Efficient synthesis of thieno[2,3-*d*]pyrimidines and related fused systems

Aly A. Aly* and Mohamed S. Behalo

Chemistry Department, Faculty of Science, Benha University, Benha, Egypt

The synthetic potency of readily accessible, ethyl 2-amino-4-methyl-5-(4-nitrophenoxy)thiophene-3-carboxylate (**1**) as a versatile precursor for the synthesis of novel polyfunctionally substituted thienopyrimidines is reported. The latter derivatives undergo further heterocyclisation to the related polycyclic fused systems *via* reactions with different reagents.

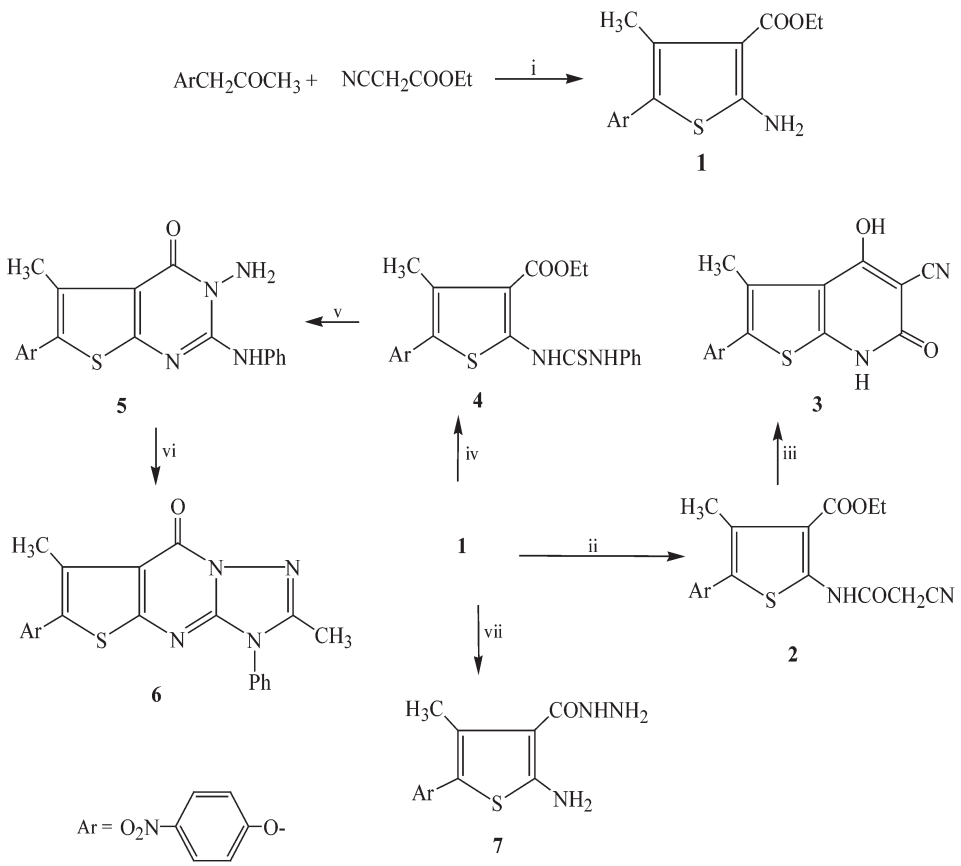
Keywords: thieno[2,3-d]pyrimidines, triazolopyrimidines, pyrimidotriazines

Our interest in the synthesis of thieno[2,3-*d*]pyrimidine derivatives arises not only from their rich and varied chemistry, but also because of their biological and physiological activities. They play important roles as antihypertensive, antipyretic, antiviral and anti-inflammatory drugs.[1–8] In addition, triazine and triazole compounds possess diverse biological uses such as antifungals, insecticides, herbicides and plant growth regulators.[9–15] Encouraged by these findings and as a continuation of our studies into the synthesis of a variety of heterocyclic systems of biological interest,[16–18] we have found that ethyl 2-aminothiophene-3-carboxylate **1** is a versatile, readily accessible building block for the synthesis of new series of fused thienopyrimidine derivatives.

Results and discussion

The synthesis of ethyl 2-amino-4-methyl-5-(4-nitrophenoxy) thiophene-3-carboxylate (**1**) needed for synthetic work can be achieved according to the Gewald method [19] from the reaction of 1-(4-nitrophenoxy)propan-2-one-ethyl cyanoacetate and sulfur in ethanol containing a few drops of piperidine. The structure of compound **1** was established on the basis of elemental analyses and spectroscopic data (Scheme 1).

The condensation of compound **1** with ethyl cyanoacetate in refluxing dioxane afforded the amide derivative **2**, which cyclised by refluxing in ethanolic solution of sodium ethoxide to give 4-hydroxy-3-methyl-2-(4-nitrophenoxy)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-5-carbonitrile (**3**). The IR spectrum of **3** exhibited absorption bands at 3410–3180 cm^{-1} due to hydroxyl and amino groups in addition to carbonitrile and carbonyl groups at 2216 and 1670 cm^{-1}. The mass spectrum of compound **3** showed a molecular ion peak at $m/z = 343$. On the other hand, the treatment of compound **1** with phenyl isothiocyanate in dry benzene yielded the corresponding thioureido derivative **4** which, in turn, converted to thieno[2,3-*d*] pyrimidinone **5** by treatment with hydrazine hydrate in ethanolic solution. The reaction of compound **5** with acetic anhydride



Scheme 1 (i) S/EtOH, piperidine, reflux 6h; (ii) $NCCH_2CO_2Et$, dioxane, reflux 3h; (iii) EtONa, EtOH, reflux 4h; (iv) PhNCS, dry benzene, reflux 30 min; (v) $N_2H_4.H_2O$, EtOH, reflux 9h; (vi) Ac_2O, reflux 4h; (vii) $N_2H_4.H_2O$, EtOH, reflux 2h.

