Heteroatom Chemistry
Volume 15, Number 7, 2004

Studies with Condensed Amino-thiophenes: Further Investigation of Reactivity of Amino-thieno-coumarines and Amino-thieno-benzo[h]coumarines toward Electron-Poor Olefins and Acetylenes

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Received 8 March 2004

ABSTRACT: *The reaction of 3-amino-5-oxa-2-thiacyclopenta[a]naphthalene-4-one* **2b** *with substituted acetylenes afforded C-1 alkylation products. On the other hand, reaction of 17-amino-15-methyl-11-oxa-16-thiacyclopenta[a]phenanthrene-12-one* **5** *with substituted acetylenes and electron-poor olefins afforded the condensed thienopyridine derivatives* **7** *and* **11a–c**. *The reaction of* **5** *with acrylonitrile and with 4-phenyl-1,2,4-triazoline-3,5-dione afforded compounds* **13** *and* **21** *with loss of H_2S via the expected [4 + 2] cycloaddition sequence.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:502–507, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20047

INTRODUCTION

The [4 + 2] cycloaddition of electron-poor olefins to condensed aminothiophenes (**1**), obtained via reacting alkylheteroaromatic carbonitriles with sulfur [1,2], has proved to be an efficient route to benzo-fused heteroaromatic amines [3,4]. This reaction is presumed to involve the formation of a cycloadduct that loses H_2S (Scheme 1).

Some times ago Döpp et al. [5] have proposed the formation of thiepin **3a** ($R_1 = CO_2Me$) from reaction of **2a** with dimethylacetylene dicarboxylate (Scheme 2). Later our group has reported as well the formation of similar thiepins [6] **3b–c** by reaction of condensed thiophenes **2b–c** with acetylenic esters. Al-Omran et al. [7,8] also claimed the formation of thiepins on reacting with other condensed aminothiophenes and dimethyl acetylenedicarboxylate (Scheme 2).

However, we observed the formation of C-1 alkylation products on the thiophene moiety upon reacting **2b** with enaminones, ϖ-nitrostyrene, and ethoxymethylenemalononitrile derivatives [9].

In the light of this last finding and in the light of well-accepted thermal instability of thiepins [5], we have decided to look further into the structure of thiepins claimed to be formed in the previous work [6] as a part of continued investigation on reactivity of condensed thiophenes toward olefins and acetylenes.

Compound **2b** reacted with ethyl propiolate at room temperature to yield 1:1 adduct that has been

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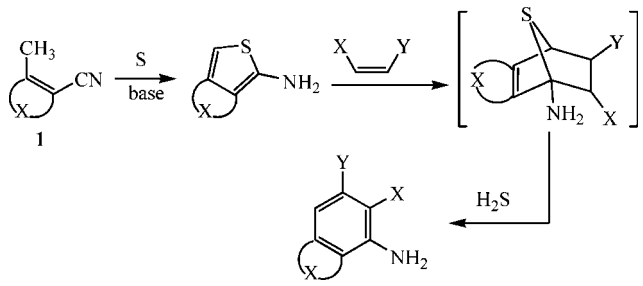


