Fused Quinoline Heterocycles VI: Synthesis of 5*H*-1-Thia-3,5,6-Triazaaceanthrylenes and 5*H*-1-Thia-3,4,5,6-Tetraazaaceanthrylenes

Ramadan Ahmed Mekheimer[a*], Kamal Usef Sadek[a], Hisham Ahmed Abd El-Nabi[a], Afaf Abd El-Hameid Mohamed[a], Ehab Anwer Ebraheem[a], Michael B. Smith[b]

[a]Department of Chemistry, Faculty of Science, El-Minia University, El-Minia 61519, Egypt
[b]Department of Chemistry, 55 N. Eagleville Rd., University of Connecticut, Storrs, CT, 06269-3060, USA
E-mail: rmekh@yahoo.com; michael.smith@uconn.edu

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Ethyl 3-amino-4-chlorothieno[3,2-*c*]quinoline-2-carboxylate (**4**) is a versatile synthon, prepared by reacting an equimolar amount of 2,4-dichloroquinoline-3-carbonitrile (**1**) with ethyl mercaptoacetate (**2**). Ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylates **9a-c**, novel perianellated tetracyclic heteroaromatics, were prepared by refluxing **4** with excess of primary amines **7a-c** to yield the corresponding aminothieno[3,2-*c*]quinolines **8a-c**. Subsequent reaction with an excess of triethyl orthoformate (TEO) furnished **9a-c**. Reaction of **4** with TEO in Ac_2O, at reflux, gave the simple acetylated compounds, thieno[3,2-*c*]-quinolines **12** and **13**. Refluxing **4** with benzylamine (**7d**) gave **10**, and subsequent treatment with TEO gave the tetracyclic compound **11**. Refluxing **13** with an excess of alkylamines **7a-d** gave the thieno[3,2-*c*]quinolines **15**. Refluxing the aminothienoquinolines **8b** with an excess of triethyl orthoacetate gave thieno[3,2-*c*]quinoline **17**, while heating with Ac_2O gave **18** and **19**, with small amounts of **16**. Reaction of **8a,b** with ethyl chloroformate and phenylisothiocyanate generated the new 1-thia-3,5,6-triazaaceanthrylenes **20a,b** and **21a,b**, respectively. Diazotization of **8a-c** afforded the novel tetracyclic ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylates **22a-c** in good yields.

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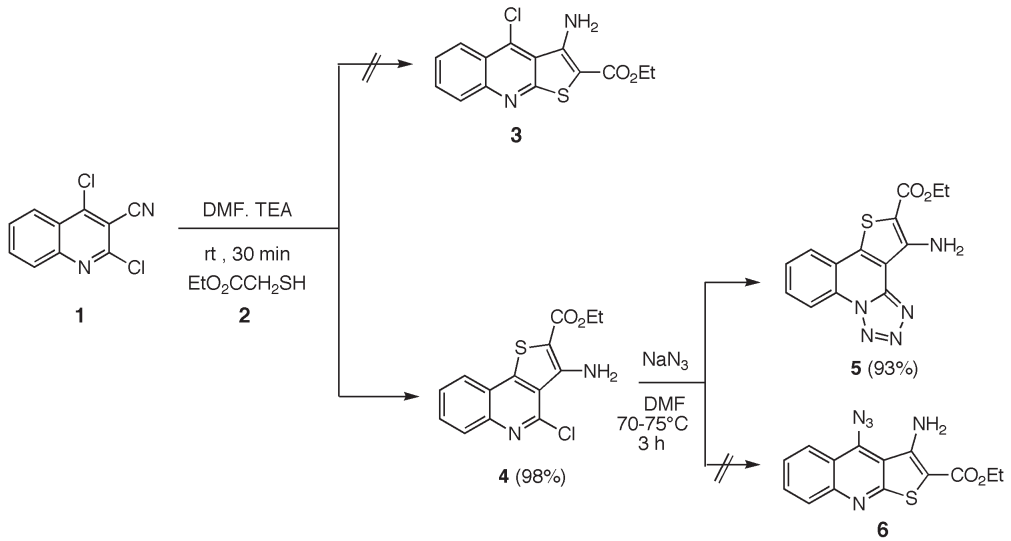
Selectively functionalized quinolines are building blocks for the synthesis of numerous tetracyclic systems with a wide variety of biological activities [1-3]. For some time, our research has focused on the synthesis of fused heterocyclic systems, particularly those containing a quinoline nucleus, with the aim of evaluating their pharmacological and/or biological activity [4-7]. As a result of this work, we recently reported a new and useful method for the synthesis of novel tetracyclic ring systems [8-12]. In pharmacological studies thieno[3,4-*d*]-pyrimidines have been shown to possess pharmacological activities including antibacterial [13], antihypertensive [14,15], antiulcer [16], fungicidal [17], gastric acid secretion inhibitory [18], insecticidal, miticidal [17] vasodilatory [14] activity, and antiallergic activity [19]. Several thienoquinolines have attracted attention over the last decade owing to their biological activities, which include antitumor [20], drug resistance modulation [21], anti-inflammatory, immunoregulatory, analgesic and antipyretic activities [22]. In addition, some compounds show potent antianaphylactic activity [23].

Our previous work [8-12] has led to the synthesis of novel tetracyclic ring systems containing both thiophene

