

Scientific paper

# A Convenient Synthesis of Some New Bioactive Diheterocyclic Thioether and Thiazolopyrimidine Derivatives

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## Abstract

2-Carboxymethylthiopyrimidinone derivative **1b** was utilized for the synthesis of some new diheterocyclic thioethers via its reaction with some acetals followed by cyclization of the products with 2-aminoheterocyclic compounds or through the reaction of **1b** with *p*-tolyl diazonium chloride followed by the reaction of the product with active methylene compounds. Also, some new thiazolopyrimidines were synthesized from 2-mercaptopyrimidine **1a** or from 5-pyrimidinylmercaptoacetic acid derivative **1c**. The molluscicidal activity of some synthesized compounds towards *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni*, was investigated.

**Keywords:** Diheterocyclic thioethers, thiazolopyrimidines, molluscicidal activity.

## 1. Introduction

Schistosomiasis, commonly known as bilharzias, is a parasitic disease caused by threadworms of the genus *Schistosoma* and is endemic throughout South America, Africa and the Far East. The reproductive cycle of *Schistosoma* involves a stage implicating aquatic snails of the genus *Biomphalaria* and *Bulinus* in which the parasite multiplies into cercariae. These cercariae can penetrate the skin of a human who comes into contact with contaminated water. Thus, the habits of Egyptian farmers being in daily contact with the Nile water canals and streams during irrigation process cause Schistosomiasis to still represent one of the main national health problems in Egypt. Great national and international efforts are being done to combat this disease. Therefore, snails control by molluscicidal agents is considered essential in schistosomal control. Copper sulphate and miclosamide were used in Egypt within a program developed by Bayer AG, however, due to their hazardous environmental effects,<sup>1</sup> the program was stopped. Therefore, the search for synthetic or naturally occurring molluscicides is still ongoing. Pre-

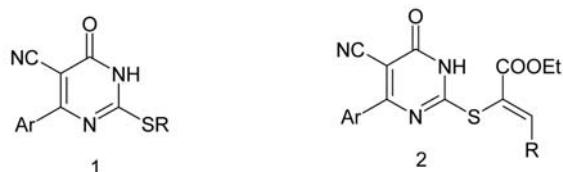
viously, as a part of our program directed towards syntheses of some new heterocyclic systems, we have tested pyrazole derivatives, pyrazolopyrimidines,<sup>2</sup> and indole derivatives<sup>3</sup> as molluscicidal agents against *Biomphalaria alexandrina* snails. The present work explores some novel pyrimidinyl heterocyclic thioethers and thiazolopyrimidines and tests some of them as molluscicidal agents.

## 2. Results and Discussion

The reactivity of thiols is in most instances sufficient to achieve the direct replacement of halides without catalyst resulting in the formation of an aryl sulfur bond.<sup>4</sup> The synthesis of bispyrimidine thioethers has been accomplished previously through direct nucleophilic attack of a thiolate anion on a pyrimidine halide<sup>5–8</sup> using Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst. Previously, we reported the synthesis of pyrimidinyl pyridyl thioether and pyrimidinyl phthalazine thioether from the reaction of 4(3*H*)-pyrimidinethione with 2-chloropyridine derivative and 1-chlorophthalazine derivative, respectively.<sup>9</sup> The present investigation deals with the synthesis of some pyrimidinyl heterocyclic

thioethers via a new route different than the reaction between thiols and heterocyclic halides.

It has been reported that pyrimidinethiols are readily alkylated on the exocyclic sulphur atom when treated with haloesters and haloacids in basic medium. Thus, when 4-(4-methoxyphenyl)-6-oxo-2-sulfanyl-1,6-dihydro-5-pyrimidine carbonitrile (**1a**)<sup>10</sup> was allowed to react with ethyl chloroacetate and with chloroacetic acid in ethanolic potassium hydroxide solution, ethyl {[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl} acetate (**1b**) and 2-carboxymethylthiopyrimidine derivative **1c**<sup>11</sup> were obtained, respectively. Compound **1c** was also obtained from alkaline hydrolysis of **1b**.



a, R= H; Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

b, R= CH<sub>2</sub>COOEt; Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

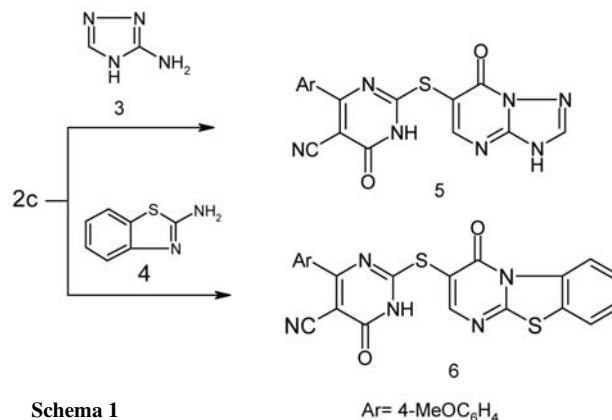
c, R= CH<sub>2</sub>COOH; Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

a, R= Me; Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

b, R= COMe; Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

c, R= NMe<sub>2</sub>; Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

Structures of compounds **1a,b** were elucidated with the help of elemental analysis and spectral data. The <sup>1</sup>H NMR spectra (DMSO-*d*<sub>6</sub>) of **1b** revealed the presence of one triplet and one quartet signal at δ 1.12 and 4.13 ppm

