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AN EFFICIENT SYNTHETIC ROUTE TOWARDS NOVEL 3*N*-SUBSTITUTED THIENO[2,3-*d*]PYRIMIDIN-4(3*H*)-ONES

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Abstract – During the last few years, condensed thienopyrimidine derivatives have received considerable attention. Herewith it has been reported the synthesis of some novel 3*N*-substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones appended to different bio-potent moieties hopping to obtain new derivatives with dual biological activities.

Heterocycles containing the thienopyrimidine moiety (Figure 1) are of interest because of their interesting pharmacological and biological activities.¹⁻⁶ Thus, over the last two decades many thienopyrimidines have been found to exhibit a variety of pronounced activities, for example, as antiinflammatory,^{3,7} antimicrobial,^{3,8} antiviral⁹ and analgesic^{7,10} agents. Some thienopyrimidine derivatives showed good antitumor activity,¹¹ while compounds with the general structure designated by C (Figure 1) showed potent and specific cytotoxicity against several leukemia cell lines.⁴ Motivated by the aforementioned biological and pharmacological importance of the title compounds, and as continuation with our previous work on the synthesis of novel heterocyclic systems,^{12,13} we report herein the synthesis of some new heterocycles incorporating a thienopyrimidine moiety.

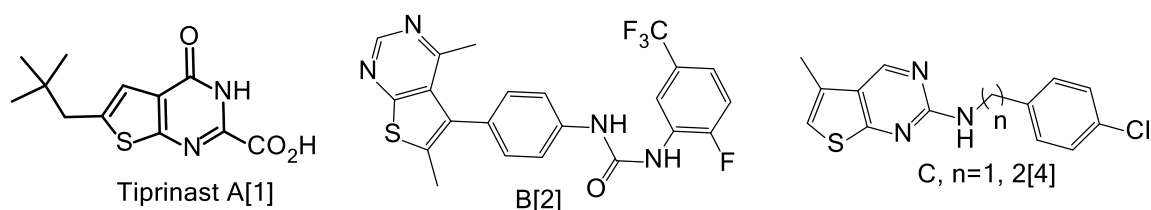
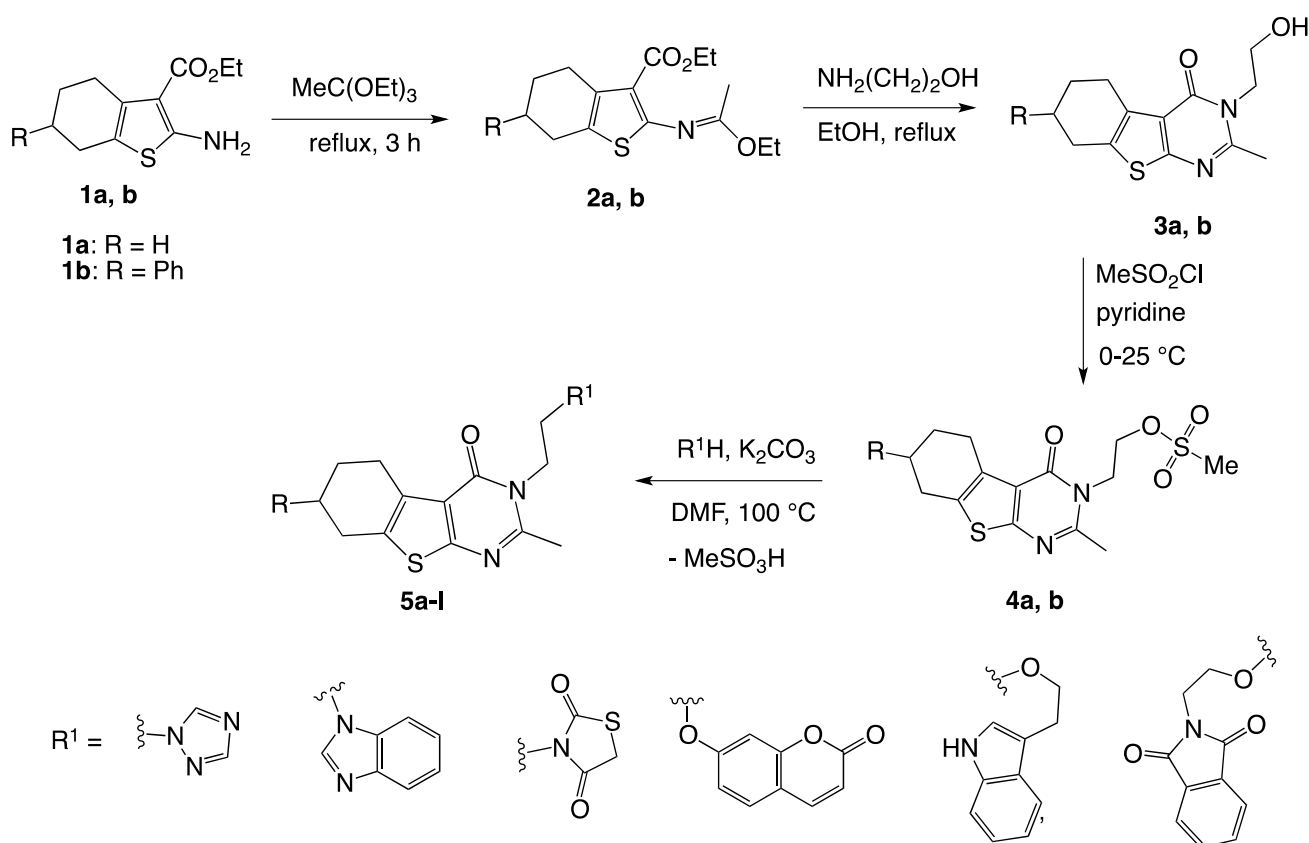


