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SYNTHESIS AND REACTIONS OF 3,8-DIPHENYL-5-(4-METHOXYPHENYL)PYRROLO[1,2-*c*][1,3]THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOHYDRAZIDE

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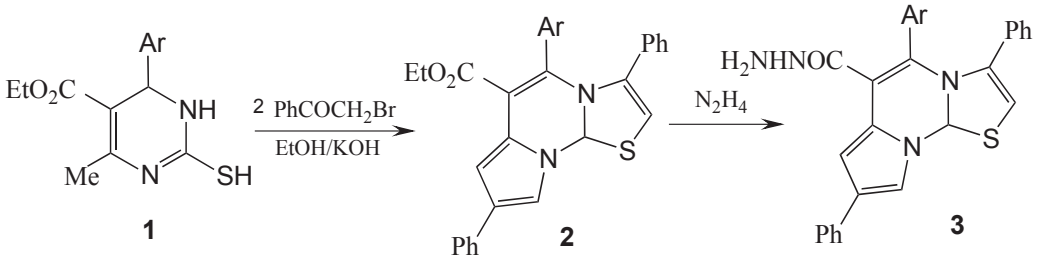
Abstract – The reaction of 2-mercaptopyrimidine **1** with phenacyl bromide gave pyrrolothiazolopyrimidine **2**, which underwent hydrazinolysis to produce the novel pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carbohydrazide **3**. Compound **3** used as a key intermediate for the synthesis of poly fused and isolated systems bearing pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine moiety *via* its reactions with some heterocyclization reagents. Structures of the newly synthesized compounds were established by elemental analysis and spectral data (IR, ^{1}H NMR, Mass spectra and ^{13}C NMR). The prepared compounds would be expected to have biological activities.

Thiazole and pyrimidine nuclei are the active core moieties of various bioactive heterocyclic compounds. The synthesis of thiazolo[3,2-*a*]pyrimidines have attracted considerable attention because of their wide spectrum biological activities such as anti-inflammatory,[1,2] antihypertensive,[3] antifungal,[4] antimicrobial,[5] anticancer,[6] and as potent and selective antagonists of the fractalkine receptor (CX3CR1).[7] These compounds have also been reported as inhibitors of CDC25B phosphatase,[8] acetylcholinesterase (AChE) enzymes,[9] and Bcl-2 family proteins.[10]

In addition, pyrrole moiety are present in a large number of bioactive compounds including HIV fusion inhibitors[11,12] and antitubercular compounds.[13,14] In view of these reports and in continuation of our work on biologically active nitrogen and sulfur heterocycles,[15-20] we planned to synthesis of novel fused pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine derivatives which would be expected to have biological activities.

Treatment of ethyl 2-mercapto-6-(4-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate **(1)**[21] with phenacyl bromide in 1:2 molar ratio in ethanolic KOH gave ethyl 5-(4-methoxyphenyl)-

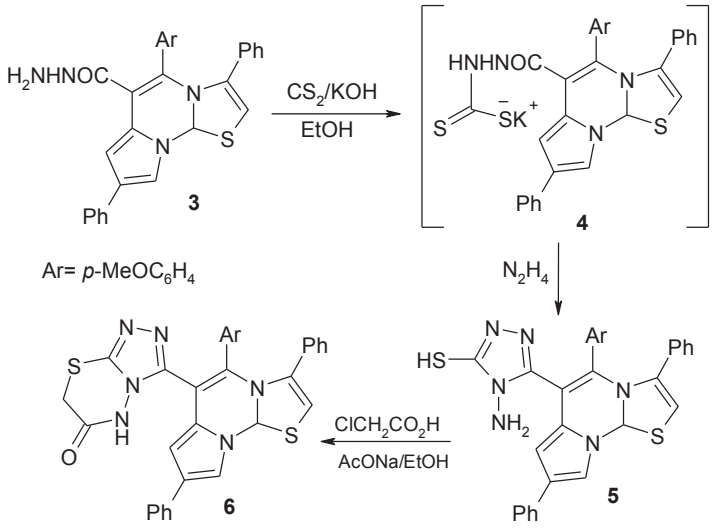
3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate **(2)**, which in turn underwent hydrazinolysis to afford 5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]-pyrimidine-6-carbohydrazide **(3)**. Compound **3** is considered as a key intermediate for the synthesis of poly fused and isolated heterocyclic compounds (Scheme1). The structures of compounds **2** and **3** were confirmed on the basis of their elemental analysis, IR, ^{1}H NMR mass spectral analysis, and ^{13}C NMR spectrum. The mass spectrum of compound **3** revealed the molecular ion peak at *m/z* 492 and confirms the postulated structure, while its ^{13}C NMR spectrum revealed the disappearance of two signals attributed to carbons of ethyl ester.