SCHEME 1

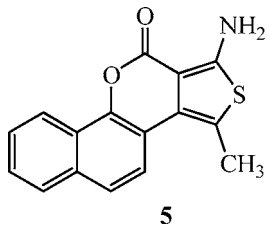


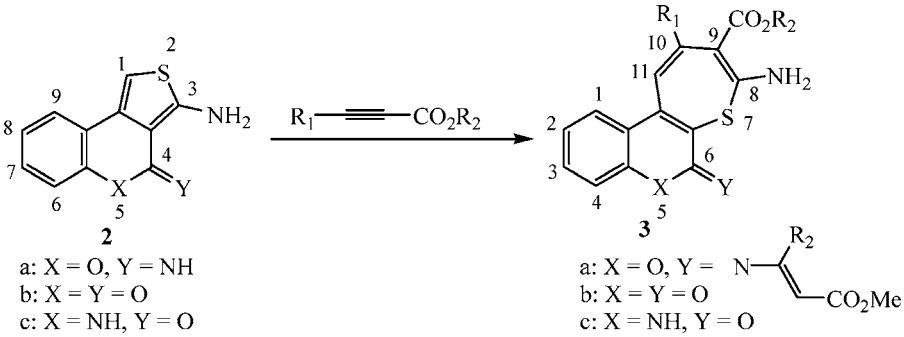
FIGURE 1

earlier assumed to be a thiepinochromone ($R_1 = H$) one **3b**. High-resolution ^{1}H NMR of this product indicated the presence of two *trans*-coupled olefinic protons at $\delta = 5.90$ and 8.23 ppm $J = 13.7$ Hz. Clearly these cannot be assigned for H-10 and H-11 protons of a thiepin ring. Furthermore, irradiation of the ^{1}H NMR signal, as previously described, at $\delta = 8.23$ ppm, produced NOE enhancements at $\delta = 5.90$ ppm along with the aromatic protons at $\delta = 7.93$ ppm. These results may be attributed to the space interaction between the two trans-olefenic protons H-9 of the C-1 alkylation of thienochromone **4** (Scheme 3) rather than what was assumed to be between H-10 and H-11 protons of the thiepinochromone **3b**. In order to eliminate possible C-1 alkylation, compound **5** was synthesized, in which C-1 is substituted by a methyl group, utilizing recently reported approach [8] (Figure 1). Thus, reaction of **5** with dimethyl acetylenedicarboxylate in refluxing xylene afforded, in contrast to the reported thiepin formation, a product of addition and subsequent water elimination. On the other hand, a 1 : 1 adduct was obtained on reaction of **5** with dimethyl acetylenedicarboxylate in refluxing dimethylformamide (Scheme 4).

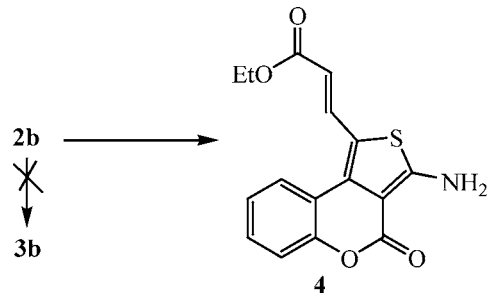
The ^{1}H NMR and IR spectra of product of reaction in refluxing DMF indicated the absence of NH_2 signal for the amino function, indicating that this product is not the claimed thiepin. We thus assumed structure **7** for this reaction product. It is assumed that **5** reacts with dimethylacetylene dicarboxylate in dimethyl formamide to yield initially **6** that rearranges into **7**. The structure of the thieno[2,3-b]-pyridine **7** was favored over **6** based on spectroscopic data in which the ^{1}H NMR revealed two D_2O exchangeable protons at $\delta = 8.62$ and 11.42 ppm for the NH and the OH group. On long reflux in xylene, compound **7** cyclized to furnish compound **8** in good yield. This same product has been found identical with product of reaction of **5** with DMAD in refluxing xylene.

Compound **5** also reacted with enaminones **9a–c** to yield product that may be formulated as **10a–c** or isomeric **11a–c**. Structure **11** was established based on ^{13}C NMR that revealed the absence of any sp3 carbon other than those for the methyl substituent (Scheme 5).

Similar to the expected behavior of condensed aminothiophenes, compound **5** reacted with acrylonitrile to yield the benzofused derivative, which may be assigned structure **13** or **14** (Scheme 6). Structure **13** was established for this reaction product based on ^{1}H NMR, which revealed the absence of aromatic signal at $\delta \approx 7.5$ ppm that is expected for structure **14**. Compound **13** condenses with dimethylformamide dimethylacetal yielding **15**. Attempted cyclization of **15** into **16** failed. Refluxing



SCHEME 2



SCHEME 3

15 with hydrazine hydrate afforded a product that may be formulated as **17** or **18**. Structure **17** was confirmed based on stability of reaction product on reflux in a mixture of EtOH/HCl, a condition that should hydrolyze an amidrazone.

The reaction of **5** with 4-phenyl-1,2,4-triazoline-3,5-dione **19** afforded product of addition and H_2S elimination to yield **21**. To our knowledge this is first reported addition of heterodienophile to condensed aminothiophene. This reaction is now being explored and will be subject to further communication (Scheme 7).

