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

Kamelia M. El-mahdy and Azza M. El-kazak*

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, 11711, Cairo, Egypt: Email: az_azelkazak@hotmail.com

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 \((\text{i})\)\(^21\) 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-carboxyhydrazide (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.

![Scheme 1](image)

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-y|]carbonylhynrazinecarbodithioato-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]-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]-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6(7H)-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 $\delta$ 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 $\delta$ 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 $\delta$ 42.7 and 162.1 ppm assigned to CH$_2$thiadiazinone and C=O carbons, respectively.
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-4H-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).

1H NMR spectrum of compound 7 agrees well with the proposed structure and revealed characteristic three D$_2$O 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) and/or 4-(4-chlorophenyl)-3-cyano-2-ethoxymethylideneamino-6-(4-methoxyphenyl)pyridine (11) 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]-1H-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(4H)-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$_2$O 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](image-url)
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(6H)-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]-5H-pyrido[3,2-f]-[1,2,4]triazolo[1,5-d][1,4]diazepin-6(7H)-one (16), respectively, (Scheme 5).

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. $^1$H 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.\textsuperscript{31}
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 H₂O 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 (CH₃ arom.), 2930 (CH₃ aliph.), 1681 (C=O), 1608 (C=C); ¹H NMR (300 MHz, DMSO-d₆) δ 1.07 (t, 3H, CH₂CH₃, J = 6.9 Hz), 3.4 (q, 2H, CH₂CH₃, J = 6.9 Hz), 3.61 (s, 3H, OCH₃), 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); ¹³C NMR (75 MHz) δ 14.4 (CH₃), 55.5 (OCH₃), 59.6 (CH₂), 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]+ 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 C₃₁H₂₆N₂O₃S (%): 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 hydrazine 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 (NH₂, NH), 3057 (CH₃ arom.), 2926 (CH₃ aliph.), 1651 (C=O), 1604 (C=C); ¹H NMR (300 MHz, DMSO-d₆) δ 3.80 (s, 3H, OCH₃), 4 (brs, 2H, NH₂ exchangeable with D₂O), 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 D₂O); ¹³C NMR (75 MHz) δ 55.2 (OCH₃), 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]+ 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 C₂₉H₂₄N₄O₂S (%): 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]-4H-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 (NH₂), 3050 (CH₃ arom.), 2916 (CH₃ aliph.), 1635 (C=N), 1600 (C=C); ¹H NMR (300 MHz, DMSO-d₆) δ 3.33 (s, 3H, OCH₃), 3.75 (brs, 2H, NH₂ exchangeable with D₂O), 5.3 (s, 1H, NCHS), 6.83-7.62 (m, 12H, Ar-H), 7.91-7.92 (dd, 4H, Ar-H), 8.1 (s, 1H, thiazole); ¹³C NMR (75 MHz) δ 55.5 (OCH₃), 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]+ 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 C₂₉H₂₄N₄O₂S (%): 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.
7.04-7.38 (m, 17H, Ar-H), 7.8 ppm (s, 1H, SH exchangeable with D$_2$O); $^{13}$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]$^+$ 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$_6$O$_2$S$_2$: 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]-5H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazin-6(7H)-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); $^1$H 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$_2$O), 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, 130.2, 130.6, 138.2, 142.3, 162.1 (C=O); MS m/z (%): [M]$^+$ 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$_6$O$_2$S$_2$: 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$_2$O 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$_{arom}$), 2924 (CH$_{aliph}$), 1650 (C=O), 1601 (C=C), 1250 (C=S); $^1$H 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, 4H, Ar-H), 8.2 (s, 1H, thiazole), 9.10 (s, 1H, NH exchangeable with D$_2$O), 10 (s, 1H, NH exchangeable with D$_2$O), 10.70 (s, 1H, NH exchangeable with D$_2$O); $^{13}$C NMR (75 MHz) δ 52 (OCH$_3$), 84.1 (NCHS), 118, 122, 124, 126, 128, 128.2, 128.8, 129.1, 129.2, 131.2, 131.5, 132, 134, 135.7, 136.9, 164.7, 169.7; MS m/z (%): [M]$^+$ 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$_6$O$_2$S$_2$: 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-4H-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=S); ¹H NMR (300 MHz, DMSO-d₆) δ 3.33 (s, 3H, OCH₃), 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 D₂O); ¹³C NMR (75 MHz) δ 48.8, 70.2, 123.2, 124.9, 126.2, 127.6, 127.8, 128.6, 129.3, 129.5, 129.7, 130.0, 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 C₃₆H₂₇N₅O₂S₂ (%): 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 H₂O 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); ¹H NMR (300 MHz, DMSO-d₆) δ 3.71 (s, 3H, OCH₃), 4.5 (brs, 2H, CH₂), 5.2 (s, 1H, NCHS), 6.84-7.58 (m, 17H, Ar-H), 8.20-8.22 (dd, 4H, Ar-H), 8.3 (s, 1H, thiazole), 9.8 (s, 1H, NH exchangeable with D₂O); ¹³C NMR (75 MHz) δ 54.8 (OCH₃), 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 C₃₈H₂₉N₅O₃S₂ (%): 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]1H-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 (NH₂, 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$_2$O), 5.4 (s, 1H, NCHS), 7.01-7.03 (dd, 13 H, 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$_2$O); $^{13}$C NMR (75 MHz) δ 55.2 (OCH$_3$), 85.5 (NCHS), 118.2, 120.3, 120.4, 122.4, 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$_7$O$_2$S (%): 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(4H)-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), 1573 (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$_2$O), 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$_2$O); $^{13}$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$_{35}$ClN$_7$O$_3$S (%): 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[1,2-c][1,3]thiazolo[3,2-a]pyrimidine-4-carboxamide (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, 4 H, Ar-H), 7.20-7.22 (dd, 4 H, 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) $\delta$ 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, 130.4, 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$_7$O$_2$S (%): 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(6H)-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), 1293, 1280, 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; $^{1}$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$_2$O), 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$_7$O$_2$S$_2$ (%): 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]-5H-pyrido[3,2-f][1,2,4]triazolo[1,5-c]pyrimidine-5(6H)-thione (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$_2$O); $^{13}$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$_7$O$_2$S (%): 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.

REFERENCES