* Correspondent. E-mail: alymaboud@yahoo.com

afforded 6-(4-nitrophenoxy)-2,7-dimethyl-3-phenylthieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-8-(3*H*)-one (**6**). Moreover, the reaction of the *ortho*-amino ester **1** with hydrazine hydrate in ethanol afforded the carbohydrazide derivative **7**. The IR spectrum of compound **7** showed the absence of a carbonyl group of ester and the presence of NH/NH_2 as well as a carbonyl group of amide. The ^1H NMR spectrum of compound **7** displayed the presence of methyl, two amino groups, aromatic protons and NH proton which were exchangeable on addition of D_2O to the NMR sample (Scheme 1).

The readily prepared carbohydrazide **7** was used as a key precursor for building other bioactive heterocyclic rings *via* intramolecular cyclisation with different reagents. Thus, the reaction of **7** with formaldehyde in methanolic solution gave thienopyrimidinone derivative **8** in good yield (Scheme 2). Furthermore, the treatment of the carbohydrazide **7** with formic acid yielded the formylamino derivative **9**. Also, the condensation of compound **7** with phthalic anhydride in *N,N*-dimethylformamide afforded phthalazine derivative **10**. Mechanistically, the formation of compound **10** involved the initial formation of a cyclic isoindole derivative, which underwent immediate intramolecular nucleophilic attack by the thiophene amino group on the isoindole carbonyl group with the elimination of water molecule.

The reaction of compound **7** with nitrous acid furnished the corresponding azide **11**, which underwent Curtius rearrangement in refluxing dry xylene to give 6-methyl-5-(4-nitrophenoxy)-1,3-dihydrothieno[2,3-*d*]imidazol-2-one (**13**) (Scheme 2).

Saponification of the *ortho*-amino ester **1** with an ethanolic sodium hydroxide solution followed by acidification afforded the corresponding amino acid derivative **14**, which underwent ring closure reaction upon treatment with acetic anhydride to yield thienooxazinone derivative **15**. The IR spectrum of compound **15** was free of the amino group and displayed the presence of carbonyl group of oxazinone at 1740 cm^{-1}. Also, the ^1H NMR displayed the presence of signals at δ = 2.25, 2.85 (2s, 6H, $2CH_3$), 7.15–8.20 (m, 4H, ArH) (Scheme 3). Treatment of compound **15** with ammonium acetate in boiling acetic acid gave 2,5-dimethyl-6-(4-nitrophenoxy)-3*H*-thieno[2,3-*d*]pyrimidin-4-one (**16**).

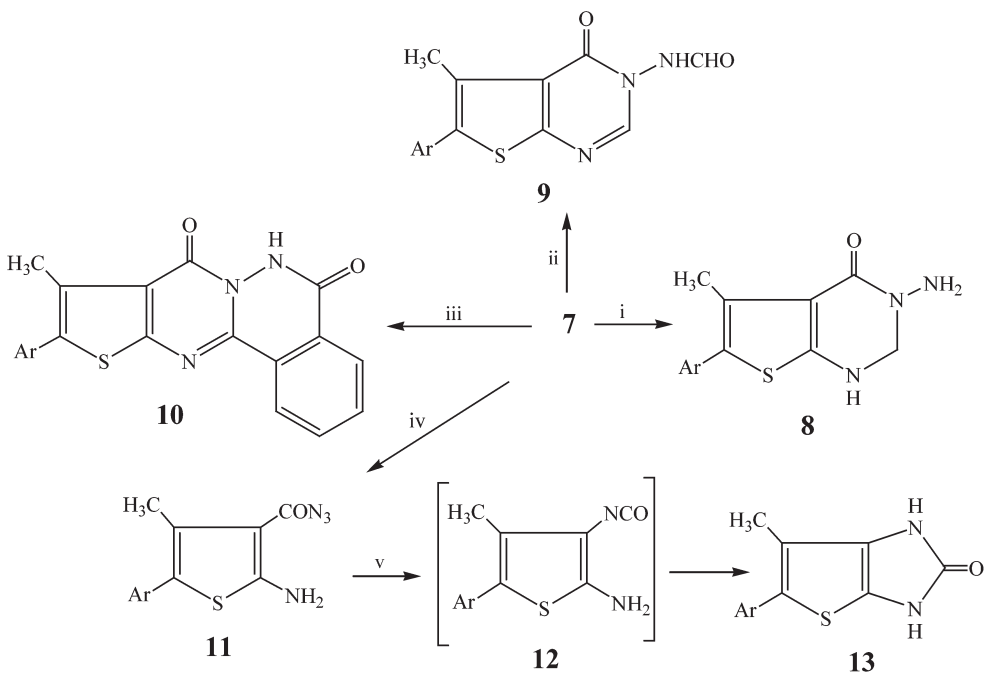
The reactivity of compound **16** was investigated through its reaction with chloroacetyl chloride in DMF to give the thienopyrimidine derivative **17**. The latter compound underwent nucleophilic displacement upon treatment with hydrazine hydrate to afford the corresponding hydrazine derivative **18**, which cyclised by fusion above its melting point to give the triazinone derivative **19** (Scheme 3).

