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Synthesis of Some Thienopyrimidine Derivatives

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Abstract: Thioxothienopyrimidinones, alkylthio- and arylalkylthiothienopyrimidinones, thienopyrimidinones, thienopyrimidines a thienopyrimidinedione and a thienotriazolo-pyrimidinone were prepared from 2-amino-3-carboethoxy-4,5-disubstituted thiophenes and 2-amino-3-cyano-4,5-disubstituted thiophenes via reactions with different reagents.

Keywords: Thioxothienopyrimidinones, alkyl- and arylalkylthiothienopyrimidinones, thienopyrimidinones, thienopyrimidines, thienopyrimidinediones, thienotriazolo-pyrimidinones.

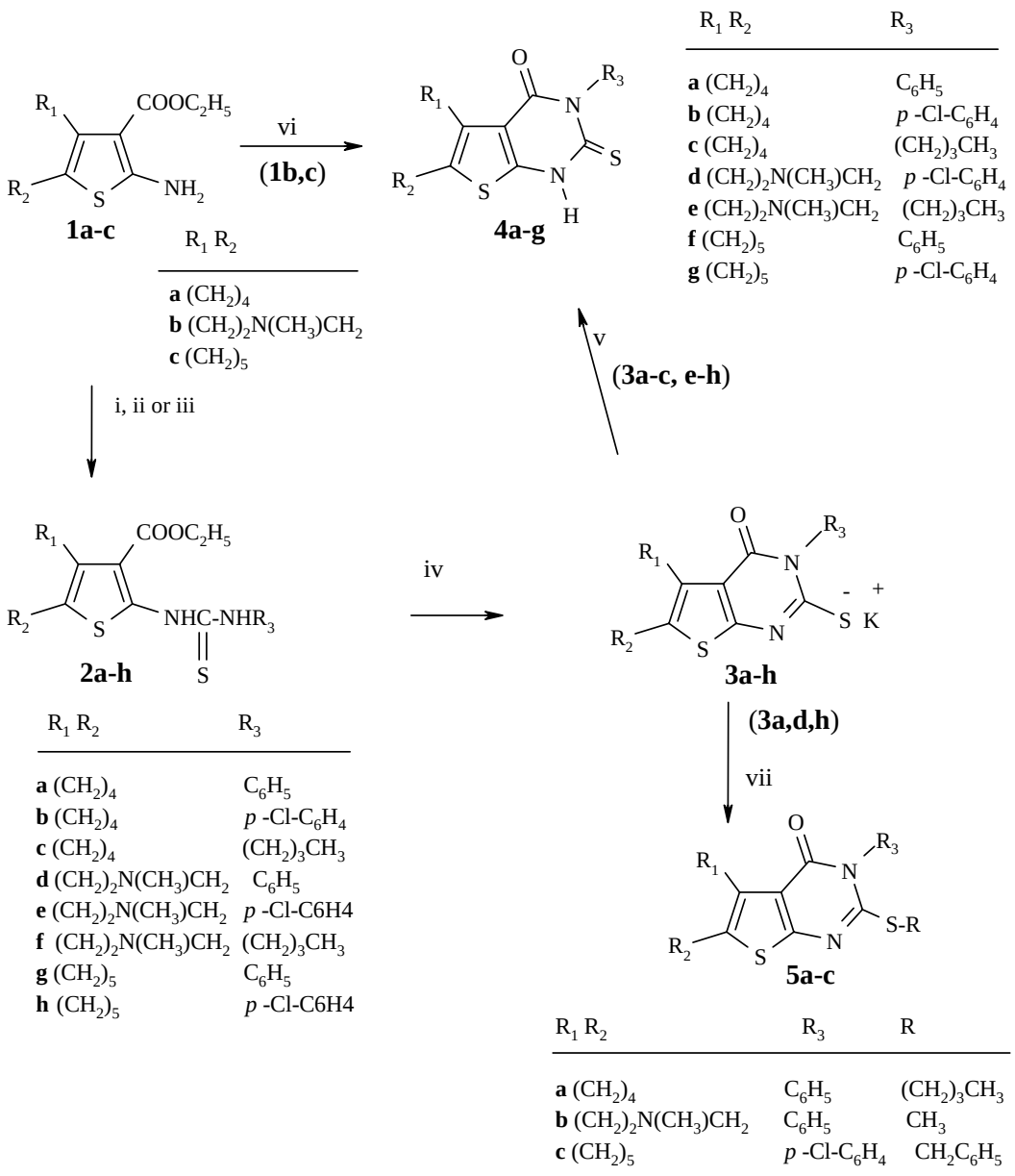
Introduction

Many thienopyrimidines are found to exhibit a variety of biological activities, including antiinflammatory [1,2], antimicrobial [3] and analgesic [4] properties, inhibition of cancer cell proliferation [5], antagonism of α_1 adrenoceptors [6] and prevention of cartilage destruction in articular diseases [7]. In continuation with our previous work on the title compounds [8,9], we report herein the synthesis of a series of novel thienopyrimidine derivatives.

Results and Discussion

The starting materials, namely 2-amino-3-ethoxycarbonyl-4,5-disubstituted thiophenes **1a-c** and 2-amino-3-cyano-4,5-disubstituted thiophenes **1d**,**e** were prepared following the corresponding literature procedures [10-12]. Thienylthiourea derivatives **2a-h** were prepared by condensation of the amino esters **1a-c** with alkyl or aryl isothiocyanates, either by heating at reflux or under microwave irradiation [8, 9, 13]; the latter method afforded higher yields of the desired products in a shorter time.

Scheme 1

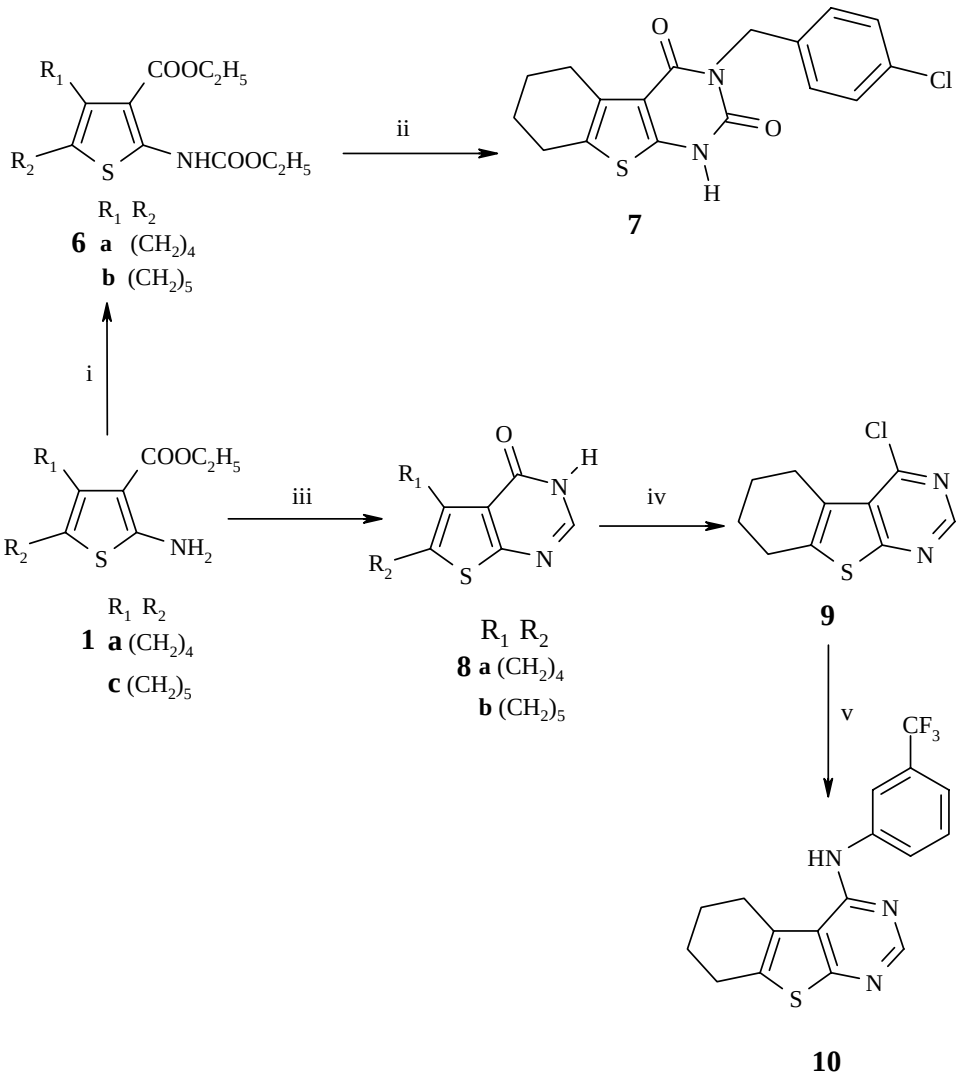


i) R_3NCS, EtOH, reflux, 1-4h
ii) R_3NCS, microwave (MW), 45 sec.
iii) phenylthiourea, EtOH, microwave (MW), 20 sec.
iv) KOH, EtOH, reflux, 2-6h
v) H_2O, HCl, r.t.
vi) *p* -Cl-C_6H_4NCS, acetonitrile, reflux, 20h
vii) R-X, EtOH, reflux, 1-8h

