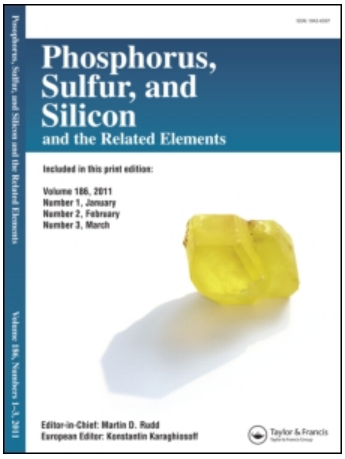

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FUSED QUINOLINE HETEROCYCLES IV. FIRST SYNTHESIS OF FOUR HETEROCYCLIC RING SYSTEMS OF lH-5-THIA-l,2,3,6-TETRA-AZAACEPHENANTHRYLENES AND 1H-5-THIA-l,3,6-TRIAZAACEPHENANTHRYLENES

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FUSED QUINOLINE HETEROCYCLES IV. FIRST SYNTHESIS OF FOUR HETEROCYCLIC RING SYSTEMS OF 1*H*-5-THIA-1,2,3,6-TETRA-AZAACEPHENANTHRYLENES AND 1*H*-5-THIA-1,3,6-TRIAZAACEPHENANTHRYLENES

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The synthesis of some novel fused tetracyclic compounds such as 1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylenes and 1*H*-5-thia-1,3,6-triazaacephenanthrylenes containing quinoline ring system have been reported.

Keywords: Synthesis; thieno[2,3-*b*]quinolines; fused tetracyclic compounds

We have reported previously[1–3] in this series on the synthesis of novel tetracyclic ring systems, containing the quinoline skeleton, with potential pharmaceutical activity, systems such as pyrazolotriazinoquinolines[1,2] and pyrrolopyrimidoquinolines.[3] Fused heterocycloquinolines are a large group of polyheterocycles with diverse, interesting biological activities. They are reported to possess significant antiinflammatory,[4,5] antitumor,[6,7] antibacterial,[8,9] and potent Bradykinin (BK) B_1 and B_2 receptor antagonist properties.[10] Moreover, some of sulfur-containing, fused quinolines and, particularly thienoquinolines, have recently drawn much attention due to their considerable biological and pharmacological activities as antitumor,[11] antibacterial,[11,12] drug resistance modulators,[13] memory enhanc-

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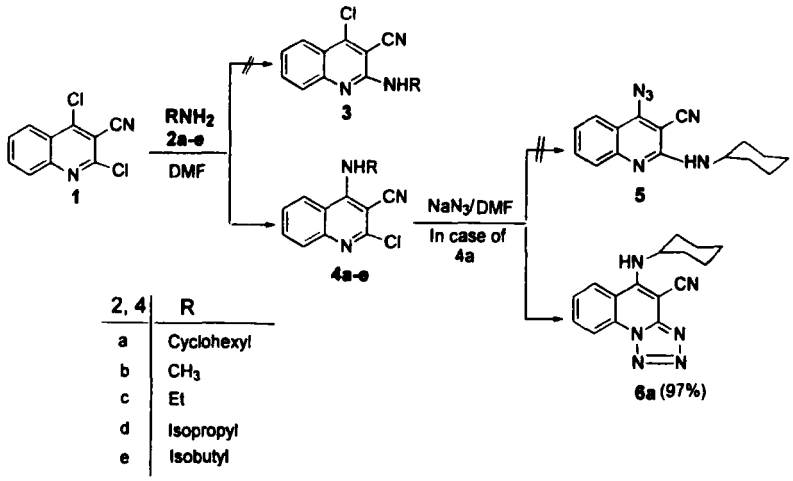
ers,[14] anti-inflammatorics, immunoregulators, analgesics and antipyretics.[15] Others are reported to exhibit a good antiallergics[16] and antianaphylactic activity.[17]

Because of these findings, our interest was focused to investigate efficient and convenient routes to construct the novel title ring systems. To the best of our knowledge, however, there are only few literature reports about the synthesis of linear, anellated pyrimidothienoquinolines[18–20] and 1,2,3-triazinothienoquinolines.[16,20] Moreover, a survey on the synthesis of perianellated tetracyclic pyrimidothienoquinoline and 1,2,3-triazinothienoquinoline ring systems revealed that such systems have been largely ignored. In connection with our ongoing program of synthesis of pharmacologically interesting new heterocyclic systems containing the quinoline moiety,[1,21–24] we have now succeeded in the synthesis of the first representatives of rarely accessible tetracyclic systems, namely, ethyl 1-alkyl-1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylates and ethyl 1-alkyl-1*H*-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylates.