EXPERIMENTAL

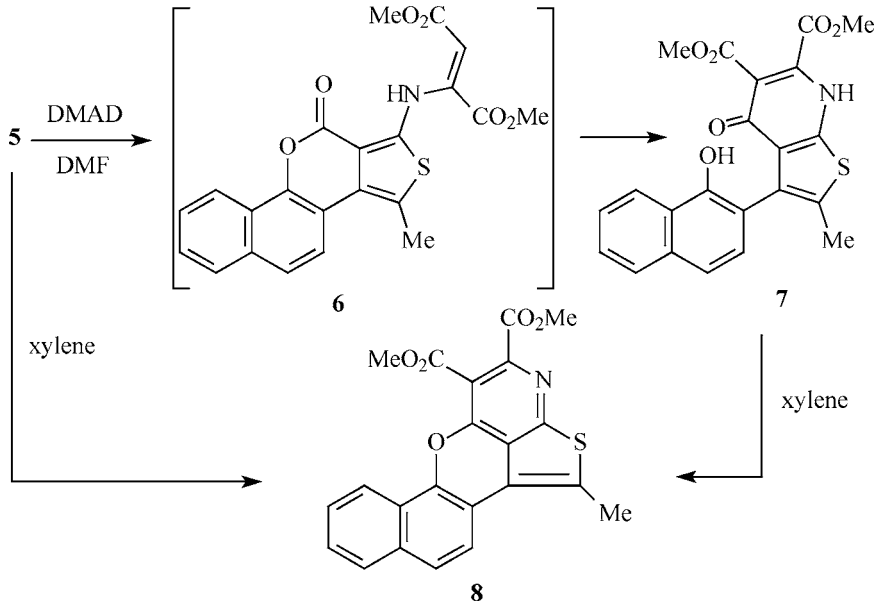
General

All melting points are uncorrected. IR spectra were recorded in KBr with a FT IR-820 IPC spectrophotometer Shimadzu (ν, cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian EM-390 300 MHz spectrometer in [$^2H_6$]DMSO as solvent and TMS as internal reference; chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. At 70 eV, microanalyses were performed on LECO CHNS-932. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

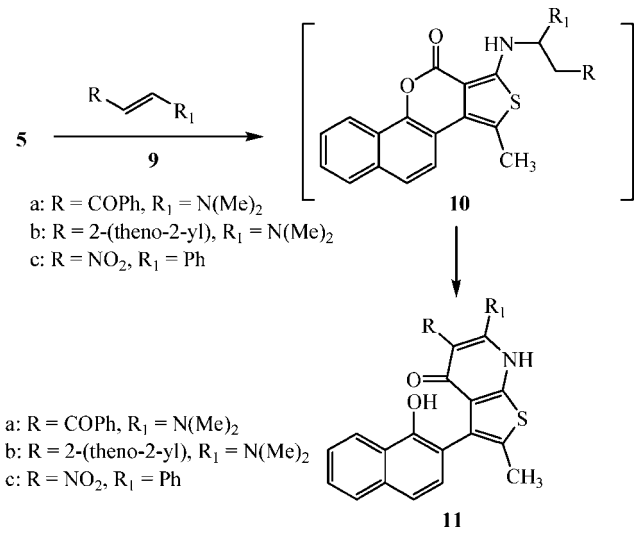
Ethyl (2E) 3-(3-amino-4-oxo-4H-thieno[3,4-c]-chromene-1-yl)-acrylate **4**

A mixture of each of **2b** (2.17 g, 10 mmol) and ethyl propiolate (1.70 g, 12 mmol) in dioxane was treated under reflux for 8 h. The reaction mixture was evaporated under vacuum till half of its volume, the solid product, so formed, was collected by filtration and crystallized from DMF.

Yield: 2.50 g (79%); mp 284–286°C (decompose). ν_{max} (KBr) 3415 and 3330 (NH_2), 1720 (ester CO) and 1662 cm^{-1} (ring CO). MS (EI, 70 eV): $m/z = 315$ (M^+). δ_H 1.26 (t, 3H, CH_3, $J = 6.8$ Hz), 4.19 (q, 2H, OCH_2, $J = 6.8$ Hz), 5.90 (d, 1H, H-2, $J = 13.7$ Hz), 7.21–7.82 (m, 3H, arom. H), 7.92–7.94 (m, 3H, arom. H), 8.23 (d, 1H, H-3, $J = 13.7$ Hz), and 8.34 ppm (br, 2H, NH2). $-\delta_C$ 166.23 (ester CO), 166.05 (C-6), 159.04 (C-4), 133.40, 135.33, 132.95, 130.43, 125.50, 124.80, 117.98, 117.70, 114.11, and 111.86 (ring carbons), 110.50 (C-3), 59.85 (OCH_2) and 14.22 (CH_3). $C_{16}H_{13}NO_4S$ (315.27): requires C 60.95, H 4.16, N 4.44, S 10.15; found C 60.73, H 4.20, N 4.48, S 10.32.