Ar= *p*-MeOC$_6$H$_4$

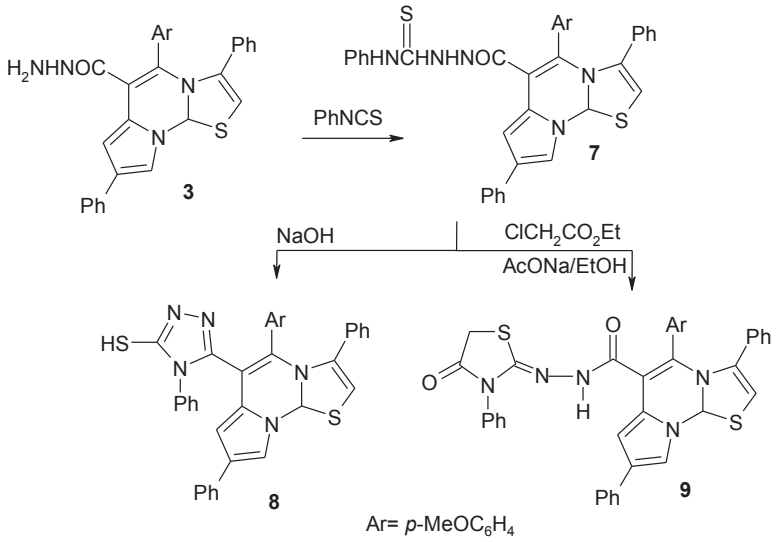
Scheme 1

Treatment of compound **3** with carbon disulfide in ethanolic KOH yielded 2-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]carbonylhydrazinecarbodithioato-kS] potassium **(4)**, which underwent hydrazinolysis to produce 4-amino-5-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-4*H*-1,2,4-triazole-3-thiol **(5)**. 3-[5-(4-Methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-5*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one **(6)** was obtained by reaction of compound **5** with monochloroacetic acid in ethanol and sodium acetate (Scheme 2). ^{1}H NMR of compound **5** showed signals at δ 3.75 ppm attributed to NH_2 group and at 7.8 ppm due to SH group. The mass spectrum of compound **5** showed the expected molecular ion peak (M^{+}) at *m/z* 548 which coincide with the molecular weight supporting the proposed identity of the structure. Also, the ^{13}C NMR spectrum of compound **5** showed downfield signal at 174.7 ppm ascribable to CSH. The IR spectrum of compound **6** reveled the absence of NH_2 group, while its ^{1}H NMR revealed signals at δ 7.57 ppm due to NH proton and at 8.61 ppm assignable to H-thiazole. The mass spectrum of **6** showed the expected molecular ion peak (M^{+}) at *m/z* 588 which supports the identity its structure. Also, the ^{13}C NMR spectrum of compound **6** showed significant signals at δ 42.7 and 162.1 ppm assigned to $CH_{2\ thiadiazinone}$ and C=O carbons, respectively.



Scheme 2

In a similar manner, interaction of compound **3** with phenyl isothiocyanate gave *N*-phenylhydrazinecarbothioamide **7**, which underwent heterocyclization by NaOH to give 5-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol **(8)**. While, 3,8-diphenyl-5-(4-methoxyphenyl)-*N*-[4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carbohydrazide **(9)** was obtained by treatment of compound **7** with ethyl chloroacetate (Scheme 3).