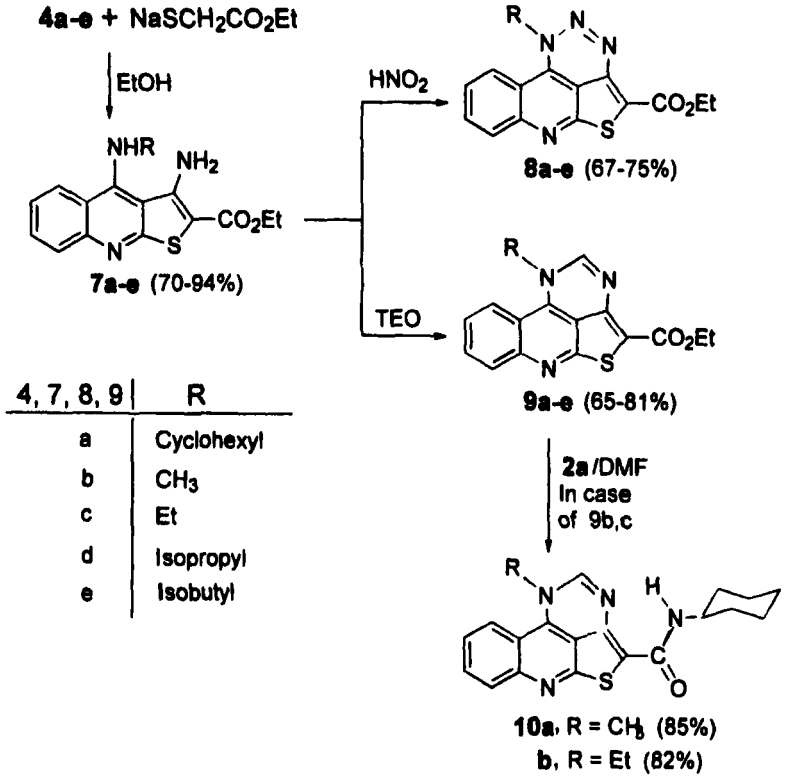
In the syntheses presented in this paper, the conveniently available 2,4-dichloroquinoline-3-carbonitrile (**1**)[1] is employed as starting material. It is known that a chlorine atom in the 4-position of **1** is more labile than that in the 2-position and is more easy to displace using nucleophiles.[25] Therefore, 1was reacted with alkylamines **2** in order to obtain the required key intermediate **4** for subsequent thiophene ring closure. Reaction of **1** with an excess of the appropriate alkylamine in DMF solution at room temperature did not afford the 2-alkylamino-4-chloroquinoline-3-carbonitriles **3**, but rather gave the expected isomeric structure, 4-alkylamino-2-chloroquinoline-3-carbonitriles **4a-e**,[1] where the nucleophilic substitution occurred first at the 4-position. In order to chemically verify the structure of **4**, we reacted **4a-e** with sodium azide, resulting in the formation of the corresponding tetrazolo[1,5-a]quinolines. The reactions of the aminoquinolines **4** with sodium azide is exemplified by the reaction of 2-chloro-4-(cyclohexylamino)quinoline-3-carbonitrile (**4a**). When **4a** was reacted with sodium azide in DMF at 70–75 °C, the ring-closed tetrazolo[1,5-a]quinolines **6** was isolated as the only reaction product, instead of the tautomeric azidoquinolines **5** (Scheme 1), based on the absence of an azido band in IR spectrum. It is difficult to obtain this reaction product **6** if the nucleophilic substitution first takes place at the 2-position.



SCHEME 1

The starting 2-carbethoxy-3-aminothieno[2,3-b]quinolines 7 required for the synthesis of novel tetracycles **8** and **9** are important synthons for the annellation of a triazine and pyrimidine ring onto the thienoquinoline ring systems. The synthesis of **7a-e** was accomplished by refluxing **4a-e** with an equimolecular amount of ethyl mercaptoacetate in dry ethanol and in the presence of an excess of sodium ethoxide (Scheme 2). The reaction takes place by nucleophilic attack of the anion of the mercaptoacetate, generated in the basic medium, at the carbon bearing the chlorine atom, followed by a 5-exo-trig cyclization to afford diaminothienoquinolines **7a-e** as stable crystalline solids (70–94%) (Scheme 2). The structures of thieno[2,3-b]quinolines **7a-e** were fully characterized by their analytical and spectroscopic data. The IR spectra showed no cyano absorption at 2200 cm^{-1}, but absorption bands for amino functions (N-H, NH_2) and ester C=O group were observed at 3450–3150 and 1680 cm^{-1}, respectively. Moreover, the ^{1}H-NMR spectra gave strong evidence for the formation of **7**, since the spectra revealed the presence of a triplet and quartet at $\delta \approx 1.28$ and 4.26, respectively, assigned to an ethoxy group at the 2-position in thiophene ring, and singlet at δ 7.04–7.27 assignable to an NH_2 group at C-3.

Since the preparation of novel tetracyclic systems was the main target of this synthetic program, the thieno[2,3-b]quinolines **7** was selected as a



SCHEME 2

model compound for studing all the reactions leading to the construction of the hitherto unknown tetracyclic systems incorporating a triazine and pyrimidine nucleus in addition to the thienoquinoline moiety. Thus, when **7a-e** were reacted with sodium nitrite in a 70% solution of H_2SO_4 at −5°C, the corresponding novel ethyl 1-alkyl-1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylates **8a-e** were indeed formed in good yield (Scheme 2). The structures of all compounds were substantiated by their elemental and spectral data (see Experimental). Both IR and ^{1}H-NMR spectra of **8a-e** disclosed the absence of signals for amino groups (NH, NH_2) The characteristic feature of the ^{1}H-NMR spectra of compounds **8a-e** was the downfield shift by ca. 0.97 ppm of the N-CH signals caused by the adjacent aza group of the triazine ring when compared with the cor-

