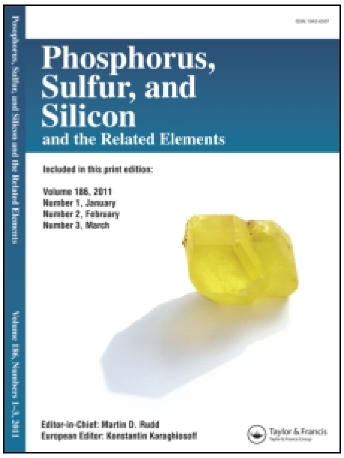

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Synthesis and Antimicrobial of Certain New Thiazolidinone, Thiazoline, and Thiophene Derivatives

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SYNTHESIS AND ANTIMICROBIAL OF CERTAIN NEW THIAZOLIDINONE, THIAZOLINE, AND THIOPHENE DERIVATIVES

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2-Cyano-*N*-(9,10-dioxo-9,10-dihydro-anthracen-2-yl)-acetamide (1) was utilized as a key intermediate for the synthesis of thiazolidin-4-one 2 and thiocarbamoyl 5 derivatives via reaction with 2-sulfanylacetic acid and phenyl isothiocyanate, respectively. Compound 5 reacted with different α-halo compounds to give thiazolidin-5-one 4, thiazolidine 7a,b, thiazolidin-4-one 8, and thiophene derivatives 10a,b. Thiazoline 6 and tetrahydro-benzothiophene 12 derivatives were obtained via a one-pot reaction of compound 1 with phenyl isothiocyanate/sulfur and cyclohexanone/sulfur, respectively. Representative compounds of the synthesized products were evaluated as antimicrobial agents. Some of these compounds exhibited promising activities.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Aminoanthraquinone; antimicrobial activity; thiazole; thiazolidinone; thiazoline; thiophene

INTRODUCTION

Many biological properties for 2-amino-9,10-anthraquinone derivatives have been reported, such as antitumor and anti-HIV activities.[1] The synthesis and antimicrobial activities of thiazole[2,3] and thiophene[4,5] compounds are well documented; however the 2-amino-9,10-anthraquinone derivatives possessing these nuclei are little known.[6] Therefore, our aim in this work was to synthesize some new thiazolidinone, thiazole, and thiophene derivatives incorporating the 2-amino-9,10-anthraquinone moiety, starting from 2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)acetamide in order to investigate their antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1–4, and compounds **2**, **4**, **5**, **7a**,**b**, and **8** prefer the (*E*) form rather than the

