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5,6,7,8-Tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-4(3*H*)one as a synthon of heterocyclic systems

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Reaction of 5,6,7,8-tetrahydrobenzo[b]thieno[2,3-*d*]pyrimidine-4(3*H*)-one with ethyl chloroacetate afforded an ester**,** which upon treatment with *p*-chlorobenzaldehyde under various conditions and with benzylamine gave new compounds. Chlorothienopyrimidine reacted with thiourea, benzoylhydrazine, thiosemicarbazide, semicarbazide, sodium azide and glycine, to give pyrimidinethione, 1,2,4-triazole, thioxo-1,2,4-triazole, oxo-1,2,4-triazole, tetrazole**,** and imidazole, respectively. The reaction of pyrimidinthione with β-aroylacrylic acid produced γ-ketoacid**,** which reacted with acetic anhydride and hydrazine hydrate to afford furanone and pyridazinone**,** respectively. Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate was utilized to synthesize the 3-aminothienopyrimidinone derivative *via* reaction with benzoyl chloride followed by hydrazine hydrate. An interesting condensation product was obtained by reaction of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate with ethyl cyanoacetate in DMF.

Key words: thieno[2,3-*d*]pyrimidin-4(3*H*)-one, triazole, tetrazole, imidazole, furanone and pyridazinone.

INTRODUCTION

In the last few decades thieno[2,3-*d*]pyrimidines have attracted attention due to their wide-scope applications and biological activity, which consists in their functioning as acaricida [1], aldose reductase inhibitory [2], angiotensin II receptor blocking [3], antiallergic [4], antibacterial [5], antibiotic [6], antidepressant [7], antihypertensive [8, 9], antimicrobial [10, 11], analgesic and antiinflammatory [12, 13], bactericidal [14], blood platelet aggregation inhibitory [15], fungicidal [16], hyper-sensitivity inhibitory [17] and insecticidal [18] activity.

The therapeutic importance of thieno[2,3-*d*]-pyrimidine derivatives directed us to synthesize several analogues by combination of other groups and active moieties. We, hereby, report the synthesis of polycyclic heterocycles containing different nuclei fused with, or attached to thieno[2,3-*d*]pyrimidines. The key intermediate for the target heterocyclic systems is 5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-pyrimidin-4(3*H*)-one (**1**), which was prepared according to the previously reported method [19].

RESULTS AND DISCUSSION

In our ongoing heterocyclic chemistry research [20–25], and continuing our synthetic study on thienopyrimidines [26], pyrimidinone **1** was allowed to react with ethyl chloroacetate in dry acetone, in the presence of anhydrous potassium carbonate, to yield ethyl (5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-yloxy)acetate (**2**) [26–28]. The ester **2** contains an active methylene group that can condense with aromatic aldehydes under different basic conditions, which strongly affect the reaction products. Thus, when ester **2** was allowed to react with 4-chlorobenzaldehyde in ethanolic sodium ethoxide solution, it afforded ethyl [3-(4-chlorophenyl)-2-(5,6,7,8-tetrahydrobenzo[*b*]-thieno[2,3-*d*] pyrimidin-4-yloxy)]propenoate (**3**) and a small amount of 3-(4-chlorophenyl)-2-(5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-yloxy) propenoic acid (**4**) (16%). On the other hand, the ester **2** reacted with 4-chlorobenzaldehyde in *tert*-butanol in the presence of potassium tert-butoxide as a stronger basic catalyst, yielding the cinnamic ester derivative **3** together with a relatively large amount of the cinnamic acid derivative **4** (25%). However, when even stronger basic catalyst, namely sodium hydride in dry benzene, was used, the product **4** was isolated as a sole product (see Scheme 1).

The reaction of ester **2** with benzylamine upon refluxing ethanol gave N-benzyl-2-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4-yloxy)acetamide (**5**) in good yield (Scheme 1).

The present work was extended aiming at introducing fused five-membered heterocyclic systems to the thienopyrimidine moiety, *via* nucleophilic substitution, followed by cyclo-condensation. Thus,