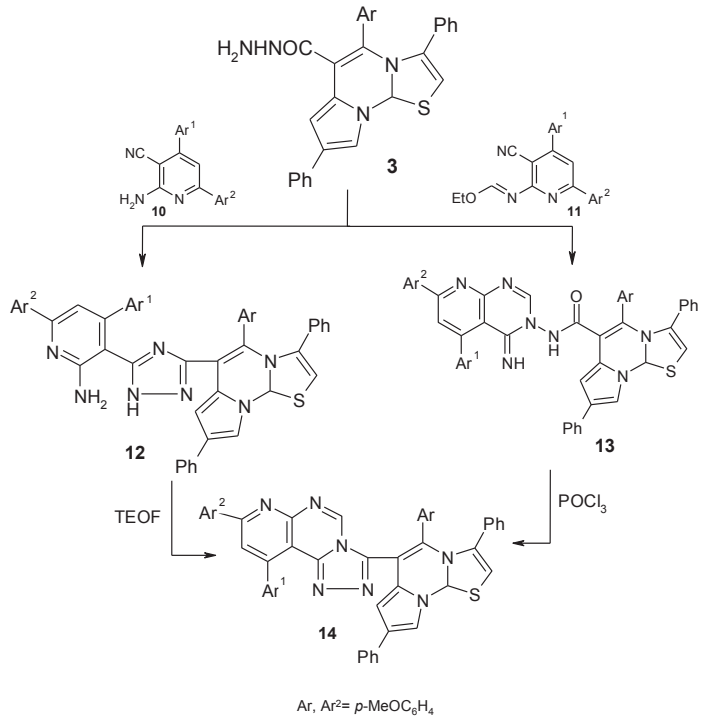


Scheme 3

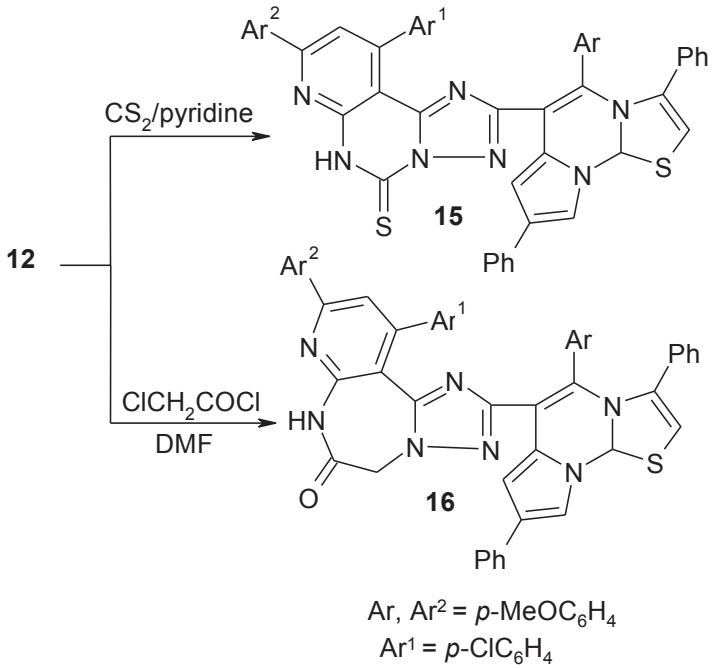
^{1}H NMR spectrum of compound **7** agrees well with the proposed structure and revealed characteristic three D_2O exchangeable signals appeared at 9.1, 10 and 10.7 ppm assignable to three NH protons. While,

compound **8** showed the presence of characteristic signal at 13.3 ppm attributed to NH proton. The mass spectrum of compounds **8** and **9** recorded the molecular ion peaks at *m/z* 609 and 667 respectively, which agree well with the formula weights and support the structures. The ^{13}C NMR spectrum of compound **7** displayed downfield signals attributed to (C=O) and (C=S) at δ 164.7 and 169.7 ppm, respectively. Also, the ^{13}C NMR spectrum of compound **9** showed characteristic signals due to the two carbonyl carbons at δ 155.7 and 161 ppm.

Also, treatment of compound **3** with 2-amino-4-(4-chlorophenyl)-3-cyano-6-(4-methoxyphenyl)pyridine **(10)**[22] and/or 4-(4-chlorophenyl)-3-cyano-2-ethoxymethylideneamino-6-(4-methoxyphenyl)pyridine **(11)**[23] in DMF afforded 4-(4-chlorophenyl)-6-(4-methoxyphenyl)-3-{3-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-1*H*-1,2,4-triazol-5-yl}pyridin-2-amine **(12)** and 5-(4-methoxyphenyl)-3,8-diphenyl-*N*-[5-(4-chlorophenyl)-4-imino-7-(4-methoxyphenyl)pyrido-[2,3-*d*]pyrimidin-3(4*H*)-yl]pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide **(13)**, respectively. Meanwhile, compounds **12** and **13** underwent heterocyclization by Triethyl orthoformate and/or $POCl_3$ respectively, to produce the same product namely 10-(4-chlorophenyl)-8-(4-methoxyphenyl)-3-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine **(14)** (Scheme 4). The IR spectrum of compound **12** showed there is no absorption band for carbonyl group. While, the ^{1}H NMR spectrum of pyrimidines **13** showed two NH protons exchangeable with D_2O at 6.95 and 9.6 ppm. The ^{13}C NMR spectrum of compounds **12, 13** and **14** showed significant signals agrees well with the proposed structures.



Scheme 4



Scheme 5

Finally, condensation of compound **12** with carbon disulfide in pyridine and/or chloroacetyl chloride in DMF gave poly fused heterocyclic compounds namely 10-(4-chlorophenyl)-2-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-8-(4-methoxyphenyl)pyrido[3,2-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidine-5(6*H*)-thione **(15)** and 11-(4-chlorophenyl)-9-(4-methoxyphenyl)-2-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-5*H*-pyrido[3,2-*f*]-[1,2,4]triazolo[1,5-*d*][1,4]diazepin-6(7*H*)-one **(16)**, respectively, (Scheme5).

IR spectra of compound **16** revealed appearance of absorption band at 1700 cm^{-1} due to (C=O). ^{13}C NMR spectra of compounds **15** and **16** showed distinct signals at δ 178.4 and 161.6 ppm attributed to C=S and C=O carbons respectively.