Figure 1. Some biologically active thienopyrimidines

The routes to thieno[2,3-*d*]pyrimidin-4(3*H*)-ones mainly involve cyclocondensation of 2-aminothiophenes with various electrophilic reagents such as α -substituted acetonitriles,¹⁴ formic acid,¹⁵ formamide,¹⁵ urea¹⁶ and guanidine.¹⁷ In this paper we wish to report the cyclocondensation of 2-aminothiophene-3-carboxylates with orthoester in combination with ethanolamine. The synthetic pathway was planned in such a way to synthesize the thieno[2,3-*d*]pyrimidin-4(3*H*)-one ring, in addition the 3-substituent was selected to incorporate well documented pharmacophoric moieties of interest such triazole, imidazole and indole. The target compounds were prepared as outlined in Scheme 1.



Scheme 1. Synthetic route for the title compounds **5a-l**

The starting materials 2-aminothiophene-3-carboxylate **1a,b** derivatives were prepared following the method of Gewald¹⁸ via the reaction of cyclohexanone and sulfur with either ethyl cyanoacetate in the presence of diethylamine.

Initially condensation of **1a,b** with orthoester in the presence of acetic acid under reflux gave product **2a,b** which was further refluxed with ethanolamine to gave **3a,b** through ring cyclization.

Compounds **3a,b** upon reaction with methanesulphonyl chloride in the presence of pyridine gave the mesylate **4a,b**. Finally the title compounds **5a-l** were obtained by reacting mesylate **4a,b** with various secondary amines and hydroxyl substituted heterocycles (Scheme 1) under mild basic condition. All the

newly synthesized compounds were characterized by IR, ^1H and ^{13}C -NMR and mass spectra. In case of IR studies, all the compounds have shown a sharp intense band at 1664-1690 cm^{-1} which corresponds to carbonyl group of thieno[2,3-*d*]pyrimidin-4(3*H*)-one ring. A medium intense band appeared around 1543-1607 cm^{-1} was attributed to C=N stretching. In case of ^1H -NMR, the C₂ methyl of thieno[2,3-*d*]pyrimidin-4(3*H*)-one ring appeared at 2.08-2.75 ppm. The signals appeared at 6.21-8.20 ppm were attributed to aromatic protons. For ^{13}C -NMR, the C₂ methyl carbon of thieno[2,3-*d*]pyrimidin-4(3*H*)-one ring resonated in the range 21.28-23.66 ppm. The ethyl carbons showed signals at 30.63-66.16 ppm. A signal resonated at 154.46-159.51 ppm was attributed to C₂ carbon of thieno[2,3-*d*]pyrimidin-4(3*H*)-one ring. The carbonyl carbon of thieno[2,3-*d*]pyrimidine ring was resonated in the range 159.42-162.17 ppm. The other rings attached to alkyl chain have shown signals at their respective positions.

In summary, the results of the study described above have led to the development of a simple approach for the synthesis of a novel class of thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives. Further studies on the bioactivity of the synthesized compounds are currently under way in our laboratory.