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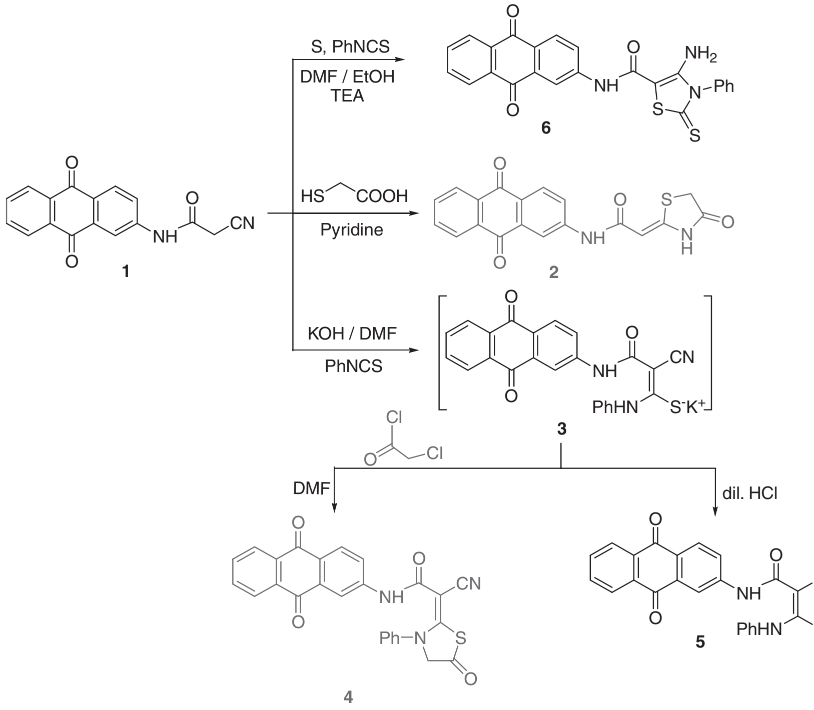
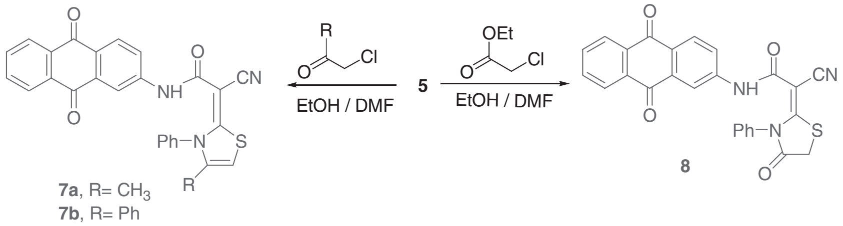
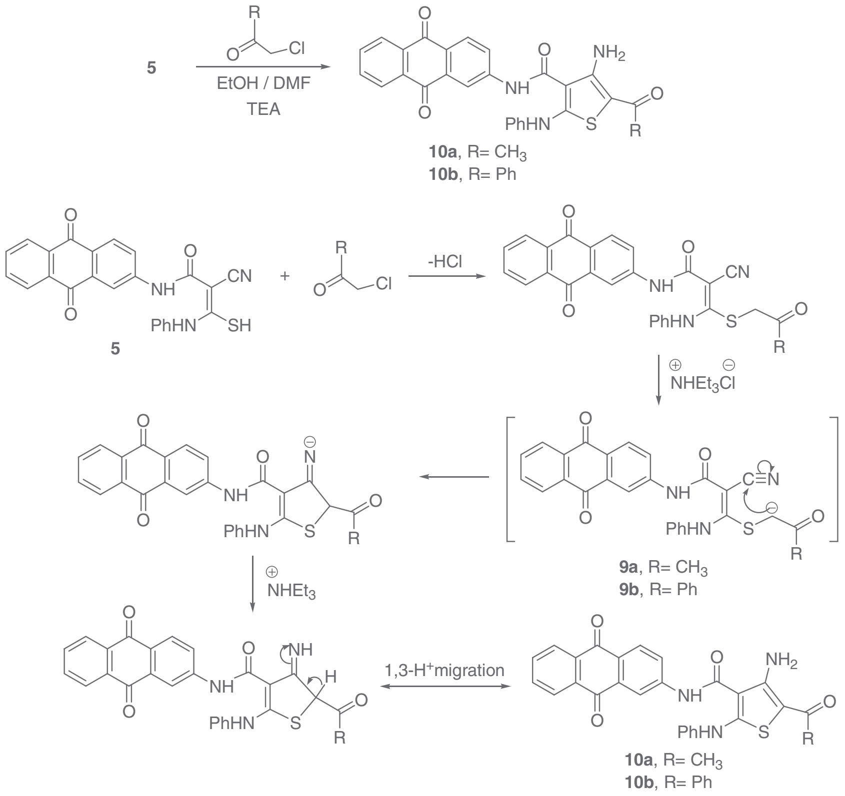