SCHEME 4



SCHEME 5

Dimethyl 3-(1-hydroxynaphthalen-2-yl)-2-methyl-4-oxo-4,7-dihydro-thieno[2,3-b] pyridine-5,6-dicarboxylate **7**

A mixture of **5** (2.81 g, 10 mmol) and dimethylacetylene dicarboxylate (1.42 g, 10 mmol) in DMF (10 mL) was treated under reflux for 5 h. The reaction mixture was evaporated under vacuum till half of its volume, the solid product, so formed, was collected by filtration and crystallized from DMF.

Yield: 3.20 g (76%); mp > 300°C. ν_{max} (KBr) 3444 (OH), 2952 (NH), 1728 br. cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 423$ (M^+). δ_H 2.65 (s, 3H, CH_3), 3.88 (s, 6H, OCH_3), 7.90 (m, 6H, arom. H), 8.62 (br s, 1H, NH D_2O exchangeable), 11.42 (s, 1H, OH D_2O exchangeable). δ_C 180.8 (CO), 167.2 (ester CO), 166.1 (ester CO), 164.5 (C-6), 150.7 (C—OH), (141.5, 140.1, 139.5, 137.5 C-thiophene ring), 135.6, 127.5, 126.5, 126.1, 125.1, 124.5, 122.4, 119.1, (C-5), 116.8, 51.5 (OCH_3), 50.7 (OCH_3) and 14.1 (CH_3). $C_{16}H_{13}NO_4S$ (315.27): requires C 60.95, H 4.16, N 4.44, S 10.15; found C 60.73, H 4.20, N 4.48, S 10.32. -$C_{22}H_{17}NO_6S$ (423.36): requires C 62.41, H 4.05, N 3.31, S 7.55; found C 62.56, H 3.86, N 3.36, S 7.42.

Dimethyl 1-methyl-6-oxa-2-thia-3-aza-benzo[j]aceanthrylene-4,5-dicarboxlyate **8**

Compound **7** (2 g) was refluxed in xylene (10 mL) for 4 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from dioxane/ethanol 3 : 1 by volume. Yield: 3.32 g (82%); mp 218–220°C (decompose). ν_{max} (KBr) 1709 br. cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 405$ (M^+). δ_H 2.73 (s, 3H, CH_3), 3.96 (s, 6H, OCH_3), 7.8 (m, 6H, arom. H). δ_C 170.2 (ester CO), 168.1 (ester CO), 160.7, 157.1, 149.8, 141.5, 134.4, 127.2, 123.1, 122.7, 121.6, 126.1, 116.6, 51.2 (OCH_3), 50.5 (OCH_3) and 18.1 (CH_3). $C_{16}H_{13}NO_4S$ (315.27): requires C 60.95, H 4.16, N 4.44, S 10.15; found C 60.73, H 4.20, N 4.48, S 10.32. $C_{22}H_{15}NO_5S$ (405.35): requires C 65.18, H 3.73, N 3.46, S 7.89; found C 64.98, H 3.67, N 3.49, S 7.72.

General Procedure for the Preparation of **11a,b**

A solution of compound **5** (2.81 g, 10 mmol) in DMF/acetic acid (30 mL) (4 : 1) by volume was treated with each of enaminones **9a, b** (10 mmol). The reaction mixture was heated under reflux for 3 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from DMF/ethanol.