Compounds **2a**,**d** were also prepared by condensation of the amino esters **1a**,**b** with phenylthiourea under microwave irradiation. Cyclization of **2a-h** using alcoholic KOH gave the monopotassium salts of the corresponding 3-substituted-2-thioxo-4,5-disubstituted-thieno[2,3-d]pyrimidin-4-ones **3a**-**h**. 2-Thioxo derivatives **4a-g** were prepared either from the appropriate potassium salts **3** by acidification or from the amino ester derivatives **1a-c** via condensation with aryl isothiocyanates [14, 15]. Alkylation of **3a**,**d**,**h** with alkyl halides gave 2-alkylthio-derivatives **5a-c**.

Condensation of the amino esters **1a**,**c** with ethyl chloroformate gave the carbamate derivatives **6a**,**b**, which were fused with *p*-chlorobenzylamine at 230-240°C to afford the dione derivative **7** [16]. The thienopyrimidinone derivatives **8a**,**b** were prepared by cyclization of the corresponding amino ester with formamide. Nucleophilic aromatic substitution with $POCl_3$ was carried out on **8a** to give the 4-chlorothienopyrimidine derivative **9**. Further substitution with an aromatic amine was carried out on this chloro derivative **9** to yield the 4-anilino derivative **10** (Scheme 2). The structures of compounds **1-10** were confirmed from their IR, ^{1}H-NMR, ^{13}C-NMR and MS spectral data.

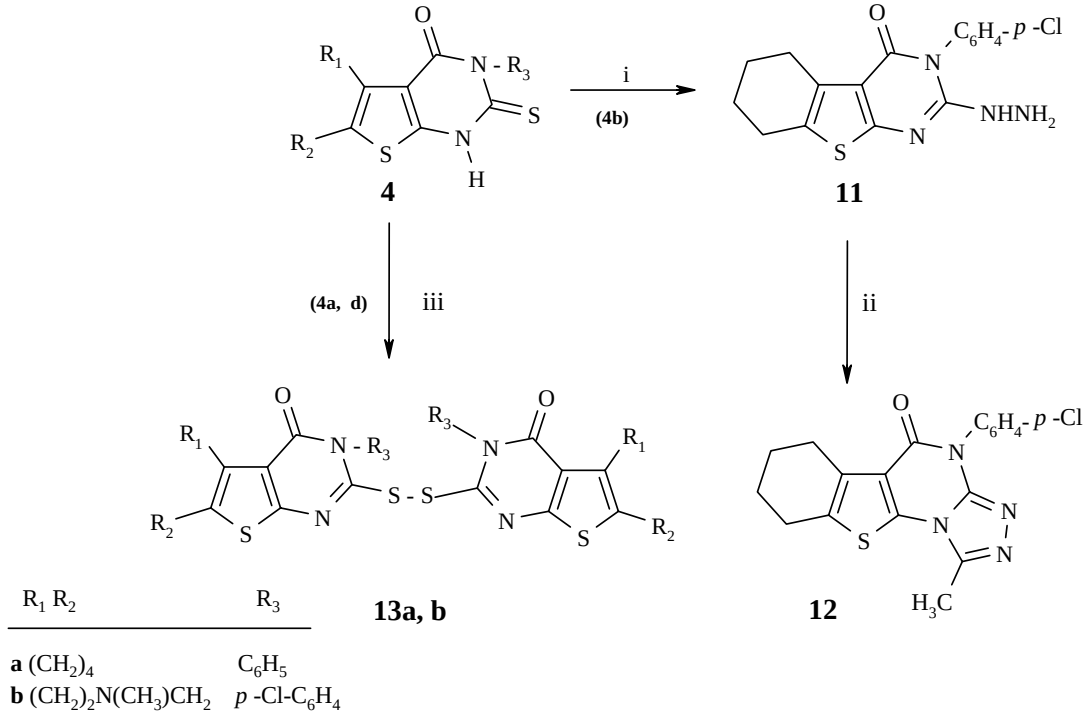
Scheme 2



i) $ClCO_2CH_2CH_3$, reflux, 3h
ii) *p* -Chlorobenzylamine, fusion, 230-240°C, 8h
iii) $HCONH_2$, reflux, 1.5h
iv) $POCl_3$, reflux, 15h
v) 3-$CF_3C_6H_4NH_2$, reflux, 3h

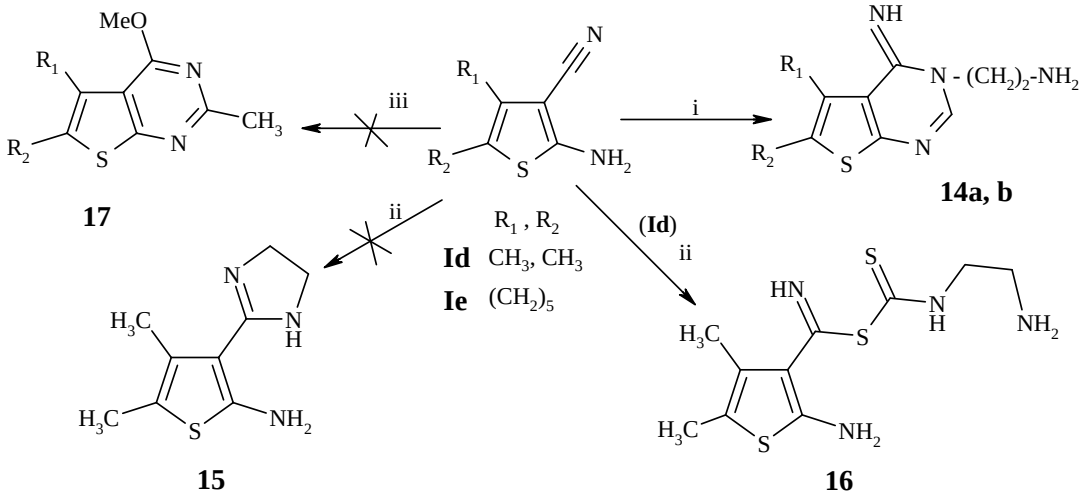
Substitution of the mercapto group in **4a**,**d** by hydrazine hydrate afforded the 2-hydrazino derivative **11** which was then cyclized by glacial acetic acid to give the triazolo derivative **12** [17, 18]; the latter compound is sparingly soluble in $CDCl_3$ and DMSO-d_6, precluding the use of ^{13}C-NMR spectroscopy as a characterization tool. Oxidation of **4a**,**d** by iodine (Scheme 3) gave the disulfides **13a**,**b** [19]. The structures of compounds **11**-**13** were also confirmed by various spectroscopic techniques.