EXPERIMENTAL

Melting points were determined on a Büchi B-545 melting point apparatus and are uncorrected. All reactions were monitored by thin layer chromatography (TLC). IR spectra were recorded in the range 4000-600 cm^{-1} using KBr disks on a Perkin Elmer 1600 series FTIR spectrometer. ^1H and ^{13}C -NMR spectra were recorded with CDCl_3 as the solvent, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm relative to TMS (internal reference). Mass spectra were determined on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. Purification of products was performed by column chromatography using silica gel 60 (Fluka).

General synthetic procedure for thienoiminoethers (2a,b).

A mixture of compound **1a** or **1b** (20 mmol), triethylorthoacetate (28 mmol) and catalytic amount of acetic acid was heated under reflux for 3 h. After the completion of the reaction, monitored by TLC, reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, eluting with EtOAc/cyclohexane (1:8) to provide products **2a,b**.

Ethyl (E)-2-((1-ethoxyethylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (2a): Yield: 89%, mp 68 °C. IR (KBr, cm^{-1}): 1656 (C=N), 1692 (C=O). ^1H -NMR (CDCl_3): 1.25 (t, $J = 7.2$ Hz, 3H),

1.31 (t, $J = 7.2$ Hz, 3H), 4.15 (q, $J = 7.2$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 1.89 (s, 3H), 1.75 (m, 4H), 2.73 (m, 2H), 2.57 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): 14.55 ($\text{CH}_3\text{CH}_2\text{O}$), 17.02 ($\text{CH}_3\text{CH}_2\text{O}$), 19.57 (CH_3), 22.81, 23.34, 26.59, 26.98 (4CH_2 cyclohexane), 59.39 ($\text{CH}_3\text{CH}_2\text{O}$), 62.52 ($\text{CH}_3\text{CH}_2\text{O}$), 115.84, 126.69, 134.40, 157.65 ($\text{C}_{\text{thiophene}}$), 163.83 (C=O), 164.25 (C=N).

Ethyl (E)-2-((1-ethoxyethylidene)amino)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (2b): Yield: 86%, mp 77 °C. IR (KBr, cm^{-1}): 1576 (C=N), 1659 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.29 (t, $J = 7.2$ Hz, 3H), 1.35 (t, $J = 7.2$ Hz, 3H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.27 (q, $J = 7.2$ Hz, 2H), 1.93 (s, 3H), 2.70-2.91 (m, 4H), 3.01 (m, 1H), 2.09 (m, 2H), 7.21-7.33 (m, 5H, CH_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 14.35 ($\text{CH}_3\text{CH}_2\text{O}$), 17.09 ($\text{CH}_3\text{CH}_2\text{O}$), 20.23 (CH_3), 27.03, 30.11, 32.75, 40.78 (CH and 3CH_2 cyclohexane), 59.73 ($\text{CH}_3\text{CH}_2\text{O}$), 62.62 ($\text{CH}_3\text{CH}_2\text{O}$), 115.66, 126.15, 126.41, 126.98, 128.57, 134.20, 146.11, 158.19 (C_{arom} and $\text{C}_{\text{thiophene}}$), 163.81 (C=O), 164.43 (C=N).

General procedure for the preparation of thieno[2,3-d]pyrimidin-4(3H)-ones (3a,b).

An equimolar mixture of the compounds, ethanamine and catalytic amount of acetic acid in EtOH (15 mL) was heated under reflux for 8 h, then left to cool and the solvent was removed under reduced pressure. Purification of the residue was carried out by flash silica gel chromatography using EtOAc/cyclohexane (3:1) as eluent to afford products **3a,b**.

3-(2-Hydroxyethyl)-2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (3a): Yield: 84%, mp 145 °C. IR (KBr, cm^{-1}): 3468 (OH), 1607 (C=N), 1690 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.82 (m, 4H), 2.66 (s, 3H), 3.97 (t, $J = 5.2$ Hz, 2H), 4.23 (t, $J = 5.2$ Hz, 2H), 2.73 (m, 2H), 2.91 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): 22.29, 22.98, 23.41, 25.21, 25.54 (4CH_2 cyclohexane, CH_3), 46.95 ($\text{CH}_2\text{CH}_2\text{OH}$), 61.14 ($\text{CH}_2\text{CH}_2\text{OH}$), 120.66, 131.33, 133.21, 146.85 ($\text{C}_{\text{thiophene}}$), 154.46 (C=N), 159.42 (C=O).