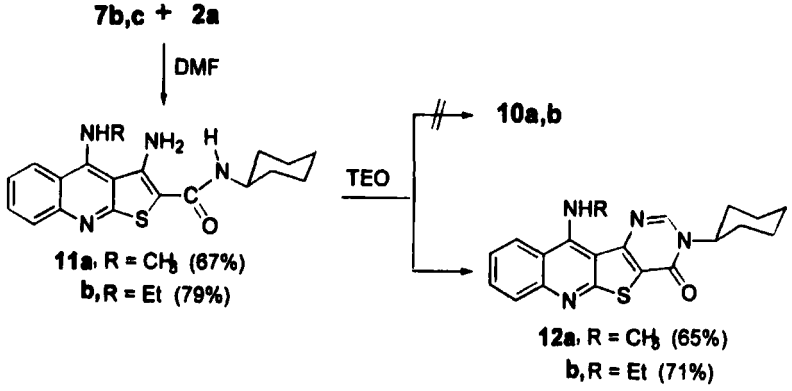
responding signals for the 4-alkylamino substituents in **7a-e**. For example, the N-CH_3 for **8b** appeared at δ 4.45, whereas these protons in **7b** resonated at δ 3.42.

Our interest in developing synthetic approaches with a view to synthesize new derivatives of the interesting heterocyclic pyrimidothienoquinoline ring system **9** led us to investigate the reaction of thienoquinolines **7** with triethyl orthoformate (TEO). When **7a-e** were refluxed with an excess of TEO for 8–11 h ethyl 1-alkyl-1*H*-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylates **9a-e** were isolated as the only reaction product (Scheme 2). These compounds, to our knowledge, are the first example of the 1,3,6-triazaacephenanthrylenes. The structure of **9a-e** were established and confirmed on the basis of their elemental and spectral data as follows: their IR spectra show no absorption bands for amino groups. In the ^{1}H-NMR spectra of **9a-e**, a singlet at δ ca 8.23 for the proton at C-2 was observed together with the signals of the other groups. Moreover, in the ^{1}H-NMR spectra the N-CH signal appears downfield in comparison with those of the corresponding thienoquinolines **7a-e** (see Experimental). The downfield shift of this N-CH signal could be explained by the anisotropic effect of the ring nitrogen. From these results, we conclude that a cyclocondensation between the amino groups in **7a-e** and TEO occured with the formation of the first example of a peri-anellated hetero-system **9a-e**.

In order to construct a new derivatives of the interesting tetracyclic ring systems of type **9**, we reacted the pyrimidothienoquinolines **9** with cyclohexylamine (**2a**) resulting in the formation of the corresponding amides. For example, reaction of **9b,c** with excess of **2a** in DMF solution at reflux temperature produced, in one step, the corresponding amide **10a,b** (Scheme 2). The structures of **10a,b** were established and confirmed on the basis of their elemental analysis and spectral data (see Experimental).

As an extension of our studies, we have been interested in preparing the interesting tetracyclic system **10** by another route starting from the thienoquinolines **7**. We envisaged that the reaction of thienoquinoline **7b,c** with **2a** might afford the corresponding amide **11a,b** and subsequent reaction with TEO would lead to the formation of the tetracyclic system **10a,b**. Interestingly, however, the isomeric linear anellated pyrimidothienoquinolines **12a,b** were obtained. Thus, pyrimido[4', 5': 4,5]thieno[2,3-b]quinolines **12a,b** were obtained in two steps starting from thienoquinolines **7b,c**. Reaction of **7b,c** with an excess of **2a**, following the same reaction condi-

tions applied for compounds **10a,b**, yielded the corresponding amide **11a,b**, in good yields. Refluxing the amides **11a,b** with excess of TEO for 8–11 h did not give the perianellated hetero-system **10a,b**, but rather gave the linear isomeric pyrimidothienoquinolines **12a,b** (Scheme 3), which were not identical in physical and spectroscopic aspects with compounds **10a,b** (see Experimental).



SCHEME 3

In summary, we have shown that the reaction between the aminoquinolines **4** and ethyl mercaptoacetate under the described conditions efficiently leads to thieno[2,3-b]quinolines **7** in good yields. These compounds are useful precursors in the preparation of a wide variety of biologically important novel 1,2,3,6-tetraazaacephenanthrylenes **8** and 1,3,6-triazaacephenanthrylenes **9**. This is the first time that such synthesis of novel peri-anellatedtetracyclic systems **8** and **9** have been described. The application of 2,4-dichloroquinoline-3-carbonitrile (**1**) to the preparation of other novel tetracyclic compounds is now in progress in our laboratory and will be published in due course.

EXPERIMENTAL

All m.p.s were recorded on a Gallenkamp melting point apparatus, and were uncorrected. IR spectra were obtained (KBr) on a Shimadzu 470 spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AC270

(270 MHz) or Bruker AM400 (400 MHz) spectrometer in $(CD_3)_2SO$ using TMS as an internal standard; the chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a GCMS- QP 1000EX mass spectrometer at 70 eV. Microanalyses were performed by the microanalytical Data Unit at Cairo University.

