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RESEARCH ARTICLE

A novel synthesis of indeno[2',1': 5,6] pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines

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Reaction of 5-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1*H*-indeno[2',1':5,6] pyrido[2,3-*d*]pyrimidine-4,6-dione with hydrazonoyl chlorides gave 1,2,4-triazolo[4,3-*a*]pyrimidine derivatives regioselectively in good yields. The structures of the newly synthesized compounds are established on the basis of chemical and spectroscopic evidence as well as their synthesis by alternative methods.

Keywords: Hydrazonoyl halides; Indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine; 1,2,4-Triazolo[4,3-*a*] pyrimidines

1. Introduction

Hydrazonyl halides have been extensively studied and are known as versatile intermediates for the synthesis of heterocyclic compounds [1]. Depending on the type of hydrazonoyl halides used and the reaction conditions, thiourea reacts with hydrazonoyl halides to give triazoles [1, 2], thiazoles [3–5] or thiadiazoles [6–8]. Recently, we have shown that the reactions of hydrazonoyl halides with cyanothioforamides provide direct, facile and new efficient methods for the synthesis of 1,3,4-thiadiazoles [9]. It is, therefore, of interest to extend our investigation to reactions of hydrazonoyl halides with heterocyclic systems containing a thiourea, such as 5-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1*H*-indeno[2',1':5,6]pyrido [2,3-*d*]pyrimidine-4,6-dione, in an attempt to develop a facile method for the preparation of 1,2,4-triazolo[4,3-*a*]pyrimidine derivatives. The latter compounds possess remarkable biological activity. They are cardiotonics, coronary vasodilators and they have antihypertensive properties [10]. They have been tested as microbicidal and bioregulator agents [11]. They act against *Aspergillus* and *Pencicillium* species [12]. They have been reported to exhibit *in vivo* leismanicidal activity against the amastigate stage of *Leishmania donovani* [13, 14] and cardiovascular activity [15, 16].

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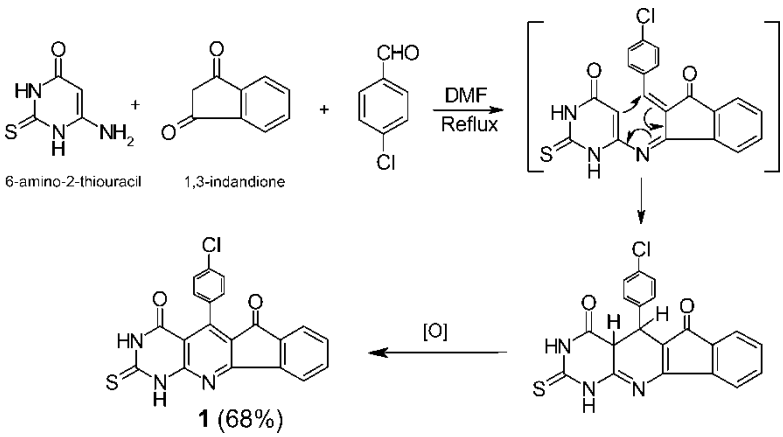
2. Results and discussion

The desired starting material 5-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1*H*-indeno[2',1':5,6]-pyrido[2,3-*d*]pyrimidine-4,6-dione (**1**) was prepared by refluxing equimolar amounts of 6-amino-2-thiouracil, 1,3-indandione and 4-chlorobenzaldehyde in DMF. Analytical data for compound **1** revealed a molecular formula $C_{20}H_{10}ClN_3O_2$ S (*m/z* 391). Its IR spectrum was characterized by the presence of an NH stretch at 3449 cm^{-1}, while stretching vibration frequencies of the carbonyl groups appeared at 1722 cm^{-1} and 1676 cm^{-1}. ^{1}H NMR spectroscopy was also used to confirm this structure; it showed the presence of aromatic protons at 7.25–7.90 ppm and two characteristic broad singlets at 12.50 ppm and 13.51 ppm assignable to the two NH groups. Finally, the formation of **1** (scheme 1) was proven using ^{13}C NMR, which revealed the presence of the expected sp^2 carbon atoms (c.f. Experimental section).