Scheme 3



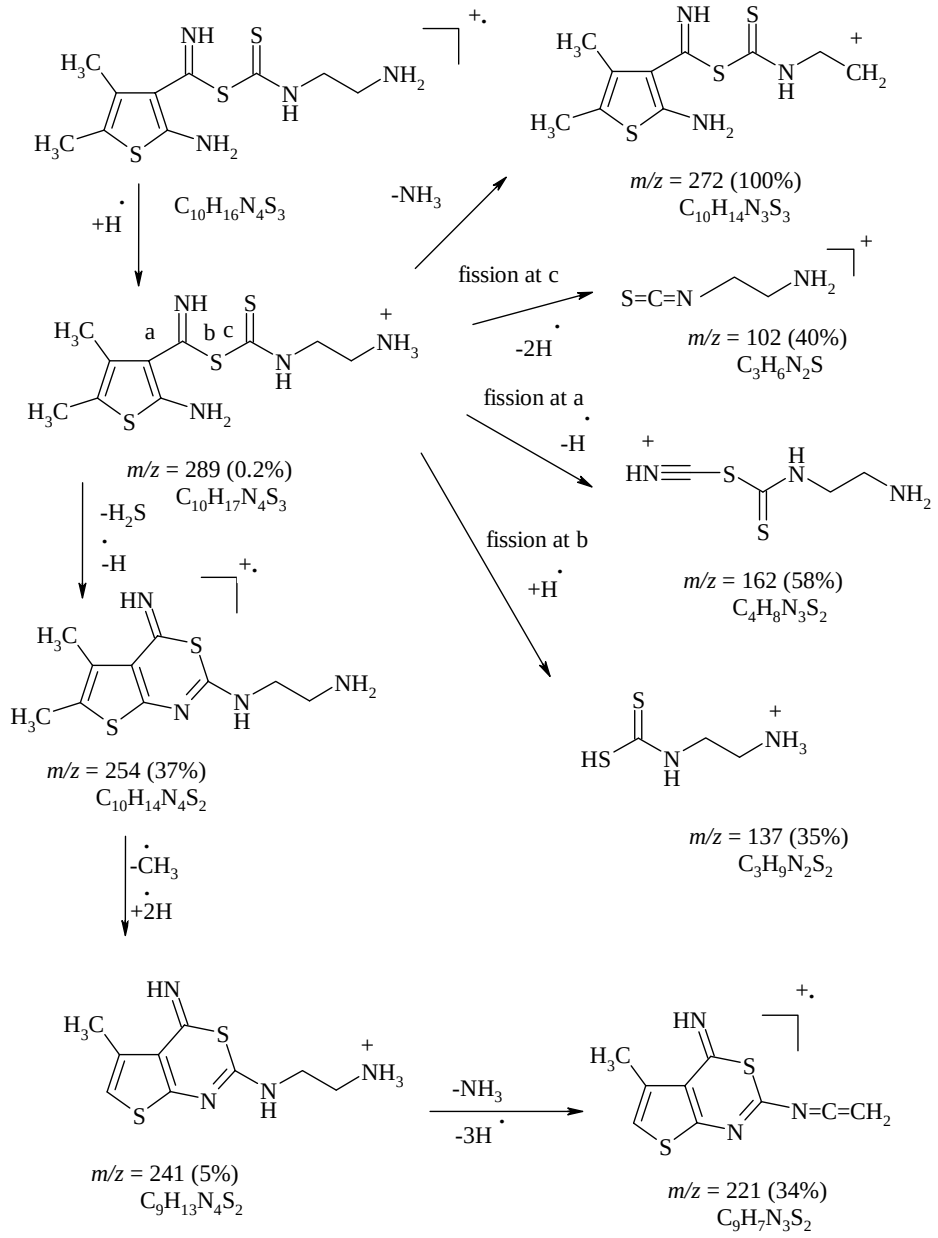
Treatment of **1d**,**e** with triethyl orthoformate followed by ethylenediamine, yielded the 3-amino-ethyl-4-imino-derivatives **14a**,**b** [20]. Compounds **13b** and **14a**,**b** could only be identified by their IR and MS spectra, as they are insoluble in the common solvents used in NMR. An attempt to prepare 2-amino-4,5-dimethyl-3-(4,5-dihydro-1*H*-2-imidazolyl)thiophene (**15**) following a published procedure [21], by reacting **1d** with ethylenediamine and carbon disulfide did not yield the expected product **15** and instead the intermediate **16** was obtained (Scheme 4). This intermediate was insoluble in the common solvents used for NMR measurements; but it could be identified by its IR spectrum, which revealed the expected C=S absorption at 1207 cm^{-1}, and by its MS spectral data (the general fragmentation patterns proposed for **16** are shown in Scheme 5). Attempts were also made to prepare 2-methyl-4-methoxythienopyrimidine **17** by reacting **1d**,**e** with acetyl chloride followed with methanol according to a published procedure [20], however, the target compound was not obtained and only the starting material was recovered.

Scheme 4



i) a: TEOF, reflux, 4h ; b: $NH_2(CH_2)_2NH_2$,100°C, 7h ii) a: $NH_2(CH_2)_2NH_2$; b: CS_2 / 100°C, 8h
iii) a: CH_3COCl; b: CH_3OH, K_2CO_3

Scheme 5



Experimental

General

Melting points were determined using an Electrothermal IA9000 series digital capillary melting point apparatus and are uncorrected. IR spectra were obtained as KBr discs on a 1000-Perkin Elmer FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL ECP-400 NMR in $CDCl_3$ (or DMSO-d_6) using TMS as an internal standard. Chemical shifts are given in ppm on the δ scale and coupling constants (*J*) are given in Hz. Electron impact (EI) MS spectra were acquired with the aid of a Shimadzu GCMSQP5050A spectrometer, equipped with a 30 m x 0.25 mm DB-1 glass column, operating with an ionization energy of 70 eV, at the Chemistry Department, College of Science, King Saud University. Compounds **2a-h** were synthesized using the reported methods [8, 9, 13], or in the case of particular examples, by the methods described below.

Method A: Synthesis of **2d**:

A mixture of **1b** (0.5 g, 2 mmol) and phenyl isothiocyanate (0.27 g, 2 mmol) was placed in a 50 mL beaker covered with a watch glass and then irradiated with microwaves (600 W) for 45 seconds. The cold reaction mixture was treated with ethanol and the solid product was filtered off and recrystallized.

Method B: Synthesis of **2a**,**d**:

A mixture of **1a**,**b** (2 mmol), phenylthiourea (2 mmol) and 5 drops of dry ethanol was placed in a 50 mL beaker, covered with a watch glass, and was then irradiated with microwave (800 W) for 20 seconds. The cold reaction mixture was treated with crushed ice; the solid product was filtered, dried and recrystallized.

3-Ethoxycarbonyl-2-(3-phenylthioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene (**2a**): Fine pale yellow needles, m.p. 191-193°C (from ethanol); Yield 64%; IR (cm^{-1}): 3416, 3179 (2NH), 1656 (C=O), 1195 (C=S); ^{1}H-NMR (DMSO-d_6): 1.30 (3H, t, *J* = 7.1, CH_2CH_3), 1.70-1.86 (4H, m, $2CH_2$ at C-5, C-6), 2.67-2.80 (4H, m, $2CH_2$ at C-4, C-7), 4.52 (2H, q, *J* = 7.1, CH_2CH_3), 7.29-7.33 (2H, m, H-2`, H-6`), 7.52-7.56 (3H, m, H-3`, H-4`, H-5`), 10.21 (1H, br. s, NH), 12.25 (1H, br. s, NH); ^{13}C-NMR: 14.31, 60.75 (Et carbons), 22.09, 23.51, 24.43, 26.42 (aliphatic ring sp^3 carbons), 113.02, 121.32, 126.94, 127.11, 130.91, 133.15, 149.85, 135.23 (sp^2 carbons), 166.73 (C=O), 176.25 (C=S).

3-Ethoxycarbonyl-2-[3-(4-chlorophenyl)thioureido]-4,5,6,7-tetrahydrobenzo[b]thiophene (**2b**): Colorless needles, m.p. 221-223°C (from ethanol); Yield 70%; IR (cm^{-1}): 3442, 3196 (2NH), 1663 (C=O), 1198 (C=S); ^{1}H-NMR (DMSO-d_6): 1.27 (3H, t, *J* = 7.3, CH_2CH_3), 1.68-1.69 (4H, m, $2CH_2$ at C-5, C-6), 2.51-2.55 (2H, m, CH_2 at C-4), 2.67-2.68 (2H, m, CH_2 at C-7), 4.18 (2H, q, *J* = 7.3, CH_2CH_3), 7.23 (2H, d, *J* = 8.8, H-2`, H-6`), 7.41 (2H, d, *J* = 8.8, H-3`, H-5`), 10.53 (1H, br. s, NH), 12.02 (1H, br. s, NH); ^{13}C-NMR: 14.37, 60.49 (Et carbons), 22.97, 23.04, 24.34, 26.43 (aliphatic ring sp^3 carbons),

112.23, 126.24, 128.93, 130.58, 137.24 150.42, 161.32, 125.71, (sp^2 carbons), 166.66 (C=O), 176.18 (C=S).