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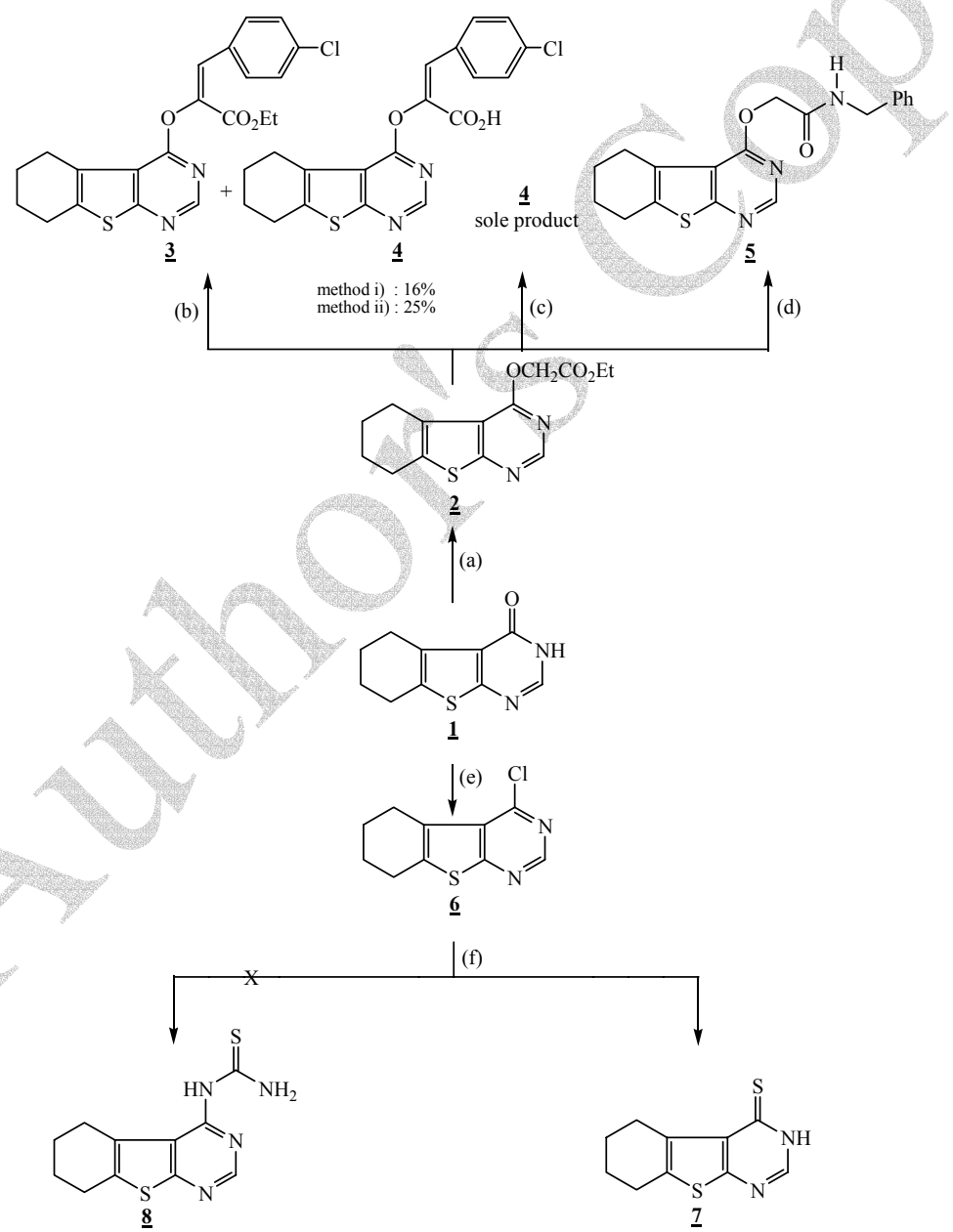
compound **1** reacted with phosphorus oxychloride to afford 4-chloro-5,6,7,8-tetrahydrobenzo[b]thieno [2,3-d]pyrimidine (**6**), which was utilized to achieve our goal. The m.p. of the pyrimidine derivative **6** is in accordance with the preceding value [12].

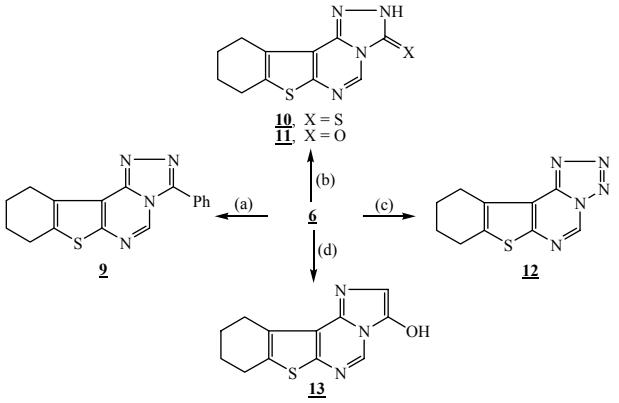
Chloropyrimidine derivative **6** reacted with thiourea in refluxing ethanol and the chlorine atom was replaced by SH [29] to afford 5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-4(3H)-thione (**7**) and not the thiourea derivative **8** (Scheme 1).