Scheme 1



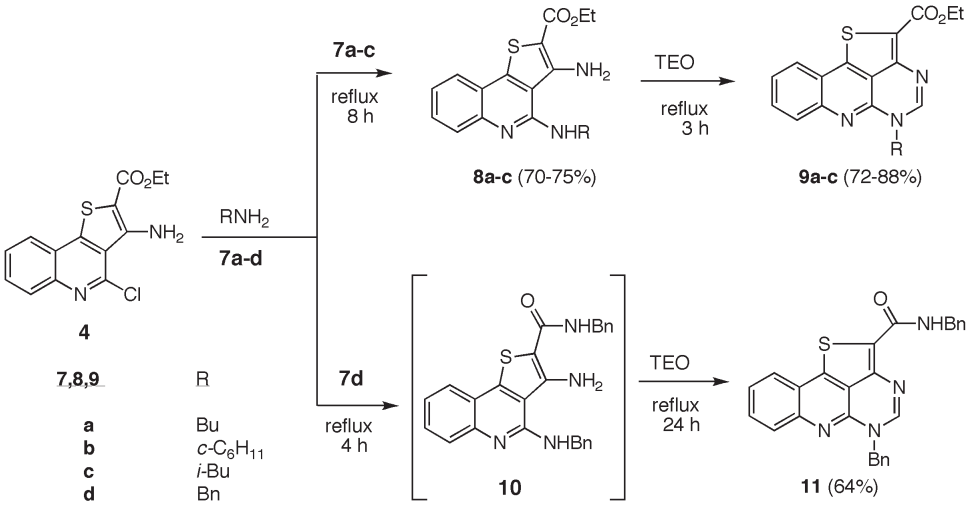
and pyrimidine moieties condensed with a quinoline nucleus. The newly synthesized perianellated tetracyclic compounds, pyrimidothienoquinolines and 1,2,3-triazinothienoquinolines, are promising targets for biological-activity evaluation studies, and to the best of our knowledge these ring systems are totally unexplored. We therefore report a novel, efficient and convenient synthesis of the first representatives, ethyl 5- alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylenes and ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylenes. The starting material is the conveniently available 2,4-dichloroquinoline-3-carbonitrile (**1**) [8]. The C-4 chlorine atom in **1** is readily displaced by nucleophiles [8,24], and reaction with ethyl mercaptoacetate (**2**) led to ethyl 3-amino-4-chlorothieno[3,2-*c*]quinoline-2-carboxylate (**4**), a precursor for the synthesis of novel tetracycles. In addition to the spectroscopic evidence for structural verification, chemical evidence was available from reaction of thienoquinoline **4** with sodium azide in DMF at 70-75 °C for 3 hours. This reaction gave the isomeric, ring-closed tetrazoloquinoline **5** rather than azidoquinolines **6**, which was consistent with formation of **4** from **1** and **2** (Scheme 1).

An interest in the pyrimido-thienoquinoline ring system **9** led us to investigate the reaction of ethyl 3-amino-4-chlorothieno[3,2-*c*]quinoline-2-carboxylate (**4**) with alkylamines **7a-d**. The resulting diaminothieno[3,2-*c*]quinolines **8a-c** were good precursors for the preparation of tetracycles **9**. Refluxing compound **4** in an excess of alkylamines **7a-c** for 8 h furnished **8a-c** as stable crystalline solids in 70-75% yield. When compounds **8a-c** were refluxed with excess of triethyl orthoformate (TEO) for 3 h, they gave ethyl 5-alkyl-5*H*-1-thia-3,5,6-triaza-aceanthrylene-2-carboxylates **9a-c** (Scheme 2). In the ^{1}H NMR spectra, the signal of the N-CH_2R attached to the pyrimidine shifted downfield in comparison with analogous signals from the N-CH_2R attached to the pyridine unit in thienoquinolines **8a-c** (see Experimental). In contrast to the other amines, when compound **4** was reacted with excess of benzylamine (**7d**), thieno[3,2-*c*]quinoline **10** was obtained as a viscous oil, which was subjected to reaction with TEO (at reflux) without further purification. Formation of **10** with benzylamine clearly involved substitution of the chlorine, and also acyl substitution with the ester unit. This behavior may be due to increased reactivity of benzylamine relative to the other amines examined, since the reaction was sluggish and required several hours to go to completion, but we did not pursue this issue. The resulting tetracyclic compound **11** was formulated to be a new derivative of 1-thia-3,5,6-triazaaceanthrylenes (Scheme 2), with this structure fully supported by analytical and spectroscopic data.

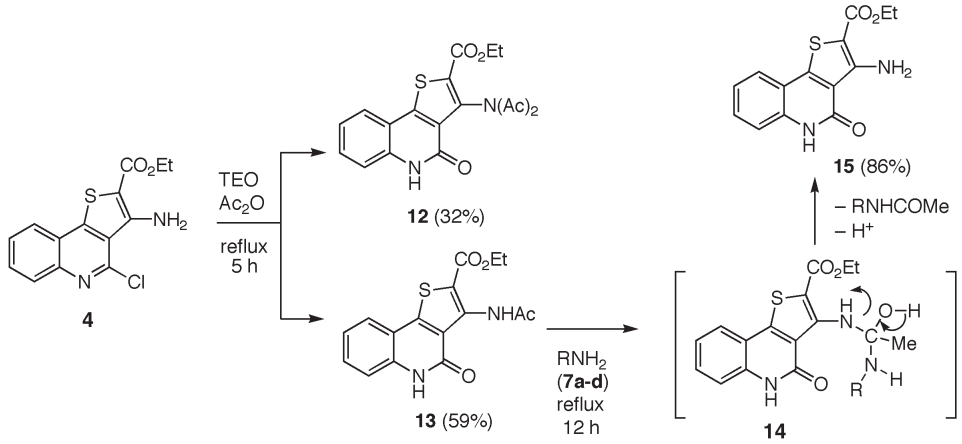
We examined the reaction of **4** with triethyl orthoformate, and found that 2-quinolones were formed, ethyl 3-(*N*,*N*-diacetylamino)-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**12**) (minor product) and the 3-acetamido analog **13** (major product). Refluxing compound **14** with excess of alkylamines **7a-d** for 12 h gave the deacetylated product, ethyl 3-amino-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**15**). Presumably, the thermal deacylation of the amides under these reaction conditions occurs *via* a highly reactive intermediate such as **14**. To the best of our knowledge, this is the first deacylation of this type reported for thieno[3,2-*c*]quinolines.

Although compound **8** was thought to be a good precursor for the synthesis of new derivatives of 1-thia-3,5,6-triazaaceanthrylenes, refluxing **8b** with excess of triethyl orthoacetate did not give the tetracylic ring system **16**. A reaction did occur, however, to give the corresponding