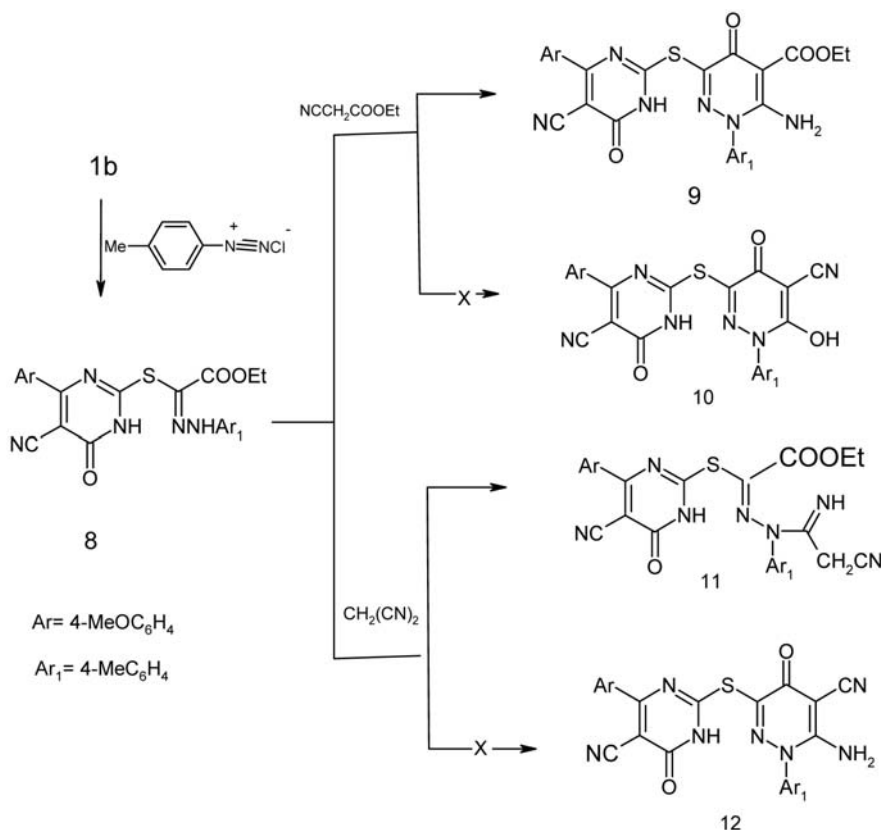


Scheme 1

Ar= 4-MeOC<sub>6</sub>H<sub>4</sub>

attributed to CH<sub>3</sub>CH<sub>2</sub> of ethyl ester, while that of compound **1c** revealed the absence of these two signals. Condensation of the active methylene compound **1b** with some acetals such as acetaldehyde diethylacetal, pyruvaldehyde dimethylacetal and dimethylformamide dimethylacetal in apolar solvents (toluene or xylene) yielded ethyl pyrimidin-2-yl thiobutenoate **2a**, ethyl pyrimidin-2-yl thiopentanoate **2b** and pyrimidin-2-ylthio(dimethylamino)arylate **2c**.

Structure of compounds **2a–c** was confirmed on the basis of elemental analyses and spectral data. The mass spectrometry of the enaminone **2c** did not exhibit a molecular ion peak but it showed a peak at *m/z* 372 attributed to M–CO. The <sup>1</sup>H NMR of **2c** furnished a signal at δ 3.19 ppm for six protons of dimethylamino group. When the



Scheme 2

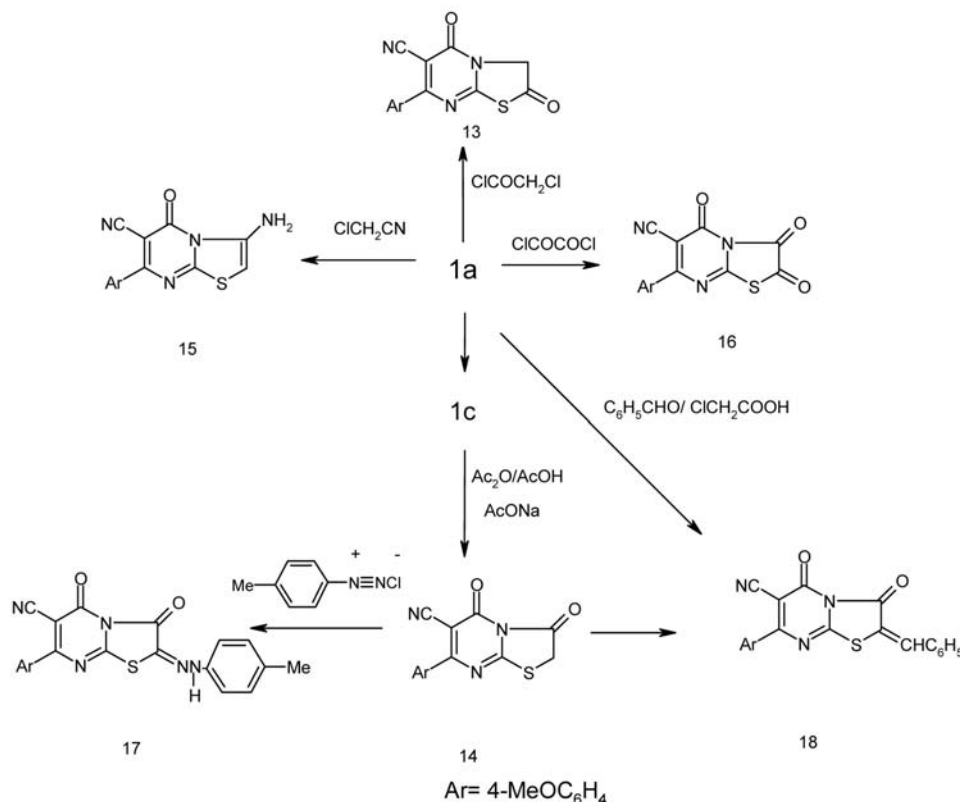
enaminone **2c** was allowed to react with 3-amino-1,2,4-triazole (**3**) and with 2-aminobenzothiazole (**4**) in boiling acetic acid, the thioethers **5** and **6**, were obtained, respectively (Scheme 1). The mass spectrometry of **6** showed a molecular ion peak at  $m/z$  459.