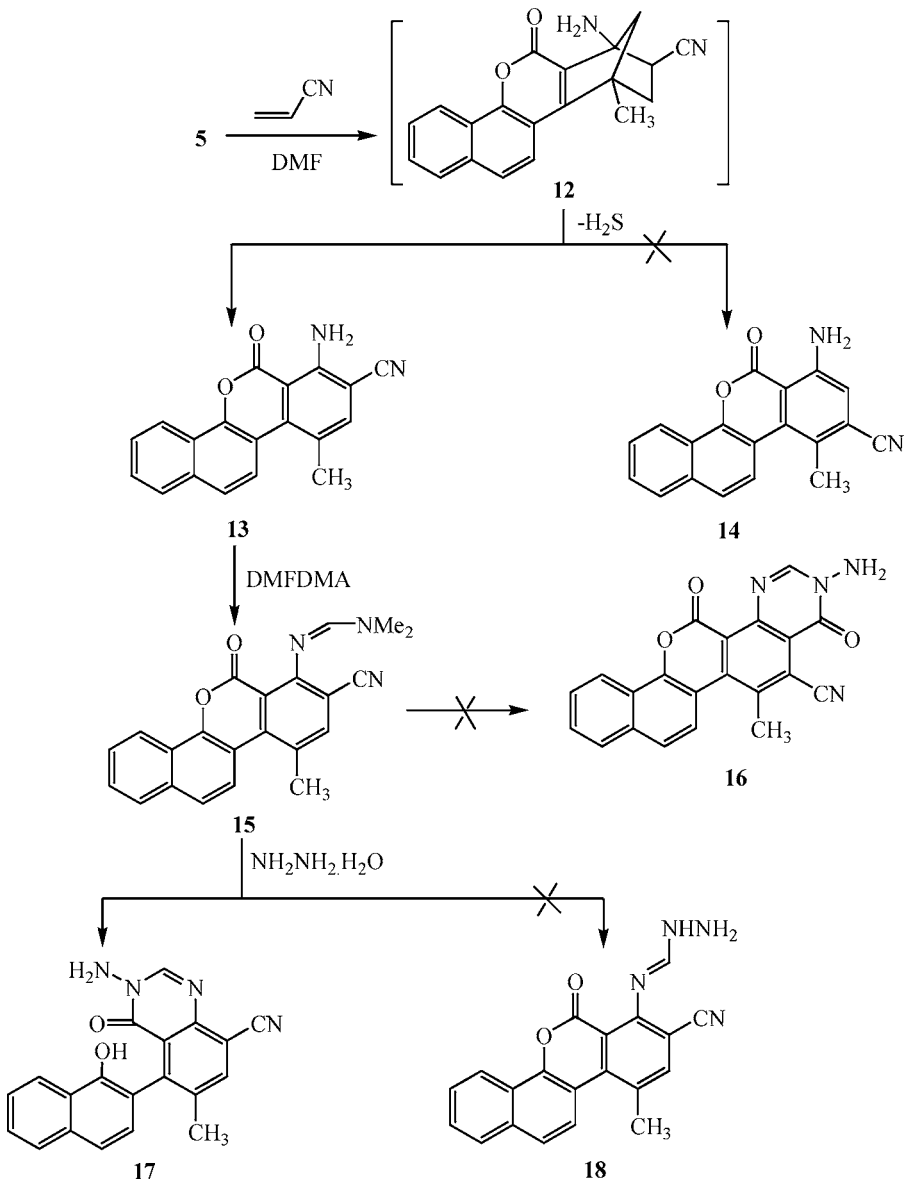
5-Benzoyl-3-(1-hydroxynaphthalen-2-yl)-2-methyl-7H-thieno[2,3-b]pyridin-4-one **11a**. Yield: 3.0 g (73%); mp 302–305°C (decompose) ν_{max} (KBr) 3434 (OH), 3278 (NH), 1709 and 1681 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 411$ (M^+). δ_H 2.77 (s, 3H, CH_3), 7.6 (m, 3H, arom. H), 7.82–7.84 (m, 5H, arom. H), 8.0 (m, 3H, arom. H), 8.29 (br s, 1H, NH D_2O exchangeable), 8.46 (s, 1H, pyridyl H-6), 11.43 (s, 1H, OH D_2O exchangeable). δ_C 186.5 (CO benzoyl), 181.8 (CO), 159.3 (C-6), 151.6 (C—OH), 141.1, 139.2, 138.9, 138.5, 137.7, 135.6, 134.5, 129.6, 129.3, 128.9, 128.5, 127.6, 126.6, 126.5, 126.1, 125.8, 122.2, 118.8, 116.7, 14.2 (CH_3). $C_{25}H_{17}NO_3S$ (411.39): requires C 72.98, H 4.17, N 3.41, S 7.78; found C 73.01, H 3.98, N 3.52, S 7.91.