Scheme 1

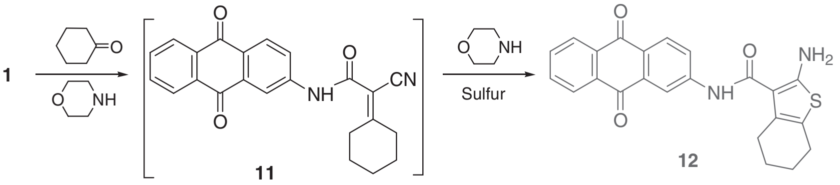


Scheme 2

(*Z*) form due to stabilization by π–π interaction (π–π stacking) between the phenyl group and anthraquinone moiety. 2-Cyano-*N*-(9,10-dioxo-9,10-dihydro-anthracen-2-yl)-acetamide (**1**) was prepared according to the previously reported procedure.[7] Thus, reaction of compound **1** with 2-sulfanylacetic acid through modification of this reported procedure[8–10] afforded (*E*)-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(4-oxothiazolidin-2-ylidene)acetamide (**2**) (Scheme 1). Compound **2** was characterized by the presence of a strong absorption band at 1716 cm^{-1} in the IR spectrum, specific for the thiazolidinone. Another piece of evidence for cyclization, in the ^{1}H NMR spectrum, is the presence of a singlet signal, equivalent to two protons at δ 3.73 ppm, which represents the C-5 protons of the thiazolidinone nucleus. The ^{13}C NMR spectrum of compound **2** revealed signals at δ 157.46 and 92.44 ppm due to C-4 and C-5 of the thiazolidinone nucleus, respectively.



Scheme 3



Scheme 4

The synthesis of 2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide (**4**) and (*E*)-2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-3-phenylamino-3-sulfanylacrylamide (**5**) were achieved as previously described method.[11] Treatment of acetamide **1** with phenyl isothiocyanate, in dry dimethylformamide in the presence of an equivalent amount of potassium hydroxide, produced the potassium 2-cyano-3-(9,10-dioxo-9,10-dihydroanthracen-2-ylamino)-3-oxo-1-(phenylamino)-prop-1-ene-1-thiolate (**3**). Cyclization of the potassium salt **3** with chloroacetyl chloride in dry dimethylformamide gave (*E*)-2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide (**4**), whereas acidification of such potassium salt **3** librated the β-sulfonylacetamide **5** (Scheme 1).

The structure of compound **4** was based on analytical and spectral data. The IR spectrum showed four absorption bands at 3300, 2191, 1720, and 1670 (br) cm^{-1} due to NH, CN, and four carbonyl functional groups. Its ^1H NMR spectrum revealed the appearance of a singlet signal, equivalent to two protons at 4.13 ppm due to C_5 protons of thiazolidinone nucleus. *N*-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)-4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxyamide (**6**) was obtained by reacting **1** with sulfur and phenyl isothiocyanate following the reported reaction conditions[12] (Scheme 1).

Refluxing of compound **5** in a mixture of DMF/EtOH with chloroacetone, phenacyl chloride, and/or ethyl chloroacetate led to the formation of 2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(4-methyl/phenyl-3-phenylthiazol-2(3*H*)-ylidene)acetamides **7a**,**b** and 2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(4-oxo-3-phenyl-thiazolidin-2-ylidene)acetamide (**8**), respectively (Scheme 2).

The IR spectra of compounds **7a**,**b** and **8** showed the presence of an NH group in 3356–3404 cm^{-1} region, a cyano group in the 2175–2002 cm^{-1} region, and three carbonyl groups in 1664–1669, 1646–1640 cm^{-1} regions. The IR of compound **8** also showed an absorption band at 1734 due to the carbonyl group of thiazolidin-4-one nucleus. The ^1H NMR of compound **7a**,**b** shows two singlet signals, equivalent to one proton at 7.03 and 7.12 ppm, respectively, due to C-5 proton of thiazoline nucleus. In addition, the ^{13}C NMR spectrum of compound **7b** reveals a signal at δ 98.95 ppm corresponding to C-5 of thiazoline ring. Moreover, the ^1H NMR spectrum of compound **8** displayed a singlet signal, equivalent to two protons at 4.05 ppm, which represents the C-5 protons of thiazolidin-4-one. In continuation of our work on the synthesis of biologically interesting heterocyclic molecules containing thiophene moiety,[13] several thiophene derivatives have been synthesized with a view to evaluating their antimicrobial activities.