Also, the reaction of oxazinone derivative **15** with hydrazine hydrate in refluxing dry benzene gave aminothienopyrimidine derivative **20**. The IR spectrum of compound **20** displayed the presence of amino group at 3390, 3350 cm^{-1}as well as carbonyl group at 1675 cm^{-1}. Also, the ^1H NMR of **20** displayed the presence of two singlet at δ = 2.22, 2.60 for two methyl groups, broad singlet at δ = 6.15 for amino group in addition to aromatic protons at δ = 7.10–8.25 (Scheme 4).

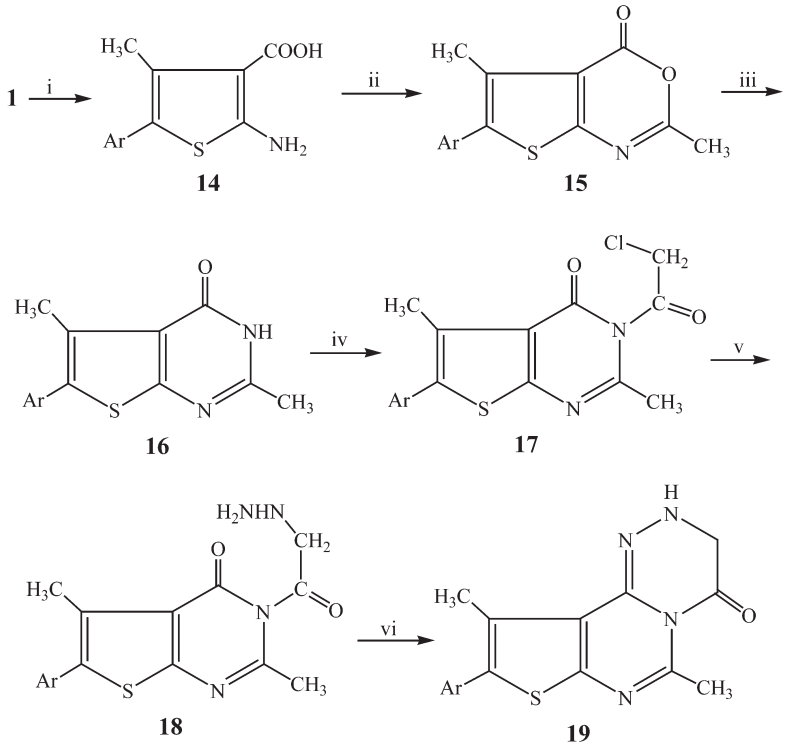
As a part of our program, directed towards developing new approaches to a variety of triazine and triazole derivatives of potential biological activity,[20–23] we report here the scope and applicability of aminothienopyrimidine derivative **20** as a key precursor for the synthesis of these heterocycles in which a thienopyrimidine moiety is incorporated. Thus, the reaction of compound **20** with chloroacetamide in DMF afforded the triazine derivative **21**. Also, the reaction of compound **20** with chloroacetyl chloride afforded acetamide derivative **22**, which gave the triazine derivative **23** upon treatment with ammonium acetate in boiling acetic acid. On the other hand, the reaction of compound **20** with acid chlorides *viz* acetyl chloride and benzoyl chloride in refluxing dry benzene afforded thienopyrimidines **24a,b**, which underwent cyclisation to triazolopyrimidines **25a,b** upon treatment with ammonium acetate in boiling acetic acid (Scheme 4). The structures of all newly synthesised compounds were elucidated on the basis of elemental analyses and spectral data. (*c.f.* Experimental).

Experimental

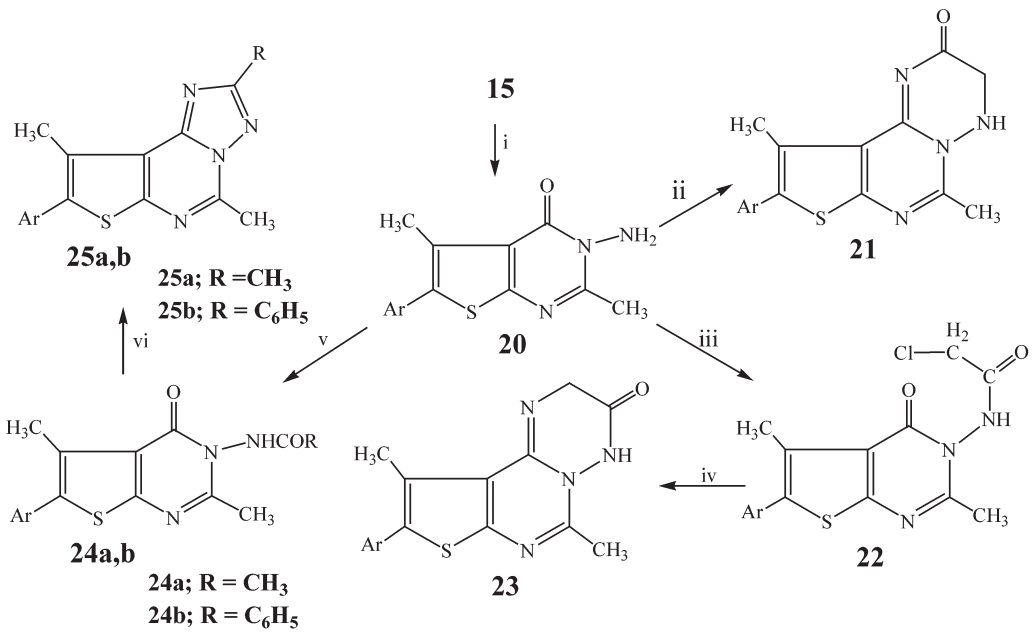
Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 298 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70 eV EI mode). Elemental analyses were carried out at the Microanalytical Center of Cairo University, Egypt.