2-(3-Butylthioureido)-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophene (**2c**): Fine pale yellow needles, m.p. 123-125°C (from ethanol); Yield 59%; IR (cm^{-1}): 3429, 3230 (2NH), 1655 (C=O), 1175 (C=S); ^{1}H-NMR ($CDCl_3$): 0.93 (3H, t, *J* = 8.0, $CH_2CH_2CH_3$), 1.35 (3H, t, *J* = 7.1, OCH_2CH_3), 1.40 (2H, sext., *J* = 8.0, $CH_2CH_2CH_3$), 1.63 (2H, quint., *J* = 8.0, $CH_2CH_2CH_2$), 1.72-1.78 (4H, m, $2CH_2$ at C-5, C-6), 2.56-2.61 (2H, m, CH_2 at C-4), 2.71-2.76 (2H, m, CH_2 at C-7), 3.45 (2H, br peak, $NHCH_2CH_2$), 4.30 (2H, q, *J* = 7.1, OCH_2CH_3), 6.44 (1H, br. s, NH), 12.10 (1H, br. s, NH); ^{13}C-NMR: 14.42, 60.71 (Et carbons), 13.81, 20.11, 30.73, 44.15 (butyl group), 22.92, 23.15, 24.42, 26.51 (aliphatic ring sp^3 carbons) 112.01, 126.32, 130.67, 151.43 (thiophene carbons), 167.25 (C=O), 177.03 (C=S).

3-Ethoxycarbonyl-6-methyl-2-(3-phenylthioureido)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (**2d**): Fine yellow needles, m.p. 186-188°C (from ethanol/chloroform); Yield 60%; IR (cm^{-1}): 3467, 3175 (2NH), 1658 (C=O), 1195 (C=S); ^{1}H-NMR ($CDCl_3$): 1.24 (3H, t, *J* = 7.2, CH_2CH_3), 2.46 (3H, s, CH_3N), 2.66 (2H, t, *J* = 5.9, CH_2 at C-4), 2.85 (2H, t, *J* = 5.8, CH_2 at C-5), 3.49 (2H, s, CH_2 at C-7), 4.12 (2H, q, *J* = 7.2, CH_2CH_3), 7.31-7.36 (3H, m, H-2`,H-4` ,H-6`), 7.47 (2H, t, *J* =7.4, H-3`,H-5`), 8.01 (1H, br. s, NH), 12.12 (1H, br. s, NH); ^{13}C-NMR: 14.25, 60.56 (Et carbons), 45.63 (CH_3N), 52.50, 26.88, 53.24 (aliphatic ring sp^3 carbons), 112.54, 124.07, 125.80, 127.95, 129.04, 130.13, 135.81 150.52, (sp^2 carbons), 166.14 (C=O), 176.29 (C=S); MS: m/z (%) 375 [M^+] (96) ($C_{18}H_{21}N_3O_2S_2$), 332 [M-CH_3-C_2H_5] (18), 282 [M-C_6H_5-CH_3-H] (13), 239 [M-C_6H_5NHCS] (100), 166 [M-C_6H_5NHCS-C_2H_5OH-C_2H_4+H] (36).

3-Ethoxycarbonyl-2-[3-(4-chlorophenyl)-6-methylthioureido]-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (**2e**): Fine yellow cubes, m.p. 206-208°C (from ethanol/ chloroform); Yield 60%; IR (cm^{-1}): 3415, 3180 (2NH), 1659 (C=O), 1195 (C=S); ^{1}H-NMR ($CDCl_3$): 1.27 (3H, t, *J* = 7.2, CH_2CH_3), 2.46 (3H, s, CH_3N), 2.67 (2H, t, *J* = 5.7, CH_2 at C-4), 2.86 (2H, t, *J* = 5.7, CH_2 at C-5), 3.50 (2H, s, CH_2 at C-7), 4.18 (2H, q, *J* = 7.2, CH_2CH_3), 7.26 (2H, d, *J* = 8.8, H-2`, H-6`), 7.41(2H, d, *J* = 8.8, H-3`, H-5`), 7.89 (1H, br. s, NH), 12.21 (1H, br. s, NH); ^{13}C-NMR: 14.25, 60.78 (Et carbons), 45.63 (CH_3N), 26.88, 52.46, 53.21 (aliphatic ring sp^3 carbons), 112.46, 123.91, 126.92, 129.04, 130.18, 133.17, 134.53, 150.27 (sp^2 carbons), 166.43 (C=O), 176.17 (C=S); MS: m/z (%) 409 [M^+] (59) ($C_{18}H_{20}{}^{35}ClN_3O_2S_2$), 411 [M+2] (22) ($C_{18}H_{20}{}^{37}ClN_3O_2S_2$), 366 [M-$CH_3$-$C_2H_4$] (12), 282 [M-$ClC_6H_4$-$CH_3$–H] (37), 239 [M-$ClC_6H_4NHCS$] (91), 169 [M-$ClC_6H_4NHCS$-$C_2H_5OH$-$C_2H_4$+3H] (58).

2-(3-Butylthioureido)-3-ethoxycarbonyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (**2f**): Fine red needles, m.p. 224-226°C (from ethanol/chloroform);Yield 60%; IR (cm^{-1}): 3434, 3162 (2NH), 1650 (C=O), 1169 (C=S); ^{1}H-NMR (DMSO-d_6): 0.89 (3H, t, *J* = 8.0, $CH_2CH_2CH_3$), 1.09 (3H, t, *J* = 7.3, OCH_2CH_3), 1.31 (2H, sext., *J* = 7.3, $CH_2CH_2CH_3$), 1.62 (2H, quint., *J* = 7.3, $CH_2CH_2CH_2$), 2.41 (3H, s, CH_3N), 2.68 (2H, t, *J* = 5.9, CH_2 at C-4), 2.91-2.95 (2H, m, CH_2 at C-5), 3.47 (2H, s, CH_2 at C-7), 3.52 (2H, t, *J* = 7.3, $NHCH_2CH_2$), 4.31 (2H, q, *J* = 7.1, OCH_2CH_3), 8.85 (1H, br. s, NH), 9.29 (1H, br. s, NH); ^{13}C-NMR: 18.59, 57.36 (Et carbons), 13.93, 20.29, 28.69, 45.98 (Bu carbons), 45.28 (CH_3N), 25.47, 51.59, 52.97 (aliphatic ring sp^3 carbons), 116.02, 125.17, 129.89, 149.62 (thiophene

carbons), 157.19 (C=O), 174.25 (C=S); MS: m/z (%) 355 [M^+] (12) ($C_{16}H_{25}N_3O_2S_2$), 309 [M-C_2H_5OH] (100), 252 [M-C_4H_9-C_2H_5OH] (13), 210 [M-C_4H_9NHCS-2CH_3+H] (35).

General procedure for the preparation of **3a-h**:

A mixture of the compounds **2a-h** (13.5 mmol) and potassium hydroxide (0.76 g, 13.5 mmol) in absolute ethanol (55 mL) was heated under reflux with stirring for 1 h. The suspension was filtered while hot and the solid was washed with hot absolute ethanol to give **3a-h**.

*General procedure for the synthesis of **4a-g**: Method A:*

A suspension of potassium salts of **3a-c**,**e-h** in water (50 mL) was acidified with concentrated hydrochloric acid and stirred at room temperature for 30 min. The solid was collected by filtration, washed with water and recrystallized from ethanol to give **4a-g**.

Method B: Synthesis of **4d**,**g**.

A mixture of **1b**,**c** (10 mmol) and the appropriate isothiocyanate (10 mmol) in acetonitrile (30 mL) was heated under reflux for 15 h in the presence of anhydrous potassium carbonate (1.4 g). The reaction mixture was then cooled, filtered, diluted with water (10 mL) and neutralized with 2M hydrochloric acid. The product obtained was filtered, washed with water, dried and recrystallized from ethanol to give **4d**,**g**.

Monopotassium salt of 3-phenyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-benzo[4,5]thieno[2,3-d]-pyrimidin-4-one (**3a**) *and its 2-thioxo derivative* **4a**: Yields: 53% (**3a**) and 73% (**4a**), respectively; Compound **4a**: white powder, m.p. 259-261°C; IR (cm^{-1}): 3413 (NH), 1705 (C=O), 1218 (C=S); ^{1}H-NMR ($CDCl_3$): 1.77-1.85 (4H, m, 2CH_2 at C-6, C-7), 2.63-2.68 (2H, m, CH_2 at C-5), 2.84-2.91 (2H, m, CH_2 at C-8), 7.24-7.26 (2H, m, H-2`, H-6`), 7.45-7.57 (3H, m, H-3`, H-4`, H-5`), 12.19 (1H, br. s, NH); ^{13}C-NMR: 21.96, 22.96, 24.72, 25.14 (aliphatic ring sp^3 carbons), 117.53, 128.52, 129.07, 129.49, 129.70, 132.64, 138.56, 148.51 (sp^2 carbons), 157.37 (C=O), 174.93 (C=S); MS: m/z (%) 314 [M^+] (100) ($C_{16}H_{14}N_2OS_2$), 179 [M-C_6H_5NCS] (89), 151 [M-C_6H_5NCS-C_2H_4] (35).