Thus, refluxing of compound **5** in DMF/EtOH containing a catalytic amount of triethylamine, chloroacetone, and/or phenacylchloride revealed formation of *N*-(9,10-dioxo-9,10-dihydro-anthracen-2-yl)-5-acetyl(or benzoyl)-4-amino-2-phenylamino-thiophene-3-carboxamides **10a**,**b**. The IR spectra of compounds **10a,b** were characterized by the disappearance of CN group and the appearance of NH_2 and CO bands. In addition, the ^1H NMR of compound **10a** showed three singlet signals at 2.26, 10.36, and 11.98 ppm due to CH_3, NHPh and NHC=O protons, respectively.

Finally, *N*-(9,10-dioxo-9,10-dihydro-anthracen-2-yl)-3-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**12**) was obtained by the reaction of compound **1** with cyclohexanone and sulfur in a mixture of DMF/EtOH containing a catalytic amount of morpholine. The reaction may be explained *via* the intermediacy of 2-cyano-2-cyclohexylidene-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-acetamide (**11**) (Scheme 4). The structure of compound **12** was established on the basis of its elemental analysis and spectral data; its ^1H NMR spectrum displayed a four multiplet signals at 1.71, 2.47, 2.64, and 7.87–8.47 ppm due to the tetrahydrobenzene and anthraquinone moieties, respectively, and another two broad signals at 6.80 and 9.57 ppm corresponding to NH_2 and NH groups, respectively. Moreover, ^{13}C NMR spectrum revealed signals at δ 26.15, 24.52, 23.35, and 22.99 due to tetrahydrobenzene nucleus.

Antimicrobial Evaluation

Twelve compounds were screened in vitro for their antimicrobial activity against two bacterial strains: *Staphylococcus epidermidis* and *Pseudomonas auregenosa*, and two fungi: *Alternaria solani* and *Fusarium solani*, using cup-plate method by measuring the zone of inhibition according to a standard procedure.[14] The results are presented in the Supplemental Materials (available online).

In conclusion, we have reported in this article a simple and convenient route for the synthesis of some new heterocyclic derivatives based on anthraquinone for antimicrobial evaluation.

EXPERIMENTAL

All melting points were recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra υ (cm^{-1}) (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157. The ^{1}H NMR spectra were obtained on a Varian Spectrophotometer at 500 MHz, using TMS as an internal reference and DMSO-d$_6$ as solvent. The ^{13}C NMR spectra were recorded on a JEOL-ECA500 (National Research Center, Egypt). The mass spectra (EI) were recorded on 70 eV with Kratos MS equipment and/or a Varian MAT 311 A spectrometer. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. 2-Cyano-*N*-(9,10-dioxo-9,10-dihydro-anthracen-2yl)acetamide was prepared according to the procedures reported in the literature.[7]

(E)-N-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)-2-(4-oxothiazolidin-2-ylidene)acetamide (2)

To 2-cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)acetamide (**1**) (0.58 g, 2 mmol) in pyridine (20 mL), 2-sulfanylacetic acid (0.184 g, 2 mmol) was added. The reaction mixture was heated under reflux for 7 h, then left to cool to room temperature. The separated crystalline product was filtered, washed with ethanol, dried, and recrystallized from DMF/ethanol to give compound **2** as brown crystals, 75% yield; mp 298°C. Analysis: Calcd. For $C_{19}H_{12}N_2O_4S$ (364.37): C, 62.63; H, 3.32; N, 7.69; Found C, 62.83%; H, 3.40%; N, 7.82%. IR (cm^{-1}) (KBr): 3337, 3290 (2NH); 1719, 1663, 1654 (3C=O). MS (*m/z*) (I%): 318 (2.1) M$^+$-CH$_2$S; 317 (1.8); 291 (0.4); 290 (96); 274 (33.9); 223 (3.2); 168 (15.0); 126 (31.1); 78 (93.2). ^{1}H NMR (DMSO-d$_6$) δ: 3.73 (s, 2H, thiazolidinone, CH$_2$); 5.82 (s, 1H, =CH); 7.87–8.43(m, 7H, Ar–H of anthraquinone ring); 10.48 (s, 1H, NH); 11.66 (s, H, NH). ^{13}C NMR (DMSO-d$_6$) δ: 183.18, 181.86, 174.95, 166.42, 157.47, 145.97, 134.74, 133.57, 129.09, 127.63, 127.28, 127.17, 123.63, 115.65, 92.44.