Scheme 2 (i) HCHO, CH_3OH, reflux 2h; (ii) HCOOH, reflux 2h; (iii) phthalic anhydride, DMF, reflux 5h; (iv) $NaNO_2$/AcOH; (v) dry xylene, reflux 30 min.



Scheme 3 (i) NaOH/EtOH, reflux 2h; (ii) Ac_2O, reflux 4h; (iii) $AcONH_4$, AcOH, reflux 4h; (iv) $ClCOCH_2Cl$, DMF, reflux 3h; (v) $N_2H_4.H_2O$, EtOH, reflux 4h; (vi) fusion 2h.



Scheme 4 (i) $N_2H_4.H_2O$, dry benzene, reflux 4h; (ii) $ClCH_2CONH_2$, DMF, reflux 12h; (iii) $ClCOCH_2Cl$, DMF, reflux 4h; (iv) $AcONH_4$, AcOH, reflux 4h; (v) RCOCl, dry benzene, reflux 3h; (vi) $AcONH_4$, AcOH, reflux 3h.

^{13}C NMR values of 4-nitrophenoxy group for compounds **2**–**25** are the same as in compound **1** with δ ± 0.1–0.5 ppm.

Ethyl 2-amino-4-methyl-5-(4-nitrophenoxy)thiophene-3-carboxylate (**1**): A mixture of 1-(4-nitrophenoxy)propan-2-one (1.95 g, 10 mmol), ethyl cyanoacetate (10 mmol) and elemental sulfur (0.32 g, 10 mmol) in ethanol (25 mL) and piperidine (1.1 mL) was heated under reflux for 6 h, then poured onto cold water (40 mL). The solid formed was filtered off and recrystallised from ethanol to give **1**. Yield, 2.0 g (62%); m.p. 165–167 °C; IR: ν = 3350, 3240 (NH_2), 1725 cm^{-1} (CO); ^{1}H NMR($CDCl_3$): δ = 1.40 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 4.30 (q, 2H, CH_2), 6.12 (brs, 2H, NH_2),7.10–7.95 (m, 4H, ArH); ^{13}CNMR: δ = 14.1, 18.7 (2CH_3), 49.5 (CH_2), 109.5 (C-4), 119.2 (C-2), 123.2 (C-3), 140.2 (C-5), 156.5 (CO), 120.5, 122.4, 136.5, 142.1 (C- of 4-nitrophenoxy group). Anal. Calcd for $C_{14}H_{14}N_2O_5S$ (322.34): C, 52.17; H, 4.38; N, 8.69. Found: C, 52.29; H, 4.50; N, 8.48%.

Ethyl 2-(2-cyanoacetylamino)-4-methyl-5-(4-nitrophenoxy)thiophene-3-carboxylate (**2**): Ethyl cyanoacetate (2 mmol) was added to a solution of compound **1** (0.64 g, 2 mmol) in dioxane (20 mL). The reaction mixture was heated under reflux for 3 h, then cooled and poured onto petroleum ether 40–60 °C (40 mL). The precipitate which formed was filtered off, dried and recrystallised from ethanol to give **2**.Yield 0.53 g (69%); m.p. 141–143 °C; IR: ν = 3385 (NH), 2215 (CN), 1720, 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.31 (q, 2H, CH_2), 4.55 (s, 2H, CH_2), 7.12–8.10

(m, 4H, ArH), 9.10 (s, 1H, NH, exchangeable), Anal. Calcd for $C_{17}H_{15}N_3O_6S$ (389.38): C, 52.44; H, 3.88; N, 10.79. Found: C, 52.26; H, 3.63; N, 10.92%.

4-Hydroxy-3-methyl-2-(4-nitrophenoxy)-6-oxo-6,7-dihydrothieno [2,3-b]- pyridine-5-carbonitrile (**3**): Compound **2** (0.78 g, 2 mmol) in a solution of sodium ethoxide (0.2 g sodium in 10 mL ethanol) was heated under reflux for 4 h. The reaction mixture was evaporated to dryness under reduced pressure, then water (25 mL) was added to the residue. The solution was cooled and acidified with hydrochloric acid (15 mL) and the solid product was filtered off and recrystallised from ethanol to give **3**. Yield, 0.48 g (70%); m.p. 173–175 °C; IR: ν = 3410–3180 (OH, NH), 2216 (CN), 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.30 (s, 3H, CH_3), 7.11–8.13 (m, 4H, ArH), 8.60 (s, 1H, NH, exchangeable), 9.50 (s, 1H, OH, exchangeable); MS: *m/z* = 343 (M^+). Anal. Calcd for $C_{15}H_9N_3O_5S$ (343.32): C, 52.48; H, 2.64; N, 12.24. Found: C, 52.30; H; 2.48; N, 12.39%.