On the other hand, when the 4-chloropyrimidine derivative **6** was allowed to react with benzoyl hydrazine in refluxing DMF, thiosemicarbazide or semicarbazide hydrochloride in ethanol, it produced 3-phenyl[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c] pyrimidine (**9**), 3-thioxo[1]benzothieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (**10**), and 3-oxo[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**11**), respectively. Compound **9** was synthesized by an alternative method from 4-hydrazino-5,6,7,8-tetrahydrobenzo[b]thienopyrimidine *via* reaction with benzaldehyde followed by treatment with bromine/acetic acid [19].

Compound **6** was also treated with sodium azide in ethanol or glycine in pyridine to produce [1]benzothieno[3,2-e]tetrazolo[1,5-c]pyrimidine (**12**) [30] and 3-oxo-[1]benzothieno-[3,2-e]pyrazolo[1,2-c]pyrimidine (**13**), respectively (Scheme 2).



Sheme 1: Reagents and conditions: a. $ClCH_2CO_2Et/K_2CO_3$; b. *p*-Chlorobenzaldehyde, i – NaOEt/EtOH or ii – ButOK/ButOH; c. *p*-Chlorobenzaldehyde, NaH/dry benzene; d. $PhCH_2NH_2$/EtOH; e. $POCl_3$; f. thiourea/EtOH.

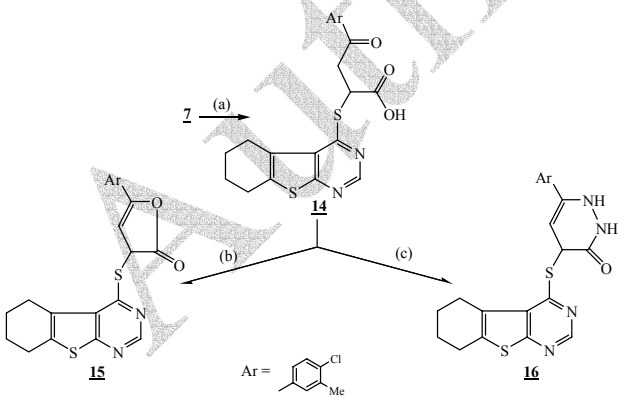


Sheme 2. Reagents and conditions:
a. $PhCONHNH_2$/DMF; b. $NH_2NHCSNH_2$ or $NH_2NHCONH_2$/EtOH/reflux; c. NaN_3/EtOH; d. NH_2CH_2COOH/pyridine.

It was interesting to investigate the behaviour of the pyrimidinethione derivative **7** towards β-aroylacrylic acid. Thus, refluxing **7** with 3-(4-chloro-3-methylbenzoyl)-2-propenoic acid in benzene produces the adduct 3-(4-chloro-3-methylbenzoyl)-2-(5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]pyrimidin-4-ylthio)propanoic acid (**14**) (Scheme 3).

Heating under reflux the γ-ketoacid **14** with freshly distilled acetic anhydride resulted in cyclodehydration reaction with the formation of 5-(4-chloro-3-methylphenyl)-3-(5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]pyrimidin-4-ylthio)furan-2(3*H*)-one (**15**).

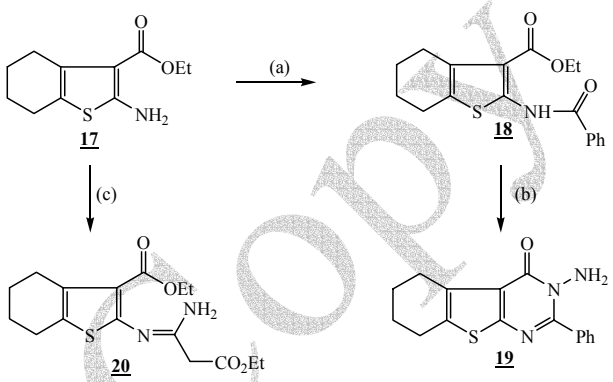
Compound **14** reacted with hydrazine hydrate in refluxing ethanol to afford 6-(4-chloro-3-methylphenyl)-4-(5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*b*] pyrimidin-4-ylthio)-1,4-dihydropyridazin-3(2*H*)-one (**16**) (Scheme 3).



Sheme 3. Reagents and conditions:
a. Ar–COCH=CH–COOH/Dry benzene/Δ; b. Ac_2O/Δ; c. N_2H_4/EtOH/Δ.

Moreover, ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**17**) [31–33] reacted with benzoyl chloride in pyridine in the cold to produce ethyl 2-benzoylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**18**), which reacted with hydrazine hydrate in refluxing DMF to afford 3-amino-2-phenyl-5,6,7,8-tetrahydrobenzo[*b*]thieno [2,3-*d*]-pyrimidin-4(3*H*)-one (**19**) [34] (Scheme 4).