Synthesis of 5-(cyclohexylamino)tetrazolo[1,5-a]quinoline-4-carbonitrile (6)

Sodium azide (0.228 g, 3.50 mmol) was added to a solution of **4a** (0.5 g, 1.75 mmol) in DMF (15 mL). The reaction mixture was stirred at 70–75 °C for 30 h. After cooling, the reaction mixture was poured into cold water, and the precipitated product was filtered, washed well with water, dried, and recrystallized (DMF) to afford compound **6** as colorless crystals, yield 0.495 g (97%), mp 254–256 °C; (Found: C, 65.91; H, 5.64; N, 28.96. $C_{16}H_{16}N_6$: C, 65.73; H, 5.52; N, 28.75%); υ_{max} /cm^{-1} 3400 (NH); 2930, 2850 (aliph. CH) and 2200 (CN); δ (DMSO-d_6) 1.17–2.11 (m, 10H, aliph H), 4.38 (m, 1H, aliph H), 7.77 (t, J = 8 Hz, 1 ArH), 7.97–8.02 (m, 2H, 1 ArH and NH), 8.43 (d, J = 8 Hz, 1 ArH), 8.61 (d, J = 8 Hz, 1 ArH).

General procedure for the synthesis of ethyl 4-alkylamino-3-aminothieno[2,3-b]quinoline-2-carboxylates 7a-e

Sodium (0.23 g) was added to dry ethanol (20 mL). The sodium was dissolved by heating under reflux, whereupon ethyl 2-mercaptoacetate (5 mmol) was slowly added. After cooling to room temperature, the solution became semisolid. The appropriate 4-alkylamino-2-chloroquinoline-3-carbonitrile **4a-e** (5 mmol) was added, and the reaction mixture was refluxed for 4–6 h. It was then poured into ice/water and acidified with cold dilute HCl to pH = 3. The resulting solid product was collected by filtration, washed with water, dried, and recrystallized from EtOH.

Ethyl 3-Amino-4-(cyclohexylamino)thieno[2,3-b] quinoline-2-carboxylate (7a)

Yellowish crystals, Yield 1.30 g (70%), m.p. 248–250 °C (dec.); (Found: C, 65.09; H, 6.22; N, 11.33; S, 8.57. $C_{20}H_{23}N_3O_2S$: C, 65.01; H, 6.27; N,

11.37; S, 8.68%); υ_{max}/cm^{-1} 3350, 3250 (NH, NH_2); 3050 (arom. CH), 2950, 2850 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.17 (m, 2H, aliph H), 1.29 (t, J = 7 Hz, 3H, CH_3), 1.59–2.07 (m, 9H, aliph H), 4.27 (q, J = 7 Hz, 2H, CH_2), 7.04 (br s, 2H, NH_2), 7.59 (t, J = 8 Hz, 1 ArH), 7.79–7.92 (m, 2 ArH), 8.53 (d, J = 8 Hz, 1 ArH).

Ethyl 3-Amino-4-(methylamino)thieno[2,3-b]quinoline-2-carboxylate (7b)

Yellowish crystals, Yield 1.41 g (94%), m.p. 260–261 °C (dec.); (Found: C, 59.68; H, 5.24; N, 14.07; S, 10.83. $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94; S, 10.64%); υ_{max}/cm^{-1} 3350, 3300, 3150 (NH, NH_2); 2980 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.28 (t, J = 7 Hz, 3H, CH_3), 3.42 (br, 3H, NCH_3), 4.26 (q, J = 7 Hz, 2H, CH_2), 7.27 (br s, 2H, NH_2), 7.56 (t, J = 8 Hz, 1 ArH), 7.75 (d, J = 8 Hz, 1 ArH), 7.89 (t, J = 8 Hz, 1 ArH), 8.49 (d, J= 8 Hz, 1ArH).

Ethyl 3-Amino-4-(ethylamino)thieno[2,3-b]quinoline-2-carboxylate (7c)

Yellowish crystals, Yield 1.22 g (77%), m.p. 247–249 °C (dec.); (Found: C, 60.75; H, 5.68; N, 13.27; S, 9.88. $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32; S, 10.17%); υ_{max}/cm^{-1} 3300, 3150 (NH, NH_2); 3050 (arom. CH), 2980 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.27 (t, J = 7 Hz, 3H, ester CH_3), 1.33 (t, J = 7 Hz, 3H, CH_3), 3.89 (m, 2H, CH_2), 4.25 (q, J = 7 Hz, 2H, ester CH_2), 7.23 (br s, 2H, NH_2), 7.55 (t, J = 8 Hz, 1ArH), 7.81 (d, J = 8 Hz, 1 ArH), 7.88 (t, J = 8 Hz, 1 ArH), 8.57 (d, J = 8 Hz, 1 ArH).

Ethyl 3-Amino-4-(isopropylamino)thieno[2,3-b] quinoline-2-carboxylate (7d)

Yellowish crystals, Yield 1.35 g (82%), m.p. 259–261 °C (dec.); (Found: C, 62.08; H, 5.94; N, 12.95; S, 9.46. $C_{17}H_{19}N_3O_2S$: C, 61.98; H, 5.81; N, 12.76; S, 9.73%); υ_{max}/cm^{-1} 3350, 3250 (NH, NH_2); 3050 (arom. CH), 2950 (aliph. CH), 1680 (ester C=O) and 1620(C=N); δ (DMSO-d_6) 1.28–1.34 (m, 9H, 3 × CH_3), 4.27 (q, J = 7 Hz, 2H, CH_2), 4.49 (m, 1H, NCH),

7.06 (br s, 2H, NH_2), 7.60 (t, J = 8 Hz, 1 ArH), 7.85–7.90 (m, 2 ArH), 8.54 (d, J = 8 Hz, 1 ArH).