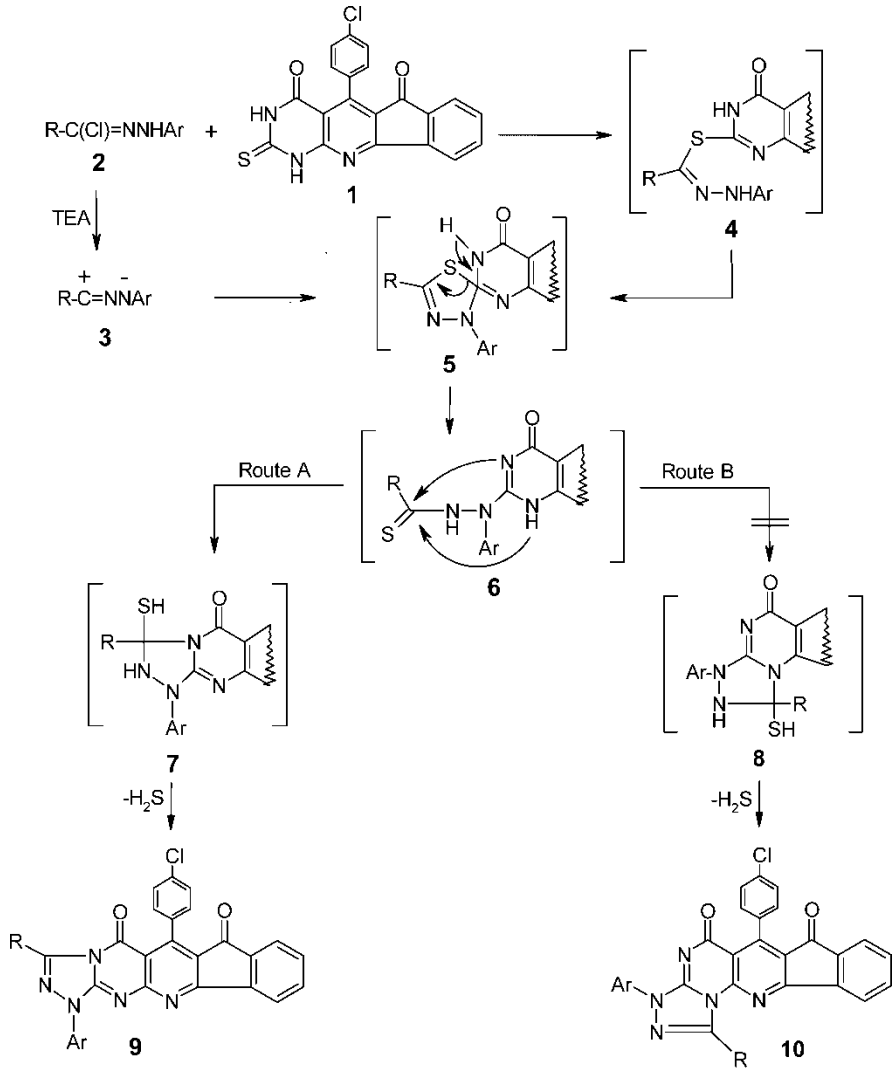


SCHEME 1

Reaction of **1** with hydrazonoyl halides **2** was carried out in THF under reflux in the presence of triethylamine or in the presence of sodium ethoxide in ethanol. The reaction proceeded cleanly, and a single product of a regioselective reaction was isolated in each case. Both spectroscopic data and elemental analyses are consistent with the structures of both **9** and **10**, respectively (scheme 2). The reaction pathway accounting for the formation of **9** or **10** is outlined in schemes 2 and 3. In scheme 2, it is proposed that the studied reactions involve an initial formation of thiohydrazonate esters **4**, which undergo a *Smiles* rearrangement to give the thiohydrazides **6** via the spiroadduct **5**. Also, compounds **6** can also be obtained via 1,3-dipolar cycloadditions of nitrilimines **3** (generated *in situ* from the reaction of hydrazonoyl chlorides **2** with TEA) onto the C=S thione group of **1**. The spiroadduct **5** cyclized with concurrent elimination of hydrogen sulfide to give the final product. As outlined in scheme 2, there are two possible routes (A and B) for the cyclization of **6** that will lead to **9** and **10** depending on the cyclization step involved. All attempts to isolate the thiohydrazonate ester **4** or the thiohydrazide open chain intermediates **6** failed.