An interesting condensation product was obtained from ester **17** *via* its reaction with ethyl cyanoacetate in DMF, during passing a current of hydrogen chloride gas in the reaction mixture. The product was identified as ethyl 3-amino-3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thieno-2-ylimino)propanoate (**20**) (Scheme 4).



Sheme 4. Reagents and conditions:
a. PhCOCl/pyridine; b. NH_2NH_2/DMF; c. $NCCH_2CO_2Et$/DMF/HCl.

EXPERIMENTAL

All reported melting points are uncorrected and were determined on a Stuart electric melting point apparatus. The IR spectra were measured on a Unicam 200 Spectrometer or Mattson infinity series FT-IR using KBr wafer technique. The ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on Varian Gemini 200 MHz instrument using TMS as internal standard with chemical shifts (δ expressed in ppm form down to up field). The mass spectrum was recorded on Shimadzu GC-MS-QP 1000 EX instrument operating at 70 eV. TLC was preformed on ready-to-use silica gel plates Merck 60 to monitor the reactions and ascertain the purity of the newly synthesized compounds. The microanalytical data were measured in microanalytical unit of the Faculty of Science, Cairo University. The title compound **1** as well as ethyl(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4-yloxy) acetate (**2**) have been synthesized in our laboratory [26].

Ethyl [3-(4-chlorophenyl)-2-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4-yloxy)]-propenoate (**3**) *and 3-(4-chlorophenyl)-2-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidin-4-yloxy)propenoic acid* (**4**)**.** *Method A*: A mixture of 4-chlorobenzaldehyde (10 mmol, 1.4 g) and ester **2** (10 mmol, 2.92 g) was added to a solution of NaOEt (prepared

from 0.5 g Na metal and 60 ml absolute ethanol) or *tert*-KOBu (1.68 g) in *tert*-BuOH (80 ml). The mixture was refluxed for 4 h. Most of the solvent was removed under reduced pressure. The cold residue was poured into water and extracted with diethyl ether. The aqueous layer was acidified with diluted hydrochloric acid. The ethereal layer was poured over dry anhydrous $MgSO_4$, evaporated to dryness to obtain oil, which on trituration afforded solid product. This product on crystallization from benzene yielded **3** as yellow crystals: m.p. 207–209°C; yield [10.5% (ethoxide), 8.56% (butoxide)]. IR: ν 3050 (CH_{ar}), 2946 (CH_{al}), 1729 (C=O ester) and 1672 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.12 (t, 3H, –$COOCH_2C\underline{H}_3$), 1.96 (br.s, 4H, C-6H and C-7H of tetrahydrobenzothienopyrimidine nucleus), 2.63 (br. s, 2H, C-5H), 2.75 (br. s, 2H, C-8H), 4.1 (q, 2H, $COOC\underline{H}_2CH_3$), 7.20 (m, 5H, Ar–H and olefinic H), 7.91 (s, 1H, C-2H); Anal. Calcd. for $C_{21}H_{19}ClN_2O_3S$ (414.5): C, 60.79; H, 4.62 ; Cl, 8.54; N, 6.75; Found: C, 60.67; H, 4.59; Cl, 8.46; N, 6.69.

On the other hand, the solid obtained from acidification of the aqueous layer was crystallized from benzene affording **4** as yellow crystals; m.p: 178–182°C yield (16% (ethoxide), 25% (butoxide)). IR: ν 3422 (OH acid), 3056 (CH_{ar}), 2933 (CH_{al}) and 1669 cm^{-1} (C=O of α,β-unsaturated acid); ^{1}H-NMR (DMSO-d_6): δ 1.81 (br.s, 4H, C-6H and C-7H), 2.61 (br.s, 2H, C-5H), 2.70 (br.s, 2H, C-8H), 7.35–7.47 (m, 5H, Ar–H and olefinic H) and 8.12 (s, 1H, C-2H); Anal. Calcd. for $C_{19}H_{15}ClN_2O_3S$ (386.5): C, 58.99 ; H, 3.91 ; Cl, 9.16; N, 7.24; Found: C, 58.89; H, 3.79; Cl, 9.07; N, 7.18.