Ethyl 3-Amino-4-(isobutylamino)thieno[2,3-b] quinoline-2-carboxylate (7e)

Yellowish crystals, Yield 1.30 g (76%), m.p. 173–175 °C (dec.); (Found: C, 63.03; H, 6.38; N, 12.19; S, 9.06. $C_{18}H_{21}N_3O_2S$: C, 62.95; H, 6.16; N, 12.24; S, 9.34%); υ_{max}/cm^{-1} 3450, 3350, 3300 (NH, NH_2); 2950 (aliph. CH), 1660 (ester C=O) and 1610 (C=N); δ (DMSO-d_6) 0.77(d, J = 6 Hz, 6H, 2 × CH_3), 1.27 (t, J = 7 Hz, 3H, CH_3), 1.91 (m, 1H, CH), 3.56 (t, J = 6 Hz, 2H, CH_2), 4.24 (q, J = 7 Hz, 2H, CH_2), 6.71(t, J = 5 Hz, 1H, NH), 7.04 (br s, 2H, NH_2), 7.45 (t, J = 8 Hz, 1 ArH), 7.70 (t, J = 8 Hz, 1 ArH), 7.80 (d, J = 8 Hz, 1 ArH), 8.47 (d, J= 8 Hz, 1 ArH).

General procedure for the synthesis of ethyl 1-alkyl-1H-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylates 8a-e

Aq. $NaNO_2$ (15 mmol in 4 mL) was added dropwise to a solution of thienoquinolines **7a-e** (5 mmol) in H_2SO_4 (12 mL, 70%) cooled in ice-salt to −10 °C, while the temperature of the reaction mixture was maintained at −10 to −5 °C. The reaction mixture was kept at −5 °C for 1 h and then was poured into ice-water. The precipitated solid product was collected by filtration, washed well with water, dried, and recrystallized (DMF) to give the corresponding tetracycles **8a-e**.

Ethyl 1-Cyclohexyl-1H-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylate (8a)

Red crystals, Yield 1.43 g (75%), m.p. 198–200°C; (Found: C, 63.04; H, 5.38; N, 14.67; S, 8.56. $C_{20}H_{20}N_4O_2S$: C, 63.14; H, 5.30; N, 14.73; S, 8.43%); υ_{max}/cm^{-1} 2950, 2850 (aliph. CH), 1680 (ester C=O) and 1610 (C=N); δ (DMSO-d_6) 1.32 (t, J = 7 Hz, 3H, CH_3), 1.55–2.29 (m, 10H, aliph H), 4.31 (q, J = 7 Hz, 2H, CH_2), 4.87 (t, J = 11 Hz, 1H, aliph H), 7.55 (t, J = 8 Hz, 1 ArH), 7.76 (d, J = 8 Hz, 1 ArH), 7.83 (d, J = 8 Hz, 1 ArH), 8.06 (d, J = 8 Hz, 1 ArH); m/z 380 (M^+, 50%), 351 (100), 323 (39), 309 (29), 281 (62), 237 (66), 224 (55), 140 (67); 83 (10), 44 (16), 29 (95).

Ethyl 1-Methyl –1H-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylate (8b)

Red crystals, Yield 1.05 g (67%), m.p. 234–236 °C; (Found: C, 57.76; H, 4.05; N, 17.99; S, 10.33. $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94; S, 10.26%); υ_{max}/cm^{-1} 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.32 (t, J = 7 Hz, 3H, CH_3), 4.33 (q, J = 7 Hz, 2H, CH_2), 4.45 (s, 3H, CH_3), 7.53 (t, J = 8 Hz, 1 ArH), 7.81 (t, J = 8 Hz, 1 ArH), 7.87 (d, J = 8 Hz, 1 ArH), 8.50 (d, J = 8 Hz, 1 ArH); m/z 312 (M^+, 51%), 283 (20), 254 (100), 240 (49), 211 (60), 140 (35), 29 (15).

Ethyl 1-Ethyl –1H-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylate (8c)

Red crystals, Yield 1.22 g (75%), m.p. 228–230 °C; (Found: C, 58.97; H, 4.41; N, 17.01; S, 10.04. $C_{16}H_{14}N_4O_2S$: C, 58.88; H, 4.32; N, 17.17; S, 9.82%); υ_{max}/cm^{-1} 2950, 2900 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.32 (t, J = 7 Hz, 3H, ester CH_3), 1.53 (t, J= 7 Hz, 3H, CH_3), 4.32 (q, J = 7 Hz, 2H, ester CH_2), 4.84 (q, J = 7 Hz, 2H, CH_2), 7.56 (t, J = 8 Hz, 1 ArH), 7.81 (t, J = 8 Hz, 1 ArH), 7.87 (d, J = 8 Hz, 1 ArH), 8.27 (d, J = 8 Hz, 1 ArH); m/z 325 (M^+-1, 83%), 298 (49), 270 (100), 255 (97), 228 (63), 184 (34), 183 (27), 140 (70), 45 (7), 29 (50).