3-(2-Hydroxyethyl)-2-methyl-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (3b): Yield: 82%, mp 169 °C. IR (KBr, cm^{-1}): 3409 (OH), 1596 (C=N), 1667 (C=O). $^1\text{H-NMR}$ (CDCl_3): 3.98 (t, $J = 5.2$ Hz, 2H); 4.26 (t, $J = 5.2$ Hz, 2H); 2.67 (s, 3H), 2.83-3.00 (m, 4H), 3.08 (m, 1H) 1.96 (m, 2H), 7.21-7.43 (m, 5H, CH_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 23.39, 25.89, 29.65, 32.98, 40.61 (CH and 3CH_2 cyclohexane, CH_3), 46.95 ($\text{CH}_2\text{CH}_2\text{OH}$), 61.12 ($\text{CH}_2\text{CH}_2\text{OH}$), 120.53, 126.61, 126.95, 128.68, 131.07, 132.76, 145.51 (C_{arom} and $\text{C}_{\text{thiophene}}$), 154.72 (C=N), 159.47 (C=O).

General procedure for the tosylation of compounds (3a,b).

A mixture of compounds (10 mmol), pyridine (20 mmol), and CHCl_3 (20 mL) was placed in a 3-neck

round flask and cooled to 0 °C in an ice bath. Methanesulfonylchloride (15 mmol) was added to the mixture. The reaction was finished within 2 h. After adding water (10 mL), the resulting mixture was extracted with Et₂O (70 mL). The ethereal layer was washed with 2 M aqueous HCl, aqueous NaHCO₃, and brine. The solvent was removed by evaporation at reduced pressure, and the residue was chromatographed on a silica gel column, eluting with EtOAc/cyclohexane (2:5) to give the mesylate **4a,b**.

2-(2-Methyl-4-oxo-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-3(4H)-yl)ethylmethanesulfonate (4a): Yield: 80%, mp 116 °C. IR (KBr, cm⁻¹): 1664 (C=O), 1567 (C=N), 1377 and 1155 (O=S=O). ¹H-NMR (CDCl₃): 1.84 (m, 4H), 2.67 (s, 3H), 3.86 (t, *J* = 6.4 Hz, 2H), 4.36 (t, *J* = 6.4 Hz, 2H), 2.74 (m, 2H), 2.97 (m, 2H), 3.66 (s, 3H). ¹³C-NMR (CDCl₃): 22.30, 22.98, 23.59, 25.20, 25.55 (4CH₂ cyclohexane, CH₃), 40.93 (CH₃-S), 46.01 (CH₂CH₂O SO₂CH₃), 52.61(CH₂CH₂OSO₂CH₃), 120.61, 131.37, 133.21, 153.70 (C_{thiophene}), 158.42 (C=N), 161.74 (C=O).

2-(2-Methyl-4-oxo-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-3(4H)-yl)ethylmethanesulfonate (4b): Yield: 78%, mp 146 °C. IR (KBr, cm⁻¹): 1666 (C=O), 1543 (C=N), 1378 and 1157 (O=S=O). ¹H-NMR (CDCl₃): 3.88 (t, *J* = 6.4 Hz, 2H), 4.38 (t, *J* = 6.4 Hz, 2H), 2.68 (s, 3H), 3.69 (s, 3H), 2.91-3.02 (m, 4H), 3.06 (m, 1H), 1.98 (m, 2H), 7.21-7.34 (m, 5H, CH_{arom}). ¹³C-NMR (CDCl₃): 23.66, 25.91, 29.67, 33.00, 40.63 (CH and 3CH₂ cyclohexane, CH₃), 40.97 (CH₃-S), 46.12 (CH₂CH₂OSO₂CH₃), 54.82 (CH₂CH₂OSO₂CH₃), 120.51, 126.60, 126.96, 128.67, 131.15, 132.77, 145.57, 154.02 (C_{arom} and C_{thiophene}), 158.53 (C=N), 162.08 (C=O).