Method B: An equimolar amount of 4-chlorobenzaldehyde (10 mmol, 1.4 g) and ester **2** (10 mmol, 2.92 g) was refluxed in 50 ml dry benzene for 4h in the presence of (0.4 g) sodium hydride. The reaction mixture was left to cool down after evaporating most of the solvent to give solid, which was dissolved in water and acidified by diluted hydrochloric acid. The crude solid was crystallized from benzene to give **4** as yellow crystals; m.p. 178–181°C; yield 56.6%.

n-Benzyl-2-(5,6,7,8-tetrahydrobenzo[b]thieno [2,3-d]pyrimidin-4-yloxy)acetamide (**5**) A mixture of thienopyrimidine **2** (10 mmol; 2.92 g) and benzyl amine (10 mmol; 1.1 ml) in ethanol (40 ml) was refluxed for 10 h. Most of the solvent was evaporated and the rest was left to cool down. The solid product that separated out was filtered off, dried and then recrystallised from ethanol to give **5** as white solid; m.p. 202–205°C; yield 33.99%. IR: ν 3298 (NH), 3057 (CH_{ar}), 2938 (CH_{al}), 1687 (C=O acyclic amide), 1653 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.79 (br.s, 4H, C-6 and C-7 H), 2.51 (br.s, 2H, C-5H), 2.88 (br.s, 2H, C-8H), 4.35 (d, 2H, OCH_2CO), 4.69 (s, 2H, benzylic proton of –$C\underline{H}_2$Ph), 7.26–7.35 (m, 5H, Ph–H), 8.28 (s, 1H, C-2H) and 8.79 (s, 1H, NH, D_2O exchangable); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$ (353): C, 64.59; H, 5.38; N, 11.89; Found: C, 64.47; H, 5.19; N, 11.76.

4-Chloro-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidine (**6**). The solution of pyrimidinone **2** (10 mmol; 2.92 g) in phosphorus oxychloride (5 ml) was heated under reflux on water bath for 1 h, left to cool down and poured onto ice water forming a solid product. Filtration and crystallization of the crude product from light petroleum (40–60°C) afforded the title product **6** as pale yellow crystals; m.p. 106–108°C; yield 89.7%. The m.p. is in satisfactory agreement with preceding value [12].

5,6,7,8-Tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)thione (**7**). An equimolar mixture of chloropyrimidine **6** (10 mmol; 2.24 g) and thiourea (10 mmol; 0.8 g) in dry methanol (30 ml) was refluxed for 5 h. Most of solvent was evaporated and the reaction mixture was left to cool down, the solid product that separated out was filtered off. Crystallization from benzene to yield the thiol **7** as orange crystals; m.p. 247–250°C; yield 85.5%. IR: ν 3132 (NH), 3045 (CH_{ar}), 2983($CH_{al.}$), 1661 (C=N), 1569 (C=C) and 1367 cm^{-1} (C=S); ^{1}H-NMR ($CDCl_3$): δ 1.87 (m, 4H, C-6H and C-7H), 2.61 (br.s, 2H, C-5H), 2.76 (br.s, 2H, C-8H), 7.85 (s, 1H, C-2H), 11.83 (br.s, 1H, NH); Anal. Calcd. for $C_{10}H_{10}N_2S_2$ (222): C, 54.05; H, 4.50; N, 12.61. Found: C, 53.89; H, 4.35; N, 12.49.

3-phenyl[1]benzothieno[3,2-e][1,2,4]triazolo [4,3-c]pyrimidine (**9**). A mixture of chloropyrimidine **6** (10 mmol; 2.24 g) and benzoylhydrazine (10 mmol; 1.36 g) in 50 ml of dimethylformamide was refluxed for 5 h. Most of solvent was evaporated and the reaction mixture was left to cool down, the solid product that separated out was filtered off. Crystallization of the crude product from dimethyl formamide yielded product **9** as orange crystals; m.p: 215–218°C; yield: 37.1%. IR: ν 3054 (CH_{ar}), 2935 (CH_{al}), 1621 cm^{-1} (C=N), with the disappearance of C=O; ^{1}H-NMR (DMSO-d_6): δ 1.82 (br.s, 4H, C-9 and C-10H), 2.60 (br.s, 2H, C-11H), 2.82 (br.s, 2H, C-8H), 7.57–7.54 (m, 5H, Ph–H), 8.22 (s, 1H, pyrimidine proton); Anal. Calcd. for $C_{17}H_{14}N_4S$ (306): C, 66.67; H, 4.57; N, 18.30; Found: C, 66.49; H, 4.51; N, 18.12.

3-(2H)-Thioxo[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**10**). To a solution of chloropyrimidine **6** (10 mmol; 2.24 g) in 30 ml of dimethylformamide, thiosemicarbazide (12 mmol; 1.58 g) was added and the reaction mixture was refluxed for 6 h, concentrated and left to cool down.