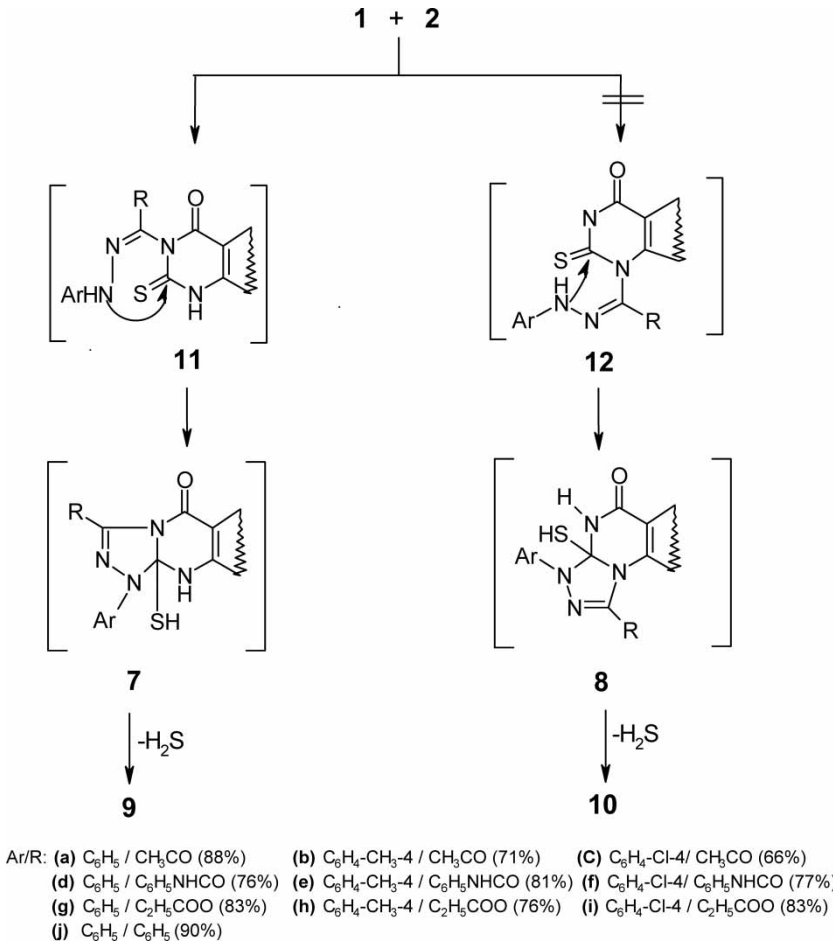
In scheme 3, it is suggested the reaction of **1** with **2** starts with nucleophilic attack on N3 or N1 to give the substitution products **11** or **12**, respectively. Cyclization of the latter intermediates and elimination of hydrogen sulfide would then give the final product **9** or **10**, respectively.

The ^{1}H NMR spectra of the isolated products were not of much help in differentiating structures **9** or **10**. An immediate distinction between these two possible pyrimidinones was



SCHEME 2

reached by comparison of the ^{13}C NMR and IR spectra. The carbonyl stretching frequencies of **9** (1660–1680 cm^{-1}) were found to be similar to those of pyrimidines of structure **14** (1680–1690 cm^{-1}), but not **13** (1640–1660 cm^{-1}) [21]. Literature reports [17–24] have shown that the chemical shift for the carbonyl carbon in 4-pyrimidinone derivatives is markedly affected by the nature of the adjacent nitrogen (N3). For example, the ^{13}C NMR carbonyl chemical shift of the imidazo[1,2-*a*]pyrimidinone derivatives of type **13** resonates between 170–175 ppm ($\geq$170 ppm) whereas that of the [1,2,4]triazolo[4,3-*a*]pyrimidinone derivatives of type **14** appears around 165 ppm (<170 ppm). The latter chemical shift is similar to those of the series prepared of type **9** (c.f. figure 1 and scheme 4). Also, we have recently reported that the