On the other hand, compound **2b** with its active methylene group was readily coupled with *p*-tolyl diazonium chloride **7** to afford 2-carboxy(*p*-tolylhydrazono)methylthiopyrimidine **8**. Treatment of **8** with ethyl cyanoacetate in benzene and ammonium acetate mixture yielded a thioether with two possible structures: either **9** or **10**. Compound **10** was ruled out based on the  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ) which revealed the absence of a triplet and quartet signals of ethyl ester. The trial to prepare another 3-pyridazinyl-2-pyrimidinyl thioether **12** from the reaction of the hydrazone **8** with malonitrile failed, however the Michael adduct **11** was obtained (Scheme 2) as clearly shown by its  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ) exhibiting signals at  $\delta$  1.12 and 4.11 ppm attributed to  $\text{CH}_3$  and  $\text{CH}_2$  protons of ethyl ester group.

reas its isomer **14**<sup>16</sup> was formed when compound **1c** was boiled in acetic anhydride, sodium acetate and acetic acid mixture (Scheme 3). Alkylation of **1a** with chloroacetonitrile in boiling ethanol containing triethyl amine afforded 3-aminothiazolopyrimidine **15**; whereas the reaction of **1a** with dioxalyl chloride gave 2,3,5-trioxothiazolopyrimidine **16** (Scheme 3).

The presence of an active methylene group in compound **14** was exploited via its ability to couple with *p*-tolyl diazonium chloride leading to the formation of hydrazono compound **17**. The mass spectrum of **17** showed a molecular ion peak at  $m/z$  417. Also, condensation of **14** with benzaldehyde confirmed the presence of an active methylene group in **14** and led to the formation of 2-benzylidene-thiazolopyrimidine derivative **18**. Assignment of the structure **18** was established via its alternative synthesis from **1a** and benzaldehyde, monochloroacetic acid, acetic anhydride, acetic acid and sodium acetate.

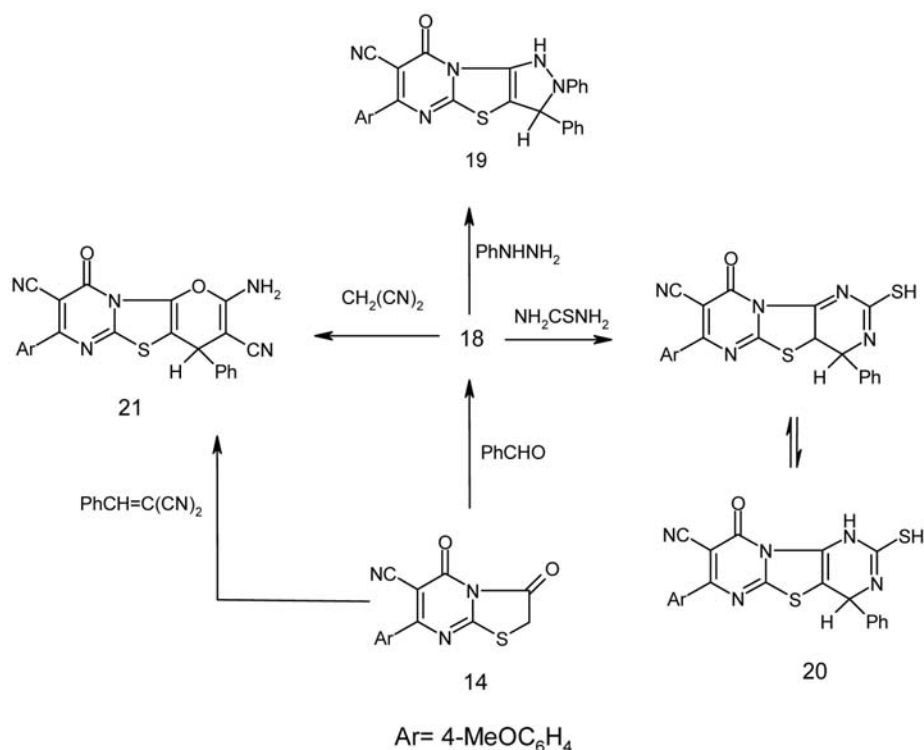
Moreover, the reactivity of the cyclic enone moiety in compound **18** towards bifunctional nucleophiles such



Scheme 3

Also, in continuation of our work on the chemistry of pyrimidines,<sup>12–13</sup> and thiazoles,<sup>14–15</sup> it was of interest to combine thiazole and pyrimidine moieties in a molecular framework to study their potential molluscicidal activity. Thus, some new thiazolopyrimidines were synthesized from 2-mercaptopyrimidine **1a** or from 5-pyrimidinemercaptoacetic acid **1c**. Therefore, thiazolopyrimidine **13** was obtained on reacting **1a** with chloroacetyl chloride whe-

as phenylhydrazine and thiourea is a good support for its structure. Thus, when compound **18** was allowed to react with phenylhydrazine, the pyrazolothiazolopyrimidinone **19** was obtained, whereas pyrimidothiazolopyrimidinone **20** was formed via cyclocondensation of **18** with thiourea in boiling ethanol containing catalytic amount of piperidine. Further, treatment of **18** with malonitrile in basic medium furnished the pyranothiazolopyrimidine **21**. The



Scheme 4

latter compound is also obtained on reacting **14** with  $\alpha$ -cyanocinnamitrile in boiling pyridine.

## 2. 1. Molluscicidal Activity

A stock solution of 1000 ppm of each tested compound was separately prepared using dechlorinated tap water on the basis of weight/volume, with the pH of water 7–7.7 and at temperature 25–27 °C. Series of 6 concentrations expressed in terms of ppm would permit to calculate the half and nearly full-lethal doses LC<sub>50</sub> and LC<sub>90</sub> according to Litchfield and Wilcoxon method.<sup>17</sup> The snails were exposed to each concentration for 24 h followed by 24 h recovery period in only dechlorinated water. The molluscicidal activity of some novel thioethers and thiazolopyrimidine derivatives against *Biomphalaria alexandrina* snails is shown in Table 1.