General procedure for the preparation of title compounds (5a-l)

A mixture of compound **4** (10 mmol), appropriate secondary amine (10 mmol) or hydroxyl substituted compound (10 mmol) and anhydrous K₂CO₃ (20 mmol) in dry DMF (20 mL) was stirred at 100 °C. The completion of the reaction was checked by TLC using EtOAc and cyclohexane (20%) as eluent. The reaction mixture was then poured into ice cold water and neutralized with dil. HCl (few drops). The precipitate thus formed was filtered and dried. All the newly prepared compounds were purified by column chromatography using EtOAc and cyclohexane (10%) as eluent.

3-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (5a): Yield: 91%, mp 147 °C. IR (KBr, cm⁻¹): 1668 (C=O), 1543 (C=N). ¹H-NMR (CDCl₃): 1.85 (m, 4H); 2.26 (s, 3H); 4.44 (t, *J* = 6.4 Hz, 2H), 4.60 (t, *J* = 6.4 Hz, 2H), 2.74 (m, 2H), 2.98 (m, 2H), 8.34 (s, 1H), 9.02 (s, 1H). ¹³C-NMR (CDCl₃): 22.32, 22.66, 22.98, 25.23, 25.61 (4CH₂ cyclohexane, CH₃), 44.64 (-NCH₂CH₂-triazole), 47.11 (-NCH₂CH₂-triazole), 120.49, 131.31, 133.66, 143.99, 152.87, 153.27 (C_{thiophene} and C_{triazole}), 158.75 (C=N), 162.17 (C=O). HRMS (EI): *m/z* calculated for C₁₅H₁₈N₅OS

(M+H)⁺: 316.12; found 316.18.

3-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (5b): Yield: 83%, mp 216 °C. IR (KBr, cm⁻¹): 1666 (C=O), 1545 (C=N). ¹H NMR (CDCl₃): 1.88 (m, 4H), 2.08 (s, 3H), 4.45 (t, *J* = 6.4 Hz, 2H), 4.69 (t, *J* = 6.4 Hz, 2H), 2.77 (m, 2H), 3.03 (m, 2H), 8.20 (s, 1H), 7.37 (m, 2H), 7.53 (m, 1H), 7.82 (m, 1H). ¹³C-NMR (CDCl₃): 22.33, 22.67, 23.00, 25.26, 25.66 (4CH₂ cyclohexane, CH₃), 42.69 (-NCH₂CH₂-imidazole), 44.61(-NCH₂CH₂-imidazole), 109.24, 120.72, 122.95, 123.86, 124.41, 131.35, 133.76, 152.83 (C_{thiophene} and C_{imidazole}), 158.72 (C=N), 161.92 (C=O). HRMS (EI): *m/z* calculated for C₂₀H₂₁N₄OS (M+H)⁺: 365.14, found 365.21.

3-(2-(2-Methyl-4-oxo-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-3(4H)-yl)ethyl)-thiazolidine-2,4-dione (5c): Yield: 68%, mp 176 °C. IR (KBr, cm⁻¹): 1739, 1701 and 1660 (C=O), 1546 (C=N). ¹H-NMR (CDCl₃): 1.82 (m, 4H), 2.56 (s, 3H), 4.39 (t, *J* = 6.4 Hz, 2H), 4.57 (t, *J* = 6.4 Hz, 2H), 2.72 (m, 2H), 2.93 (m, 2H), 3.63 (s, 2H). ¹³C-NMR (CDCl₃): 22.29, 22.71, 22.96, 25.21, 25.69 (4CH₂ cyclohexane, CH₃), 36.59 (CH₂ thiazolidine), 42.37 (-NCH₂CH₂-thiazoline), 46.84 (-NCH₂CH₂-thiazoline), 119.92, 131.17, 133.46, 153.28 (C_{thiophene}) 158.34 (C=N), 161.51 (C=O), 166.37, 167.90 (2C=O thiazoline). HRMS (EI): *m/z* calculated for C₁₆H₁₈N₃O₃S₂ (M+H)⁺: 364.08; found 364.13.