Scheme 2



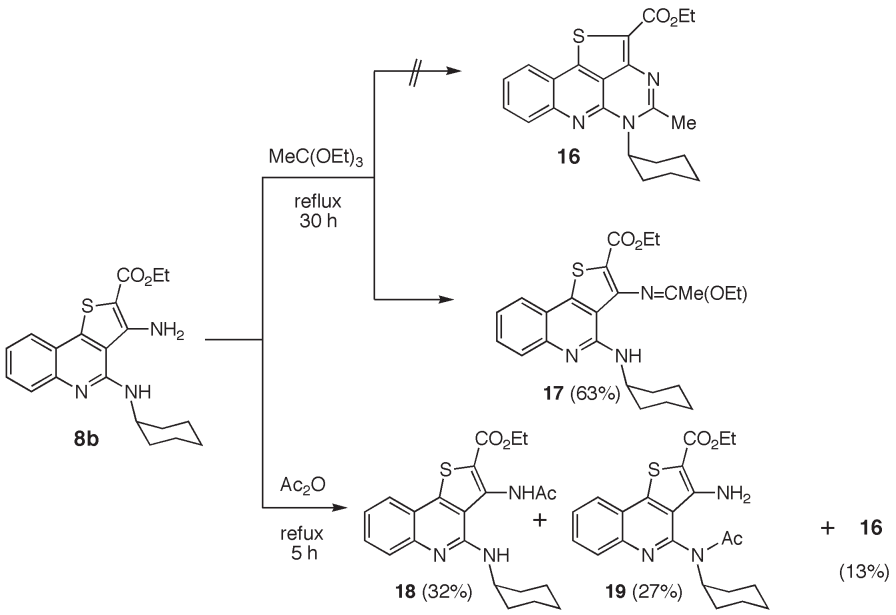
Scheme 3



thieno[3,2-*c*]quinoline derivative **17**. Refluxing compound **8b** with acetic anhydride gave several products, and three identifiable and separable compounds were isolated in a ratio of 32:27:13, in 72% yield. Compounds **18** and **19** were identified as the major components, along with a small amount of **16** (see Scheme 4). Refluxing **8a,b** with ethyl chloroformate yielded the tetracyclic ethyl 4-oxo-5-substituted-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylates, **20a,b**.

In an attempt to synthesize new derivatives related to **22**, we reacted **8a,b** with phenylisothiocyanate, in refluxing dry pyridine for 5 h, and obtained ethyl 5-substituted-4-thioxo-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylates **23a,b**. Thieno[3,2-*c*]quinolines **8** were believed to be viable precursors to the hitherto unknown tetracyclic systems that incorporated both a triazine nucleus and the thienoquinoline moiety. Indeed, reaction of **8a-c** with sodium nitrite in 70% solution of H_2SO_4 at -5 °C, gave the corresponding ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraaza-aceanthrylene-2-carboxylates **22a-c** in good yields (Scheme 5). The ^{1}H NMR spectra of compounds **22a-c** showed a characteristic downfield shift for the N-CH signals (alkyl substituents on the triazine ring) of about 0.85 ppm, when compared with the corresponding signals for the 4-alkylamino substituents in **8a-c** ($NHCH_2R$ attached to the pyridine ring), due the adjacent aza group of the triazine ring. The N-CH_2 (N-$CH_2CH_2CH_2CH_3$ on the triazine ring) for **22a** appeared at δ = 4.42 ppm, for example,

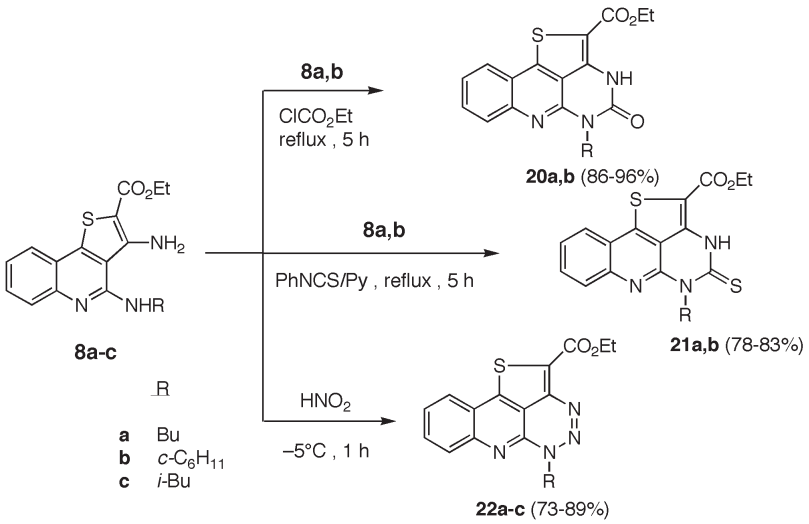
Scheme 4



compared with the N-CH_2 ($NHCH_2CH_2CH_2CH_3$ of the amino substituent attached to the pyridine ring) signal at δ = 3.53 ppm for **8a**.

In summary, this work is the sixth in a series that gives the first report of new, simple and general methodology for the construction of several 5*H*-1-thia-3,5,6-triazaaceanthrylenes and 5*H*-1-thia-3,4,5,6-tetraazaaceanthrylenes that contain various substituents at the pyrimidine ring. This route is convenient for its simplicity, availability of the starting materials, and good yields were obtained. Our use of 2,4-dichloroquinoline-3-carbonitrile (**1**) as a precursor for the synthesis of other novel tetracyclic compounds continues, and will be published in due course.

Scheme 5



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM400 spectrometer at 400 MHz with DMSO-d_6 as the solvent, and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in ppm downfield of TMS. Mass spectra were measured on a GCMS-QP1000EX mass spectrometer. Microanalyses were performed at the Microanalytical Data Unit, Cairo University. Analytical TLC was performed using silica gel 60 PF254 (Merck).

Ethyl 3-Amino-4-chlorothieno[3,2-*c*]quinoline-2-carboxylate (**4**).

Et_3N (0.363 g, 3.59 mmol) was added to stirred solution of **1** (0.20 g, 0.90 mmol) and **2** (0.108 g, 0.90 mmol) in DMF (10 mL). Stirring was continued for a further 30 min. at ambient temperature, and then poured into H_2O. The precipitated solid product was collected by filtration, washed with H_2O, dried and finally recrystallized from EtOH to give 0.270 g (98%) of compound **4** as yellowish crystals, mp: 178-18 °C; IR (KBr): ν = 3500, 3400 (NH_2), 2950 (aliph. CH), 1685 (CO, ester) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.31 (t, 3H, *J* = 7Hz, CH_3), 4.28 (q, 2H, *J* = 7Hz, CH_2), 7.12 (s, 2H, NH_2), 7.67 (t, 1H$_{arom}$, *J* = 8Hz), 7.81 (t, 1H$_{arom}$, *J* = 8Hz), 7.95 (d, 1H$_{arom}$, *J* = 8Hz), 8.12 (d, 1H$_{arom}$, *J* = 8Hz); MS: *m/z* (%) = 306/308 (M^+, 20), 278 (24), 277 (84), 234 (41), 233 (91), 194 (13), 195 (90), 170 (88), 153 (100), 126 (69), 99 (49), 45 (39), 29 (60).

Anal. Calcd. for $C_{14}H_{11}ClN_2O_2S$ (306.80): C, 54.80; H, 3.61; Cl, 11.57; N, 9.13; S, 10.45. Found: C, 54.69; H, 3.70; Cl, 11.49; N, 9.29; S, 10.33.

Tetrazoloquinolines **5**.