EXPERIMENTAL

All the reported melting points were uncorrected. The IR spectra were recorded on FT-IR Jasco 4100 spectrophotometer using KBr wafer technique. ^1H NMR spectra and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as an internal standard. Elemental microanalyses were recorded on a Perkin Elmer series II CHNS analyzer 2400. Mass spectra were obtained using gas chromatography GCMS qp-2010 and on a Shimadzu instrument mass spectrometer (70 eV). The purity of the synthesized compounds was checked by thin layer chromatography (TLC). Compound **1** has been prepared according to the reported method.[21]

Ethyl 3,8-diphenyl-5-(4-methoxyphenyl)pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (2). A mixture of compound **1** (0.306 g, 1 mmol) and phenacyl bromide (0.398 g, 2 mmol) in KOH (0.112 g, 2 mmol) in EtOH (20 mL) was refluxed for 6 h, then pour onto ice and H_2O the solid obtained was filtered off and recrystallized from EtOH to give compound **2** as brown crystals (0.445 g, 88%): mp 111-113 °C; IR (ν cm^{-1}) 3050 ($CH_{arom.}$), 2930 ($CH_{aliph.}$), 1681 (C=O), 1608 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (t, 3H, CH_2***CH*****$_3$**, *J* = 6.9 Hz), 3.4 (q, 2H, ***CH*****$_2$**CH_3, *J* = 6.9 Hz), 3.61 (s, 3H, OCH_3), 5.20 (s, 1H, NCHS), 6.83-7.62 (m, 12H, Ar-H), 7.91-7.92 (dd, 4H, Ar-H), 8.1 (s, 1H, thiazole); ^{13}C NMR (75 MHz) δ 14.4 (CH_3), 55.5 (OCH_3), 59.6 (CH_2), 60.02 (NCHS), 124.1, 124.3, 126.4, 127.8, 128.09, 128.4, 129.03, 129.2, 129.7, 130.3, 133.3, 134.1, 134.6, 136.1, 145.2, 152.2, 165.6 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 506 (13.3), [M+1] 507 (6.8), [M+2] 508 (3.5), 489 (11.6), 475 (5.1), 387 (5.7), 329 (8.4), 267 (8.9), 105 (100), 91 (4.5), 77 (31.4); Anal. Calcd for $C_{31}H_{26}N_2O_3S$ (%): C, 73.49; H, 5.17; N, 5.53; S, 6.33. Found: C, 73.40; H, 5.10; N, 5.50; S, 6.30.

3,8-Diphenyl-5-(4-methoxyphenyl)pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carbohydrazide (3). A mixture of compound **2** (0.506 g, 1 mmol) and hydazine hydrate (1 mL) was heated under reflux for **2** h in MeOH (10 mL). The reaction mixture was left overnight at room temperature. The solid obtained was collected and recrystallized from MeOH to give compound **3** as brown crystals (0.359 g, 73%): mp 118-120 °C; IR (ν cm^{-1}) 3400-3250 (NH_2, NH), 3057 ($CH_{arom.}$), 2926 ($CH_{aliph.}$), 1651 (C=O), 1604 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H, OCH_3), 4 (brs, 2H, NH_2 exchangeable with D_2O), 5.2 (s, 1H, NCHS), 6.90-7.94 (m, 12H, Ar-H), 8.21-8.29 (dd, 4H, Ar-H), 8.1 (s, 1H, thiazole), 9.6 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 55.2 (OCH_3), 69.7 (NCHS), 120.3, 120.4, 120.5, 122.2, 122.6, 124.5, 124.6, 126.6, 127.2, 127.4, 128.2, 128.6, 128.8, 129.8, 130.2, 130.6, 160.1 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 492 (5.9), [M+1] 493 (5.5), 455 (3.8), 422 (6.5), 360 (5.2), 318 (5.2), 265 (3.8), 207 (3.6), 184 (5.1), 134 (6), 104 (11.7), 91 (15.7), 77 (100), 57 (62.7); Anal. Calcd for $C_{29}H_{24}N_4O_2S$ (%): C, 70.71; H, 4.91; N, 11.37; S, 6.51. Found: C, 70.69; H, 4.88; N, 11.34; S, 6.48.