**Table 1:** The molluscicidal activity of some new synthesized compounds

Compound	Concentration (ppm)					
	200	100	75	50	20	10
<b>1a</b>	0	0	0	0	0	0
<b>1b</b>	0	0	0	0	0	0
<b>13</b>	50	10	0	0	0	0
<b>15</b>	0	0	0	0	0	0
<b>17</b>	0	0	0	0	0	0
<b>18</b>	100	100	80	40	20	0
<b>20</b>	100	60	10	0	0	0
<b>21</b>	0	0	0	0	0	0

**Table 2:** Susceptibility of *Biomphalaria alexandrina* snails to certain compounds after 24 and 48 h.

Compound	Time (h)	LC50 ppm	LC90 ppm	S (slope)
<b>18</b>	24	42 (32.95–53.82)	73	1.32
	48	40 (28.54–50.91)	70	1.31
<b>20</b>	24	44 (32.89–58.43)	70	1.31
	48	41 (29.75–49.82)	68	1.26

The results showed that the introduction of arylidene moiety to the thiazolopyrimidine or another pyrimidinethione moiety to thiazolopyrimidine led to an increase in the molluscicidal activity. Also, the presence of sulfur in their structures enhances the molluscicidal activity compared with that shown in the case of our previous studies on pyrazolopyrimidines<sup>2</sup> and indole derivatives.<sup>3</sup>

## 3. Experimental

All reported melting points are uncorrected. The IR spectra were recorded on FTIR Bruker Vector 22 spectrophotometer using KBr wafer technique. <sup>1</sup>H NMR spectra were measured on Varian Gemini spectrophotometer 200 MHz using TMS ( $\delta$  ppm) as an internal standard. Mass spectra were obtained using GCMS Qp 1000 ex Shimadzu instrument (70 eV). Elemental analyses were carried out at Microanalysis center, Cairo University.

**4-(4-Methoxyphenyl)-6-oxo-2-sulfanyl-1,6-dihydro-5-pyrimidine carbonitrile (1a).** This compound was prepared using the reported method.<sup>10</sup>

**Ethyl {[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl}acetate (1b).**<sup>11</sup> A mixture of **1a** (10 mmol) and ethyl chloroacetate (15 mmol) in ethanolic potassium hydroxide solution (prepared by dissolving 0.56 g (10 mmol) of KOH in 50 mL ethanol) 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 ethanol. Yield 78%, mp 180–182 °C, yellow crystals. IR (KBr)  $\nu$  3488 (NH), 3030 (aromatic CH), 2982 (aliphatic CH), 2221 (CN), 1738 (C=O of ester), 1653 (C=O of cyclic amide), 1599, 1554 (C=N, C=C)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.12 (t, *J* = 7.5 Hz, 3H, CH<sub>3</sub> of ethyl ester), 3.36 (s, 2H, SCH<sub>2</sub>CO), 3.86 (s, 3H, OCH<sub>3</sub>), 4.13 (q, *J* = 7.5 Hz, 2H, CH<sub>2</sub> of ethyl ester), 7.99–8.09 (m, 4H, ArH), 8.27 (s, 1H, NH). MS *m/z* 345 (M, 2), 301 (M–CO<sub>2</sub>, 1), 228 (100%). Anal. Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>S: C, 55.65; H, 4.34; N, 12.17; S, 9.27. Found: C, 55.40; H, 4.30; N, 12.19; S, 9.22.

**{[5-Cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl}acetic acid (1c).**<sup>11</sup> **Method A:** A mixture of **1a** (10 mmol) and chloroacetic acid (10 mmol) in ethanolic potassium hydroxide solution (prepared by dissolving 0.56 g (10 mmol) of KOH in 50 mL ethanol) was heated under reflux for 5 h. The solid obtained upon dilution with water was filtered off and recrystallized from methanol. Yield 65%, mp 208–210 °C.

**Method B:** A mixture of **1b** (30 mmol) and aqueous sodium hydroxide (100 mL, 2.0 M NaOH) was heated under reflux for 2 h, then filtered while hot. The filtrate was acidified with hydrochloric acid and the solid formed was filtered off. The crude material was purified by dissolving in aqueous sodium carbonate and then reprecipitated using hydrochloric acid. The solid obtained was filtered off and recrystallized from methanol. Yield 75%, mp 208–210 °C, yellow crystals. IR (KBr)  $\nu$  3600–3250 (broad OH), 3100 (NH), 3015 (aromatic CH), 2978 (aliphatic CH), 2222 (CN), 1715 (C=O of carboxylic group), 1668 (C=O of cyclic amide), 1600, 1536 (C=N, C=C)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.88 (s, 3H, OCH<sub>3</sub>), 4.07 (s, 2H, CH<sub>2</sub>), 7.20–8.04 (m, 5H, ArH, NH), 8.33 (s, 1H, OH). MS *m/z* 317 (M, 6), 273 (M–CO<sub>2</sub>), 229 (100%). Anal. Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>S: C, 52.99; H, 3.47; N, 13.24; S, 10.09. Found: C, 52.45; H, 3.43; N, 13.30; S, 10.40.

**Reaction of 1b with acetals; formation of 2a–c.** To a solution of **1b** (10 mmol) in dry xylene (15 mL) acetaldehyde diethyl acetal, pyruvaldehyde dimethyl acetal or dimethylformamide dimethyl acetal (0.01 mol) was added. The reaction mixture was heated under reflux for 3

h. The solid obtained on evaporation of the excess solvent was filtered off and recrystallized from methanol to produce **2a–c**.