Sodium azide (0.252 g, 3.88 mmol) was added to a solution of **4** (0.60 g, 1.95 mmol) in DMF (15 mL) and the reaction mixture was stirred at 70-75 °C for 3 h. After cooling, the reaction mixture was poured into cold H_2O and the precipitated solid product was collected b filtration, washed well with H_2O, dried and recrystallized from DMF to afford 0.570 g (93%) of compound **5** as yellow crystals, mp: 258-259 °C; IR (KBr): ν = 3500, 3400 (NH_2), 1675 (CO, ester) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.35 (t, 3H, *J* = 7Hz, CH_3), 4.35 (q, 2H, *J* = 7Hz, CH_2), 6.91 (s, 2H, NH_2), 7.83 (t, 1H$_{arom}$, *J* = 8Hz), 7.98 (t, 1H$_{arom}$, *J* = 8Hz), 8.27 (d, 1H$_{arom}$, *J* = 8Hz), 8.63 (d, 1H$_{arom}$, *J* = 8Hz); MS: *m/z* (%) = 312 (M^+-1, 98), 284 (53), 255 (47), 239 (76), 211 (99), 184 (78), 145 (100), 130 (38), 45 (25), 29 (55).

Anal. Calcd. for $C_{14}H_{11}N_5O_2S$ (313.32): C, 53.66; H, 3.54; N, 22.35; S, 10.23. Found: C, 53.80; H, 3.73; N, 22.14; S, 10.34.

Ethyl 4-alkylamino-3-aminothieno[3,2-*c*]quinoline-2-carboxylates (**8a-c**).

General Procedure.

A solution of **4** (0.50 g, 1.63 mmol) in excess of alkylamines (**7a-c**, 10 mL) was refluxed for 8 h. After cooling, the mixture was evaporated to dryness *in vacuo*. The remaining oily residue

was triturated with EtOH. The resulting solid product was collected by filtration, washed with EtOH, dried and recrystallized from EtOH to give **8a-c**.

Ethyl 3-Amino-4-(butylamino)thieno[3,2-*c*]quinoline-2-carboxylate (**8a**) .

This compound was obtained as yellow crystals, yield: 0.390 g (70%); mp: 123-124 °C; IR (KBr): ν = 3400, 3350 (NH, NH_2), 2950, 2850 (aliph. CH), 1670 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.94 (t, 3H, *J* = 7Hz, CH_3), 1.30 (t, 3H, *J* = 7Hz, CH_3), 1.39 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 3.53 (q, 2H, *J* = 7Hz, CH_2), 4.28 (q, 2H, *J* = 7Hz, CH_2), 6.57 (t, 1H, *J* = 5Hz, NH), 6.92 (s, 2H, NH_2), 7.22 (t, $1H_{arom}$, *J* = 8Hz), 7.51-7.57 (m, $2H_{arom}$), 7.83 (d, $1H_{arom}$, *J* = 8Hz).

Anal. Calcd. for $C_{18}H_{21}N_3O_2S$ (343.43): C, 62.95; H, 6.16; N, 12.24; S, 9.34. Found: C, 63.09; H, 6.23; N, 12.39; S, 9.19.

Ethyl 3-Amino-4-(cyclohexylamino)thieno[3,2-*c*]quinoline-2-carboxylate (**8b**).

This compound was obtained as yellow crystals; yield: 0.450 g (75%), mp: 179-180 °C; IR (KBr): ν = 3450, 3350 (NH, NH_2), 2950, 2850 (aliph. CH), 1670 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.30 (t, 3H, *J* = 7Hz, CH_3), 1.34-1.44 (m, 5H, H_{aliph}), 1.61-1.75 (m, 3H, H_{aliph}), 2.04 (br, 2H, H_{aliph}), 4.20 (br, 1H, H_{aliph}), 4.28 (q, 2H, *J* = 7Hz, CH_2), 6.23 (d, 1H, *J* = 7Hz, NH), 6.80 (s, 2H, NH_2), 7.21 (t, $1H_{arom}$, *J* = 8Hz), 7.49-7.56 (m, $2H_{arom}$), 7.81 (d, $1H_{arom}$, *J* = 8Hz).

Anal. Calcd. for $C_{20}H_{23}N_3O_2S$ (369.46): C, 65.01; H, 6.27; N, 11.37; S, 8.68. Found: C, 65.19; H, 6.22; N, 11.49; S, 8.91.

Ethyl 3-Amino-4-(*iso*-butylamino)thieno[3,2-*c*]quinoline-2-carboxylate (**8c**) .

This compound was obtained as yellow crystals; yield: 0.410 g (73%), mp: 148-150 °C.; IR (KBr): ν = 3450, 3300 (NH, NH_2), 2950 (aliph. CH), 1670 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.95 (d, 6H, *J* = 7Hz, 2 x CH_3), 1.30 (t , 3H, *J* = 7Hz, CH_3), 2.07 (m, 1H, CH), 3.49 (d, 2H, *J* = 6Hz, CH_2), 4.28 (q, 2H, *J* = 7Hz, CH_2), 6.60 (t, 1H, *J* = 5Hz, NH), 6.90 (s, 2H, NH_2), 7.22 (t, $1H_{arom}$, *J* = 8Hz), 7.54 (m, $2H_{arom}$), 7.84 (d, $1H_{arom}$, *J* = 8Hz).

Anal. Calcd. for $C_{18}H_{21}N_3O_2S$ (343.43): C, 62.95; H, 6.16; N, 12.24; S, 9.34. Found: C, 63.13; H, 6.28; N, 12.36; S, 9.17.

Ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylates (**9a-c**); General procedure (Route A).

A mixture of aminothienoquinolines **8a-c** (1.35 mmol) and triethyl orthoformate (15 mL) was heated under reflux for 3 h. After concentration and cooling to ambient temperature, the resulting precipitate was collected by filtration, washed with MeOH, dried and recrystallized from DMF.

Ethyl 5-Cyclohexyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylate (**9b**) (Route B).

A solution of **8b** (0.250 g, 0.68 mmol) in acetic anhydride (5 mL) was refluxed for 5 h. After concentration and cooling to ambient temperature, the resulting solid product was chromatographed on a preparative TLC using (toluene:ethyl acetate, 8:2) as eluent to give **9b** after extraction with acetone followed by recrystallization form EtOH.

Ethyl 5-Butyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylate (**9a**).