Ethyl 4-methyl-5-(4-nitrophenoxy)-2-(3-phenylthioureido)thiophene-3-carboxylate (**4**): A mixture of compound **1** (0.64 g, 2 mmol) and phenyl isothiocyanate (2 mmol) in dry benzene (25 mL) was heated gently under reflux for 30 min. The reaction mixture was cooled and the solid formed was collected, dried and recrystallised from benzene to give **4**. Yield, 0.58 g (64%); m.p. 187–189 °C; IR: ν = 3390–3285 (NH), 1722 (CO), 1255 cm^{-1} (CS); ^1H NMR ($CDCl_3$): δ = 1.35 (t, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.31 (q, 2H, CH_2), 7.10–8.16 (m, 9H, ArH), 8.40, 8.50 (2s, 2H, 2NH, exchangeable). Anal. Calcd for $C_{21}H_{19}N_3O_5S_2$ (457.52); C, 55.13; H, 4.19; N, 9.18. Found: C, 55.28; H, 4.31; N, 9.09%.

3-Amino-6-(4-nitrophenoxy)-5-methyl-2-(phenylamino)thieno[2,3-d] pyrimidin-4-(3H)-one (**5**): A mixture of **4** (0.91 g, 2 mmol) and hydrazine hydrate (2 mmol) in ethanol (20 mL) was heated under reflux for 9 h. The solid that separated upon cooling was filtered off, washed with water, dried and recrystallised from ethanol to give **5**. Yield, 0.58 g (71%); m.p. 217–219 °C; IR: ν = 3430–3230 (NH_2, NH), 1670 cm^{-1} (CO); ^1H NMR($CDCl_3$): δ = 2.23 (s, 3H, CH_3), 5.9 (brs, 2H, NH_2), 7.05–8.10 (m, 9H, ArH); 8.50(s, H, NH, exchangeable). Anal. Calcd for $C_{19}H_{15}N_5O_4S$ (409.42): C, 55.74; H, 3.69; N, 17.11. Found: C, 55.95; H, 3.89; N, 17.26%.

6-(4-Nitrophenoxy)-2,7-dimethyl-3-phenylthieno[2,3-d][1,2,4] triazolo[1,5-a]pyrimidin-8(3H)-one (**6**): A mixture of compound **5** (0.82 g, 2 mmol) and acetic anhydride (15 mL) was heated under reflux for 4 h. On cooling, the separated solid was filtered off, dried and recrystallised from butan-1-ol to give **6**.Yield, 0.50 g (58%); m.p. 180–182 C °; IR: ν = 1673 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.22, 2.30 (2s, 6H, $2CH_3$), 7.05–8.13 (m, 9H, ArH). Anal. Calcd for $C_{21}H_{15}N_5O_4S$ (433.44): C, 58.19; H, 3.49; N, 16.16. Found: C, 58.02; H, 3.31; N, 16.32%.

2-Amino-4-methyl-5-(4-nitrophenoxy)thiophene-3-carboxylic acid hydrazide (**7**): A mixture of **1** (1.6 g, 5 mmol) and hydrazine hydrate (5mmol) in ethanol (25 mL) was heated under relfux for 2 h, then allowed to cool. The solid precipitate was filtered off, washed with water and recrystallised from ethanol to give **7**. Yield, 1.2 g (81%); 210–212 °C; IR: ν = 3390–3185 (NH_2, NH) 1675 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 5.95 (brs, 2H, NH_2 of carbohydrazide), 6.10 (brs, 2H, NH_2), 7.25–8.30 (m, 4H, ArH), 8.55 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{12}H_{12}N_4O_4S$ (308.31): C, 46.75; H, 3.92; N, 18.17. Found: C, 46. 89; H, 4.10; N, 18.31%.

3-Amino-5-methyl-6-(4-nitrophenoxy)-2,3-dihydro-1H-thieno[2,3-d] pyrimidin-4-one (**8**): To a solution of compound **7** (0.62 g, 2 mmol) in methanol (20 mL) was added formaldehyde (6 mL), and the reaction mixture was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with cold water (30 mL). The formed precipitate was filtered off, dried and recrystallised from dioxane to give **8**.Yield, 0.55 g (86%); m.p. 186–188 °C; IR: ν = 3400–3210 (NH_2, NH), 1678 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 5.90 (brs, 2H, NH_2), 7.11–8.20 (m, 4H, ArH), 8.55 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 17.7 (CH_3),44.8 (CH_2), 107.8 (C-5), 115.9 (C-7a), 134.7 (C-4a), 152.3 (C-6), 161.9 (CO). Anal. Calcd for $C_{13}H_{12}N_4O_4S$ (320.32): C, 48.74; H, 3.78; N, 17.49. Found: C, 48.96; H, 3.91; N, 17.32%;

N-[5-Methyl-6-(4-nitrophenoxy)-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl]formamide (**9**): A mixture of compound **7** (0.62 g, 2 mmol) and formic acid (12 mL) was heated under reflux for 2 h. The reaction mixture was poured onto cold water (40 mL) and the formed precipitate was filtered off, dried and recrystallised from dioxane to give **9**. Yield, 0.58 g (72%); m.p. 163–165 °C; IR: ν = 3210 (NH), 1690, 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.27 (s, 3H, CH_3), 6.99–8.10 (m, 6H, ArH and CH of CHO), 8.65 (s, 1H, NH, exchangeable); MS: *m/z* = 346 (M^+). Anal. Calcd for $C_{14}H_{10}N_4O_5S$ (346.32): C, 48.55; H, 2.91; N, 16.18. Found: C, 48.26; H, 2.75; N, 16.31%.