Ethyl 1-Isopropyl –1H-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylate (8d)

Red crystals, Yield 1.22 g (72%), m.p. 180–181 °C; (Found: C, 59.96; H, 4.89; N, 16.54; S, 9.61. $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46; S, 9.42%); υ_{max} /cm^{-1} 2980, 2950 (aliph. CH), 1670 (ester C=O) and 1610 (C=N); δ (DMSO-d_6) 1.31 (t, J = 7 Hz, 3H, CH_3), 1.67 (d, J = 6 Hz, 6H, 2 × CH_3), 4.30 (q, J = 7 Hz, 2H, CH_2), 5.35 (m, 1H, NCH), 7.50 (t, J = 8 Hz, 1 ArH), 7.75 (t, J = 8 Hz, 1 ArH), 7.81 (d, J = 8 Hz, 1 ArH), 8.21 (d, J = 8Hz, 1 ArH); m/z 339 (M^+-1, 76%), 311 (74), 296 (47), 283 (42), 268 (56), 255 (57), 239 (76), 224 (64), 153 (67), 140 (93), 102 (61), 43 (78), 29 (100).

Ethyl 1-Isobutyl-1H-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylate (8e)

Red crystals, Yield 1.24 g (70%), m.p. 170–172 °C; (Found: C, 61.16; H, 5.25; N, 15.98; S, 9.25. $C_{18}H_{18}N_4O_2S$: C, 61.00; H, 5.12; N, 15.81; S, 9.05%); υ_{max}/cm^{-1} 2980, 2900 (aliph. CH), 1680 (ester C=O) and 1610 (C=N); δ (DMSO-$\underline{d}_6$) 1.03 (d, J = 6 Hz, 6H, 2 × CH_3), 1.32 (t, J = 7 Hz, 3H, CH_3), 2.19 (m, 1H, CH), 4.30 (q, J= 7 Hz, 2H, CH_2), 4.61 (d, J = 6 Hz, 2H, CH_2), 7.55 (t, J = 8 Hz, 1 ArH), 7.77 (t, J = 8 Hz, 1 ArH), 7.82 (d, J = 8 Hz, 1 ArH), 8.11 (d, J = 8 Hz, 1 ArH); m/z 354 (M^+, 8%), 326 (47), 296 (68), 283 (42), 254 (100), 227 (28), 184 (13), 140 (12).

General procedure for the synthesis of ethyl 1-alkyl-1H-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylates 9a-e and pyrimido[4',5':4,5] thieno[2,3-b]quinolines 12a,b

A mixture of thienoquinolines **7a-e** or **11a,b** (5 mmol) and triethyl orthoformate (30 mL) was heated under reflux for 8–11 h. After concentration and cooling to room temperature, the resulting precipitate was filtered off, washed with methanol, dried, and recrystallized from DMF.

Ethyl 1-Cyclohexyl-1H-5-thia-1,3,6--triazaacephenanthrylene-4-carboxylate (9a)

Yellow crystals, Yield 1.33 g (70%), m.p. 240–241 °C; (Found: C, 66.34; H, 5.61; N, 11.00; S, 8.51. $C_{21}H_{21}N_3O_2S$: C, 66.47; H, 5.58; N, 11.07; S, 8.45%); υ_{max}/cm^{-1} 2950, 2850 (aliph. CH), 1700 (ester C=O) and 1620 (C=N); δ (DMSO-$\underline{d}_6$) 1.27 (t, J = 7Hz, 3H, CH_3), 1.45–2.21(m, 10H, aliph H), 4.24 (q, J = 7 Hz, 2H, CH_2), 4.60 (t, J = 10 Hz, 1H, aliph H), 7.51 (t, J = 8 Hz, 1 ArH), 7.73 (t, J = 8 Hz, 1 ArH), 7.86 (d, J = 8 Hz, 1 ArH), 7.99 (d, J = 8 Hz, 1 ArH), 8.41(s, 1H, pyrimidine CH); m/z 378 (M^+-1, 100%), 310 (17), 296 (88), 251 (27), 250 (73), 224 (62), 223 (40), 195 (25), 83 (18), 55 (49), 41 (32), 28 (37).

Ethyl 1-Methyl-1H-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylate (9b)

Yellow crystals, Yield 1.09 g (70%), m.p. 264–265 °C (dec.); (Found: C, 61.79; H, 4.35; N, 13.40; S, 10.15. $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N,

13.50; S, 10.30%); υ_{max} / cm^{-1} 2950 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.27 (t, *J* = 7 Hz, 3H, CH_3), 4.04 (s, 3H, CH_3), 4.23 (q, *J* = 7 Hz, 2H, CH_2), 7.42 (t, *J* = 8 Hz, 1 ArH), 7.73 (t, *J* = 8 Hz, 1 ArH), 7.83 (d, *J* = 8 Hz, 1 ArH), 8.07 (s, 1H, pyrimidine CH), 852 (d, J = 8 Hz, 1 ArH); m/z 310 (M^+-1, 100%), 265 (19), 238 (59), 223 (36), 28 (34).