This compound was obtained as yellow crystals; yield: 0.385 g (81%), mp: 280-282 °C; IR (KBr): ν = 2950 (aliph. CH), 1700 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.93 (t, 3H, *J* = 7Hz, CH_3), 1.31 (t, 3H, *J* = 7Hz, CH_3), 1.36 (m, 2H, CH_2) 1.78 (m, 2H, CH_2), 4.12 (t, 2H, *J* = Hz, CH_2), 4.30 (q, 2H, *J* = 7Hz, CH_2), 7.46 (t, $1H_{arom}$, *J* = 8Hz), 7.68 (t, $1H_{arom}$, *J* = 8Hz), 7.83 (d, $1H_{arom}$, *J* = 8Hz), 8.01 (d, $1H_{arom}$, *J* = 8Hz), 8.21 (s, 1H, pyrimidine CH); MS: *m/z* (%) = 352 (M^+-1, 71), 323 (15), 310 (57), 296 (54), 280 (37), 251 (55), 238 (66), 224 (100), 196 (60), 169 (21), 41 (11), 29 (25).

Anal. Calcd. for $C_{19}H_{19}N_3O_2S$ (353.42): C, 64.57; H, 5.42; N, 11.89; S, 9.07. Found: C, 64.49; H, 5.32; N, 12.02; S, 9.23.

Ethyl 5-Cyclohexyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylate (**9b**).

This compound was obtained as yellow crystals, yield: [0.370 g (72%) (route A) and 0.023 g (9%) (route B)], mp: 212-213 °C; IR (KBr): ν = 2950, 2850 (aliph. CH), 1700 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.30 (t, 3H, *J* = 7Hz, CH_3) 1.47 (m, 3H, H_{aliph}), 1.69-1.93 (m, 7H, H_{aliph}), 4.28 (q, 2H, *J* = 7Hz, CH_2), 4.84 (br t, 1H, *J* = 12Hz, H_{aliph}), 7.41 (t, $1H_{arom}$, *J* = 8Hz), 7.63 (t, $1H_{arom}$, *J* = 8Hz), 7.79 (d, $1H_{arom}$, *J* = 8Hz), 7.92 (d, $1H_{arom}$, *J* = 8Hz), 8.30 (s, 1H, pyrimidine CH); MS: *m/z* (%) = 379 (M^+, 1), 378 (M^+-1, 46), 348 (8), 305 (20), 296 (86), 251 (74), 224 (100), 196 (72), 195 (43), 169 (29), 152 (43), 83 (7), 55 (44), 41 (45), 29 (21).

Anal. Calcd. for $C_{21}H_{21}N_3O_2S$ (379.46): C, 66.47; H, 5.58; N, 11.07; S, 8.45. Found: C, 66.29; H, 5.49; N, 11.13; S, 8.63.

Ethyl 5-*iso*-Butyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylate (**9c**).

This compound was obtained as yellow crystals, yield: 0.420 g (88%), mp: 274-276 °C; IR (KBr): ν = 2950 (aliph. CH), 1700 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.05 (d, 6H, *J* = 7Hz, 2 x CH_3), 1.47 (t, 3H, *J* = 7Hz, CH_3), 2.51 (m, 1H, CH), 4.37 (d, 2H, *J* = 7Hz, CH_2), 4.51 (q, 2H, *J* = 7Hz, CH_2), 7.39 (t, $1H_{arom}$, *J* = 8Hz), 7.61 (t, $1H_{arom}$, *J* = 8Hz), 7.83 (d, $1H_{arom}$, *J* = 8Hz), 7.90 (d, $1H_{arom}$, *J* = 8Hz), 8.25 (s, 1H, pyrimidine CH); MS: *m/z* (%) = 353 (M^+, 13), 297 (18), 282 (4), 252 (7), 239 (6), 225 (100), 197 (17), 153 (7), 57 (3).

Anal. Calcd. for $C_{19}H_{19}N_3O_2S$ (353.42): C, 64.57; H, 5.42; N, 11.89; S, 9.07. Found: C, 64.73; H, 5.29; N, 11.99; S, 8.89.

5-Benzyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylic Acid Benzylamide (**11**).

A solution of **4** (1.53 g, 5 mmol) in excess of benzylamine (**7d**, 15 mL) was heated at reflux for 4 h. The mixture was evaporated to dryness *in vacuo* to give **10**, as a clear oil. Triethyl orthoformate (15 mL) was added to **10**, and the mixture was refluxed for 24 h (monitored by TLC). After concentration and cooling to ambient temperature, the resulting solid product was collected by filtration, washed with a small amount of EtOH, dried and recrystallized from DMF to afford 1.43 g (64%) of **11** as colorless crystals, mp: 239-240 °C; IR (KBr): ν = 3350 (NH), 3050 (arom. CH), 1680 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 4.81 (d, 2H, *J* = 5Hz, CH_2), 5.32 (s, 2H, CH_2), 6.98 (d, $1H_{arom}$, *J* = 8Hz), 7.21-7.73 (m, 13H, $12H_{arom}$ + pyrimidine CH), 8.09 (d, $1H_{arom}$, *J* = 8Hz), 8.32 (t, 1H, *J* = 5Hz, NH); MS: *m/z* (%) = 447 (M^+-1, 3), 432 (100), 329 (88), 301 (11), 199 (11), 106 (7), 91 (93), 77 (8).

Anal. Calcd. for $C_{27}H_{20}N_4OS$ (448.54): C, 72.30; H, 4.49; N, 12.49; S, 7.15. Found: C, 72.25; H, 4.65; N, 12.31; S, 7.24.

Ethyl 3-(*N*,*N*-Diacetylamino)-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**12**) and Ethyl 3-Acetamido-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**13**).

Triethyl orthoformate (0.965 g, 6.52 mmol) was added to a solution of **4** (0.50 g, 1.63 mmol) in Ac_2O (5 mL) and the mixture was refluxed for 5 h. After concentration and cooling to ambient temperature, the resulting solid product was chromatographed *via* preparative TLC using (toluene:acetone, 2:1 as eluent) to give two zones. Extraction with acetone followed by recrystallization from EtOH gave compounds **12** and **13**.

Ethyl 3-(*N*,*N*-Diacetylamino)-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**12**) .

This compound was obtained as colorless crystals, yield: 0.195 g (32%), mp: 320-321 °C; IR (KBr): ν = 3400 (NH), 3000 (arom. CH), 2900 (aliph. CH), 1720 (CO, ester), 1700 (CO, acetyl), 1650 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.27 (t, 3H, *J* = 7Hz, CH_3), 2.22 (s, 6H, 2 x $COCH_3$), 4.30 (q, 2H, *J* = 7Hz, CH_2), 7.29 (t, $1H_{arom}$, *J* = 8Hz), 7.43 (d, $1H_{arom}$, *J* = 8Hz), 7.59 (t, $1H_{arom}$, *J* = 8Hz), 8.01 (d, $1H_{arom}$, *J* = 8Hz), 11.89 (s, 1H, quinoline NH); MS: *m/z (%)* = 372 (M^+, 4), 330 (17), 288 (100), 260 (22), 242 (21), 216 (43), 197 (6), 188 (8), 153 (7), 142 (5), 100 (2).