An oily substance was formed, which solidified upon trituration with ethanol gave a solid product. The solid product was collected by filtration, dried and then recrystallised from ethanol to give **10** as orange solid; m.p. 284–286°C; yield 41.6%. IR: ν 3120 (NH), 3050 (CH_{ar}), 2930 (CH_{al}), 1635 cm^{-1} (C=N) ;^{1}H-NMR (DMSO-d_6): δ 1.86 (br.s, 4H, C-9 and C-10H, 2.65 (br.s, 2H, C-4H), 2.74 (br.s, 2H, C-8H), 8.40 (s, 1H, C-5H) and 9.14 and 9.57 (two s, 1H, HN–C=S ⇆ N=CSH). Anal. Calcd. for $C_{11}H_{10}N_4S_2$ (262): C, 50.38; H, 3.82; N, 21.37; Found: C, 50.18; H, 3.79; N, 21.27.

3-(2H)-Oxo[1]benzothieno[3,2-e][1,2,4]triazolo [4,3-c]pyrimidine **(11)** A mixture of chloropyrimidine **6** (10 mmol; 2.24 g) and semicarbazide hydrochloride (12 mmol; 1.34 g) in dimethyl formamide (30 ml) was heated under reflux for 6 h. Most of the solvent was evaporated, the residual was left to cool down. The solid product that separated out was filtered off, dried and then recrystallised from benzene to give **11** as orange solid; m.p. 230°C (*d*); yield 48.3%. IR: ν 3115 (NH), 3073 (CH_{ar}), 2936 (CH_{al}), 1753 (C=O) and 1616 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.88 (br.s, 4H, C-9 and C-10H), 2.67 (br.s, 2H, C-11H), 2.77 (br.s, 2H, C-8H), 8.43 (s, 1H, C-5H) and 9.28 and 9.62 (two s, 1H, NH–C=O ⇆ N=C–OH); Anal. Calcd. for $C_{11}H_{10}N_4OS$ (246): C, 53.66; H, 4.07; N, 22.76; Found: C, 53.57; H, 3.99; N, 22.45.

[1]benzothieno[3,2-e]tetrazolo[1,5-c]pyrimidine **(12).** To a solution of chloropyrimidine **6** (10 mmol; 2.24 g) in 30 ml of ethanol, sodium azide (10 mmol; 0.65 g) was added and the reaction mixture was stirred for 1 h and left to cool down. The solid product that precipitated down was filtered off by suction, dried and then recrystallised from ethanol to give **12** as white solid; m.p. 141–143°C; yield 49.13%. IR: ν 3069 (CH_{ar}), 2935 (CH_{al}), 1641 (C=N), 1605 cm^{-1} (C=C); ^{1}H-NMR (DMSO-d_6): δ 1.83 (br.s, 4H, C-9H and C-10H), 2.70 (br.s, 2H, C-11H), 2.82 (br.s, 2H, C-8H), 8.12 (s, 1H, C-2H); Anal. Calcd. for $C_{10}H_9N_5S$ (231): C, 51.95; H, 3.90; N, 30.30, Found: C, 52.12; H, 4.09; N, 30.49.

3-hydroxy[1]benzothieno[3,2-e]pyrazolo[1,2-c] pyrimidine **(13).** A mixture of chloropyrimidine **6** (10 mmol; 2.24 g) and glycine (10 mmol; 0.75 g) was fused for 2 h at temperature not higher than 140°C, left to cool down and treated by light petroleum (60–80°C). The solid product that separated out was filtered off, dried and then recrystallised from benzene to give **13** as violet solid; m.p. 188–190°C; yield 48.3%. IR: ν 3425 (OH), 3060 (CH_{ar}), 2937 cm^{-1} (CH_{al}); ^{1}H-NMR (DMSO-d_6): δ 1.86 (br.s, 4H, C-6H and C-7H), 2.64 (br.s, 2H, C-5H), 2.86 (br.s, 2H, C-8H), 5.79 (s, 1H, pyrazole), 8.21 (s, 1H, C-2H), 9.43 (br.s, 1H, OH, D_2O exchangeable); MS: m/e: 245 (M^+, 42.9), 228 (3.2), 226 (19.0), 224 (61.9), 196 (100), 169 (14.1), 134 (16.2); Anal. Calcd. for $C_{12}H_{11}N_3OS$ (245): C, 58.77; H, 4.49; N, 17.14; Found: C, 58.64; H, 4.41; N, 16.99.