**Ethyl 2-[[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl]-2-butenate (2a).** Yield 72%, mp 210–212 °C, colourless crystals. IR (KBr)  $\nu$  3311 (NH), 3010 (aromatic CH), 2937 (aliphatic CH), 2216 (CN), 1736 (C=O of ester), 1661 (C=O of cyclic amide), 1604, 1548 (C=N, C=C)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.12 (t, *J* = 7.5 Hz, 3H, CH<sub>3</sub> of ethyl ester), 2.08 (s, 3H, CH<sub>3</sub> of ethylidene group), 3.85 (s, 3H, OCH<sub>3</sub>), 4.10 (q, *J* = 7.5 Hz, 2H, CH<sub>2</sub> of ethyl ester), 7.09–7.12 (m, 4H, ArH), 7.95 (s, 1H, olefinic CH), 7.98 (s, 1H, NH). MS *m/z* 371 (M, 2), 340 (1), 228 (100%). Anal. Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S: C, 58.22; H, 4.58; N, 11.32. Found: C, 58.30; H, 4.50; N, 11.10.

**Ethyl 2-[[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl]-4-oxo-2-pentenoate (2b).** Yield 58%, mp 204–206 °C, colourless crystals. IR (KBr)  $\nu$  3442 (NH), 3005 (aromatic CH), 2971 (aliphatic CH), 2208 (CN), 1731, 1700 (C=O of ester and acetyl), 1660 (C=O of cyclic amide), 1600, 1571 (C=N, C=C)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.12 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub> of ethyl ester), 2.49 (s, 3H, CH<sub>3</sub>CO), 3.85 (s, 3H, OCH<sub>3</sub>), 4.12 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub> of ethyl ester), 7.09–7.12 (m, 4H, ArH), 7.96 (s, 1H, olefinic CH), 7.98 (s, 1H, NH). MS *m/z* 339 (M, 9), 356 (12), 229 (100%). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub>S: C, 57.14; H, 4.26; N, 10.52. Found: C, 57.25; H, 4.30; N, 10.60.

**Ethyl 2-[[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl]-3-(dimethylamino)-2-propenoate (2c).** Yield 60%, mp 110–112 °C, yellow crystals. IR (KBr)  $\nu$  3394 (NH), 3020 (aromatic CH), 2936 (aliphatic CH), 2206 (CN), 1734 (C=O of ester), 1654 (C=O of cyclic amide), 1607, 1588 (C=N, C=C)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.12 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub> of ethyl ester), 3.19 (s, 6H, 2CH<sub>3</sub> of *N,N*-dimethylamino group), 3.72 (s, 3H, OCH<sub>3</sub>), 4.22 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub> of ethyl ester), 6.98–7.13 (m, 4H, ArH), 7.77 (s, 1H, olefinic CH), 7.80 (s, 1H, NH). MS *m/z* 372 (M–CO, 1), 242 (C<sub>11</sub>H<sub>4</sub>N<sub>3</sub>O<sub>2</sub>S, 100%), 303 (2), 270 (35), 214 (28), 200 (81), 159 (59), 148 (44). Anal. Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S: C, 56.99; H, 5.03; N, 13.99; S, 8.01. Found: C, 57.30; H, 4.94; N, 13.91; S, 8.11.

**4-(4-Methoxyphenyl)-6-oxo-2-[(7-oxo-3,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)sulfanyl]-1,6-dihydro-5-pyrimidinecarbonitrile (5).** A mixture of **2c** (10 mmol) and 2-aminotriazole (**3**) (10 mmol) in acetic acid (5 mL) was refluxed for 2 h. The solid obtained was filtered off and recrystallized from butan-1-ol. Yield 55%, mp 312–314 °C, yellow crystals. IR (KBr)  $\nu$  3337, 3211 (NH), 3060 (aromatic CH), 2929 (aliphatic CH), 2215

(CN), 1700, 1655 (C=O), 1599, 1550 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  3.84 (s, 3H, OCH<sub>3</sub>), 7.07–7.89 (m, 8H, ArH, C<sub>2</sub>-H, C<sub>7</sub>-H, 2  $\times$  NH). MS  $m/z$  393 (M, 2), 339. Anal. Calcd for C<sub>17</sub>H<sub>11</sub>N<sub>7</sub>O<sub>3</sub>S: C, 51.90; H, 2.79; N, 24.93. Found: C, 51.46; H, 2.83; N, 24.80.

**4-(4-Methoxyphenyl)-6-oxo-2-[(4-oxo-4H-pyrimido[2,1-*b*][1,3]benzothiazol-3-yl)sulfanyl]-1,6-dihydro-5-pyrimidinecarbonitrile (6).** A mixture of **2c** (1 mmol) and 2-aminobenzothiazole (**4**) (1 mmol) in acetic acid (5 mL) was refluxed for 2.5 h. The solid obtained was filtered off and recrystallized from DMF. Yield 60%, mp > 320 °C, colourless crystals. IR (KBr)  $\nu$  3422 (NH), 3069 (aromatic CH), 2968 (aliphatic CH), 2221 (CN), 1710, 1650 (C=O), 1606, 1573 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  3.75 (s, 3H, OCH<sub>3</sub>), 6.89 (m, 10H, ArH, NH). MS  $m/z$  459 (M, 2), 84 (C<sub>3</sub>H<sub>4</sub>N<sub>2</sub>O, 100), 383 (6), 313 (11), 264 (12), 213 (15), 157 (13), 129 (36), 55 (93%). Anal. Calcd for C<sub>22</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub>S<sub>2</sub>: C, 57.51; H, 2.83; N, 15.25; S, 13.94. Found: C, 57.95; H, 2.89; N, 15.47; S, 13.75.

