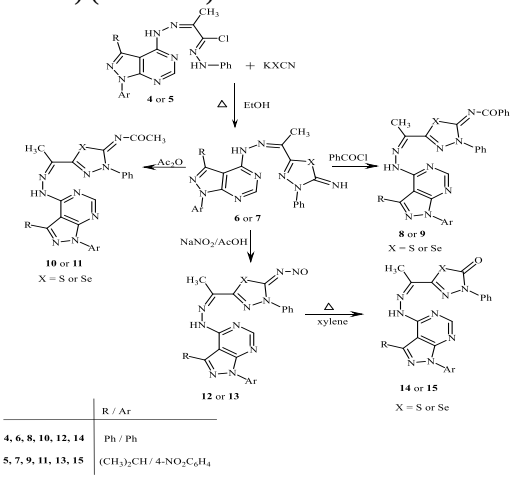
their analyses (see Experimental). For example, their IR spectra revealed the presence of band in the region ν 3352–3329 cm^{-1} due to two NH groups. The ^1H NMR spectrum of compound **4** revealed three singlet signals at δ 2.20 (3H, CH_3), 10.12 (1H, NH) and 11.31 (1H, NH), in addition to multiplet signal at δ 7.28-8.42 (16H) revealed to aromatic protons.

Treatment of each of hydrazonoyl chlorides **4** and **5** with each of potassium thiocyanate and potassium selenocyanate in refluxing ethanol yielded the corresponding 1,3,4-thiadiazol-2(3*H*)-imine **6** and its selenadiazol analog **7** (Scheme 2). The structures of the products **6** and **7** were elucidated by their spectral and elemental analyses, in addition to some chemical reactions. For example, their IR spectra showed imino NH band in region 3326-3320 cm^{-1} (see Experimental). In addition, treatment of each of **6** and **7** with benzoyl chloride and acetic anhydride yielded the *N*-benzoyl **8** and **9** and *N*-acetyl **10** and **11** derivatives, respectively (Scheme 2). Furthermore, synthesis of *N*-nitroso derivatives **12** and **13** *via* treatment of each of **6** and **7** with sodium nitrite in acetic acid which underwent thermolysis upon boiling in xylene to give the corresponding 1,3,4-thiadiazol-2(3*H*)-one **14** and its selenadiazol analog **15** (Scheme 2).

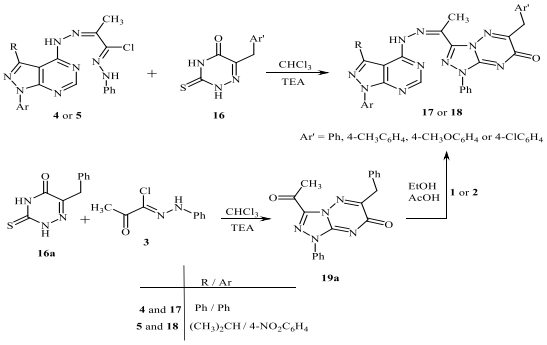


Scheme 1. Synthesis of 2-(2-(1,3-diaryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazono)-*N*-phenylpropanehydrazonoyl chlorides **4** and **5**.

Reaction of each of the hydrazonoyl chlorides **4** and **5** with 6-arylmethylene-2,3-dihydro-3- thioxo-1,2,4-triazin-5(4*H*)-ones (**16**) [33] in refluxing chloroform in the presence of triethylamine gave, in each case, a single product as evidenced by TLC analysis of the crude products **17** and **18** (Scheme 3). Both mass spectra and elemental analyses of the products indicated that they are free of sulfur. It was reported that the reaction involves the initial formation of spiro intermediate I which converted to thiohydrazide II *via* S→N migration. The latter thiohydrazide II undergo cyclization followed by elimination of hydrogen sulphide to give the final product (Figure 1).[34] The structures of the isolated products **17** and **18** were confirmed by alternative method via refluxing of 6-arylmethylene-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4*H*)-ones (**16**) with *N*-phenyl-*C*-acetylmethanohydrazonoyl chloride (**3**) in chloroform in the presence of triethylamine to give 3-acetyl-6-benzyl-1-phenyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7(1*H*)-one (**19**) that heated with hydrazine derivatives **1** and **2** in ethanol in the presence of few drops of acetic acid afforded the corresponding pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazono)ethyl)-1-phenyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7(1*H*)-ones (**17** and **18**) (Scheme 3).



Scheme 2. Synthesis of thiadiazole and Selenadiazole derivatives **8**-**15**.



Scheme 3. Synthesis of triazolo-triazine derivatives **17** and **18**.

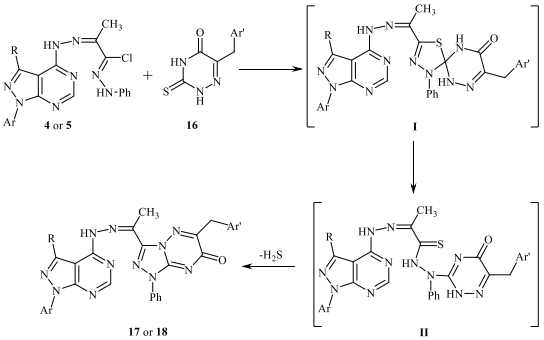


Figure 1. The proposed mechanism of synthesis of triazolo-triazine derivatives **17** and **18**.

Conclusions

In summary, 2-(2-(1,3-diaryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazono)-*N*-phenylpropanehydrazonoyl chlorides, generated from condensation reaction of hydrazine derivatives

of pyrazozlopyrimidine with *N*-phenyl-*C*-acetylmethanohydrazonoyl chloride, represented to be a useful precursors for synthesis of various new heterocyclic compounds like thiadiazoles and selenadiazoles by nucleophilic substitution reaction followed by cyclization with each of thiocyanate and selenocyanate, respectively. In addition the synthesis of triazolotriazines *via* addition reaction followed by cyclization with triazinethione derivatives.

Conflict of interest

The authors declare there is no conflict of interest.

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