2-Methyl-3-(2-((2-oxo-2H-chromen-7-yl)oxy)ethyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (5d): Yield: 94%, mp 224 °C. IR (KBr, cm⁻¹): 1716 and 1660 (C=O), 1544 (C=N). ¹H-NMR (CDCl₃): 1.82 (m, 4H), 2.74 (s, 3H), 4.35 (t, *J* = 5.2 Hz, 2H), 4.50 (t, *J* = 5.2 Hz, 2H), 2.70 (m, 2H), 2.95 (m, 2H), 6.21 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 12 Hz, 1H), 7.60 (d, *J* = 9.6 Hz, 1H), 6.76 (s, 1H), 6.78 (d, *J* = 2.8 Hz, 1H). ¹³C-NMR (CDCl₃): 22.33, 23.00, 23.52, 25.23, 25.59 (4CH₂ cyclohexane, CH₃), 44.00 (-NCH₂CH₂O), 66.16 (-NCH₂CH₂O), 101.65, 112.46, 113.12, 113.67, 120.65, 129.00, 131.40, 133.22, 143.26, 154.16, 155.80 (C_{thiophene} and C_{chromenone}), 158.72 (C=N), 161.21 (C=O), 161.90 (C=O). HRMS (EI): *m/z* calculated for C₂₂H₂₁N₂O₄S (M+H)⁺: 409.12; found 409.20.

3-(2-(2-(1H-Indol-3-yl)ethoxy)ethyl)-2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (5e): Yield: 77%, mp 203 °C. IR (KBr, cm⁻¹): 3312 (NH), 1658 (C=O), 1541 (C=N). ¹H-NMR (CDCl₃): 1.81 (m, 4H), 2.62 (s, 3H), 4.43 (t, *J* = 5.2 Hz, 2H), 4.60 (t, *J* = 5.2 Hz, 2H), 3.17 (t, *J* = 6.4 Hz, 2H), 4.33 (t, *J* = 6.4 Hz, 2H), 2.73 (m, 2H), 2.91 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.18 (m, 1H), 7.10 (m, 1H), 7.05 (s, 1H), 8.25 (br s, 1H). ¹³C-NMR (CDCl₃): 22.30, 22.98, 23.53, 25.21, 25.57 (4CH₂ cyclohexane, CH₃), 28.80 (indole-CH₂CH₂O), 46.86 (-NCH₂CH₂O), 60.92 (-NCH₂CH₂O), 62.66 (indole-CH₂CH₂O), 111.32, 112.27, 118.86, 119.45, 120.59, 122.17, 122.65, 127.48, 131.25, 133.07, 136.52, 154.41 (C_{thiophene} and C_{indole}), 159.51 (C=N), 161.86 (C=O). HRMS (EI):

m/z calculated for $C_{23}H_{26}N_3O_2S$ ($M+H$)⁺: 408.17; found 408.22.

2-(2-(2-(2-Methyl-4-oxo-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-3(4H)-yl)ethoxy)ethyl)isoindoline-1,3-dione (**5f**): Yield: 79%, mp 133 °C. IR (KBr, cm^{-1}): 1694 and 1660 (C=O), 1545 (C=N). ¹H-NMR (CDCl₃): 1.85 (m, 4H), 2.66 (s, 3H), 4.53 (t, $J = 5.2$ Hz, 2H), 4.60 (t, $J = 5.2$ Hz, 2H), 4.29 (t, $J = 6.4$ Hz, 2H), 4.33 (t, $J = 6.4$ Hz, 2H), 2.74 (m, 2H), 2.90 (m, 2H), 7.84-7.92 (m, 2H), 7.72-7.79 (m, 2H). ¹³C-NMR (CDCl₃): 22.27, 22.93, 23.33, 25.19, 25.76 (4CH₂ cyclohexane, CH₃), 43.64 (isoindoline-CH₂CH₂O), 46.71 (-NCH₂CH₂O), 61.02 (isoindoline-CH₂CH₂O), 62.46 (-NCH₂CH₂O), 120.42, 123.39, 131.43, 131.98, 133.12, 135.18, 154.37 (C_{thiophene} and C_{isoindoline}), 158.13 (C=N), 161.79 (C=O), 165.37 (2C=O). HRMS (EI): m/z calculated for $C_{23}H_{24}N_3O_4S$ ($M+H$)⁺: 438.14; found 438.18.