3-(1-Hydroxynaphthalen-2-yl)-2-methyl-5-(thieno-2-yl)-7H-thieno[2,3-b]pyridin-4-one **11b**. Yield: 2.80 g (68%); mp 238–240°C (decompose) ν_{max} (KBr) 3428 (OH), 3288 (NH), 1708 and 1685 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 417$ (M^+). δ_H (300 MHz, DMSO-d_6) 2.66 (s, 3H, CH_3), 7.8 (m, 9H, arom. H), 8.2 (br s, 1H, NH D_2O exchangeable), 8.53 (s, 1H, pyridyl H-6), 11.44 (s, 1H, OH D_2O exchangeable). δ_C 181.8 (CO), 179.9 (CO thenyl), 160.3 (C-6), 150.9 (C—OH), 146.5, 140.2, 139.1, 138.5, 137.8, 137.1, 136.7, 136.1, 135.6, 129.5, 127.8, 126.5, 126.2, 125.1, 124.8, 118.1, 117.6, 15.1 (CH_3). $C_{23}H_{15}NO_3S_2$ (417.36): calcd C 66.19, H 3.62, N 3.36, S 15.33; found C 66.21, H 3.62, N 3.49, S 15.21.

3-(1-Hydroxy-naphthalen-2-yl)-2-methyl-5-nitro-6-phenyl-7H–thieno[2,3-b]pyridin-4-one **11c**

Similar reaction condition as for compounds **11a**–**b** but using ϖ-nitrostyrene **9c** (1.49 g, 10 mmol). The target product **11c** was crystallized from dioxane.

Yield: 3.0 g (70%); mp > 300°C. ν_{max} (KBr) 3425 (OH), 3286 (NH), 1685 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 428$ (M^+). δ_H (300 MHz, DMSO-d_6) 2.65 (s, 3H,



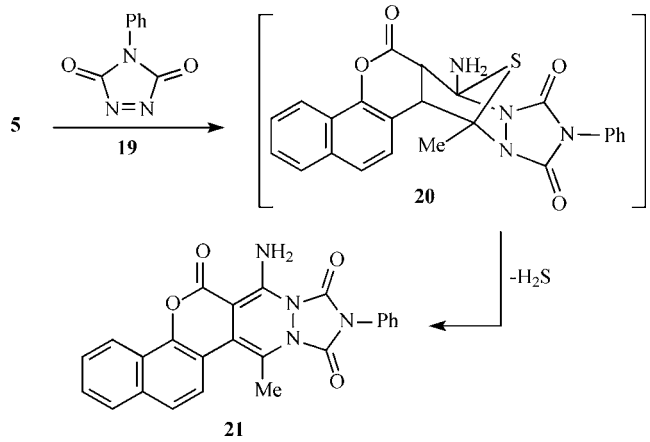
SCHEME 6

CH_3), 7.6 (m, 5H, arom. H), 7.8 (m, 5H, arom. H), 8.2 (m, 1H, arom. H), 8.38 (br s, 1H, NH), 1143 (s, 1H, OH). δ_C 181.8 (CO), 161.9 (C-6), 150.7 (C—OH), 142.1, 139.9, 138.7, 138.1, 136.1, 135.6, 128.2, 128.4, 127.9, 126.8, 126.4, 126.1, 125.2, 124.5, 122.2, 121.4, 117.7, 115.6, 13.8 (CH_3). $C_{24}H_{16}N_2O_4S$ (428.38): calcd C 67.29, H 3.76, N 6.54, S 7.47; found C 6.10, H 3.81, N 6.41, S 7.32.

7-Amino-10-methyl-6-oxo-6H-dibenzo[c,h]-chromene-8-carbonitrile **13**

A solution of compound **5** (2.81 g, 10 mmol) in DMF (20 mL) was treated with acrylonitrile (0.52 g, 10 mmol). The reaction mixture was heated under reflux for 3 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from dioxane/ethanol.

Yield: 2.35 g (78%); mp 178–290°C (decompose). ν_{max} (KBr) 3428 and 3327 (NH_2), 2213 (CN), 1694 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 300$ (M^+). δ_H 2.71 (s, 3H, CH_3), 7.8 (m, 7H, arom. H), 8.3 (m, 2H, NH_2 D_2O exchangeable). δ_C 166.4 (CO), 152.1, 150.2, 146.1, 139.5, 135.5, 128.1, 127.2, 126.8, 126.4, 124.7, 122.2, 121.8, 117.7, 116.9, 117.5 (CN), 99.8, 16.8 (CH_3). $C_{19}H_{12}N_2O_2$(300.30): requires C 75.99, H 4.03, N 9.33; found C 75.82, H 3.92, N 9.20.