Anal. Calcd. for $C_{18}H_{16}N_2O_5S$ (372.38): C, 58.05; H, 4.33; N, 7.52; S, 8.61. Found: C, 57.94; H, 4.39; N, 7.46; S, 8.79.

Ethyl 3-Acetamido-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**13**) .

This compound was obtained as colorless crystals, yield: 0.315 g (59%), mp: 313-315 °C; IR (KBr): ν = 3350 (NH), 2950, 2850 (aliph. CH), 1720 (CO, ester), 1700 (CO, acetyl), 1640 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.27 (t, 3H, *J* = 7Hz, CH_3), 2.10 (s, 3H, $COCH_3$), 4.24 (q, 2H, *J* = 7Hz, CH_2), 7.26 (t, $1H_{arom}$, *J* = 8Hz), 7.42 (d, $1H_{arom}$, *J* = 8Hz), 7.56 (t, $1H_{arom}$, *J* = 8Hz), 7.91 (d, $1H_{arom}$, *J* = 8Hz), 10.08 (s, 1H, NH at C-3), 11.94 (s, 1H, quinoline NH); MS: *m/z* (%) = 329 (M^+-1, 8), 328 (M^+-2, 48), 287 (100), 284 (18), 259 (55), 241 (58), 215 (74), 213 (38), 170 (10), 141 (10), 114 (11), 89 (7), 43 (24).

Anal. Calcd. for $C_{16}H_{14}N_2O_4S$ (330.34): C, 58.17; H, 4.27; N, 8.48; S, 9.71. Found: C, 58.10; H, 4.31; N, 8.56; S, 9.64.

Ethyl 3-Amino-4-oxo-5(4*H*)-thieno[3,2-*c*]quinoline-2-carboxylate (**15**) .

A solution of **13** (0.40 g, 1.21 mmol) in excess of alkylamines **7a-d** (10 mL) was refluxed for 12 h. After concentration and cooling to ambient temperature, the resulting solid product was collected by filtration, washed with EtOH and dried to give 0.30 g (86%) of **15**, mp: 316-318 °C; IR (KBr): ν = 3500, 3350 (NH, NH_2), 2800 (aliph. CH), 1680 (CO, ester), 1640 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.29 (t, 3H, *J* = 7Hz, CH_3), 4.26 (q, 2H, *J* = 7Hz, CH_2), 7.05 (br, 2H, NH_2), 7.25 (t, $1H_{arom}$, *J* = 8Hz), 7.39 (d, $1H_{arom}$, *J* = 8Hz), 7.56 (t, $1H_{arom}$, *J* = 8Hz), 7.82 (d, $1H_{arom}$, *J* = 8Hz), 11.90 (s, 1H, quinoline NH).

Anal. Calcd. for $C_{14}H_{12}N_2O_3S$ (288.31): C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.23; H, 3.98; N, 9.83; S, 11.28.

Ethyl 4-Cyclohexylamino-3-(2-ethoxyethyleneamino)thieno[3,2-*c*]-quinoline-2-carboxylate (**17**).

A mixture of **8b** (0.20 g, 0.542 mmol) and triethyl orthoacetate (5 mL) was refluxed for 30 h. After cooling to ambient temperature, the precipitated solid product was collected by filtration, washed with a small amount of EtOH, dried and recrystallized from EtOH to afford 0.150 g (63%) of compound **17** as colorless crystals, mp: 145-146 °C; IR (KBr): ν = 3400 (NH), 2950, 2850 (aliph. CH), 1700 (CO, ester), 1650 (conj. C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.27 (t, 3H, *J* = 7Hz, CH_3), 1.38 (t, 3H, *J* = 7Hz, CH_3), 1.44 (br, 5H, H_{aliph}), 1.60 (m, 3H, H_{aliph}), 1.90 (s, 3H, CH_3), 2.03 (br, 2H, H_{aliph}), 4.11 (q, 2H, *J* = 7Hz, CH_2), 4.26 (q, 2H, *J* = 7Hz, CH_2), 4.45 (br, 1H, H_{aliph}), 6.60 (d, 1H, *J* = 7Hz, NH), 7.22 (t, $1H_{arom}$, *J* = 8Hz), 7.55 (m, $2H_{arom}$), 7.89 (d, $1H_{arom}$, *J* = 8Hz).

Anal. Calcd. for $C_{24}H_{29}N_3O_3S$ (439.55): C, 65.58; H, 6.65; N, 9.56; S, 7.29. Found: C, 65.73; H, 6.55; N, 9.44; S, 7.35.

5*H*-1-Thia-3,5,6-triazaaceanthrylenes **16** and Thieno[3,2-*c*]-quinolines **18** and **19**.

The experimental procedure for preparation of compound **9b** was followed to give compounds **16**, **18** and **19**.

Ethyl 5-Cyclohexyl-4-methyl-5*H* -1-thia-3,5,6-triazaaceanthrylene-2-carboxylate (**16**).

This compound was obtained as yellowish crystals, yield: 0.035 g (13%), mp: 240-242 °C; IR (KBr): δ =2900, 2850 (aliph. CH), 1690 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ =1.49 (t, 3H, *J* = 7Hz, CH_3), 1.56 (m, 2H, H_{aliph}), 1.81 (m, 5H, H_{aliph}), 2.01 (m, 3H, H_{aliph}), 2.24 (s, 3H, CH_3), 4.51 (q, 2H, *J* = 7Hz, CH_2), 4.70 (br, 1H, H_{aliph}), 7.42 (t, $1H_{arom}$, *J* = 8Hz), 7.64 (t, $1H_{arom}$, *J* = 8Hz), 7.85 (d, $1H_{arom}$, *J* = 8Hz), 7.91 (d, $1H_{arom}$, *J* = 8Hz).

Anal. Calcd. for $C_{22}H_{23}N_3O_2S$ (393.48): C, 67.15; H, 5.89; N, 10.68; S, 8.15. Found: C, 66.98; H, 6.03; N, 10.77; S, 8.23.

Ethyl 3-Acetamido-4-cyclohexylaminothieno[3,2-*c*]quinoline-2-carboxylate (**18**).