Monopotassium salt of 3-(4-chlorophenyl)-2-thioxo-2,3,5,6,7,8-hexahydro-1H-benzo[4,5]thieno[2,3-d]-pyrimidin-4-one (**3b**) *and its 2-thioxo derivative* **4b**: Yields: 75% (**3b**) and 89% (**4b**), respectively; Compound **4b**: white scales, m.p. 289-292°C; IR (cm^{-1}): 3129 (NH), 1706 (C=O), 1219 (C=S); ^{1}H-NMR (DMSO-d_6): 1.70-1.71 (2H, m, CH_2 at C-6), 1.77-1.78 (2H, m, CH_2 at C-7), 2.66-2.70 (2H, m, CH_2 at C-5), 2.71-2.75 (2H, m, CH_2 at C-8), 7.28 (2H, d, *J* =8.1, H-2`, H-6`), 7.52 (2H, d, *J* = 8.1, H-3`, H-5`), 13.71 (1H, br. s, NH); ^{13}C-NMR: 22.10, 23.02, 24.52, 25.38 (aliphatic ring sp^3 carbons), 116.67, 128.97, 129.57, 131.62, 131.69, 133.17, 138.81, 149.92 (sp^2 carbons), 157.38 (C=O), 174.88 (C=S); MS: m/z (%) 348 [M^+] (86) ($C_{16}H_{13}{}^{35}ClN_2OS_2$), 350 [M+2] (35) ($C_{16}H_{13}{}^{37}ClN_2OS_2$), 179 [M-$ClC_6H_4NCS$] (100), 151 [M-$ClC_6H_4NCS$-$C_2H_4$] (38).

*Monopotassium salt of 3-butyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (**3c**) and its 2-thioxo derivative* **4c**: Yields: 40% (**3c**) and 78% (**4c**), respectively; Compound **4c**: white scales, m.p. 234-236°C; IR (cm^{-1}): 3254 (NH), 1689 (C=O), 1220 (C=S); ^{1}H-NMR ($CDCl_3$): 0.97 (3H, t, J = 7.3, CH_2CH_3), 1.42 (2H, sext., *J* =7.3, $CH_2CH_2CH_3$), 1.71-1.87 (6H, m, $3CH_2$ at C-6, C-7, C-2`), 2.66 (2H, t, *J* = 5.8, CH_2 at C-5), 2.91 (2H, t, *J* = 5.8, CH_2 at C-8), 4.43 (2H, t, *J* = 7.7, NCH_2CH_2), 12.31 (1H, br. s, NH); ^{13}C-NMR: 13.88, 20.33, 28.82, 46.59, (Bu carbons), 21.99, 22.97, 24.76, 25.31 (aliphatic ring sp^3 carbons), 117.31, 129.32 132.29, 147.89 (thiophene carbons), 156.85 (C=O), 173.52 (C=S); MS: m/z (%) 294 [M^+] (71) ($C_{16}H_{18}N_2OS_2$), 261 [M-SH] (100), 238 [M-C_4H_9+H] (40), 179 [M-C_4H_9NCS] (75), 151 [M-C_4H_9NCS-C_2H_4] (29).

Monopotassium salt of 7-methyl-3-phenyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-pyrido[3`,4`:5,4]-thieno[2,3-d]pyrimidin-4-one (**3d**): Yield 45%; IR (cm^{-1}): 1650 (C=O); ^{1}H-NMR (DMSO-d_6): 2.31 (3H, s, CH_3N), 3.21 (2H, t, *J* = 5.9, CH_2 at C-5), 3.38-3.42 (2H, m, CH_2 at C-6), 4.33 (2H, s, CH_2 at C-8), 7.31-7.33 (3H, m, H-2`, H-4`, H-6`), 7.45-7.52 (2H, t, *J* =7.8, H-3`, H-5`); ^{13}C-NMR: 46.44 (CH_3N), 26.24, 53.50, 54.31 (aliphatic ring sp^3 carbons), 118.79,122.37, 128.37, 129.83, 131.45, 131.65, 142.13, 157.74, (sp^2 carbons), 165.68 (C=O), 176.23 (C=S).

Monopotassium salt of 3-(4-chloro-phenyl)-7-methyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-pyrido-[3`,4`:5,4]thieno[2,3-d]pyrimidin-4-one (**3e**) *and its 2-thioxo derivative* **4d**: Yields: 85% (**3e**) and 89% (**4d**), respectively; Compound **4d**: pale orange scales, m.p. 256-258°C; IR (cm^{-1}): 3137 (NH), 1691 (C=O), 1213 (C=S); ^{1}H-NMR (DMSO-d_6): 2.88 (3H, s, CH_3N), 2.98-3.12 (2H, m, CH_2 at C-5), 3.36-3.46 (2H, m, CH_2 at C-6), 4.39 (2H, s, CH_2 at C-8), 7.29 (2H, d, *J* = 8.1, H-2`, H-6`), 7.53 (2H, d, *J* = 8.1, H-3`, H-5`), 11.18 (1H, br. s, NH); ^{13}C-NMR: 42.22 (CH_3N), 22.79, 49.89, 50.55 (aliphatic ring sp^3 carbons), 115.56, 120.55, 128.83, 129.64, 131.56, 133.31, 138.57, 151.80, (sp^2 carbons), 157.32 (C=O), 175.38 (C=S); MS: m/z (%) 363 [M^+] (84) ($C_{16}H_{14}{}^{35}ClN_3OS_2$), 365 [M+2] (35) ($C_{16}H_{14}{}^{37}ClN_3OS_2$), 193 [M-$ClC_6H_4NCS$] (21), 151 [M-$ClC_6H_4NCS$-$C_2H_4$-$CH_3$] (100).

Monopotassium salt of 7-methyl-3-butyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-pyrido[3`,4`:5,4]thieno-[2,3-d]pyrimidin-4-one (**3f**) *and its 2-thioxo derivative* **4e**: Yields: 51% (**3f**) and 45% (**4e**), respectively; Compound **4e**: yellow scales, m.p. 297-299°C; IR (cm^{-1}): 3176 (NH), 1687 (C=O), 1200 (C=S); ^{1}H-NMR (DMSO-d_6): 0.92 (3H, t, *J* = 7.3, CH_2CH_3), 1.32 (2H, sext., *J* =7.3, $CH_2CH_2CH_3$), 1.62 (2H, quint., *J* =7.3, $CH_2CH_2CH_2$),4.41 (2H, t, *J* = 7.7 NCH_2CH_2), 2.49 (3H, s, CH_3N), 2.84-2.89 (2H, m, CH_2 at C-5), 3.14-3.20 (2H, m, CH_2 at C-6), 3.34 (2H s,, CH_2 at C-8), 13.71 (1H, br. s, NH); ^{13}C-NMR: 14.47, 20.25, 28.69, 45.93 (Bu carbons), 45.42 (CH_3N), 26.81, 52.54, 53.22 (aliphatic ring sp^3 carbons), 114.42, 124.98, 130.76, 149.81 (thiophene carbons), 156.38 (C=O), 175.94 (C=S); MS: m/z (%) 309 [M^+] (100) ($C_{14}H_{19}N_3OS_2$), 193 [M-C_4H_9NCS-H] (15), 151 [M-C_4H_9NCS-C_2H_4-CH_3] (14).

Monopotassium salt of 3-phenyl-2-thioxo-1,2,3,5,6,7,8,9-octahydrocyclohepta[4,5]thieno[2,3-d]-pyrimidin-4-one (**3g**) *and its 2-thioxo derivative* **4f**: Yields: 42% (**3g**) and 83% (**4f**); Compound **4f**: pale yellow powder, m.p. 306-308°C; IR (cm^{-1}): 3141 (NH), 1698 (C=O), 1221 (C=S); ^{1}H-NMR (DMSO-d_6): 1.54-1.62 ($2CH_2$ m, 4H at C-6, C-7), 1.81 (2H, br. peak, CH_2 at C-8), 2.76 (2H, br. peak, CH_2 at C-5), 3.09 (2H, br. peak, CH_2 at C-9), 7.20-7.21 (2H, d, *J* = 7.1, H-2`, H-6`), 7.38 (1H, t, *J* = 7.3, H-4`), 7.45 (2H, t, *J* = 7.3, H-3`, H-5`), 13.57 (1H, br. s, NH); ^{13}C-NMR: 27.17 (2C), 27.86, 28.95,

32.26 (aliphatic ring sp^3 carbons), 117.23, 128.47, 129.38, 129.58, 132.66, 137.20, 139.99, 148.57 (sp^2 carbons), 157.94 (C=O), 174.87 (C=S); MS: m/z (%) 328 [M^+] (100) ($C_{17}H_{16}N_2OS_2$), 193 [M-C_6H_5NCS] (39), 151 [M-C_6H_5NCS-C_2H_4-NH+H] (6).