(*E*)-2-Cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide (4)

To a cold suspension of finally divided KOH (0.112 g, 2 mmol) in dry dimethylformamide (10 mL), the cyanoacetamide derivative **1** (0.58 g, 2 mmol) followed by phenyl isothiocyanate (0.24 mL, 2 mmol) were added. The mixture was stirred at room temperature for 12 h, and then cooled again to 0°C, treated with the chloroacetyl chloride, and left to stand at room temperature for 24 h. Then the mixture was poured into ice-cold water. The resulting precipitate was filtered off, dried, and crystallized from DMF/ethanol gave compound **4**, brown crystals, 60% yield; mp 310°C. Analysis: Calcd. For $C_{26}H_{15}N_3O_4S$ (465.48): C, 67.09; H, 3.25; N, 9.03; Found C 67.20,%; H 3.39,%; N 9.25,%. IR (cm^{-1}) (KBr): 3300 (NH); 2081 (CN); 1720–1670 (4C = O). MS (*m/z*) (I%): 464 (46.2) M$^+$-1;

463 (46.2); 296 (15.4); 294 (46.2); 241 (100); 131 (46.2); 74 (61.5). ^{1}H NMR (DMSO-d$_6$) δ: 4.13 (s, 2H, thiazolidin-5-one); 7.20–8.83 (m, 7H, Ar–H) and 11.50 (s, 1H, NH).

(*E*)-2-Cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-3-phenylamino-3-sulfanylacrylamide (5)

To a cold suspension of finally divided KOH (0.22 g, 4 mmol) in dry dimethylformamide (10 mL), the cyanoacetamide derivative **1** (1.16 g, 4 mmol) followed by phenyl isothiocyanate (0.48 mL, 4 mmol) were added. The mixture was stirred at room temperature over night, then poured into ice-cold water and acidified with 0.1 N HCl to a pH 3–4. The resulting precipitate was filtered off, dried, and crystallized from aqueous ethanol to give compound **5**, as reddish brown crystals; 72% yield, mp 244°C. Analysis: Calcd. For $C_{24}H_{15}N_3O_3S$ (425.46): C, 67.75; H, 3.55; N, 9.88; Found C, 67.62%; H, 3.46%; N, 9.87%. IR (cm^{-1}) (KBr): 3294 (br. NH), 2548 (SH), 2201 (CN) and 1672, 1637 (3 C=O). MS (*m/z*) (I%): 425 (M$^+$, 2.5), 291 (15.00), 265 (47.00), 251 (17.5), 223 (100.0), 164 (42.5), 76 (67.5). ^{1}H NMR (DMSO-d$_6$) δ: 6.91–8.80 (m, 14H, Ar–H, SH, $\underline{\text{NH}}$-Ph) and 11.71 (s, 1H, NH).

N-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)-4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxyamide (6)

To a suspension of compound **1** (0.58 g, 2 mmol) in ethanol (20 mL), finely divided sulfur (0.064 g, 2 mmol), triethylamine (0.28 mL, 2 mmol), phenyl isothiocyanate (0.24 mL, 2 mmol), and dimethylformamide (5 mL) were added. The reaction mixture was stirred at 60°C for 4 h, then left to cool at room temperature. The separated product was filtered, washed with ethanol, dried, and crystallized from DMF/benzene (2:1) to give compound **6**; brown crystals; 70% yield, mp 270°C. Analysis: Calcd. For $C_{24}H_{15}N_3O_3S_2$ (457.52): C, 63.00; H, 3.30; N, 9.18; Found C, 63.28%; H, 3.47%; N, 9.33%. IR (cm^{-1}) (KBr): 3412, 3325 (br., NH); 1674 (3 C=O) and 1324 (C=S). MS (*m/z*) (I%): 264 (M$^+$-$C_8H_8N_2S_2$, 12.0), 263 (38.6), 224 (15.8), 223 (100), 195 (16.5), 167 (25.3), 142 (82.3), 114 (44.9), 86 (50.0), 68 (90.5), 50 (22.2). ^{1}H-NMR (DMSO-d$_6$) δ: 7.69–8.55 (m, 14H, 12Ar–H, NH$_2$), 11.02 (s, 1H, NH).