4-Amino-5-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin6-yl]-4*H*-1,2,4-triazole-3-thiol (5). In alcoholic solution of KOH (0.84 g, 1.5 mmol KOH in 100 mL EtOH), compounds **3** (0.492 g, 1 mmol) and carbon disulfide (1 mL) were stirred at room temp for 4 h. The salt obtained **4** was collected and added directly to hydrazine hydrate (0.5 mL). The reaction mixture was heated under reflux for 3 h. Cool and acidified with conc. HCl. The solid obtained was filtered off and recrystallized from MeOH to give compound **5** as brown crystals (0.378 g, 69%): mp 128-130 °C; IR (ν cm^{-1}) 3446 (NH_2), 3050 ($CH_{arom.}$), 2916 ($CH_{aliph.}$), 1635 (C=N), 1600 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (s, 3H, OCH_3), 3.75 (brs, 2H, NH_2 exchangeable with D_2O), 5.3 (s, 1H, NCHS),

7.04-7.38 (m, 17H, Ar-H), 7.8 ppm (s, 1H, SH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 55.7, 60.1, 124.1, 124.3, 127.9, 128.1, 129.0, 129.1, 129.20, 129.26, 129.34, 129.7, 133.5, 136.2, 137.3, 145.3, 148.6, 152.8, 174.7; MS *m/z* (%): $[M]^{\cdot+}$ 548 (0.1), [M+1] 549 (0.1), [M+2] 550 (0.1), 479 (0.2), 404 (0.3), 363 (0.6), 317 (0.8), 227 (1.5), 149 (4.6), 129 (6.9), 91 (8.1), 77 (13.5), 59 (100); Anal. Calcd for $C_{30}H_{24}N_6OS_2$ (%): C, 65.67; H, 4.41; N, 15.32; S, 11.69. Found: C, 65.65; H, 4.40; N, 15.30; S, 11.65.

3-[5-(4-Methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-5*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one (6). A mixture of compound **5** (0.548 g, 1 mmol) and monochloroacetic acid (0.1 g, 1 mmol) in EtOH (10 mL) containing freshly fused sodium acetate (0.1 g) was heated under reflux for 6 h. The excess solvent was evaporated. The solid obtained was collected and recrystallized from EtOH to give compound **6** as pale brown crystals (0.341 g, 58%): mp 150-152 °C; IR (ν cm^{-1}) 3207 (NH), 3059 ($CH_{arom.}$), 2924 ($CH_{aliph.}$), 1723 (C=O), 1603 (C=N), 1580 (C=C); ^1H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H, OCH_3), 4.2 (brs, 2H, CH_2), 5.6 (s, 1H, NCHS), 7.05-7.81 (m, 12H, Ar-H), 7.57 (s, 1H, NH exchangeable with D_2O), 8.22-8.30 (dd, 4H, Ar-H), 8.61 (s, 1H, thiazole); ^{13}C NMR (75 MHz) δ 42.7 (CH_2), 55.2 (OCH_3), 69.7 (NCHS), 120.3, 121.4, 121.5, 122.2, 122.6, 124.5, 124.6, 125.1, 127.2, 127.7, 128.2, 128.5, 128.8, 129.8, 130.2, 130.6, 138.2, 142.3, 162.1 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 588 (0.2), [M+1] 589 (0.5), [M+2] 590 (0.8), 551 (63.7), 424 (11.2), 367 (15.5), 313 (54.7), 269 (6.4), 239 (58.1), 150 (10.7), 135 (30.7), 91 (20.4), 77 (51.2), 57 (100); Anal. Calcd for $C_{32}H_{24}N_6O_2S_2$ (%): C, 65.29; H, 4.11; N, 14.28; S, 10.89. Found: C, 65.27; H, 4.10; N, 14.26; S, 10.85.

2-{[5-(4-Methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]carbonyl}-*N*-phenylhydrazinecarbothioamide (7). A mixture of compound **3** (0.492 g, 1 mmol) and phenyl isothiocyanate (0.12 mL, 1 mmol) in dioxane (10 mL) was heated at 80 °C for 2 h. The reaction mixture was left at room temperature overnight. The solid obtained was filtered off and washed with Et_2O to give compound **7** as pale brown crystals (0.35 g, 56%): mp 185-187 °C; IR (ν cm^{-1}) 3392-3181 (3NH), 3056 ($CH_{arom.}$), 2929 ($CH_{aliph.}$), 1650 (C=O), 1601 (C=C), 1250 (C=S); ^1H NMR (300 MHz, DMSO-d_6) δ 3.36 (s, 3H, OCH_3), 5.4 (s, 1H, NCHS), 6.87-7.46 (m, 17H, Ar-H), 7.54-7.57 (dd, 4 H, Ar-H), 8.2 (s, 1H, thiazole), 9.10 (s, 1H, NH exchangeable with D_2O), 10 (s, 1H, NH exchangeable with D_2O), 10.70 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 52 (OCH_3), 84.1 (NCHS), 118, 122, 124, 126, 128, 128.2, 128.8, 128.9, 129.1, 129.2, 131.2, 131.5, 132, 134, 135.7, 136.9, 164.7, 169.7; MS *m/z* (%): $[M]^{\cdot+}$ 627 (0.2), 340 (15.6), 290 (46.5), 289 (100), 246 (15.6), 217 (13), 189 (10.9), 137 (7.5), 77 (9.2); Anal. Calcd for $C_{36}H_{29}N_5O_2S_2$ (%): C, 68.88; H, 4.66; N, 11.16; S, 10.22. Found: C, 68.80; H, 4.63; N, 11.12; S, 10.20.