Monopotassium salt of 3-(4-chlorophenyl)-2-thioxo-1,2,3,5,6,7,8,9-octahydrocyclohepta[4,5]thieno-[2,3-d]pyrimidin-4-one (**3h**) *and its 2-thioxo derivative* **4g**: Yields: 88% (**3h**) and 85% (**4g**), respectively; Compound **4g**: white scales, m.p. 263-265°C, 3123 (NH), 1710 (C=O), 1220 (C=S); ^{1}H-NMR (DMSO-d_6): 1.53 (2H, br. peak, CH_2 at C-7), 1.61 (2H, br. peak, CH_2 at C-6), 1.82 (2H, br. peak, CH_2 at C-8), 2.77 (2H, br. peak, CH_2 at C-5), 3.08 (2H, br. peak, CH_2 at C-9), 7.28 (2H, d, *J* = 8.8, H-2`,H-6`), 7.52 (2H, d, *J* = 8.8, H-3`,H-5`), 13.68 (1H, br. s, NH); ^{13}C-NMR: 27.14 (2C), 27.86, 28.93, 32.33 (aliphatic ring sp^3 carbons), 117.20, 129.52, 131.65, 132.79, 133.12, 137.21, 138.95, 148.63 (sp^2 carbons), 157.90 (C=O), 174.62 (C=S); MS: m/z (%) 362 [M^+] (100) ($C_{17}H_{15}{}^{35}ClN_2OS_2$), 364 [M+2] (44) ($C_{17}H_{15}{}^{37}ClN_2OS_2$), 193 [M-$ClC_6H_4NCS$] (74), 151 [M-$ClC_6H_4NCS$-$C_2H_4$-NH+H] (19).

General procedure for synthesis of **5a-c**:

A mixture of potassium salt of **3a**, **d**, **h** (3.6 mmol) and the appropriate alkyl halide (4.32 mmol) in ethanol (15 mL) was heated under reflux with stirring for 1 h (for compounds **5a**,**b**) and for 8 h (for compound **5c**). The solid obtained was filtered, washed with water, dried and recrystallized from ethanol/chloroform.

2-Butylthio-3-phenyl-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (**5a**): Colorless scales, m.p. 230-232°C; Yield 90%; IR (cm^{-1}): 1689 (C=O); ^{1}H-NMR ($CDCl_3$): 0.90 (3H, t, J = 7.3, CH_2CH_3), 1.39 (sext., 2H, *J* =7.3, $CH_2CH_2CH_3$), 1.61 (2H, quint., *J* =7.3, $CH_2CH_2CH_2$), 1.79-1.87 (4H, m, 2CH_2 at C-6, C-7), 2.70-2.76 (2H, m, CH_2 at C-5), 2.91-2.94 (m, 2H, CH_2 at C-8), 3.12 (2H, t, *J* = 7.3, NCH_2CH_2), 7.25-7.27 (2H, m, H-2`, H-6`), 7.51-7.53 (3H, m, H-3`, H-4`, H-5`); ^{13}C-NMR: 13.73, 22.04, 30.59, 32.59 (Bu carbons), 22.38, 23.10, 25.17, 25.46 (aliphatic ring sp^3 carbons), 119.15, 129.12, 129.76, 129.89, 131.68, 131.74, 136.04, 157.75 (sp^2 carbons), 158.69 (C=O), 162.11 (C=S); MS: m/z (%) 370 [M^+] (100) ($C_{20}H_{22}N_2OS_2$), 314 [M-C_4H_9+H] (74), 281 [M-SC_4H_9] (39), 253 [M-SC_4H_9-C_2H_4] (6), 179 [M-SC_4H_9-C_2H_4-C_6H_5+3H] (79), 151 [M-C_4H_9-C_2H_4-C_6H_5NCS+H] (16).

3-Phenyl-7-methyl-2-methylthio-5,6,7,8-tetrahydro-3H–pyrido[3`,4`:5,4]thieno[2,3-d]pyrimidin-4-one (**5b**): Fine yellow needles, m.p. 296-298°C; Yield 75%; IR (cm^{-1}): 1692 (C=O); ^{1}H-NMR (DMSO-d_6): 2.45 (3H, s, NCH_3), 3.17-3.21 (2H, m, CH_2 at C-5), 3.36 (3H, s, SCH_3), 3.71 (2H, t, *J* = 5.9, CH_2 at C-6), 4.75 (2H, s, CH_2 at C-8), 7.41-7.42 (2H, m, H-2`, H-6`), 7.55-7.62 (3H, m, H-3`, H-4`, H-5`); ^{13}C-NMR: 15.93 (SCH_3), 51.44 (CH_3N), 22.20, 58.51, 60.01 (aliphatic ring sp^3 carbons), 117.88, 121.26, 127.43, 129.71, 130.24, 130.63, , 136.02, 157.84 (sp^2 carbons), 161.18 (C=O), 163.85 (C=S); MS: m/z (%) 343 [M^+] (88) ($C_{17}H_{17}N_3OS_2$), 328 [M-CH_3] (47), 300 [M-CH_3-C_2H_4] (100), 253 [M-CH_3-C_2H_4-SCH_3] (83), 193 [M-CH_3-C_6H_5NCS] (6), 150 [M-2CH_3-C_6H_5NCS-C_2H_4] (27).

2-Benzylthio-3-(4-chloro-phenyl)3,5,6,7,8,9-hexahydrocyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (**5c**): Fine colorless needles, m.p. 264-266°C; Yield 88%; IR (cm^{-1}): 1680 (C=O); ^{1}H-NMR ($CDCl_3$): 1.61-1.74 (4H, m, 2CH_2 at C-6, C-7), 1.84-1.88 (2H, m, CH_2 at C-8), 2.82-2.85 (2H, m, CH_2 at C-5),

3.23-3.26(2H, m, CH_2 at C-9), 4.33 (2H, s, SCH_2Ph), 7.19 (2H, d, *J* = 8.8, H-2`, H-6`), 7.23-7.34 (5H, m, Ar-H), 7.46 (d, 2H, *J* = 8.8, H-3`, H-5`); ^{13}C-NMR: 27.32, 27.78, 27.90, 29.94, 32.69 (aliphatic ring sp^3 carbons), 37.31 (SCH_2Ph), 119.70, 127.71, 128.68, 129.44, 130.06, 130.60, 134.33, 135.91, 136.06, 136.60, 137.37, 156.14 (sp^2 carbons), 159.04 (C=O), 160.90 (C=S); MS: m/z (%) 452 [M^+] (67) ($C_{24}H_{21}{}^{35}ClN_2OS_2$), 454 [M+2] (30) ($C_{24}H_{21}{}^{37}ClN_2OS_2$), 419 [M-Cl+2H] (29), 361 [M-$CH_2C_6H_5$] (6), 326 [M-Cl-$CH_2C_6H_5$] (9), 201 [M-$SHCH_2C_6H_5$-$ClC_6H_4NH_2$] (100).

General procedure for synthesis of **6a**,**b**:

A mixture of **1a**,**c** (15.8 mmol) and ethyl chloroformate (40 mL) was refluxed for 3h. After cooling, the reaction mixture was evaporated under reduced pressure and the residue was recrystallized from ethanol.

2-Ethoxycarbonylamino-3-ethoxycarbonyl-5,6,7,8-tetrahydrobenzo[b]thiophene (**6a**): Fine pale brown needles, m.p. 66-68 °C; Yield 87%; IR (cm^{-1}): 3246 (NH), 1724, 1662 (2C=O); ^{1}H-NMR (DMSO-d_6): 1.25 (3H, t, *J* = 7.3 CH_2CH_3), 1.28 (3H, t, *J* = 6.9 CH_2CH_3), 1.68-1.70 (4H, m, $2CH_2$ at C-5, C-6), 2.54-2.56 (2H, m, CH_2 at C-4), 2.64-2.66 (2H, m, CH_2 at C-7), 4.19 (2H, q, *J* = 7.3 OCH_2CH_3), 4.23 (2H, q, *J* = 7.3 OCH_2CH_3), 10.34 (1H, br s, NH); ^{13}C-NMR: 14.56, 62.59 (Et carbons), 14.78, 60.89 (Et carbons), 22.77, 23.01, 24.27, 26.42 (aliphatic ring sp^3 carbons), 111.01, 125.69, 131.32, 148.62 (thiophene carbons), 165.85 (C=O), 152.75 (carbamate C=O); MS: m/z (%) 297 [M^+] (100) ($C_{14}H_{19}NO_4S$), 251 [M-C_2H_5OH] (89), 223 [M-C_2H_5COOH] (30), 205 [M-$2C_2H_5OH$] (38), 195 [M-C_2H_5COOH-C_2H_4] (10), 179 [M-$COOC_2H_5$-C_2H_5O] (54), 151 [M-$COOC_2H_5$-C_2H_5O-C_2H_4] (32).