**Ethyl {[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl}[(4-methylphenyl)hydrazono]ethanoate (8).** To a cold solution of compound **1b** (10 mmol) in ethanol (80 mL), containing sodium acetate (2 g) was added *p*-tolyl diazonium chloride (**7**) [prepared by adding concentrated hydrochloric acid (3 mL) to *p*-toluidine (10 mmol) at 0–5 °C and treating the resulting hydrochloride solution with a cold solution of sodium nitrite (10 mmol) in water (5 mL)] dropwise with stirring at 0–5 °C. The reaction mixture was stirred at room temperature for 2 h and then diluted with (30 mL) water. The solid obtained was filtered off and recrystallized from methanol. Yield 68%, mp 200–202 °C, orange crystals. IR (KBr)  $\nu$  3468, 3295 (NH), 3060 (aromatic CH), 2979 (aliphatic CH), 2218 (CN), 1741 (C=O of ester), 1653 (C=O of cyclic amide), 1599, 1556 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  1.12 (t,  $J = 7.3$  Hz, 3H, CH<sub>3</sub> of ethyl ester), 3.30 (s, 3H, CH<sub>3</sub> of *p*-tolyl), 3.85 (s, 3H, OCH<sub>3</sub>), 4.11 (q,  $J = 7.3$  Hz, 2H, CH<sub>2</sub> of ethyl ester), 7.08–7.98 (m, 10H, ArH, 2  $\times$  NH). MS  $m/z$  463 (M, 4), 419 (6), 373 (14), 229 (100%). Anal. Calcd for C<sub>23</sub>H<sub>21</sub>N<sub>5</sub>O<sub>4</sub>S: C, 59.61; H, 4.53; N, 15.11; S, 6.91. Found: C, 59.33; H, 4.50; N, 15.17; S, 6.74.

**6-[[5-Cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl]-3-hydroxy-2-(4-methylphenyl)-5-oxo-2,5-dihydro-4-pyridazinecarbonitrile (9).** A suspension of **8** (1 mmol), ethyl cyanoacetate (1 mmol) in benzene (30 mL) and ammonium acetate (1.0 g) was heated at 180 °C for 5 min. The reaction mixture was left overnight at room temperature and then triturated with ethanol. The solid obtained was filtered off and recrystallized from ethanol. Yield 60%, mp 215–217 °C, colourless crystals. IR (KBr)  $\nu$  3250, 3177, 3100 (NH<sub>2</sub>, NH), 3005

(aromatic CH), 2937 (aliphatic CH), 2207 (CN), 1740 (C=O of ester), 1680, 1655 (C=O), 1604, 1550 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  1.13 (t,  $J = 7.4$  Hz, 3H, CH<sub>3</sub> of ethyl ester), 2.50 (s, 3H, CH<sub>3</sub> of *p*-tolyl), 3.64 (s, br, 2H, NH<sub>2</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.10 (q,  $J = 7.4$  Hz, 2H, CH<sub>2</sub> of ethyl ester), 7.08–7.99 (m, 9H, ArH, NH). MS  $m/z$  530 (M, 1), 489 (7), 442 (2), 314 (100%). Anal. Calcd for C<sub>26</sub>H<sub>22</sub>N<sub>6</sub>O<sub>5</sub>S: C, 58.86; H, 4.15; N, 15.84; S, 6.03. Found: C, 58.63; H, 4.22; N, 15.54; S, 6.40.

**Ethyl [(2-Cyanoethanimidoyl)(4-methylphenyl)hydrazono][5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]sulfanyl]ethanoate (11).** A suspension of **8** (1 mmol), malononitrile (1 mmol) in benzene (30 mL) and ammonium acetate (1.0 g) was heated at 180 °C for 5 min. The reaction mixture was left overnight at room temperature and then triturated with ethanol. The solid obtained was filtered off and recrystallized from ethanol. Yield 58%, mp 218–219 °C, yellow crystals. IR (KBr)  $\nu$  3453, 3220 (NH), 3004 (aromatic CH), 2970 (aliphatic CH), 2220, 2208 (CN), 1750 (C=O of ester), 1651 (C=O of cyclic amide), 1602, 1550  $\text{cm}^{-1}$  (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  1.12 (t,  $J = 7.5$  Hz, 3H, CH<sub>3</sub> of ethyl ester), 2.07 (s, 3H, CH<sub>3</sub> of *p*-tolyl), 3.29 (s, br, 2H, NH<sub>2</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.11 (q,  $J = 7.5$  Hz, 2H, CH<sub>2</sub> of ethyl ester), 7.07–7.97 (m, 10H, ArH, =CH, NH). MS  $m/z$  529 (M, 28), 497 (16), 441 (12), 228 (100%). Anal. Calcd for C<sub>26</sub>H<sub>23</sub>N<sub>7</sub>O<sub>4</sub>S: C, 58.97; H, 4.34; N, 18.52. Found: C, 59.14; H, 4.35; N, 18.46.

**7-(4-Methoxyphenyl)-2,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (13).** To a solution of **1a** (16 mmol) in benzene (15 mL), triethyl amine (0.3 mmole) and chloroacetyl chloride (16 mmol) were added in small portions with stirring and the mixture was refluxed for 3 h on a water-bath. The solid obtained was filtered off and recrystallized from ethanol. Yield 87%, mp 258–260 °C, yellow crystals. IR (KBr)  $\nu$  3040 (aromatic CH), 2940 (aliphatic CH), 2225 (CN), 1797 (C=O of thiazolidinone ring), 1672 (C=O of pyrimidine ring), 1591, 1556 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  3.84 (s, 3H, OCH<sub>3</sub>), 6.55 (s, 2H, CH<sub>2</sub>, thiazolidine), 7.06–7.96 (m, 4H, ArH). MS  $m/z$  301 (M+2, 25), 259 (M–CH<sub>2</sub>CN, 100), 231 (21), 200 (8), 186 (34), 158 (32), 134 (51), 69 (17%). Anal. Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>S: C, 56.18; H, 3.01; N, 14.04; S, 10.70. Found: C, 56.23; H, 3.00; N, 14.20; S, 10.86.