SCHEME 3

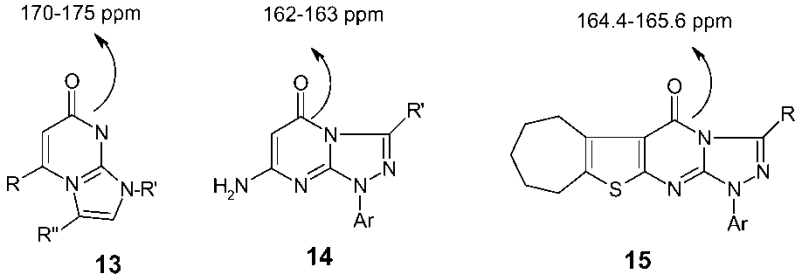
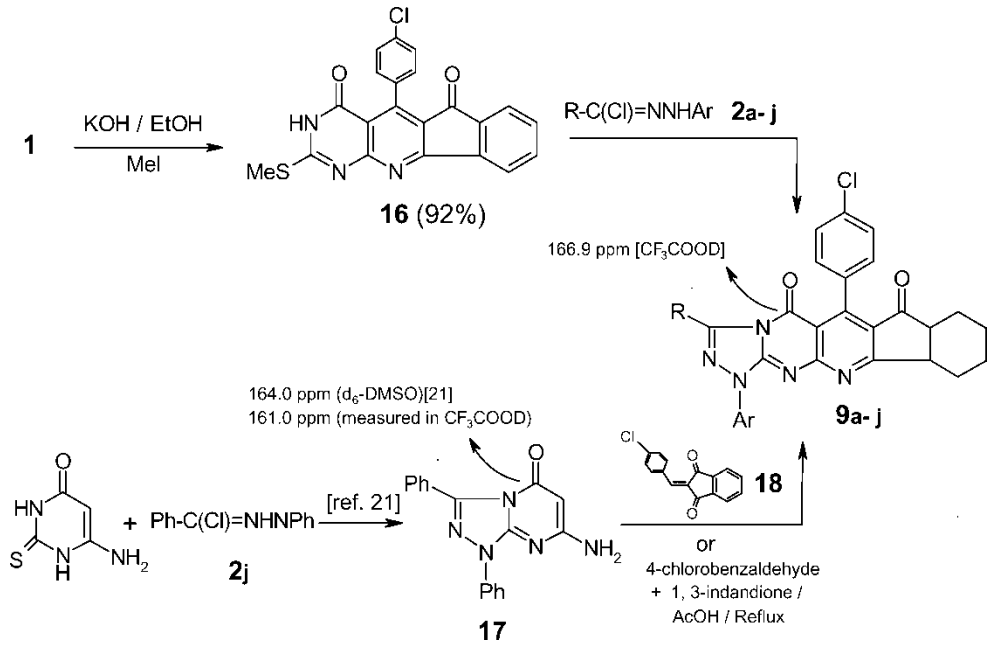


Figure 1. ^{13}C NMR shifts of strategic carbon atoms.

reaction of 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one or its methylthio derivative with hydrazonoyl halides led to the formation of product **15** whose angular structure was confirmed by X-ray crystallographic analysis [24]. Furthermore, reactions of 2-thiouracil derivatives and 1,2-dihydro-2-thioxopteridin-4(3*H*)-one with various hydrazonoyl halides yielded S-substituted products in all reported cases [18–23].

The final structural evidence was judged chemically by two alternative pathways. In the first pathway, the starting material **1** was converted to its 2-methylthio derivative **16** by treatment



SCHEME 4

with methyl iodide in presence of ethanolic sodium hydroxide. Then, the latter product was subjected to reaction with hydrazonoyl chlorides in the presence of sodium ethoxide to afford products that have identical chemical and physical properties with those obtained from **1** and **2**.

Moreover, in a simple experimental procedure, reaction of 7-amino-1,3-diphenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one **17** [21] with 2-(4-chlorobenzylidine)indan-1,3-dione **18** [24] or with 1,3-indandione and 4-chlorobenzaldehyde in acetic acid afforded **9j**, which were shown to be the same as those obtained from the reaction of **1** with **2j** by their melting point and spectral data (scheme 4). Based on these findings, the mechanism proposed in scheme 2 seems to be acceptable and the mechanism in scheme 3 should be discarded.

3. Conclusion

The above results indicate that reactions of **1** or **16** with hydrazonyl chlorides **2** provide facile and novel regioselective routes for the synthesis of indeno[2',1':5,6]pyrido[2,3-d][1,2,4]-triazolo[4,3-*a*]pyrimidinedione derivatives.