2-Ethoxycarbonylamino-3-ethoxycarbonyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene (**6b**): Fine pale brown needles, m.p. 78-80 °C; Yield 70%; IR (cm^{-1}): 3241 (NH), 1728, 1662 (2C=O); ^{1}H-NMR (DMSO-d_6): 1.25 (3H, t, *J* = 6.9 CH_2CH_3), 1.28 (3H, t, *J* = 7.1, CH_2CH_3), 1.52-1.58 (4H, m, $2CH_2$ at C-5, C-6), 1.76-1.78 (2H, m, CH_2 at C-7), 2.65-2.69 (2H, m, CH_2 at C-4), 2.90-2.93 (2H, m, CH_2 at C-8), 4.18 (2H, q, *J* = 7.1 OCH_2CH_3), 4.26 (2H, q, *J* = 7.4 OCH_2CH_3), 10.11 (1H, br. s, NH); ^{13}C-NMR: 14.82, 62.40 (Et carbons), 14.53, 61.05 (Et carbons), 27.12, 27.98, 28.14, 28.45, 32.11 (aliphatic ring sp^3 carbons), 116.25, 130.13, 137.03, 145.61 (thiophene carbons), 165.55, (C=O), 153.04 (carbamate C=O); MS: m/z (%) 311 [M^+] (100) ($C_{15}H_{21}NO_4S$), 283 [M-C_2H_4] (8), 265 [M-C_2H_5OH] (72), 237 [M-$HCOOC_2H_5$] (26), 219 [M-$HCOOC_2H_5$-CH_3-3H] (35), 193 [M-$COOC_2H_5$-C_2H_5O] (33), 165 [M-$COOC_2H_5$-C_2H_5O-C_2H_4] (17), 151 [M-$COOC_2H_5$-C_2H_5O-C_2H_4-CH_3+H] (7), 139 [M-$COOC_2H_5$-C_2H_5O-C_2H_4-HCN+H] (10).

3-(4-Chlorobenzyl)-5,6,7,8-tetrahydro-1H-benzo[4,5]thieno[2,3-d]pyrimidine-2,4-dione (**7**):

A mixture of **6a** (1.2 g, 3.7 mmol) and 4-chlorobenzylamine (1.0 g, 7.1 mmol) was heated to 230-240 °C for 8 h. After cooling, the crude solid was recrystallized from ethanol/water to give **7** as a brown powder, m.p.236-238 °C; Yield 60%; IR (cm^{-1}): 3232 (NH), 1724 (C=O at 4 position), 1660 (C=O at 2 position); ^{1}H-NMR ($CDCl_3$): 1.78-1.85 (4H, m, 2 CH_2 at C-6, C-7) 2.61-2.63 (2H, m, CH_2 at C-5) 2.87-2.89 (2H, m, CH_2 at C-8),5.09 (2H, s, N*C*$H_2C_6H_4Cl$), 7.23 (2H, d, *J* = 8.8, H-2`, H-6`),7.41 (2H, d, *J* = 8.8, H-3`, H-5`), 10.27 (1H, br. s, NH); ^{13}C-NMR: 22.07, 23.15, 24.59, 25.45

(aliphatic ring sp^3 carbons), 43.13 (NCH_2 Ar), 113.91, 126.98, 128.57, 130.44, 132.34, 133.84, 135.58, 148.52, (sp^2 carbons), 152.41 (C=O at C-2), 158.90 (C=O at C-4); Ms: m/z (%) 346 [M^+] (41) ($C_{17}H_{15}{}^{37}ClN_2O_2S$), 348 [M+2] (17) ($C_{17}H_{15}{}^{35}ClN_2O_2S$), 179 (30) [M-$OCNCH_2C_6H_4Cl$], 308 (22) [M-HCl-2H], 221 (61) [M-$CH_2C_6H_4Cl$], 151 (17) [M-$OCNCH_2C_6H_4Cl$-CO], 140 (98) [M-$C_{10}H_8NO_2S$], 125 (100) [M-$C_{10}H_9N_2O_2S$].

General procedure for synthesis of **8a**,**b**:

A mixture of **1a**,**c** (2 mmol) and formamide (20 mL) was heated under reflux for 1.5 h, then left to cool to room temperature overnight. The solid formed was filtered, washed with water, dried and recrystallized from ethanol.

5,6,7,8-Tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (**8a**): Fine pale brown needles, m.p. 255-257 °C; Yield 92%; IR (cm^{-1}): 3415 (NH), 1693 (C=O); ^{1}H-NMR (DMSO-d_6): 1.73-1.79 (4H, m, $2CH_2$ at C-6, C-7), 2.71-2.74 (2H, m, CH_2 at C-5), 2.85-2.87 (2H, m, CH_2 at C-8), 7.99 (1H, s, H-2), 12.29 (1H, br. s, NH); ^{13}C-NMR: 22.32, 23.01, 24.99, 25.89 (aliphatic ring sp^3 carbons), 123.23, 131.36, 136.77, 145.39 (thiophene carbons), 158.26 (C-2), 162.97 (C=O); Ms: m/z (%) 206 [M^+] (100) ($C_{10}H_{10}N_2OS$), 191 [M-NH] (36), 178 [M-CO] (91), 165 [M-CONH+2H] (7), 150 [M-CO-C_2H_4] (7), 136 [M-CONH-HCN] (3).

3,5,6,7,8,9-Hexahydrocyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (**8b**): Fine pale brown needles, m.p. 209-211 °C; Yield 90%; IR (cm^{-1}): 3411 (NH), 1705 (C=O); ^{1}H-NMR (DMSO-d_6): 1.53-1.65 (4H, m, $2CH_2$ at C-6, C-7), 1.80-1.87 (2H, m, CH_2 at C-8), 2.80-2.83 (2H, m, CH_2 at C-5), 3.23-3.26 (2H, m, CH_2 at C-9) 7.98 (1H, s, H-2), 12.31 (1H, br. s, NH); ^{13}C-NMR: 27.42, 27.80, 27.86, 29.57, 32.56 (aliphatic ring sp^3 carbons), 123.76, 132.15, 137.01,145.07 (thiophene carbons), 158.75 (C-2), 161.39 (C=O); MS: m/z (%) 220 [M^+] (100) ($C_{11}H_{12}N_2OS$), 205 [M-NH] (67), 191 [M-CHO] (46), 192 [M-CO] (48), 178 [M-CONH+H] (23), 165 [M-CO-C_2H_4+H] (25), 148 [M-$HCONH_2$-HCN] (6).

4-Chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (**9**):

A mixture of **8a** (1 g, 5 mmol) and phosphorus oxychloride (10 mL) was heated under reflux for 15 h. The excess phosphorus oxychloride was removed by distillation under reduced pressure, the residue treated with dry benzene (5 mL) and the solvent distilled under reduced pressure to remove the last traces of phosphorus oxychloride. The residue left was triturated with ice and sodium bicarbonate solution (10 %), the solid thus obtained was collected, washed with water and recrystallized from toluene to give a 48% yield of the title compound **9** as fine pale brown needles, m.p. 90-92 °C; ^{1}H-NMR ($CDCl_3$): 1.89-1.91 (4H, m, $2CH_2$ at C-6, C-7), 2.86-2.87 (2H, m, CH_2 at C-5), 3.05-3.06 (2H, m, CH_2 at C-8), 8.68 (1H, s, H-2); ^{13}CNMR: 22.27, 22.50, 26.12, 26.36 (aliphatic ring sp^3 carbons), 127.23, 128.91, 139.72, 153.23, 168.89, 151.57 (sp^2 carbons); Ms: m/z (%) 224 [M^+] (65) ($C_{10}H_9{}^{35}ClN_2S$); 226 [M+2] (25) ($C_{10}H_9{}^{37}ClN_2S$), 196 (100) [M-C_2H_4], 161 (10) [M-HCN-HCl].