**7-(4-Methoxyphenyl)-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (14).**<sup>16</sup> A mixture of **1c** (10 mmol) and 2 g of anhydrous sodium acetate was refluxed in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 3 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from ethanol. Yield

80%, mp 250–252 °C, brown crystals. IR (KBr)  $\nu$  3069 (aromatic CH), 2936 (aliphatic CH), 2212 (CN), 1751 (C=O of thiazolidinone ring), 1684 (C=O of pyrimidine ring), 1579, 1550 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  3.34 (s, 2H, cyclic  $\text{CH}_2$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 7.17–8.15 (m, 4H, ArH). Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{N}_3\text{O}_3\text{S}$ : C, 56.18; H, 3.01; N, 14.04. Found: C, 56.28; H, 3.02; N, 14.10.

**3-Amino-7-(4-methoxyphenyl)-5-oxo-5H-[1,3]thiazolo [3,2-a]pyrimidine-6-carbonitrile (15).** To a solution of **1a** (10 mol) in ethanol (10 mL), triethyl amine (15 mL) and chloroacetonitrile (112 mmol) were added in small portions while stirring and the mixture was refluxed for 30 min. The solid obtained upon dilution with water and acidification with HCl was filtered off and recrystallized from ethanol. Yield 60%, mp 214–216 °C, brown crystals. IR (KBr)  $\nu$  3554, 3459 ( $\text{NH}_2$ ), 3086 (aromatic CH), 2984 (aliphatic CH), 2222 (CN), 1683 (C=O of pyrimidine ring), 1602, 1541 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  3.89 (s, 3H,  $\text{OCH}_3$ ), 4.37 (br s, 2H,  $\text{NH}_2$ ), 7.15–8.16 (m, 5H, ArH,  $\text{C}_2$ -H). MS  $m/z$  298 ( $\text{M}^+$ , 34), 84 ( $\text{C}_3\text{H}_4\text{N}_2\text{O}$ , 100), 297 (38), 271 (14), 256 (17), 227 (16), 185 (16), 149 (18), 129 (45), 97 (64), 57 (85%). Anal. Calcd for  $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_2\text{S}$ : C, 56.37; H, 3.35; N, 18.79; S, 10.73. Found: C, 56.30; H, 3.33; N, 18.70; S, 10.48.

**7-(4-Methoxyphenyl)-2,3,5-trioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carbonitrile (16).** A solution of **1a** (10 mmol) in benzene (10 mL) was stirred at room temperature for 10 min and then oxalyl chloride (10 mmol) in benzene (10 mL) was added dropwise in the presence of triethyl amine (1 mL) during 30 min. The mixture was stirred for 4 h and then left over night; the solid obtained was filtered off and recrystallized from ethanol. Yield 65%, mp 255–257 °C, yellow crystals. IR (KBr)  $\nu$  3010 (aromatic CH), 2940 (aliphatic CH), 2221 (CN), 1760, 1710 (C=O of thiazolidinone ring), 1672 (C=O of pyrimidine ring), 1585, 1559 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  3.86 (s, 3H,  $\text{OCH}_3$ ), 7.15–8.16 (m, 4H, ArH). MS  $m/z$  287 (M-CN, 22), 259 (M-[CO+CN], 100), 231 (23), 201 (72), 158 (19), 134 (35), 114 (29), 78 (41%). Anal. Calcd for  $\text{C}_{14}\text{H}_7\text{N}_3\text{O}_4\text{S}$ : C, 53.67; H, 2.23; N, 13.41; S, 10.22. Found: C, 53.52; H, 2.20; N, 13.49; S, 10.10.

**7-(4-Methoxyphenyl)-2-[(4-methylphenyl)hydrazono]-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo [3,2-a]pyrimidine-6-carbonitrile (17).** To a cold solution of compound **14** (10 mmol) in ethanol (80 mL), containing sodium acetate (2 g) was added *p*-tolyl diazonium chloride [prepared by adding concentrated hydrochloric acid (3 mL) to *p*-toluidine (10 mmol) at 0–5 °C and treating the resulting hydrochloride solution with a cold solution of sodium nitrite (10 mmol) in water (5 mL)] dropwise with stirring at

0–5 °C. The reaction mixture was stirred at room temperature for 2 h and then diluted with (30 mL) water. The solid obtained was filtered off and recrystallized from ethanol. Yield 62%, mp 289–291 °C, yellow crystals. IR (KBr)  $\nu$  3394 (NH), 3009 (aromatic CH), 2936 (aliphatic CH), 2212 (CN), 1751 (C=O of thiazolidinone ring), 1684 (C=O of pyrimidine ring), 1579, 1552 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  3.32 (s, 3H,  $\text{CH}_3$  of *p*-tolyl), 3.89 (s, 3H,  $\text{OCH}_3$ ), 7.17–8.10 (m, 8H, ArH), 8.15 (s, 1H, NH). MS  $m/z$  417 (M, 44), 344 (100), 200 (40), 164 (51), 134 (47), 102 (34), 69 (42%). Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_5\text{O}_3\text{S}$ : C, 60.43; H, 3.59; N, 16.78; S, 7.67. Found: C, 60.35; H, 3.56; N, 16.80; S, 7.30.

**2-Benzylidene-7-(4-methoxyphenyl)-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carbonitrile (18).**<sup>11</sup> **Method A:** A mixture of **1a** (10 mmol), chloroacetic acid (10 mmol), benzaldehyde (10 mmol) and 2 g of anhydrous sodium acetate was refluxed in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 5 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from the mixture of dioxane and water.

**Method B:** A mixture of **14** (10 mmol), benzaldehyde (10 mol) and 2 g of anhydrous sodium acetate was refluxed in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 5 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from the mixture of dioxane and water. Yield 75%, mp 170–172 °C, pale brown crystals. IR (KBr)  $\nu$  3017 (aromatic CH), 2934 (aliphatic CH), 2218 (CN), 1762 (C=O of thiazolidinone ring), 1695 (C=O of pyrimidine ring), 1595, 1574 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  3.86 (s, 3H,  $\text{OCH}_3$ ), 5.56 (s, 1H, =CH), 7.07 (m, 9H, ArH). MS  $m/z$  387 ( $\text{M}^+$ , 47), 360 (100), 281 (24), 226 (15), 159 (23), 134 (43), 112 (55), 91 (21), 69 (60%). Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$ : C, 65.11; H, 3.35; N, 10.85; S, 8.26. Found: C, 65.28; H, 3.32; N, 10.78; S, 8.50.