3-(4-Chloro-3-methylphenyl)carboxy-2-(5,6,7,8-tetrahydro[b]benzothieno[2,3-d]pyrimidin-4-ylthio) propanoic acid (**14**). A mixture of pyrimidine **7** (10 mmol; 2.22 g) and β-aroylacrylic acid namely 3-(4-chloro-3-methylbenzoyl)-2-propenoic acid (10 mmol; 2.24 g) in 40 ml of benzene was heated under reflux for 5 h. Most of the solvent was evaporated and left to cool down. The solid product that separated out was filtered off, dried and then recrystallised from benzene affording **14** as yellow solid; m.p. 168–170°C; yield: 94.1%. IR: ν 3037 (CH_{ar}), 2934 (ν_{CHal}), 1736 (CO acid) and 1684 cm^{-1} (CO ketone); ^{1}H-NMR (DMSO-d_6): δ 1.77 (br.s, 4H, C-6 and C-7H), 2.41 (s, 3H, CH_3), 2.59 (br.s, 2H, C-5H), 2.78 (br.s, 2H, C-8H), 2.98 (d, 2H, Ar–CO–CH_2–), 4.14 (d, 1H, –S–CH–), 7.82–7.91 (m, 3H, Ar–H), 8.17 (s, 1H, C-2H pyrimidine), 13.69 (br.s, 1H, CO_2H, D_2O exchangeable); Anal. Calcd. for $C_{21}H_{19}ClN_2O_3S_2$ (446.5): C, 56.44; H, 4.26; Cl, 7.95; N, 6.27; Found: C, 56.08; H, 4.09; Cl, 7.76; N, 6.14.

5-(4-Chloro-3-methylphenyl)-3-(5,6,7,8-tetrahydro[b]benzothieno[2,3-d]pyrimidin-4-ylthio)furan-2(3H)-one (**15).** To a gently warmed solution of acetic anhydride (5 ml), the acid **14** (10 mmol; 2.4 g) was added and the mixture heated under reflux for 0.5 h and then left to cool down. The solid that separated out was filtered off and washed by light petroleum (60–80°C), dried and then recrystal-lised from benzene to give **15** as violet solid; m.p. 223–225°C; yield 46.5%. IR: ν 3089 and 3057 (CH_{ar}), 2929 (CH_{al}), 1787 (C=O furanone), 1641 cm^{-1} (C=N); δ 1.80 (br.s, 4H, C-6 and C-7H), 2.44 (s, 3H, CH_3), 2.63 (br.s, 2H, C-5H), 2.81 (br.s, 2H, C-8H), 4.25 (d, 1H, –S–CH–), 6.12 (d, 1H, CH=), 7.77–7.92 (m, 3H, Ar–H), 8.21 (s, 1H, C-2H pyrimidine); MS: m/z: 428 (M^+, 90.3), 222 (100), 207 (78.7), 153 (89.9), 125 (53.2), 89 (45), 53 (25); Anal. Calcd. for $C_{21}H_{17}ClN_2O_2S_2$ (428.5): C, 58.81; H, 3.97; Cl, 8.28; N, 6.53; Found: C, 58.68; H, 3.77; Cl, 8.04; N, 6.67.

6-(4-Chloro-3-methylphenyl)-4-(5,6,7,8-tetrahydro[b]benzothieno[2,3-d]pyrimidin-4-ylthio)-1,4-dihydropyridazin-3(2H)-one (**16**). A mixture of **14** (10 mmol; 2.4g) and hydrazine hydrate (10 mmol; 0.5 ml) in ethanol (40 ml) was refluxed for 12 hrs, left to cool down, then filtered off, dried and then recrystallised from benzene to afford **16** as yellow crystals; m.p. 202–204°C; yield 54.5%. IR: ν 3145 (NH), 3056 (CH_{ar}), 2932 (CH_{al}), 1672 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.85 (br s, 4H, C-6 and C-7H),

2.42 (s, 3H, CH_3), 2.57 (br s, 2H, C-5H), 2.83 (br s, 2H, C-8H), 4.23 (d, 1H, –S–CH–, 6.18 (d, 1H, CH=), 7.59–7.84 (m, 3H, Ar–H), 8.27 (s, 1H, C-2H), 12.98 and 13.31 (two s, 2H, 2NH, D_2O exchangeable); Anal. Calcd. for $C_{21}H_{19}ClN_4OS_2$ (442.5): C, 56.95; H, 4.29; Cl, 8.02; N, 12.66; Found: C, 56.78; H, 4.11; Cl, 7.81; N, 12.47.

Ethyl 2-(benzoylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**18**)**.** To a solution of thiophene ester **17** (10 mmol; 2.25 g) in 30 ml of pyridine, benzoyl chloride (10 mmol; 1.4 ml) was added and the reaction mixture was stirred at room temperature for 2 h, poured onto ice water, acidified with cold diluted HCl to give a solid product, which was filtered off, dried and then recrystallised from benzene to give **18** as yellow solid; m.p. 178–180°C; yield: 68.19%. IR: ν 3238 (NH), 3071 and 3033 (CH_{ar}), 2932 (CH_{al}), 1658 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): δ 1.39 (t, J = 7.08 Hz, 3H, $CH_2C\underline{H}_3$), 1.80 (br s, 4H, C-5 and C-6H), 2.68 (br s, 2H, C-4H), 2.80 (br s, 2H, C-7H), 4.36 (q, J = 7.18 Hz, 2H, $C\underline{H}_2CH_3$), 7.48-8.03 (m, 5H, Ar-H), 12.33 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{19}NO_3S$ (329): C, 65.65; H, 5.78; N, 4.26; Found: C, 65.57; H, 5.74; N, 4.07.