3-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-methyl-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (**5g**): Yield: 89%, mp 94 °C. IR (KBr, cm^{-1}): 3050 (CH_{arom}), 1655 (C=O), 1545 (C=N). ¹H-NMR (CDCl₃): 4.65 (t, $J = 5.6$ Hz, 2H), 4.48 (t, $J = 5.6$ Hz, 2H), 2.67 (s, 3H), 2.83-2.96 (m, 4H), 3.14 (m, 1H), 1.95 (m, 2H), 7.98 (s, 1H), 8.48 (s, 1H), 7.18-7.30 (m, 5H, CH_{phenyl}). ¹³C-NMR (CDCl₃): 21.28, 25.55, 29.49, 32.30, 34.03 (CH and 3CH₂ cyclohexane, CH₃), 40.52 (-NCH₂CH₂-triazole), 43.68 (-NCH₂CH₂-triazole), 119.98, 126.19, 126.59, 128.28, 130.76, 132.88, 145.53, 148.27, 154.96 (C_{thiophene}, C_{triazole} and C_{phenyl}), 158.69 (C=N), 161.67 (C=O). HRMS (EI): m/z calculated for $C_{21}H_{22}N_5OS$ ($M+H$)⁺: 392.15; found 392.41.

3-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-2-methyl-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (**5h**): Yield: 77%, mp 163 °C. IR (KBr, cm^{-1}): 3042 (CH_{arom}), 1677 (C=O), 1556 (C=N). ¹H-NMR (CDCl₃): $\delta = 4.55$ (t, $J = 5.6$ Hz, 2H), 4.47 (t, $J = 5.6$ Hz, 2H), 2.70 (s, 3H), 2.81-2.98 (m, 4H), 3.11 (m, 1H), 1.89 (m, 2H), 7.20-7.32 (m, 5H, CH_{phenyl}), 8.12 (s, 1H), 7.41 (m, 2H), 7.52 (m, 1H), 7.78 (m, 1H). ¹³C-NMR (CDCl₃): $\delta = 22.18, 24.97, 29.32, 31.98, 34.14$ (CH and 3CH₂ cyclohexane, CH₃), 40.47 (-NCH₂CH₂-imidazole), 43.53 (-NCH₂CH₂-imidazole), 120.08, 122.87, 123.93, 124.67, 126.23, 126.74, 128.17, 130.41, 132.49, 144.83, 148.37, 155.04 (C_{thiophene}, C_{imidazole} and C_{phenyl}), 158.34 (C=N), 161.08 (C=O). HRMS (EI): m/z calculated for $C_{26}H_{25}N_4OS$ ($M+H$)⁺: 441.17; found 441.34.

3-(2-(2-Methyl-4-oxo-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-3(4H)-yl)ethyl)thiazolidine-2,4-dione (**5i**): Yield: 67%, mp 211 °C. IR (KBr, cm^{-1}): 3047 (CH_{arom}), 1730, 1706 and 1678 (C=O), 1547 (C=N). ¹H-NMR (CDCl₃): 4.41 (t, $J = 6.4$ Hz, 2H), 4.58 (t, $J = 6.4$ Hz, 2H), 2.73 (s, 3H), 2.80-2.93 (m, 4H), 3.07 (m, 1H), 1.90 (m, 2H), 7.22-7.31 (m, 5H, CH_{phenyl}), 3.66 (s, 2H). ¹³C-NMR (CDCl₃): 21.32, 25.47, 29.52, 32.27, 33.86 (CH and 3CH₂ cyclohexane, CH₃), 36.44 (CH₂thiazolidine), 40.48 (-NCH₂CH₂-thiazolidine), 43.61 (-NCH₂CH₂-thiazolidine), 120.03, 126.33, 126.71, 129.04, 130.84,

132.82, 145.39, 148.19, 154.79 ($C_{\text{thiophene}}$ and C_{phenyl}), 158.44 (C=N), 161.51 (C=O), 167.32 (2C=O). HRMS (EI): m/z calculated for $C_{22}H_{22}N_3O_3S_2$ (M+H)⁺: 440.11; found 440.17.

2-Methyl-3-(2-((2-oxo-2H-chromen-7-yl)oxy)ethyl)-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (5j): Yield: 92%, mp 189 °C. IR (KBr, cm^{-1}): 3055 (CH_{arom}), 1703 and 1656 (C=O), 1547 (C=N). $^1\text{H-NMR}$ (CDCl_3): 4.57 (t, $J = 5.6$ Hz, 2H), 4.42 (t, $J = 5.6$ Hz, 2H), 2.73 (s, 3H), 2.77-2.92 (m, 4H), 3.05 (m, 1H) 1.92 (m, 2H), 7.19-7.31 (m, 5H, $\text{CH}_{\text{phenyl}}$), 6.32 (d, $J = 9.2$ Hz, 1H), 7.37 (d, $J = 12$ Hz, 1H), 7.64 (d, $J = 9.2$ Hz, 1H), 6.80 (s, 1H), 6.83 (d, $J = 3.2$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3): 22.38, 25.06, 29.17, 32.03, 34.23 (CH and 3 CH_2 cyclohexane, CH_3), 43.62 ($-\text{NCH}_2\text{CH}_2\text{O}$), 63.03 ($-\text{NCH}_2\text{CH}_2\text{O}$), 120.17, 123.81, 124.71, 126.21, 126.68, 128.88, 131.47, 132.56, 144.27, 150.12, 155.21 ($C_{\text{thiophene}}$, C_{phenyle} and $C_{\text{chromenone}}$), 158.37 (C=N), 161.18 (C=O), 162.24 (C=O). HRMS (EI): m/z calculated for $C_{28}H_{25}N_2O_4S$ (M+H)⁺: 485.15; found 485.38.