**6-(4-Methoxyphenyl)-8-oxo-2,3-diphenyl-2,3-dihydro-1H,8H-pyrazolo- [3',4':4,5][1,3]thiazolo[3,2-a]pyrimidine-7-carbonitrile (19).** A mixture of **18** (10 mmol) and phenylhydrazine (10 mmol) in ethanol (30 mL) and few drops of piperidine was refluxed for 4 h. The solid obtained was filtered off and recrystallized from methanol. Yield 77%, mp 163–165 °C, brown crystals. IR (KBr)  $\nu$  3445 (NH), 3006 (aromatic CH), 2936 (aliphatic CH), 2215 (CN), 1654 (C=O of pyrimidine ring), 1602, 1540 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  3.67 (s, 3H,  $\text{OCH}_3$ ), 6.98 (m, 16H, ArH, NH). MS  $m/z$  461 (M- $\text{NH}_2$ , 54), 77 (100), 390 (41), 361 (51), 310 (30), 259 (20), 134 (88), 84 (51%). Anal. Calcd for  $\text{C}_{27}\text{H}_{19}\text{N}_5\text{O}_2\text{S}$ : C, 67.92; H, 3.98; N, 14.67; S, 6.70. Found: C, 67.80; H, 4.00; N, 14.63; S, 6.39.

**2-Mercapto-7-(4-methoxyphenyl)-9-oxo-4-phenyl-1,4-dihydro-9H-pyrimido[4',5':4,5][1,3]thiazolo[3,2-a]pyrimidine-8-carbonitrile (20).** A mixture of **18** (10 mmol) and thiourea (10 mmol) in ethanol (30 mL) and few drops of piperidine was refluxed for 3 h. The solid obtained was filtered off and recrystallized from the mixture of ethanol and water. Yield 83%, mp 210–212 °C, yellow crystals. IR (KBr)  $\nu$  3424 (NH), 3020 (aromatic CH), 2937 (aliphatic CH), 2371 (SH), 2213 (CN), 1645 (C=O of pyrimidine ring), 1601, 1570 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  3.45 (s, 3H, OCH<sub>3</sub>), 3.78 (d, 1H, C<sub>4</sub>-H), 3.89 (d, 1H, bridged C-H), 4.96 (s, 1H, SH), 6.42–8.05 (m, 9H, ArH). MS  $m/z$  447 (M+2, 1), 310 (M-[anisole+HCN], 100), 295 (37), 281 (64), 271 (25), 267 (26), 227 (19), 201 (18), 134 (24), 84 (25%). Anal. Calcd for C<sub>22</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 59.32; H, 3.37; N, 15.73; S, 14.38. Found: C, 59.30; H, 3.34; N, 15.80; S, 14.60.

**2-Amino-7-(4-methoxyphenyl)-9-oxo-4-phenyl-4H,9H-pyrano[2',3':4,5][1,3]thiazolo [3,2-a]pyrimidine-3,8-dicarbonitrile (21).** **Method A:** A solution of **18** (10 mmol) and malononitrile (10 mmol) in ethanol (30 mL) and few drops of piperidine was refluxed for 3 h. The solid obtained was filtered off and recrystallized from methanol.

**Method B:** A mixture of **14** (10 mmol) and  $\alpha$ -cyanocinnamonnitrile (10 mmol) in pyridine (25 mL) was refluxed for 12 h. The reaction mixture was poured onto cold water then neutralized with diluted HCl, filtered off and recrystallized from methanol. Yield 72%, mp 138–140 °C, brown crystals. IR (KBr)  $\nu$  3400, 3336 (NH<sub>2</sub>), 3005 (aromatic CH), 2939 (aliphatic CH), 2209, 2190 (CN), 1644 (C=O of pyrimidine ring), 1602, 1560 (C=N, C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ )  $\delta$  3.82 (s, 3H, OCH<sub>3</sub>), 5.65 (br s, 2H, NH<sub>2</sub>), 7.06–7.98 (m, 10H, ArH). MS  $m/z$  452 (M–1, 1), 84 (C<sub>3</sub>H<sub>4</sub>N<sub>2</sub>O, 100), 379 (1), 313 (1), 256 (4), 213 (6), 199 (3), 161 (10), 129 (15), 77 (13%). Anal. Calcd for C<sub>24</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>S: C, 63.57; H, 3.31; N, 15.45; S, 7.06. Found: C, 63.50; H, 3.33; N, 15.40; S, 7.55.

## Povzetek

2-Karboetoksimetiltiopirimidinonski derivat **1b** smo uporabili za sintezo novih diheterocikličnih tioetrov s pomočjo reakcije z nekaterimi acetali s sledečo ciklizacijo produktov z 2-aminoheterocikličnimi spojinami ali pa s pomočjo reakcije **1b** s *p*-tolildiazonijevim kloridom s sledečo reakcijo produkta preko aktivne metilenske skupine. Iz 2-merkaptopirimidina **1a** ali iz derivata 5-pirimidinilmerkaptocetne kisline **1c** smo tudi pripravili nekaj novih tiazolopirimidinskih derivatov. Raziskali smo moluskicidno aktivnost pripravljenih spojin proti polžem *Biomphalaria alexandrina*, ki so gostitelji zajedalca *Schistosoma mansoni*.

## 4. Conclusion

Enaminones and hydrazones produced from the interaction of ethyl 1-pyrimidinyl acetate with DMFDMA and aryldiazonium salts are suitable synthons for the preparation of diheterocyclic thioethers. Also, ethyl 1-pyrimidinylacetate is considered a good intermediate for the synthesis of thiazolopyrimidinederivatives.

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