5-[5-(4-Methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol (8). Compound **7** (0.627 g, 1 mmol) was dissolved in aqueous sodium hydroxide (5 mL, 2%) and was heated under reflux for 2 h. The reaction mixture was cooled and poured gradually onto crushed ice and neutralized with HCl. The solid obtained was filtered off and recrystallized from dioxane to give compound **8** as brown crystals (0.292 g, 48%): mp 179-180 °C; IR (ν cm^{-1}) 3352 (NH), 3058 ($CH_{arom.}$), 2929 ($CH_{aliph.}$), 1603 (C=N), 1553 (C=C), 1250 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (s, 3H, OCH_3), 5.1 (s, 1H, NCHS), 6.79-7.54 (m, 17H, Ar-H), 7.61-7.63 (dd, 4H, Ar-H), 8.3 (s, 1H, thiazole), 13.3 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 48.8, 70.2, 123.2, 124.9, 126.16, 126.3, 127.6, 127.8, 128.6, 129.3, 129.5, 129.7, 130.07, 130.7, 133.8, 139.1, 139.7, 142.2, 146.6, 168.8; MS *m/z* (%): $[M]^{+}$ 609 (0.1), [M-1] 608 (0.2), 580 (0.4), 515 (0.9), 457 (3.8), 377 (3.2), 287 (21.3), 269 (21.6), 216 (10.6), 159 (8.9), 135 (13.2), 91 (26.7), 77 (69.5), 59 (100); Anal. Calcd for $C_{36}H_{27}N_5OS_2$ (%): C, 70.91; H, 4.46; N, 11.49; S, 10.52. Found: C, 70.88; H, 4.43; N, 11.48; S, 10.50.

3,8-Diphenyl-5-(4-methoxyphenyl)-*N*-[4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]pyrrolo[1,2-*c*][1,3]-thiazolo[3,2-*a*]pyrimidine-6-carbohydrazide (9). A mixture of compound **7** (0.627 g, 1 mmol), ethyl chloroacetate (0.1 mL, 1 mmol) and anhydrous sodium acetate (0.12 g, 1.5 mmol) in absolute EtOH (10 mL) was heated under reflux for 3 h. The reaction mixture was cooled, poured onto cold H_2O and stand overnight. The solid obtained was filtered off and recrystallized from MeOH to give compound **9** as pale brown crystals (0.46 g, 69%): mp 136-138 °C; IR (ν cm^{-1}) 3194 (NH), 3058 ($CH_{arom.}$), 2923 ($CH_{aliph.}$), 1729, 1658 (2C=O), 1601 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.71 (s, 3H, OCH_3), 4.5 (brs, 2H, CH_2), 5.2 (s, 1H, NCHS), 6.84-7.58 (m, 17H, Ar-H), 8.20-8.22 (dd, 4 H, Ar-H), 8.3 (s, 1H, thiazole), 9.8 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 54.8 (OCH_3), 70 (NCHS),118.1, 120.3, 120.5, 120.9, 124.5, 125, 126.6, 128.3, 128.4, 128.6, 128.8, 128.9, 129.1, 129.4, 129.8, 130.9, 131.8, 134.1, 141.2, 155.7 (C=O), 161 (C=O); MS *m/z* (%): $[M]^{+}$ 667 (0.1), [(M+1] 668 (0.1), [M+2] 669 (0.1), 606 (0.3), 537 (0.6), 479 (2.1), 377 (8), 287 (9.6), 268 (26.7), 216 (10.6), 150 (15), 135 (22.4), 91 (35.2), 77 (100), 57 (92.8); Anal. Calcd for $C_{38}H_{29}N_5O_3S_2$ (%): C, 68.34; H, 4.38; N, 10.49; S, 9.60. Found: C, 68.30; H, 4.33; N, 10.40; S, 9.56.

4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-3-{3-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*]-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]1*H*-1,2,4-triazol-5-yl}pyridin-2-amine (12). A mixture of compound **3** (0.492 g, 1 mmol) and pyridine **10** (0.335 g, 1 mmol) in DMF (10 mL) containing few drops of triethylamine was heated under reflux for 5 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from dioxane to give compound **12** as brown crystals (0.47 g, 58%): mp 151-153 °C; IR (ν cm^{-1}) 3457, 3362, 3231 (NH_2, NH), 3068