9-Methyl-10-(4-nitrophenoxy)-6H-thieno[2′,3′:4,5]pyrimido[2,1-a] phthalazine-5,8-dione (**10**): To a solution of compound **7** (0.62 g, 2 mmol) in *N,N*-dimethylformamide (15 mL) was added phthalic anhydride (0.3 g, 2 mmol). The reaction mixture was refluxed for 5 h, then cooled and poured onto cold water (40 mL). The formed precipitate was filtered off, washed with ethanol (25 mL) and recrystallised from butan-1-ol to give **10**. Yield, 0.48 g (56%). m.p. 236–238 °C; IR: ν = 3335 (NH), 1675–1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.23 (s, 3H, CH_3), 7.15–8.21 (m, 8H, ArH), 8.9 (s, 1H, NH, exchangeble). Anal. Calcd for $C_{20}H_{12}N_4O_5S$ (420.40): C, 57.14; H, 2.88; N, 13.33. Found: C, 57.30; H, 2.99; N, 13.12%.

2-Amino-4-methyl-5-(4-nitrophenoxy)thiophene- 3-carbonyl azide (**11**): A solution of sodium nitrite (1g) in water (10 mL) was added with stirring to a solution of compound **7** (0.62 g, 2 mmol) in acetic acid (15 mL) during 10 min at room temperature. The formed solid was filtered off, washed with cold water to give **11**. Yield, 0.57 g (76%); m.p. 140–143 °C (dec); IR: ν = 3420, 3360 (NH_2), 2210 (CON_3), 1665 cm^{-1} (CO).

6-Methyl-5-(4-nitrophenoxy)-1,3-dihydrothieno[2,3-d]imidazol-2-one (**13**): The azide **11** (0.64 g, 2 mmol) was heated under reflux in dry xylene (25 mL) for 30 min, then was allowed to cool. The formed solid was filtered off and recrystallised from butan-1-ol to give **13**. Yield, 0.4 g (69%) m.p. 221–223 °C; IR: ν = 3360–3310 (NH), 1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.24 (s, 3H, CH_3), 7.30–8.25 (m, 4H, ArH), 8.6–9.1 (brs, 2H, 2NH, exchangeable). Anal. Calcd for $C_{12}H_9N_3O_4S$ (291.28): C, 49.48; H, 3.11; N, 14.43. Found: C, 49.61; H, 3.25; N, 14.25%.

2-Amino-4-methyl-5-(4-nitrophenoxy)thiophene-3-carboxylic acid (**14**): Compound **1** (1g) was heated under reflux for 2 h in ethanolic sodium hydroxide solution (20 mL, 10%). The reaction mixture was cooled then acidified by conc. HCl (25 mL). The solid product obtained after cooling was filtered off, washed with ethanol and dried to give **14**. Yield, 0.69 g (76%) m.p. 220–222 °C; IR: ν = 3460–3120 (multiple bands, OH, NH_2), 1690 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 6.10 (brs, 2H, NH_2) 7.12–8.15 (m, 4H, ArH), 9.85 (s, 1H, OH, exchangeable). Anal. Calcd for $C_{12}H_{10}N_2O_5S$ (294.28): C, 48.98; H, 3.43; N, 9.52. Found: C, 48.65; H, 3.21; N, 9.73%.

2,5-Dimethyl-6-(4-nitrophenoxy)thieno[2,3-d][1,3]oxazin-4-one (**15**): Compound **14** (1.58 g, 5 mmol) was heated under reflux in acetic anhydride (20 mL) for 4 h. The solid precipitate obtained on cooling was filtered off and recrystallised from butan-1-ol to give **15**. Yield, 1.02 g (64%); m.p. 226–228 °C; IR: ν = 1740 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.25, 2.85 (2s, 6H, $2CH_3$), 7.15–8.20 (m, 4H, ArH). Anal. Calcd for $C_{14}H_{10}N_2O_5S$ (318.31): C, 52.83; H, 3.17; N, 8.80. Found: C, 52.70; H, 3.02, N, 8.95%.

2,5-Dimethyl-6-(4-nitrophenoxy)-3H-thieno[2,3-d]pyrimidin-4-one (**16**): A mixture of compound **15** (0.64 g, 2 mmol) and ammonium acetate (0.31 g, 4 mmol) in glacial acetic acid (15 mL) was heated under reflux for 4 h. The solid product obtained after cooling was filtered off and recrystallised from dioxane to give **16**. Yield, 0.39 g (61%); m.p. 240–242 °C; IR: ν = 3210 (NH), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.23, 2.65 (2s, 6H, $2CH_3$), 7.10–8.20 (m, 4H, ArH), 9.10 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{14}H_{11}N_3O_4S$ (317.32): C, 52. 99; H, 3.49; N, 13.24. Found: C, 52. 81; H, 3.32; N, 13.38%.