4. Experimental

The melting points are uncorrected and were measured on a Gallenkamp apparatus. The IR spectra were recorded as potassium bromide pellets on a Nexus 670 spectrophotometer; wave numbers $\nu(cm^{-1})$ are reported. The ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Varian Mercury VXR-300 spectrometer (Cairo University, Egypt) and Bruker 300 MHz (Guelph University and Brock University, Canada). Coupling constants J are reported in Hz and chemical shifts in ppm (δ values) against TMS as internal reference. Mass spectra were

recorded on EI + Q1 MSLMR UPLR spectrometers. Microanalyses were carried out with a Vario El Elmentar apparatus, their results were found to be in good agreement with the calculated values.

4.1 *5-(4-Chlorophenyl)-2-thioxo-2,3-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d] pyrimidine-4,6-dione(1)*

A mixture of equimolar amounts of 6-aminothiouracil (1.43 g, 10 mmol), 1,3-indandione (1.46 g, 10 mmol) and *p*-chlorobenzaldehyde (1.40 g, 10 mmol) in DMF (30 ml) was refluxed under stirring for 48 h. The solid product, so formed, was collected by filtration, washing with ethanol, drying and recrystallized from DMF. Yield 2.66 g (68%). M.p.: 374–376 °C; IR (KBr) υ (cm^{-1}): 3449 (NH), 1722, 1676 (CO); ^{1}H-NMR (300 MHz, *DMSO*-d_6): $\delta = 7.25$–7.90 (m, 8H, Ar), 12.50 (bs, 1H, NH, exchangeable with D_2O), 13.51 (br, 1H, NH, exchangeable with D_2O); ^{13}C-NMR (*DMSO*-d_6): 109.0, 121.4, 121.8, 123.6, 127.1, 129.8, 132.7, 133.2, 135.6, 136.0, 140.0, 149.8, 156.0, 158.6, 168.4, 175.5, 188.0; MS, m/z (M^+): 391. Anal. Calcd. for $C_{20}H_{10}ClN_3O_2S$ (391.8): C, 61.31; H, 2.57; N, 10.72, S, 8.18 Found: C, 61.52; H, 2.57; N, 10.71, S, 8.28.

4.2 *5-(4-Chlorophenyl)-2-methylthio-3H-indeno[2',1':5,6]pyrido[2,3-d] pyrimidine-4,6-dione(16)*

To a warm solution of KOH (0.14 g, 2.50 mmol) in EtOH (20 mL) was added **1** (2.50 mmol). The mixture was heated gently for 1 h. After cooling to room temperature, a solution of iodomethane (0.43 g, 3 mmol) in EtOH (5 mL) was added. The reaction mixture was stirred at 40 °C for 12 h. The separated solid was filtered off, washed with H_2O (3 × 5 mL), cold EtOH (2 × 2 mL), dried and crystallized from DMF to afford **16.** Yield 0.93 g (92%). M.p.: 297–299 °C; IR (KBr) υ (cm^{-1}): 3448 (NH), 1722, 1659 (CO); ^{1}H-NMR (300 MHz, *DMSO*-d_6): $\delta = 2.59$ (s, 3H, CH_3), 7.29–7.90 (m, 8H, Ar), 12.05 (bs, 1H, NH, exchangeable with D_2O); MS, m/z (M^+): 405. Anal. Calcd. for $C_{21}H_{12}ClN_3O_2S$ (405.9): C, 62.15; H, 2.98; N, 10.35, S, 7.90 Found: C, 62.25; H, 3.01; N, 10.35, S, 7.89.

4.3 *General procedure for the syntheses of indeno[2',1':5,6]pyrido[2,3-d][1,2,4] triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione derivatives(9)*

4.3.1 Method A. To a mixture of equimolar amounts of **1** and the appropriate hydrazonoyl chlorides **2** (10 mmol each) in absolute ethanol (60 ml) (and 5 ml DMF if necessary for solubility reasons), triethylamine (1.40 ml, 10 mmol) was added, and the resulting mixture was refluxed until hydrogen sulfide gas evolution ceased (6–8 h). The solid product, so formed, was collected by filtration, washed with H_2O (2 × 5 ml), cold EtOH (2 × 5 ml), dried and crystallized from the proper solvent to afford **9**.