3-(2-(2-(1H-Indol-3-yl)ethoxy)ethyl)-2-methyl-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (5k): Yield: 69%, mp 266 °C. IR (KBr, cm^{-1}): 3320 (NH), 3037 (CH_{arom}), 1667 (C=O), 1551 (C=N). $^1\text{H-NMR}$ (CDCl_3): 4.41 (t, $J = 5.6$ Hz, 2H), 4.62 (t, $J = 5.6$ Hz, 2H), 3.23 (t, $J = 6.4$ Hz, 2H), 4.36 (t, $J = 6.4$ Hz, 2H), 2.75 (s, 3H), 2.79-2.91 (m, 4H), 3.02 (m, 1H) 1.88 (m, 2H), 7.20-7.32 (m, 5H), 7.58 (d, $J = 7.2$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 7.00 (s, 1H), 8.13 (br s, 1H). $^{13}\text{C-NMR}$ (CDCl_3): 22.35, 25.19, 29.21, 32.15, 34.13 (CH and 3 CH_2 cyclohexane, CH_3), 30.63 (indole- $\text{CH}_2\text{CH}_2\text{O}$), 43.71 ($-\text{NCH}_2\text{CH}_2\text{O}$), 61.18 ($-\text{NCH}_2\text{CH}_2\text{O}$), 62.93 (indole- $\text{CH}_2\text{CH}_2\text{O}$), 120.33, 123.17, 124.91, 126.18, 126.73, 128.54, 131.52, 132.17, 136.32, 143.13, 152.23, 155.21 ($C_{\text{thiophene}}$, C_{phenyl} and C_{indole}), 158.22 (C=N), 160.83 (C=O). HRMS (EI); m/z calculated for $C_{29}H_{30}N_3O_2S$ (M+H)⁺: 484.20; found 484.31.

2-(2-(2-(2-Methyl-4-oxo-7-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-yl)ethoxy)ethyl)-isoindoline-1,3-dione (5l): Yield: 75%, mp 173 °C. IR (KBr, cm^{-1}): 2966 and 2873 (CH_{arom}), 1690 and 1668 (C=O), 1548 (C=N). $^1\text{H-NMR}$ (CDCl_3): 4.51 (t, $J = 5.2$ Hz, 2H), 4.58 (t, $J = 5.2$ Hz, 2H), 4.31 (t, $J = 6.4$ Hz, 2H), 4.37 (t, $J = 6.4$ Hz, 2H), 2.67 (s, 3H), 2.86-2.94 (m, 4H), 3.17 (m, 1H), 1.97 (m, 2H), 7.20-7.34 (m, 5H), 7.80-7.88 (m, 2H), 7.71-7.77 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3): 23.50, 25.91, 29.67, 29.78, 32.98 (CH and 3 CH_2 cyclohexane, CH_3), 40.62 (isoindoline- $\text{CH}_2\text{CH}_2\text{O}$), 46.91 ($-\text{NCH}_2\text{CH}_2\text{O}$), 59.12 (isoindoline- $\text{CH}_2\text{CH}_2\text{O}$), 61.22 ($-\text{NCH}_2\text{CH}_2\text{O}$), 120.49, 126.60, 126.95, 128.67, 131.04, 132.62, 145.55, 154.58 ($C_{\text{thiophene}}$, C_{phenyl} and $C_{\text{isoindoline}}$), 157.64 (C=N), 160.69 (C=O), 164.87 (2C=O). HRMS (EI): m/z calculated for $C_{29}H_{28}N_3O_4S$ (M+H)⁺: 514.18; found 514.24.

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