Ethyl 1-Ethyl-1H-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylate (9c)

Yellow crystals, Yield 1.06 g (65%), m.p. 276–278 °C; (Found: C, 62.67; H, 4.59; N, 13.08; S, 9.72. $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91; S, 9.85%); υ_{max} /cm^{-1} 2980, 2900 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.28 (t, *J* = 7 Hz, 3H, ester CH_3), 1.46 (t, *J* = 7 Hz, 3H, CH_3), 4.24 (q, *J* = 7 Hz, 2H, ester CH_2), 4.46 (q, *J* = 7 Hz, 2H, CH_2), 7.50 (t, *J* = 8 Hz, 1 ArH), 7.75 (t, *J* = 8 Hz, 1 ArH), 7.86 (d, *J* = 8 Hz, 1 ArH), 8.15 (s, 1H, pyrimidine CH), 8.29 (d, *J* = 8 Hz, 1 ArH).

Ethyl 1-Isopropyl-1H-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylate (9d)

Yellow crystals, Yield 1.16 g (68%), m.p. 200–202 °C (dec.); (Found: C, 63.82; H, 5.11; N, 12.29; S, 9.59. $C_{18}H_{17}N_3O_2S$: C, 63.69; H, 5.05; N, 12.38; S, 9.45%); υ_{max} /cm^{-1} 2980, 2950 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 1.26 (t, *J* = 7 Hz, 3H, CH_3), 1.64 (d, *J*= 6 Hz, 6H, 2 × CH_3), 4.24 (q, *J* = 7 Hz, 2H, CH_2), 5.12 (m, 1H, NCH), 7.46 (t, J = 8 Hz, 1 ArH), 7.73 (t, *J* = 8 Hz, 1 ArH), 7.85 (d, *J* = 8 Hz, 1 ArH), 8.15 (d, *J* = 8 Hz, 1 ArH), 8.41 (s, 1H, pyrimidine CH).

Ethyl 1-Isobutyl-1H-5-thia-1,3,6-triazaacephenanthrylene-4-carboxylate (9e)

Yellow crystals, Yield 1.43 g (81%), m.p. 272–274 °C; (Found: C, 64.41; H, 5.39; N, 11.85; S, 9.18. $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89; S, 9.07%); υ_{max} /cm^{-1} 2980, 2900, 2850 (aliph. CH), 1680 (ester C=O) and 1620 (C=N); δ (DMSO-d_6) 0.96 (d, *J* = 6 Hz, 6H, 2 × CH_3), 1.27 (t, *J* = 7 Hz, 3H, CH_3), 2.10 (m, 1H, CH), 4.24 (m, 4H, 2 × CH_2), 7.49 (t,

J = 8 Hz, 1 ArH), 7.72 (t, J = 8 Hz, 1 ArH), 7.84 (d, J = 8 Hz, 1 ArH), 8.10 (s, 1H, pyrimidine CH), 8.18 (d, J = 8 Hz, 1 ArH); m/z 352 (M^+-1, 68%), 324 (8), 308 (7), 297 (11), 281 (15), 251 (62), 225 (100), 224 (84), 196 (67), 170 (29), 57 (49), 41 (61), 29 (83).

3-Cyclohexyl-11-(methylamino)pyrimido[4',5':4,5]thieno[2,3-b] quinoline-4(3H)-one(12a)

Yellow crystals, Yield 1.18 g (65%), m.p. 332–333 °C; (Found: C, 66.07; H, 5.60; N, 15.22; S, 9.01. $C_{20}H_{20}N_4OS$: C, 65.91; H, 5.53; N, 15.37; S, 8.80%); υ_{max}/cm^{-1}3530, 3420 (NH), 2930, 2850 (aliph. CH), 1690 (C=O) and 1620 (C=N); δ (DMSO-d_6) 1.40–1.89 (m, 10H, aliph H), 4.02 (d, J = 5 Hz, 3H, NCH_3), 4.71 (t, J = 9 Hz, 1H, aliph H), 7.41 (t, J = 8 Hz, 1 ArH), 7.74 (t, J= 8 Hz, 1 ArH), 7.83 (d, J = 8 Hz, 1 ArH), 8.47(d, J = 8 Hz, 1 ArH), 8.80 (s, 1H, pyrimidine CH).

3-Cyclohexyl-11-(ethylamino)pyrimido[4',5':4,5]thieno[2,3-b] quinoline-4(3H)-one (12b)

Yellow crystals, Yield 1.34 g (71%), m.p. 243–245 °C (dec.); (Found: C, 66.78; H, 5.66; N, 14.84; S, 8.36. $C_{21}H_{22}N_4OS$: C, 66.64; H, 5.86; N, 14.80; S, 8.47%); υ_{max}/cm^{-1}3530, 3420 (NH), 2930, 2850 (aliph. CH), 1690 (C=O) and 1620 (C=N); δ (DMSO-d_6) 1.28 (t, J = 7 Hz, 3H, CH_3), 1.42–2.21 (m, 10H, aliph H), 4.23 (m, 2H, CH_2), 4.60 (t, J = 9 Hz, 1H, aliph H), 7.51 (t, J = 8 Hz, 1 ArH), 7.74 (t, J = 8 Hz, 1 ArH), 7.87 (d, J = 8 Hz, 1 ArH), 8.0 (d, J = 8 Hz, 1 ArH), 8.42 (s, 1H, pyrimidine CH).