This compound was obtained as colorless crystals, yield: 0.090 g (32%), mp: 238-240 °C; IR (KBr): ν = 3300 (NH), 2950, 2850 (aliph. CH), 1720 (CO, ester), 1660 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.31 (t, 3H, *J* = 7Hz, CH_3), 1.57 (m, 5H, H_{aliph}), 1.70 (m, 3H, H_{aliph}), 2.04 (s, 3H, CH_3), 2.16 (m, 2H, H_{aliph}), 4.24 (br, 1H, H_{aliph}), 4.31 (q, 2H, *J* = 7Hz, CH_2), 6.24 (d, 1H, *J* = 7Hz, NH), 7.98 (t, $1H_{arom}$, *J* = 8Hz), 7.89 (t, $1H_{arom}$, *J* = 8Hz), 8.13 (d, $1H_{arom}$, *J* = 8Hz), 8.38 (d, $1H_{arom}$, *J* = 8Hz), 9.68 (s, 1H, NH); MS: *m/z* (%) = 412 (M^++1, 9), 411 (M^+, 25), 410 (100), 364 (20), 356 (53), 314 (21), 269 (19), 239 (20), 197 (10), 128 (3), 83 (8), 55 (20).

Anal. Calcd. for $C_{22}H_{25}N_3O_3S$ (411.50): C, 64.21; H, 6.12; N, 10.21; S, 7.79. Found: C, 64.38; H, 5.98; N, 10.29; S, 7.99.

Ethyl 3-Amino-4-(*N*-acetyl, *N*-cyclohexylamino)thieno[3,2-*c*]quinoline-2-carboxylate (**19**).

This compound was obtained as yellowish crystals, yield: 0.075 g (27%), mp: 220-222 °C; IR (KBr): ν = 3400, 3250 (NH_2), 2900, 2850 (aliph. CH), 1700 (CO, ester), 1680 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.39 (t, 3H, *J* = 7Hz, CH_3), 1.49-1.67 (m, 8H, H_{aliph}), 2.16 (m, 2H, H_{aliph}), 2.28 (s, 3H, CH_3), 4.30 (br, 1H, H_{aliph}), 4.43 (q, 2H, *J* = 7Hz, CH_2), 7.0 (s, 2H, NH_2), 7.20 (t, $1H_{arom}$, *J* = 8Hz), 7.52 (t, $1H_{arom}$, *J* = 8Hz), 7.69 (d, $1H_{arom}$, *J* = 8Hz), 7.81 (d, $1H_{arom}$, *J* = 8Hz), MS: *m/z* (%) = 411 (M^+, 19), 364 (2), 329 (100), 314 (78), 287 (23), 286 (11), 266 (19), 252 (18), 239 (22), 215 (30), 197 (13), 128 (7), 82 (2), 55 (25).

Anal. Calcd. for $C_{22}H_{25}N_3O_3S$ (411.50): C, 64.21; H, 6.12; N, 10.21; S, 7.79. Found: C, 64.29; H, 6.31; N, 10.13; S, 7.62.

Ethyl 4-Oxo-5-substituted-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylates (**20a,b**); General Procedure.

A mixture of **8a,b** (1.46 mmol) and ethyl chloroformate (10 mL) was refluxed for 5 h (monitored by TLC). After concentration and cooling to ambient temperature, the resulting solid product was collected by filtration, washed with a small amount of MeOH, dried and recrystallized from DMF to afford **20a,b**.

Ethyl 5-Butyl-4-oxo-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylate (**20a**).

This compound was obtained as colorless crystals, yield: 0.465 g (86%), mp: 223-225 °C; IR (KBr): ν = 3200 (NH), 2950 (aliph. CH), 1680 (CO, ester), 1640 (CO, amide) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.94 (t, 3H, *J* = 7Hz, CH_3), 1.32 (t, 3H, *J* = 7Hz, CH_3), 1.38 (m, 2H, CH_2), 1.68 (m, 2H, CH_2), 4.14 (t, 2H, *J* = 7Hz, CH_2), 4.34 (q, 2H, *J* = 7Hz, CH_2), 7.48 (t, $1H_{arom}$, *J* = 8Hz), 7.70 (t, $1H_{arom}$, *J* = 8Hz), 7.84 (d, $1H_{arom}$, *J* = 8Hz), 8.0 (d, $1H_{arom}$, *J* = 8Hz), 10.32 (s, 1H, pyrimidine NH); MS: *m/z* (%) = 368 (M^+-1, 7) 367 (M^+-2, 88), 326 (81), 312 (99), 297 (74), 279 (67), 266 (61), 251 (80), 240 (100), 196 (68), 169 (37), 170 (14), 152 (57), 125 (23), 41(32), 29 (52).

Anal. Calcd. for $C_{19}H_{19}N_3O_3S$ (369.42): C, 61.77; H, 5.18; N, 11.37; S, 8.68. Found: C, 61.55; H, 5.25; N, 11.22; S, 8.72.

Ethyl 5-Cyclohexyl-4-oxo-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylate (**20b**).

This compound was obtained as yellowish crystals, yield: 0.550 g (96%), mp: 248-250 °C; IR (KBr): ν = 3300 (NH), 2900, 2850 (aliph. CH), 1680 (CO, ester), 1640 (CO, amide) $cm^{-;}$ ^1H NMR (DMSO-d_6): δ = 1.31 (t, 3H, *J* = 7Hz, CH_3); 1.37-1.46 (m, 5H, H_{aliph}), 1.63-1.78 (m, 3H, H_{aliph}), 2.07 (m, 2H, H_{aliph}), 4.23 (br, 1H, H_{aliph}), 4.31 (q, 2H, *J* = 7Hz, CH_2), 7.51 (t, $1H_{arom}$, *J* = 8Hz), 7.73 (t, $1H_{arom}$, *J* = 8Hz), 7.89 (d, $1H_{arom}$, *J* = 8Hz), 8.04 (d, $1H_{arom}$, *J* = 8Hz), 10.20 (s, 1H, pyrimidine NH).

Anal. Calcd. for $C_{21}H_{21}N_3O_3S$ (395.46): C, 63.78; H, 5.35; N, 10.63; S, 8.11. Found: C, 63.59; H, 5.49; N, 10.57; S, 7.94.

Ethyl 5-Substituted-4-thioxo-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylates **21a,b**; General Procedure .

Phenyl isothiocyanate (0.472 g, 3.50 mmol) was added to a solution of **8a,b** (1.75 mmol) in pyridine (15 mL). The mixture was refluxed for 5 h. After concentration and cooling to ambient temperature, the precipitated solid product was collected by filtration, washed with ethanol, dried and recrystallized from $CHCl_3$ to give **21a,b**.

Ethyl 5-Butyl-4-thioxo-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylate (**21a**).