3-(Chloroacetyl)-2,5-dimethyl-6-(4-nitrophenoxy)thieno[2,3-d]pyrimidin-4-(3H)-one (**17**): A mixture of compound **16** (0.63 g, 2 mmol) and chloroacetyl chloride (2 mmol) in DMF (20 mL) was heated under reflux for 3 h. The reaction mixture after cooling was poured onto cold water (30 mL) and the solid precipitate obtained was filtered off and recrystallised from benzene to give **17**. Yield, 0.54 g (68%); m.p. 230–232 °C; IR: ν = 1680–1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.25, 2.84 (2s, 6H, $2CH_3$), 4.30 (s, 2H, CH_2), 7.16–8.21 (m, 4H, ArH). Anal. Calcd for $C_{16}H_{12}ClN_3O_5S$ (393.80): C, 48. 80; H, 3.07; N, 10.67. Found: C, 48.95; H, 3.20; N, 10.43%.

3-(Hydrazinylacetyl)-2,5-dimethyl-6-(4-nitrophenoxy)thieno[2,3-d] pyrimidin-4-(3H)-one (**18**): A mixture of **17** (0.79 g, 2 mmol) and hydrazine hydrate (2 mmol) in ethanol (15 mL) was heated under reflux for 4 h, then cooled and poured onto crushed ice (30 g). The solid product which formed was filtered off, washed with water and recrystallised from ethanol to give **18**. Yield, 0.47 g (60%); m.p. 257–259 °C; IR: ν = 3410–3190 (NH_2, NH), 1675–1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.21, 2.80 (2s, 6H, $2CH_3$), 4.10 (s, 2H, CH_2),

5.90 (brs, 2H, NH_2), 7.15–8.25 (m, 4H, ArH), 8.65 (s,1H, NH, exchangeable). Anal. Calcd for $C_{16}H_{15}N_5O_5S$ (389.39): C, 49.35; H, 3.88; N, 17.99. Found:. C, 49.51; H, 3.98; N, 17.81%.

6,10-Dimethyl-9-(4-nitrophenoxy)-2,3-dihydro-4H-thieno[2′,3′:4,5] pyrimido[6,1-c][1,2,4]triazin-4-one (**19**): Compound **18** (1 g) was fused above its melting point in an oil bath for 2 h. After cooling, cold water (25 mL) was added and the solid obtained was filtered off and recrystallised from benzene to give **19**. Yield, 0.65 g (68%); m.p. 210–212 °C. IR: ν = 3210 (NH), 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.33, 2.81 (2s, 6H, $2CH_3$), 4.51 (s, 2H, CH_2), 7.11–8.30 (m, 4H, ArH), 9.30 (s,1H, NH, exchangeable). Anal. Calcd for $C_{16}H_{13}N_5O_4S$ (371.37): C, 51.75; H, 3.53; N, 18.86. Found: C, 51.93, H, 3.72; N, 18.72%;

3-Amino-2,5-dimethyl-6-(4-nitrophenoxy)-3H-thieno[2,3-d]pyrimidin-4-one (**20**): A solution of compound **15** (0.64 g, 2 mmol) in dry benzene (20 mL) and hydrazine hydrate (2 mmol) was heated under reflux for 4 h. The reaction mixture was cooled and the precipitated solid was filtered off and recrystallised from ethanol to give **20**.Yield, 0.48 g (71%); m.p. 241–243 °C; IR: ν = 3390, 3350 (NH_2), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.22, 2.60 (2s, 6H, $2CH_3$), 6.15 (brs, 2H, NH_2), 7.10-8.25 (m, 4H, ArH). Anal. Calcd for $C_{14}H_{12}N_4O_4S$ (332.34): C, 50.60; H, 3.64; N, 16.86. Found: C, 50.76; H, 3.89; N, 16.61%.

6,10-Dimethyl-9-(4-nitrophenoxy)-3,4-dihydro-2H-thieno[2′,3′:4,5] pyrimido[1, 6-b][1,2,4]triazin-2-one (**21**): A mixture of **20** (0.66 g, 2 mmol) and chloroacetamide (0.28 g, 3 mmol) in *N,N*-dimethylformamide (20 mL) was heated under reflux for 12 h. The reaction mixture was cooled, then poured onto cold water (30 mL). The precipitated solid was filtered off, dried and recrystallised from DMF to give **21**. Yield, 0.45 g (60%); m.p. 201–203 °C; IR: ν = 3240 (NH), 1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.20, 2.60 (2s, 6H, $2CH_3$), 4.20 (s, 2H, CH_2), 7.11–8.19 (m, 4H, ArH), 8.60 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{16}H_{13}N_5O_4S$ (371.37): C, 51.75; H, 3.53; N, 18.86. Found: C, 51.61; H, 3.39; N, 18.97%.