4.3.2 Method B. To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 10 mg atom) and absolute ethanol (20 ml) (and 5 ml DMF if necessary for solubility reasons), was added **16** (4.06 g, 10 mmol). To the resulting solution was added the appropriate hydrazonoyl chlorides **2** (10 mmol) portionwise under stirring. After the addition was complete, the reaction mixture was refluxed until methanethiol ceased to evolve (6–11 h) and complete as described for method A. The products obtained by this method were found to be identical in all respects with those obtained by method A.

4.3.3 Method C. A mixture of **17** [21] (2.69 g, 10 mmol), 1,3-indandione (1.46 g,10 mmol) and *p*-chlorobenzaldehyde (1.40 g, 10 mmol) in 50 ml of AcOH was refluxed for 10 h, the precipitated solid was collected, dried, and recrystallized from dioxane to give the corresponding product **9**, which proved to be identical in all respects with that obtained by either method A or method B.

4.4 *3-Acetyl-1-phenyl-6-(4-chlorophenyl)indeno[2',1':5,6]pyrido[2,3-d][1,2,4] triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9a)*

Yield 4.56 g (88%). M.p.: 387–389 °C; IR (KBr) υ (cm^{-1}): 1721, 1676; ^{1}H-NMR (300 MHz, *DMSO*-d_6): $\delta = 2.63$ (s, 3H, CH_3), 7.37–8.20 (m, 13H, Ar); ^{13}C-NMR (*CF_3COOD*): 29.5, 112.0, 123.5, 124.7, 125.0, 126.5, 127.5, 128.2, 130.0, 130.2, 131.1, 131.3, 131.5, 132.0, 132.8, 134.9, 136.4, 138.6, 139.3, 139.9, 140.1, 144.8, 150.9, 155.2, 158.3, 166.9, 189.1, 190.7; MS, m/z (M^+): 517; Anal. Calcd. for $C_{29}H_{16}ClN_5O_3$ (517.94): C, 67.25; H, 3.11; N, 13.52 Found: C, 67.29; H, 3.09; N, 13.51.

4.5 *3-Acetyl-1-(4-methylphenyl)-6-(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d] [1,2,4]triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9b)*

Yield 3.78 g (71%). M.p.: 361–363 °C; IR (KBr) υ (cm^{-1}): 1710, 1672; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 2.49$ (S, 3H, CH_3), 2.62 (s, 3H, **C**H_3CO), 7.37–8.20 (m, 12H, Ar); MS, m/z (M^+): 531; Anal. Calcd. for $C_{30}H_{18}ClN_5O_3$ (531.96): C, 67.74; H, 3.41; N, 13.17 Found: C, 67.73; H, 3.40; N, 13.15.

4.6 *3-Acetyl-1,6-di(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d][1,2,4]triazolo-[4,3-a] pyrimidin-5,7(1H,7H)-dione(9c)*

Yield 3.64 g (66%). M.p.: 342–344 °C; IR (KBr) 1713, 1671 υ (cm^{-1}): 1715, 1674; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 2.62$ (s, 3H, CH_3CO), 7.38–8.21 (m, 12H, Ar); ^{13}C-NMR (*CF_3COOD*): $\delta = 112.1$, 123.6, 125.7, 127.5, 128.2, 130.1, 130.3, 131.1, 131.4, 131.5, 132.2, 134.8, 134.9, 138.6, 139.2, 139.3, 139.7, 140.1, 144.8, 150.8, 155.0, 158.2, 166.9, 188.9, 190.4; MS, m/z (M^+): 552; Anal. Calcd. for $C_{29}H_{15}Cl_2N_5O_3$ (552.38): C, 63.06; H, 2.74; N, 12.68 Found: C, 63.17; H, 2.81; N, 12.65.

4.7 *3-Phenylcarbamoyl-1-phenyl-6-(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d] [1,2,4]triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9d)*

Yield 4.52 g (76%). M.p.: 351–353 °C; IR (KBr) υ (cm^{-1}): 3410, 1716, 1680, 1644; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 7.34$–8.00 (m, 18H, Ar), 9.01 (s, 1H, NH, exchangeable with D_2O); MS, m/z (M^+): 595; Anal. Calcd. for $C_{34}H_{19}ClN_6O_3$ (595.02): C, 68.63; H, 3.22; N, 14.12 Found: C, 68.85; H, 3.33; N, 14.16.