3-Amino-2-phenyl-5,6,7,8-tetrahydro[b]benzothieno[2,3-d]pyrimidin-4(3H)-one (**19**)**.** Compound **18** (10 mmol; 3.33 g) and hydrazine hydrate (10 mmol; 0.5 ml) were dissolved in dimethylformamide (30 ml) and refluxed for 5 h. It was left to cool down, poured onto ice water, filtered off, dried and then recrystallised from ethanol to afford **19** as yellow crystals; m.p. 145–146°C; yield 60.14%. IR: ν 3289 and 3213 (NH_2), 3055 and 3028 (CH_{ar}), 2951 (CH_{al}) and 1658 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): δ 1.88 (br.s, 4H, C-6 and C-7H), 2.59 (br s, 2H, C-5H), 2.73 (br.s, 2H, C-8H), 5.02 (s, 2H, NH_2, D_2O exchangeable), 7.47–7.88 (m, 5H, Ar-H), Anal. Calcd. for $C_{16}H_{15}N_3OS$ (297): C, 64.64; H, 5.05; N, 14.14; Found: C, 64.57; H, 4.89; N, 14.07.

Ethyl 2-ethoxycarbonylmethylaminomethylideneamino-4,5-tetrahydrobenzo[b]thiophene-3-carboxylate (**20**)**.** To a solution of thiophene ester **17** (40 mmol; 9 g) in 30 ml dimethylformamide, ethyl cyanoacetate (40 mmol; 5 ml) was added and HCl gas was passed through the reaction mixture at room temperature for 2 h. The reaction mixture was poured onto ice water, the solid product that precipitated was filtered off, dried and recrystallised from light petroleum (60–80°C) giving **20** as yellow solid; m.p. 98–101°C; yield 59.19%. IR: ν 3406 and 3300 (NH_2), 3077 (CH_{ar}), 2984 and 2937 (CH_{al}), 1744 (CO ester), 1647 cm^{-1} ($\nu_{C=N}$) in addition to the disappearance of $\nu_{C\equiv N}$; ^{1}H-NMR ($CDCl_3$): δ 1.29 (t, 3H, CH_2–$COOCH_2C\underline{H}_3$), 1.39 (t, 3H, C3–$COOCH_2C\underline{H}_3$), 1.79 (m, 4H, C-5 and C-6H), 2.48 (br.s, 2H, C-4H), 2.72 (br.s, 2H, C-7H), 3.21 (s, 2H, $C\underline{H}_2$–COOEt), 4.05 (q, 2H, –CH_2–$COOC\underline{H}_2CH_3$), 4.25 (q, 2H, C3–$COOC\underline{H}_2CH_3$), 5.93 (br.s, 2H, NH_2, D_2O exchangeable); Anal. Calcd. for $C_{16}H_{22}N_2O_4S$ (338): C, 56.80; H, 6.51; N, 8.28; Found: C, 56.67; H, 6.34; N, 8.17.

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5,6,7,8-ТЕТРАХИДРОБЕНЗО[B]ТИЕНО[2,3-D]ПИРИМИДИН-4(3H)-ОН КАТО СИНТОН ЗА ХЕТЕРОЦИКЛЕНИ СИСТЕМИ

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(Резюме)

При реакцията на тетрахидробензо[b]тиено[2,3-d]пиримидин-4(3*H*)-он с етилхлорацетат е получен естер, който при взаимодействие с *p*-хлоробензалдехид в различни условия и с бензиламин дава нови съединения. При реакцията на хлоротиенопиримидин с тиокарбамид, бензоилхидразин, тиосемикарбазид, семикарбазид, натриев азид и глицин са получени съответно пиримидинтион, 1,2,3-триазол, тиооксо-1,2,4-триазол, оксо-1,2,4-триазол, тетразол и имидазол. При реакцията на пиримидинтион с β-арилакрилова киселина е получена γ-кетокиселина, която при реакция с оцетен анхидрид и хидразинхидрат дава съответно фуранон и пиридазинон. Етил-2-амино-4,5,6,7-тетрахидробензо[b]тиофен-3-карбоксилат е използван при синтеза на производно на 3-аминотиено-пиримидинон чрез реакция с бензоилхлорид и хидразинхидрат. Получен е интересен продукт на кондензация при реакцията на етил-2-амино-4,5,6,7-тетрахидро[b]тиофен-3-карбоксилат с етилцианоацетат в диметил-формамид.