2-Chloro-N-[2,5-dimethyl-6-(4-nitrophenoxy)-4-oxo-4H-thieno [2,3-d]pyrimidin-3-yl]acetamide (**22**): A mixture of **20** (0.66 g, 2 mmol) and chloroacetyl chloride (2 mmol) in *N,N*-dimethylformamide (20 mL) was heated under reflux for 4 h. The reaction mixture was cooled and then poured onto cold water (30 mL). The precipitated solid was filtered off, dried and recrystallised from DMF to give **22**. Yield, 0.55 g (67%); m.p. 223–225 °C; IR: ν = 3260 (NH), 1678–1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.20, 2.60 (2s, 6H, $2CH_3$), 4.10 (s, 2H, CH_2), 7.15–8.10 (m, 4H, ArH), 8.60 (s, H, NH, exchangeable). Anal. Calcd for $C_{16}H_{13}ClN_4O_5S$ (408.82): C, 47.01; H, 3.21; N, 13.70. Found: C, 47.21; H, 3.39; N, 13.97%.

6,10-Dimethyl-9-(4-nitrophenoxy)-2H-thieno[2′,3′:4,5]pyrimido[1, 6-b][1,2,4]triazin-3(4H)-one (**23**): A mixture of **22** (0.82 g, 2 mmol) and ammonium acetate (0.31 g, 4 mmol) in glacial acetic acid (20 mL) was heated under reflux for 4 h. The reaction mixture was cooled and then poured onto crushed ice (30 g). The precipitated solid was filtered off and recrystallised from ethanol to give **23**. Yield, 0.49 g (65%); m.p. 171–173 °C; IR: ν = 3240 (NH),1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.30, 2.67 (2s, 6H, $2CH_3$), 4.45 (s, 2H, CH_2), 7.12–8.25 (m, 4H, ArH), 9.40 (s,1H, NH, exchangeable); ^{13}C NMR: δ = 17.4, 18.9 (2 CH_3), 45.2 (CH_2), 109.8 (C-7a), 111.6 (C-10), 123.9 (C-10a), 145.6 (C-10b), 151.5 (C-9), 154.9 (C-6), 165.3 (CO). Anal. Calcd for $C_{16}H_{13}N_5O_4S$ (371.37): C, 51.75; H, 3.53; N, 18.86. Found: C, 51.91; H, 3.72; N, 18.65%.

Preparation of compounds **24a,b***; general procedure*

A mixture of compound **20** (0.66 g, 2 mmol) and acid chlorides *viz* acetyl chloride and benzoyl chloride (2 mmol) in dry benzene (20 mL) was heated under reflux for 3 h. The excess solvent was removed under reduced pressure and the residue was recrystallised from suitable solvent to give **24a,b**.

N-[2,5-Dimethyl-6-(4-nitrophenoxy)-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl]acetamide (**24a**): Yield, 0.46 g (61%, benzene); m.p. 230–232 °C; IR: ν = 3240 (NH), 1670–1665 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 1.60, 2.30, 2.65 (3s, 9H, $3CH_3$), 7.14–8.10 (m, 4H, ArH), 9.30 (s, 1H, NH, exchangeable); MS: *m/z* = 374 (M^+). Anal. Calcd for $C_{16}H_{14}N_4O_5S$ (374.37): C, 51.33; H, 3.77; N, 14.97%; Found: C, 51.57; H, 3.92; N, 14.81%.

N-[2,5-Dimethyl-6-(4-nitrophenoxy)-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl]benzamide (**24b**): Yield, 0.52 g (59%, benzene); m.p. 231–233 °C; IR: ν = 3230 (NH), 1675–1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.21, 2.60 (2s, 6H, $2CH_3$), 7.10–8.20 (m, 9H, ArH), 8.60 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{21}H_{16}N_4O_5S$ (436.44): C, 57.79; H, 3.70; N, 12.84. Found: C, 57.90; H, 3.91; N, 12.61%.

Preparation of compounds **25 a,b***; general procedure*

A mixture of compound **24a** and/or **24b** (2 mmol) and ammonium acetate (0.31 g, 4 mmol) in glacial acetic acid (20 mL) was heated under reflux for 3 h. The reaction mixture was cooled, then poured onto cold water (30 mL). The separated solid was filtered off and recrystallised from suitable solvent to give **25a,b**.

2,5,9-Trimethyl-8-(4-nitrophenoxy)thieno[3,2-e][1,2,4]triazolo [1,5-c]pyrimidine (**25a**): Yield, 0.50 g (70%, butan-1-ol); m.p. 197–199 °C; IR: ν = 1610–1600 cm^{-1} (CN); ^1H NMR (DMSO-d_6): δ = 2.20, 2.41, 2.63 (3s, 9H, $3CH_3$), 7.01–8.11 (m, 4H, ArH); MS: *m/z* = 355 (M^+) Anal. Calcd for $C_{16}H_{13}N_5O_3S$ (355.37): C, 54.08; H, 3.69; N, 19.71. Found: C, 54.23; H, 3.93; N, 19.51%.

5,9-Dimethyl-8-(4-nitrophenoxy)-2-phenylthieno[3,2-e][1,2,4] triazolo[1,5-c]pyrimidine (**25b**): Yield, 0.60 g (72%); m.p. 183–185 °C; IR: ν = 1605–1600 cm^{-1} (CN); ^1H NMR (DMSO-d_6): δ = 2.22, 2.51 (2s, 6H, $2CH_3$), 7.15–8.10 (m, 9H, ArH). Anal. Calcd for $C_{21}H_{15}N_5O_3S$ (417.44): C, 60.42; H, 3.62; N, 16.78. Found: C, 60.61; H, 3.76; N, 16.53%.

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