4.8 *3-Phenylcarbamoyl-1-(4-methylphenyl)-6-(4-chlorophenyl)-indeno[2',1':5,6] pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9e)*

Yield 4.93 g (81%). M.p.: 345–347 °C; IR (KBr) υ (cm^{-1}): 3398, 1719, 1678, 1648; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 2.43$ (S, 3H, CH_3), 7.34–8.06 (m, 17H, Ar), 9.00 (s, 1H, NH, exchangeable with D_2O); MS, m/z (M^+): 609; Anal. Calcd. for $C_{35}H_{21}ClN_6O_3$ (609.05): C, 69.02; H, 3.46; N, 13.80 Found: C, 69.11; H, 3.48; N, 13.78.

4.9 *3-Phenylcarbamoyl-1,6-di(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d][1,2,4] triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9f)*

Yield 4.85 g (77%). M.p.: 322–324 °C; IR (KBr) υ (cm^{-1}): 3401, 1722, 1676, 1643; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 7.36$–8.26 (m, 17H, Ar), 9.10 (s, 1H, NH, exchangeable with D_2O); MS, m/z (M^+): 629; Anal. Calcd. for $C_{34}H_{18}Cl_2N_6O_3$ (629.47): C, 64.88; H, 2.88; N, 13.35 Found: C, 64.79; H, 2.87; N, 13.36.

4.10 *3-Ethoxycarbonyl-1-phenyl-6-(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d] [1,2,4]triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9g)*

Yield 4.55 g (83%). M.p.: 313–315 °C; IR (KBr) υ (cm^{-1}): 1711, 1662; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 1.29$ (t, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.35–8.22 (m, 13H, Ar); MS, m/z (M^+): 547; Anal. Calcd. for $C_{30}H_{18}ClN_5O_4$ (547.96): C, 65.76; H, 3.31; N, 12.78 Found: C, 65.73; H, 3.29; N, 12.73.

4.11 *3-Ethoxycarbonyl-1-(4-methylphenyl)-6-(4-chlorophenyl)indeno-[2',1':5,6] pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9h)*

Yield 4.27 g (76%). M.p.: 303–305 °C; IR (KBr) υ (cm^{-1}): 1710, 1671; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 1.28$ (t, 3H, CH_3), 2.49 (S, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.35–8.08 (m, 12H, Ar); MS, m/z (M^+): 561; Anal. Calcd. for $C_{31}H_{20}ClN_5O_4$ (561.99): C, 66.25; H, 3.59; N, 12.46 Found: C, 66.27; H, 3.64; N, 12.48.

4.12 *3-Ethoxycarbonyl-1,6-di(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d][1,2,4] triazolo[4,3-a]pyrimidin-5,7(1H,7H)-dione(9i)*

Yield 4.60 g (83%). M.p.: 317–319 °C; IR (KBr) υ (cm^{-1}): 1712, 1669; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 1.29$ (t, 3H, CH_3), 4.42 (q, 2H, CH_2), 7.36–8.20 (m, 12H, Ar); ^{13}C-NMR (CF_3COOD): $\delta = 14.3$, 68.6, 111.8, 123.4, 125.6, 127.5, 128.2, 130.4, 131.1, 131.2, 134.9, 138.6, 139.2, 139.3, 139.4, 139.9, 140.0, 149.9, 154.9, 158.5, 159.2, 166.9, 189.0; MS, m/z (M^+): 582; Anal. Calcd. for $C_{30}H_{17}Cl_2N_5O_4$ (582.41): C, 61.87; H, 2.94; N, 12.02 Found: C, 61.88; H, 2.92; N, 12.03.

4.13 *1,3-Diphenyl-6-(4-chlorophenyl)-indeno[2',1':5,6]pyrido[2,3-d][1,2,4]triazolo [4,3-a]pyrimidin-5,7(1H,7H)-dione(9j)*

Yield 4.97 g (90%). M.p.: 362–364 °C; IR (KBr) υ (cm^{-1}): 1716, 1667; ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 7.35$–8.22 (m, Ar); MS, m/z (M^+): 552; Anal. Calcd. for $C_{33}H_{18}ClN_5O_2$ (552.00): C, 71.81; H, 3.29; N, 12.69 Found: 71.79; H, 3.27; N, 12.70.

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