Synthesis of (*E*)-2-Cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(4-methyl/phenyl-3-phenylthiazol-2(3*H*)-ylidene)acetamides 7a,b and (*E*)-2-Cyano-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(4-oxo-3-phenyl-thiazolidin-2-ylidene)acetamide (8)

To compound **5** (0.85 g, 2 mmol) in dimethylformamide (20 mL) and chloroacetone (0.16 mL, 2 mmol), phenacyl chloride (0.23 mL, 2 mmol), or ethyl chloroacetate (0.21 mL, 2 mmol) was added. The reaction mixture was heated under reflux for 6 h, then cooled and neutralized with saturated sodium acetate solution. The resulting precipitate was filtered off, dried, and crystallized from DMF/ethanol to give compounds **7a**,**b** and **8**, respectively.

7a: Red crystals, 55% yield, mp >320°C; Analysis: Calcd. For $C_{27}H_{17}N_3O_3S$ (463.51): C, 69.96; H, 3.70; N, 9.07; Found C, 70.05%; H, 3.91%; N, 9.14%. IR (cm^{-1}) (KBr): 3404 (NH); 2175 (CN); 1664–1646 (3C=O). MS (*m/z*) (I%): 463 (M$^+$, 32.5), 344 (17.50), 340 (12.50), 339 (17.50), 291 (20.0), 241 (100), 192 (17.5), 139 (35.0), 105 (22.5), 73 (80.0). ^{1}H-NMR (DMSO-d$_6$) δ: 1.88 (s, 3H, CH$_3$), 7.03 (s, 1H,=C$_5$-H, thiazoline ring), 7.56–8.51 (m, 12H, Ar–H), 9.53 (s, 1H, NH).

7b: Brown crystals; 60% yield, mp 175°C; Analysis: Calcd. For $C_{32}H_{19}N_3O_3S$ (525.58): C, 73.13; H, 3.64; N, 8.00; Found C, 73.06%; H, 3.51%; N, 7.84%. IR (cm^{-1}) (KBr): 2180 (CN); 1669 (3C=O). MS (*m/z*) (I%): 525 (M$^+$, 17.1), 304 (28.0), 303 (59.8), 278 (1.2), 167 (12.2), 134 (31.7), 89 (26.8), 51 (100). ^{1}H NMR (DMSO-d$_6$) δ: 7.12 (s, 1H,=C$_5$-H, thiazoline ring), 7.38–8.47 (m, 17H, Ar–H), 11.20 (br., 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ: 183.98, 181.85, 166.84, 155.21, 145.49, 142.88, 140.62, 138.33, 137.11, 135.40, 134.98, 134.91, 134.84, 134.72, 134.53, 134.23, 133.57, 133.50, 131.00, 130.42, 130.07, 129.098, 129.58, 128.96, 128.55, 127.14, 127.02, 125.09, 124.70, 123.51, 121.56, 121.42, 118.58, 117.39, 116.22, 110.83 and 98.95.

8: Brown crystals, 75% yield, mp 285°C; Analysis: Calcd. For $C_{26}H_{15}N_3O_4S$ (465.48): C, 67.09; H, 3.25; N, 9.03; Found C, 67.27%; H, 3.41%; N, 9.24%. IR (cm^{-1}) (KBr): 3356 (NH); 2202 (CN); 1734–1665 (4C=O). MS (*m/z*) (I%): 398 (M$^+$-CH$_2$=C=O, 16.5), CN; 397 (0.9), 352 (0.8), 326 (13.1), 153 (6.1), 77 (100). ^{1}H NMR (DMSO-d$_6$) δ: 4.05 (s, 2H, CH$_2$, thiazolidinone), 7.48–8.48 (m, 12H, Ar–H), 10.14 (s, 1H, NH).