($CH_{arom.}$), 2929 ($CH_{aliph.}$), 1633 (C=N), 1573 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 6H, $2OCH_3$), 6.51 (brs, 2H, NH_2 exchangeable with D_2O), 5.4 (s, 1H, NCHS), 7.01-7.03 (dd, 4H, Ar-H), 7.08-7.09 (dd, 4H, Ar-H), 7.20-7.66 (m, 13 H, Ar-H), 8.08-8.10 (dd, 4 H, Ar-H), 8.00 (s, 1H, thiazole), 8.2 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 55.2 (OCH_3), 85.5 (NCHS), 118.2, 120.3, 120.4, 122.4, 122.8, 124.5, 126.6, 128.5, 128.7, 128.8, 129.7, 130.1, 130.7, 132.3, 134.3, 135.8, 138.7, 142.2., 148.8, 153.2, 158.3; MS *m/z* (%): [M-2H_2] 806 (0.2), 690 (0.3), 593 (0.5), 551 (8.3), 423 (2.7), 359 (2.4), 287 (13.4), 269 (3), 215 (4.6), 134 (12.2), 91 (17), 77 (34), 59 (100); Anal. Calcd for $C_{48}H_{36}ClN_7O_2S$ (%): C, 71.14; H, 4.48; N, 12.1; S, 3.96. Found: C, 71.10; H, 4.50; N, 12.00; S, 3.90.

5-(4-Methoxyphenyl)-3,8-diphenyl-*N*-[5-(4-chlorophenyl)-4-imino-7-(4-methoxyphenyl)pyrido-[2,3-*d*]pyrimidin-3(4*H*)-yl]pyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (13). A mixture of compound **3** (0.492 g, 1 mmol) and compound **11** (0.391 g, 1 mmol) in DMF (10 mL) was heated under reflux for 6 h. The reaction mixture was cooled and poured onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH to give compound **13** as brown crystals (0.46 g, 55%): mp 128-129 °C; IR (ν cm^{-1}) 3361, 3230 (2NH), 3062 ($CH_{arom.}$), 2928 ($CH_{aliph.}$), 1651 (C=O), 1605 (C=N), 1543 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 6H, $2OCH_3$), 5.1 (s, 1H, NCHS), 6.95 (s, 1H, NH exchangeable with D_2O), 7.02-7.05 (dd, 4 H, Ar-H), 7.09-7.22 (dd, 4 H, Ar-H), 7.44-7.71 (m, 14 H, Ar-H), 8.09-8.12 (dd, 4 H, Ar-H), 8.6 (s, 1H, thiazole), 9.6 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 55.7 (OCH_3), 85.9 (NCHS),118.3, 120.2, 122.1, 123.4, 124.4, 124.8, 125.3, 127.2, 128.3, 129.2, 129.3, 129.5, 130.2, 130.7, 132.02, 133.1, 133.7, 134.8, 135.7, 136.3, 142, 153.8, 161.5; MS *m/z* (%): [M-1] 837 (0.1), 700 (8.6), 671 (9.6), 505 (1.5), 431 (1.5), 418 (2.5), 336 (6.7), 327 (2.2), 269 (2.9), 135 (13.6), 91 (16.7), 77 (39.6), 59 (100); Anal. Calcd for $C_{49}H_{36}ClN_7O_3S$ (%): C, 70.20; H, 4.33; N, 11.69; S, 3.82. Found: C, 70.18; H, 4.35; N, 11.70; S, 3.80.

10-(4-Chlorophenyl)-8-(4-methoxyphenyl)-3-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]-thiazolo[3,2-*a*]pyrimidin-6-yl]pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (14)

Method A. A mixture of compound **12** (0.810 g, 1 mmol) and triethyl orthoformate (0.5 mL) was fused for 12 h. The solid obtained was triturated with MeOH and filtered off and recrystallized from DMF to give compound **14** as pale brown crystals (0.484 g, 59%): mp 122-124 °C.

Method B. In $POCl_3$ (10 mL), compound **13** (0.838 g, 1 mmol) was heated on a water-bath for 3 h. The reaction mixture was cooled and poured onto crushed ice. The solid obtained was filtered off and recrystallized from DMF to give compound **14** as pale brown crystals (0.426 g, 52%): mp 122-124 °C; IR (ν cm^{-1}) 3054 ($CH_{arom.}$), 2930 ($CH_{aliph.}$), 1605 (C=N), 1574 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 6H, $2OCH_3$), 6.7 (s, 1H, NCHS), 6.97-7.03 (dd, 4H, Ar-H), 7.20-7.22 (dd, 4H, Ar-H), 7.57-7.69 (m,

14H, Ar-H), 8.08-8.11 (dd, 4H, Ar-H), 8.2 (s, 1H, thiazole); ^{13}C NMR (75 MHz) δ 55.1 (OCH_3), 85.5 (NCHS), 118.4, 120, 121, 121.5, 122.1, 123.2, 124.8, 126, 126.4, 126.6, 127.1, 127.4, 127.8, 128.3, 128.5, 128.7, 129.6, 129.8, 130, 134.3, 135.7, 136.5, 137.6; MS *m/z* (%): [M-1] 819 (0.1), 712 (0.2), 621 (0.3), 507 (1), 433 (1.1), 387 (2.7), 327 (1.2), 269 (2.5), 135 (8.3), 91 (16.6), 77 (24.2), 59 (100); Anal. Calcd for $C_{49}H_{34}ClN_7O_2S$ (%): C, 71.74; H, 4.18; N, 11.95; S, 3.91. Found: C, 71.71; H, 4.17; N, 11.97; S, 3.88.