4-N-(3-Trifluoromethylphenyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (**10**):

A mixture of **9** (0.5 g, 2 mmol) and 3-trifluoromethyl aniline (5 g, 40 mmol) was heated under reflux for 3 h and left overnight. The oily product was treated several times with petroleum ether (b.p. 40-60°C) and the separated solid was washed several times with petroleum ether to give a 15% yield of compound **10** as a brown powder, m.p. 224-226 °C; IR (cm^{-1}): 3450 (NH); ^{1}H-NMR ($CDCl_3$): 1.91-2.01 (4H, m, $2CH_2$ at C-6, C-7), 2.84-2.86 (2H, m, CH_2 at C-5), 3.06-3.07 (2H, m, CH_2 at C-8), 7.29 (1H, s, H-2`), 7.35 (1H, d, *J* = 8.1, H-6`), 7.47 (1H, t, *J* = 7.6, H-5`), 7.89 (1H, d, *J* = 8.1 , H-4`), 7.95 (1H, br. s, NH); ^{13}C-NMR: 22.41, 22.55, 25.62, 26.58 (aliphatic ring sp^3 carbons), 120.51 (CF_3), 116.93, 117.69, 117.73, 120.47, 124.22, 124.67, 129.62, 135.78, 139.03, 151.82,, 154.67, 165.66 (sp^2 carbons); MS: m/z (%) 349 [M^+] (100) ($C_{17}H_{14}F_3N_3S$), 334 [M-F+4H] (20), 320 [M-C_2H_4-H] (10), 304 [M-C_2H_4-F+2H] (5), 294 [M-3F+2H] (2), 204 [M-$C_6H_4CF_3$] (16).

3-(4-Chlorophenyl)-2-hydrazino-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (**11**):

A mixture of **4b** (1.4 g, 4 mmol) and 99% hydrazine hydrate (4 mL, 80 mmol) in pyridine (20 mL) was heated under reflux for 15 h. The mixture was evaporated under reduced pressure and the residue was treated with ethanol. The solid product was filtered and washed several times with ethanol to give a 75% yield of **11** as colorless needles, m.p. 204-204 °C; IR (cm^{-1}): 3488-3272 (NH, NH_2); ^{1}H-NMR (acetic acid-d_4): 1.74-1.86 (4H, m, $2CH_2$ at C-6, C-7), 2.67-2.68 (2H, m, CH_2 at C-5), 2.81-2.83 (2H, m, CH_2 at C-8), 7.38 (1H, br. s, NH), 7.39 (1H, br. s, NH), 7.56 (1H, br. s, NH), 7.43 (2H, d, *J* = 8.7, H-2`, H-6`), 7.58 (2H, d, *J* = 8.7, H-3`, H-5`); MS: m/z (%) 346 [M^+] (89) ($C_{16}H_{15}{}^{35}ClN_4OS$), 348 [M+2] (34) $C_{16}H_{15}{}^{37}ClN_4OS$), 331 [M-$NH_2$+H] (100), 316 [M-$N_2H_4$+2H] (32), 303 [M-$NH_2$+H-$C_2H_4$] (63), 220 [M-NH-$C_6H_4Cl$] (22).

4-(4-Chlorophenyl)-1-methyl-6,7,8,9-tetrahydro-4H-benzo[4,5]thieno[2,3-d][1,2,4]triazolo[3,4-b]-pyrimidin-5-one (**12**):

A mixture of **11** (1.4 g, 4 mmol) and glacial acetic acid (15 mL) was heated under reflux with stirring for 8 h. The reaction mixture was allowed to cool to room temperature and was poured into water (50 mL). The formed solid was collected by filtration, washed with ethanol, dried and recrystallized from ethanol to give **12** as colorless fine needles, m.p. 300-300 °C; Yield 72%; IR (cm^{-1}): 1676 (C=O); ^{1}H-NMR ($CDCl_3$): 1.83-1.91 (4H, m, $2CH_2$ at C-7, C-8), 2.79- 2.81 (5H, m, CH_3, CH_2 at C-6), 3.00 (2H, t, *J* = 6.2, CH_2 at C-9), 7.37 (2H, d, *J* = 8.8, H-2`, H-6`), 7.51 (2H, d, *J* = 8.8, H-3`, H-5`); MS: m/z (%) 370 [M^+] (100) ($C_{18}H_{15}{}^{35}ClN_4OS$), 372 [M+2] (38) $C_{18}H_{15}{}^{37}ClN_4OS$), 355 [M-$CH_3$] (4), 328 [M-$CH_3$-$C_2H_4$+H] (22).

General procedure for synthesis of **13a**,**b**:

A solution of iodine (50.76 g, 20 mmol), in 5% KI solution (100 mL) was added dropwise with stirring to a solution of **4a**,**d** (10 mmol) in 10% aqueous sodium hydroxide (10 mL) until the color of iodine persisted. The solid formed was filtered and dried.

Bis{3-phenyl-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-on-2-yl}disulfide (**13a**): Pale yellow cubes, m.p. 277-279 °C (from toluene/chloroform); Yield 73%; IR (cm^{-1}): 1651 (C=O); ^{1}H-NMR ($CDCl_3$): 1.79-1.87 (8H, m, $4CH_2$ at C-6, C-7), 2.74-2.77 (4H, m, $2CH_2$ at C-5), 2.91-2.95 (4H, m, $2CH_2$ at C-8), 7.39-7.42 (4H, m, H-2`, H-6`), 7.55-7.63 (6H, m, H-3`, H-4`, H-5`), 7.39-7.42 (4H, m, H-2`, H-6`); ^{13}C-NMR: 22.30, 23.01, 25.24, 25.35 (aliphatic ring sp^3 carbons), 119.98, 129.40, 130.11, 130.60, 131.87, 133.21, 135.28, 153.09, 161.92 (sp^2 carbons); 158.42 (C=O); (C-2); MS: m/z (%) 626 [M^+] (0.4) ($C_{32}H_{26}N_4O_2S_4$); 314 (100) [M-$C_{16}H_{13}N_2OS_2$]; 281 [M-$C_{16}H_{13}N_2OS_2$-SH+H] (19).

Bis{3-(4-Chlorophenyl)-7-methyl-5,6,7,8-tetrahydro-3H–pyrido[3`,4`:5,4]thieno[2,3-d]pyrimidin-4-on-2-yl}disulfide (**13b**): Yield 65%; m.p. 254-256 °C; IR (cm^{-1}): 1651 (C=O); MS: m/z (%) 363 (91) [M-$C_{16}H_{13}ClN_3OS_2$+H].

General procedure for the synthesis of **14a**,**b**:

A mixture of **1d**,**e** (20 mmol) and triethyl orthoformate (20 mL) was heated under reflux for 4h, and then evaporated to dryness under reduced pressure. Ethylenediamine (3 g, 50 mmol) was added dropwise with stirring and the reaction mixture was heated at 100°C for 7 h. The solid product that separated after cooling was collected by filtration, washed with ethanol, dried and recrystallized from DMF.

3-(2-Aminoethyl)-4-imino-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine (**14a**): Fine colorless needles, m.p. 300-302 °C; Yield 40%; IR (cm^{-1}): 3437-3312 (NH, NH_2), 1573, 1564 (2C=N); MS: m/z (%) 222 [M^+] (0.22) ($C_{10}H_{14}N_4S$), 205 [M-NH_3] (17), 180 [M-NH_3-C_2H_4+3H] (100).

3-(2-Aminoethyl)-4-imino-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]-thieno[2,3-d]pyrimidine (**14b**): Fine colorless needles, m.p. 218-220 °C; Yield 75%; IR (cm^{-1}): 3371-3319 (NH, NH_2), 1580, 1555 (2C=N); MS: m/z (%) 262 [M^+] (0.4) ($C_{13}H_{18}N_4S$), 245 [M-NH_3] (22), 220 [M-NH_3-C_2H_4+3H] (100).

Attempted preparation of 2-amino-4,5-dimethyl-3-(4,5-dihydro-1H-2-imidazolyl)thiophene (**15**):

Carbon disulfide (1 g, 13 mmol) was added gradually to a suspension of **1d** (0.3 g, 2 mmol) and ethylenediamine (3 g, 50 mmol). The mixture was heated at 100 °C, for 8 h; the solid formed after cooling was filtered off and washed several times with DMF to give **16** as fine yellow needles, m.p. 217-219 °C; Yield 90%; IR (cm^{-1}): 3245-3167 (NH_2, NH), 1207 (C=S); MS: m/z (%) 289 [M+H] (0.2), 272 [M-NH_2] (100), 254 [M-H_2S-H] (37), 241 [M-H_2S-CH_3+2H], 221 [M-H_2S-CH_3-NH_2-2H] (34), 162 [M-C_6H_8NS] (100), 137 [M-$C_7H_9N_2S$+2H] (35), 102 [M-$C_7H_{10}N_2S_2$] (40).

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