General procedure for the synthesis of 1H-5-thia-1,3,6-triazaacephenanthrylenes 10a,b and thieno[2,3-b]quinolines 11a,b

Cyclohexylamine (**2a**) (4.97 g, 50 mmol) was added to a solution of **9b,c** or **7b,c** (5 mmol) in DMF (10 mL). The mixture was refluxed for 10–12 h. After cooling, the mixture was evaporated to dryness *in vacuo*. Cold water (10 mL) was added to the remaining oily residue with stirring. The solution was neutralized with conc. HCl, and the precipitated solid product was collected by filtration, washed with water, dried, and recrystallized from DMF/MeOH.

N4-Cyclohexyl-1-methyl-1H-5-thia-1,3,6-triazaacephenanthrylenecarboxamide (10a)

Yellow crystals, Yield 1.55 g (85%), m.p. 345–346 °C; (Found: C, 65.99; H, 5.49; N, 15.48; S, 8.90. $C_{20}H_{20}N_4OS$: C, 65.91; H, 5.53; N, 15.37; S, 8.80%); υ_{max}/cm^{-1} 3300, 3200 (NH), 2920, 2850 (aliph. CH), 1660 (C=O) and 1620 (C=N); δ (DMSO-d_6) 1.19–1.92 (m, 10H, aliph H), 3.55 (s, 3H, CH_3), 4.68 (m, 1H, aliph H), 7.35 (t, J = 8 Hz, 1 ArH), 7.69 (t, J = 8 Hz, 1 ArH), 7.79 (d, J = 8 Hz, 1 ArH), 8.51 (d, J = 8 Hz, 1 ArH), 8.71 (s, 1H, pyrimidine CH), 8.97 (d, J = 6 Hz, 1H, NH).

N4-Cyclohexyl-1-ethyl-1H-5-thia-1,3,6-triazaacephenanthrylenecarboxamide (10b)

Yellow crystals, Yield 1.55 g (82%), m.p. 288–289 °C; (Found: C, 66.71; H, 5.73; N, 14.84; S, 8.66. $C_{21}H_{22}N_4OS$: C, 66.64; H, 5.86; N, 14.80; S, 8.47%); υ_{max}/cm^{-1} 3300, 3200 (NH), 2920, 2850 (aliph. CH), 1660 (C=O) and 1620 (C=N); δ (DMSO-d_6) 1.19 (m, 2H, aliph H), 1.42 (t, J = 7 Hz, 3H, CH_3), 1.67–1.89 (m, 8H, aliph H), 4.01 (q, J = 7 Hz, 2H, CH_2), 4.71 (m, 1H, aliph H), 7.41 (t, J = 8 Hz, 1 ArH), 7.74 (t, J = 8 Hz, 1 ArH), 7.82 (d, J = 8 Hz, 1 ArH), 8.46 (d, J = 8 Hz, 1 ArH), 8.80 (s, 1H, pyrimidine CH), 8.91 (d, J = 6 Hz, 1H, NH).

N2-Cyclohexyl-3-amino-4-(methylamino)thieno[2,3-b]quinolinecarboxamide (11a)

Yellow crystals, Yield 1.19 g (67%), m.p. 244–246 °C (dec.); (Found: C, 64.34; H, 6.13; N, 16.03; S, 9.19. $C_{19}H_{22}N_4OS$: C, 64.38; H, 6.26; N, 15.80; S, 9.04%); υ_{max}/cm^{-1} 3450, 3320 (NH, NH_2), 3050 (arom. CH), 2930, 2850 (aliph. CH), 1670 (C=O) and 1620 (C=N); δ (DMSO-d_6) 1.18 (m, 2H, aliph H), 1.60–1.98 (m, 9H, aliph H), 3.38 (br, 3H, NCH_3), 4.14 (br, 1H, NH), 7.08 (br s, 2H, NH_2), 7.58 (t, J = 8 Hz, 1 ArH), 7.83–7.92 (m, 3H, 2 ArH and NH), 8.49 (d, J = 8 Hz, 1ArH).

N2-Cyclohexyl-3-amino-4-(ethylamino)thieno[2,3-b]quinolinecarboxamide (11b)

Yellow crystals, Yield 1.45 g (79%), m.p. 223–225 °C (dec.); (Found: C, 65.30; H, 6.60; N, 15.32; S, 8.59. $C_{20}H_{24}N_4OS$: C, 65.19; H, 6.56; N,

15.20; S, 8.70%); υ_{max} /cm^{-1} 3450, 3320 (NH, NH_2), 3050 (arom. CH), 2930, 2850 (aliph. CH), 1670 (C=O) and 1620 (C=N); δ (DMSO-$\underline{d}_6$) 1.17 (m, 2H, aliph H), 1.29 (t, J = 7 Hz, 3H, CH_3), 1.59–2.0 (m, 9H, aliph H), 4.13 (br, 1H, NH), 4.28 (m, 2H, CH_2), 7.04 (br s, 2H, NH_2), 7.60 (t, J= 8 Hz, 1 ArH), 7.84–7.93 (m, 3H, 2 ArH and NH), 8.52 (d, J = 8 Hz, 1 ArH).

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