10-(4-Chlorophenyl)-2-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]thiazolo[3,2-*a*]pyrimidin-6-yl]-8-(4-methoxyphenyl)pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thione (15). A mixture of compound **12** (0.810 g, 1 mmol) and carbon disulfide (0.5 mL) in pyridine (10 mL) was heated under reflux for 4 h. The reaction mixture was cooled and poured gradually onto crushed ice containing few drops of dil. HCl. The solid obtained was filtered off and recrystallized from dioxane to give compound **15** as brown crystals (0.494 g, 58%): mp 173-175 °C; IR (ν cm^{-1}) 3230 (NH), 3059 ($CH_{arom.}$), 2927 ($CH_{aliph.}$), 1635 (C=N), 1606 (C=C), 1239 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 6H, 2 OCH_3), 6.8 (s, 1H, NCHS), 7.02 (s, 1H, NH exchangeable with D_2O), 7.04-7.05 (dd, 4 H, Ar-H), 7.22-7.23 (dd, 4H, Ar-H), 7.60-7.71 (m, 13H, Ar-H), 8.09-8.12 (dd, 4H, Ar-H), 8.2 (s, 1H, thiazole); ^{13}C NMR (75 MHz) δ 55.7 (OCH_3), 78.2 (NCHS), 118.8, 121.1, 122.4, 124.4, 127.5, 128.0, 129.2, 129.3, 130.2, 130.7, 134.9,136.3, 139.2, 140.0, 142.1, 148.3, 150.2, 153.8,161.2, 161.5, 178.4; MS *m/z* (%): [M+1] 853 (0.03), [M+2] 854 (0.05), 725 (0.1), 654 (0.8), 552 (1.8), 431 (1.5), 418 (6.8), 335 (21), 327 (2.5), 269 (3.6), 135 (11.4), 91 (12.5), 77 (24), 57 (100); Anal. Calcd for $C_{49}H_{34}ClN_7O_2S_2$ (%): C, 69.04; H, 4.02; N, 11.50; S, 7.52. Found: C, 69.00; H, 4.00; N, 11.50; S, 7.50.

11-(4-Chlorophenyl)-9-(4-methoxyphenyl)-2-[5-(4-methoxyphenyl)-3,8-diphenylpyrrolo[1,2-*c*][1,3]-thiazolo[3,2-*a*]pyrimidin-6-yl]-5*H*-pyrido[3,2-*f*][1,2,4]triazolo[1,5-*d*][1,4]diazepin-6(7*H*)-one (16). A mixture of compound **12** (0.810 g, 1 mmol) and chloroacetyl chloride (0.1 mL, 1 mmol) in DMF (5 mL) was heated under reflux for 5 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from dioxane to give compound **16** as brown crystals (0.493 g, 58%): mp 138-140 °C; IR (ν cm^{-1}) 3363 (NH), 3060 ($CH_{arom.}$), 2924 ($CH_{aliph.}$), 1700 (C=O), 1635 (C=N), 1605 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 6H, 2 OCH_3), 3.85 (s, 2H, CH_2), 6.7 (s, 1H, NCHS), 7.01-7.04 (dd, 4H, Ar-H), 7.11-7.22 (dd, 4H, Ar-H), 7.59-7.70 (m, 14H, Ar-H), 8.09-8.12 (dd, 4H, Ar-H), 8.2 (s, 1H, thiazole), 8.7 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 34.6 (CH_2), 70.2 (OCH_3), 86.1 (NCHS), 118.8, 124.6, 127.4, 128.0, 129.2, 129.4, 130.0, 130.7, 131.1, 133.4, 134.9, 135.8, 136.3, 138.2, 138.5, 140.7, 142.0, 146.7, 153.9, 158.7, 161.1, 161.6; MS *m/z* (%): 771 (0.2), 631 (0.3), 552 (1.5), 430 (1.34), 421 (1.1), 393 (1.2), 335 (12.4), 268 (4.5), 216 (4.9), 135 (12.4), 91 (22), 77 (50.6), 59 (100); Anal. Calcd for $C_{50}H_{36}ClN_7O_3S$ (%): C, 70.62; H, 4.27; N, 11.53; S,

3.77. Found: C, 70.60; H, 4.30; N, 11.50; S, 3.70.

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