This compound was obtained as yellow crystals, yield: 0.560 g (83%), mp: 204-206 °C; IR (KBr): ν = 3400 (NH), 2950, 2850 (aliph. CH), 1710 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.98 (t, 3H, *J* = 7Hz, CH_3), 1.36 (t, 3H, *J* = 7Hz, CH_3), 1.44 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 4.36 (q, 2H, *J* = 7Hz, CH_2), 4.63 (t, 2H, *J* = 7Hz, CH_2), 7.54 (t, $1H_{arom}$, *J* = 8Hz), 7.71 (t, $1H_{arom}$, *J* = 8Hz), 7.88 (d, $1H_{arom}$, *J* = 8Hz), 8.01 (d, $1H_{arom}$, *J* = 8Hz), 10.15 (s, 1H, pyrimidine NH); MS: *m/z* (%) = 385 (M^+, 16), 340 (3), 329 (37), 312 (3), 311 (8), 283 (100), 255 (10), 229 (3), 197 (13), 196 (14), 182 (3), 126 (5).

Anal. Calcd. for $C_{19}H_{19}N_3O_2S_2$ (385.48): C, 59.20; H, 4.97; N, 10.90; S, 16.63. Found: C, 59.01; H, 5.12; N, 10.79; S, 16.55.

Ethyl 5-Cyclohexyl-4-thioxo-1-thia-4(3*H*)-3,5,6-triazaaceanthrylene-2-carboxylate (**21b**).

This compound was obtained as yellow crystals, yield: 0.560 g (78%), mp: 246-248 °C; IR (KBr): ν = 3400 (NH), 2900, 2850 (aliph. CH), 1680 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.36 (t, 3H, *J* = 7Hz, CH_3), 1.74-1.90 (m, 8H, H_{aliph}), 3.02 (m, 2H, H_{aliph}), 4.37 (q, 2H, *J* = 7Hz, CH_2), 5.96 (br t, 1H, *J* = 11Hz, H_{aliph}), 7.55 (t, $1H_{arom}$, *J* = 8Hz), 7.76 (t, $1H_{arom}$, *J* = 8Hz), 7.94 (d, $1H_{arom}$, *J* = 8Hz), 8.02 (d, $1H_{arom}$, *J* = 8Hz), 10.16 (s, 1H, pyrimidine NH); MS: *m/z* (%) = 411 (M^+, 7), 329 (72), 283 (100), 257 (10), 229 (3), 197 (10), 196 (13), 183 (4), 55 (13).

Anal. Calcd. for $C_{21}H_{21}N_3O_2S_2$ (411.52): C, 61.29; H, 5.14; N, 10.21; S, 15.58. Found: C, 61.40; H, 5.06; N, 10.13; S, 15.41.

Ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylates (**22a-c**);

General Procedure.

Aqueous $NaNO_2$ (5.25 mmol in 2 mL) was added (dropwise) to a solution of thienoquinolines **8a-c** (1.75 mmol) in H_2SO_4 (5 mL, 70%), cooled in ice-salt to -10 °C, while the temperature of the reaction mixture was maintained at -10 °C to -5 °C. The reaction mixture was kept at -5 °C for 1 h and then poured into ice/H_2O. The precipitated solid product was collected by filtration, washed well with H_2O, dried and recrystallized from EtOH to afford the corresponding tetracycles **22a-c**.

Ethyl 5-Butyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylate (**22a**) .

This compound was obtained as orange crystals, yield: 0.480 g (77%), mp: 162-164 °C; IR (KBr): ν = 2950 (aliph. CH), 1690 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.94 (t, 3H, *J* = 7Hz, CH_3), 1.34 (t, 3H, *J* = 7Hz, CH_3), 1.41 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 4.35 (q, 2H, *J* = 7Hz, CH_2), 4.42 (t, 2H, *J* = 7Hz, CH_2), 7.44 (t, $1H_{arom}$, *J* = 8Hz), 7.66 (t, $1H_{arom}$, *J* = 8Hz), 7.78 (d, $1H_{arom}$, *J* = 8Hz), 7.95 (d, $1H_{arom}$, *J* = 8Hz); MS: *m/z* (%) = 354 (M^+, 66), 353 (M^+-1, 59), 310 (100), 296 (33), 283 (32), 268 (28), 256 (48), 228 (48), 227 (51), 211 (56), 183 (28), 140 (73), 70 (8), 29 (29).

Anal. Calcd. for $C_{18}H_{18}N_4O_2S$ (354.40): C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 60.94; H, 5.23; N, 15.67; S, 9.23.

Ethyl 5-Cyclohexyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylate (**22b**).

This compound was obtained as orange crystals, yield: 0.595 g (89%), mp: 228-230 °C; IR (KBr): ν = 2900, 2850 (aliph. CH), 1680 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.34 (t, 3H, *J* = 7Hz, CH_3), 1.42-2.08 (m, 10H, H_{aliph}), 4.38 (q, 2H, *J* = 7Hz, CH_2), 5.05 (m, 1H, H_{aliph}), 7.49 (t, $1H_{arom}$, *J* = 8Hz), 7.70 (t, $1H_{arom}$, *J* = 8Hz), 7.87 (d, $1H_{arom}$, *J* = 8Hz), 8.05 (d, $1H_{arom}$, *J* = 8Hz).

Anal. Calcd. for $C_{20}H_{20}N_4O_2S$ (380.44): C, 63.14; H, 5.30; N, 14.73; S, 8.43. Found: C, 63.24; H, 5.43; N, 14.63; S, 8.64.

Ethyl 5-*iso*-Butyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylate (**22c**).

This compound was obtained as orange crystals, yield: 0.450 g (73%), mp: 192-194 °C; IR (KBr): ν = 2950 (aliph. CH), 1680 (CO, ester) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.01 (d, 6H, *J* = 7Hz, 2 x CH_3), 1.37 (t, 3H, *J* = 7Hz, CH_3), 2.41 (m, 1H, CH), 4.31 (d, 2H, *J* = 7Hz, CH_2), 4.40 (q, 2H, *J* = 7Hz, CH_2), 7.50 (t, $1H_{arom}$, *J*

= 8Hz), 7.71 (t, 1H$_{arom}$, *J* = 8Hz), 7.86 (d, 1H$_{arom}$, *J* = 8Hz), 8.04 (d, 1H$_{arom}$, *J* = 8Hz); MS: *m/z* (%) = 354 (M^+, 6), 353 (M^+-1, 92), 324 (26), 310 (69), 296 (25), 282 (47), 256 (38), 255 (100), 237 (28), 227 (98), 211 (68), 183 (64), 182 (73), 155 (14), 140 (28), 139 (97), 138 (45), 43 (40), 41 (37), 29 (55).

Anal. Calcd. for $C_{18}H_{18}N_4O_2S$ (354.40): C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 61.13; H, 5.02; N, 16.03; S, 9.19.

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