5-Acetyl-4-amino-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(phenylamino)thiophene-3-carboxamide (10a) and 4-Amino-5-benzoyl-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(phenylamino)thiophene-3-carboxamide (10b)

To compound **5** (0.85 g, 2 mmol) in dimethylformamide (20 mL), chloroacetone (0.16 mL, 2 mmol) or phenacyl chloride (0.23 mL, 2 mmol) and triethylamine (0.2 mL) were added. The reaction mixture was heated under reflux for 6 h, then cooled and neutralized with saturated sodium acetate solution. The resulting precipitate was filtered off, dried, and crystallized from the DMF/methanol to give **10a** and **10b**.

10a: Brown crystals, 60% yield, mp 290°C; Analysis: Calcd. For $C_{27}H_{19}N_3O_4S$ (481.52): C, 67.35; H, 3.98; N, 8.73; Found C, 67.52%; H, 4.08%; N, 8.94%. IR (cm^{-1}) (KBr): 3416 (br), 3321, 3259 (NH), 1667 (3C=O). ^{1}H NMR (DMSO-d$_6$) δ: 2.26 (s, 3H, CH$_3$), 7.17–8.7 (m, 14H, Ar-H, NH$_2$), 10.36, 11.98 (2s, 2H, 2NH).

10b: Brown crystals, 65% yield mp 185°C; Analysis: Calcd. For $C_{32}H_{21}N_3O_4S$ (543.59): C, 70.70; H, 3.89; N, 7.73; Found C, 70.93%; H, 3.95%; N, 7.94%. IR (cm^{-1}) (KBr): 3379 (br); 3313 (br) (NH); 1668 (br) (3C=O). ^{1}H NMR (DMSO-d$_6$) δ: 7.18–8.65 (m, 19H, Ar-H, NH$_2$), 9.57, 9.82 (2s, 2H, 2NH).

2-Amino-*N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (12)

To compound **1** (0.58 g, 2 mmol) in absolute ethanol (20 mL), morpholine (0.52 mL, 6 mmol), cyclohexanone (0.19 mL, 2 mmol), and sulfur (0.06 g, 2 mmol) were added. The reaction mixture was heated under reflux for 3 h. The separated crystalline product was filtered, dried, and recrystallized from DMF/EtOH (1:2) to give compound **12**. Brown crystals, 60% yield, mp 290°C; Analysis: Calcd. For $C_{23}H_{18}N_2O_3S$ (402.47): C, 68.64; H, 4.51; N, 6.96; Found C, 68.80%; H, 4.73%; N, 7.08%. IR (cm^{-1}) (KBr): 3436 (br.), 3303 (NH), 1761–1667 (3C=O). MS (*m/z*) (I%): 403 (M$^+$ +1, 5.3), 402 (M$^+$, 20.4), 401 (3.3), 249 (9.0), 223 (37.1), 179 (100.0), 125 (44.9), 91 (30.2), 50 (31.0). ^{1}H NMR (DMSO-d$_6$)

δ: 1.66–1.73 (m, 4H, C_5-H_2, C_6-H_2 of cyclohexene ring), 2.47 (M, 2H, C_4-H_2 of cyclohexane ring), 2.64 (m, 2H, C_7-H_2 of cyclohexene ring; 6.80 (s, NH_2), 7.87–8.47 (m, 7H, Ar–H of anthraquinone ring), 9.57 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 183.06, 181.79, 164.80, 145.78, 135.01, 134.64, 134.49, 133.60, 130.38, 128.72, 127.76, 127.21, 127.31, 124.50, 26.15, 24.52, 23.35 and 22.99.

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