SCHEME 7

N′-(8-Cyano-10-methyl-6-oxo-6H-dibenzo[c,h]chromen-7-yl)-N,N-dimethyl-formamidine **15**

A solution of compound **13** (3 g, 10 mmol) and *N,N*-dimethylformamide dimethylacetal (1,46 g, 11 mmol) in dioxane (30 mL) was refluxed for 4 h. The solid product obtained upon cooling was recrystallized from dioxane.

Yield: 2.8 g (79%); mp 250–252°C (decompose). ν_{max} (KBr) 2224 (CN), 1733 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 355$ (M^+). δ_H 2.72 (s, 3H, CH_3), 3.08 (s, 6H, $-NMe_2$), 7.6 (m, 3H, arom. H), 7.8 (m, 3H, arom. H), 8.22 (m, 1H, arom. H), 8.30 (s, 1H, amidine-H). δ_C 165.4 (CO), 159.8, 151.4, 146.5, 145.7, 139.2, 135.5, 128.1, 127.1, 126.8, 126.1, 125.5, 124.7, 122.4, 121.8, 118.5 (CN), 105.7, 38.7 (NCH_3), 15.9 (CH_3). $C_{22}H_{17}N_3O_2$ (355.38): requires C 74.35, H 4.82, N 11.84; found C 74.25, H 4.66, N 11.74.

3-Amino-5-(1-hydroxynaphthalen-2yl)-6-methyl-4-oxo-3,4-dihydro-quinazoline-8-carbonitrile **17**

A solution of compound **15** (3.55 g, 10 mmol) and hydrazine hydrate (3 mL) in dioxane (30 mL) was refluxed for 2 h. The solid product obtained upon cooling was recrystallized from dioxane.

Yield: 2.2 g (65%); mp > 300°C. IR (KBr): ν = 3445 br. (OH), 3410 and 3380 (NH_2), 2220 (CN), 1695 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 342$ (M^+). ^1H NMR (300 MHz, DMSO): $\delta = 2.69$ (s, 3H, CH_3), 7.8 (m, 7H, arom. H), 8.9 (m, 2H, NH_2 D_2O exchangeable), 9.32 (S, 1H, quinazoline H-2), 11.80 (br s, 1H, OH D_2O exchangeable). δ_C 170.1 (CO), 160.8, 151.5, 149.8, 142.2, 138.9, 136.1, 134.5, 128.6, 127.5, 126.6, 126.1, 125.7, 125.2, 122.4, 121.8, 117.8, 116.5 (CN), 106.2, 15.8 (CH_3). $C_{20}H_{14}N_4O_2$ (342.34): calcd C 70.16, H 4.12, N 16.37; found C 70.08, H 4.22, N 16.24.

7-Amino-11-methyl-9-phenyl-5-oxa-7a,9,10a-triaza-cyclopenta[b]chrysene-6,8,10-trione **21**

A solution of compound **5** (2.81 g, 10 mmol) in dichloromethane (20 mL) was treated with 4-phenyl-1,2,4-triazoline-3,5-dione (1.75 g, 10 mmol). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from dioxan/ethanol.

Yield: 3.5 g (85%); mp 226–228°C (decompose). IR (KBr): $\nu = 3402$ and 3309 (NH_2), 1710 and 1689 cm^{-1} (C=O). MS (EI, 70 eV): $m/z = 424$ (M^+). ^1H NMR (300 MHz, DMSO): $\delta = 2.59$ (s, 3H, CH_3), 7.6 (m, 3H, arom. H), 7.7 (m, 5H, arom. H), 7.9 (m, 3H, arom. H), 8.2 (m, 2H, NH_2, D_2O exchangeable). δ_C 166.4 (CO), 160.1, 160.4, 156.4, 151.2, 147.6, 144.8, 139.4, 135.6, 129.1, 127.8, 127.1, 126.8, 125.2, 124.8, 123.8, 122.4, 118.8, 116.6, 121.4, 120.8, 15.2 (CH_3). $C_{24}H_{16}N_4O_4$ (424.40): calcd C 67.92, H 3.80, N 13.20; found C 67.70, H 3.94, N 13.59.

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