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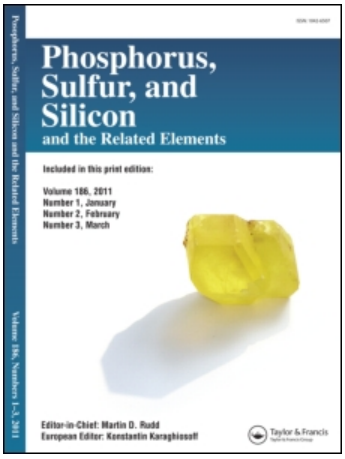

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3-Arylidene-pent-2,4-dione in the Synthesis of Heterocyclic Systemes. Facile One-Pot Synthesis of Novel Pentasubstituted 1,8-Naphthyridine-2-thione

Mohamed Ali Khalil[a]

[a] Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

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3-Arylidene-pent-2,4-dione in the Synthesis of Heterocyclic Systemes. Facile One-Pot Synthesis of Novel Pentasubstituted 1,8-Naphthyridine-2-thione

Mohamed Ali Khalil
Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

*Novel pentasubstituted 1,8-naphthyridin-2-thione derivatives **9** have been isolated in high yield via a facile one-pot reaction of 3-arylidene-pent-2,4-dione derivatives **3** and cyanothio-acetamide **4**. Plausible mechanistic pathways are presented to account for the unexpected product. The new compounds were established via IR, ^{1}H-, ^{13}C NMR, and MS analysis.*

Keywords Cyanothioacetamide; mass fragment; mechanism; pentasubstituted 1,8-naphthyridin-2-thiones; spectra

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2-Cyanothioacetamide is a highly reactive and readily obtainable starting material that has been extensively utilized in heterocyclic synthesis.[1–5] The reaction of 2-cyanothioacetamide with 1,3-diketones mainly afforded pyridine-2-thiones.[4,5] Annelated pyridine-2-thiones have shown remarkable pharmaceutical,[6–8] and biological activities.[9,10] Shuttleworth[11] reported a parallel solution synthesis of pyridine-2-thione core via reaction of cyanothioacetamide with alkylated 1,3-diketones in the presence of excess of 4-methylmorpholine, as is shown in Scheme 1. Synthesis of similar pyridine-2-thiones core using the same starting materials has been recently reported.[12] In continuation with our previous interest in the synthesis of azaheterocycles,[13–17] we report herein different and unexpected results for the reaction of cyanothioacetamide with the well-known 3-arylidenacetylacetone derivatives under the same conditions.

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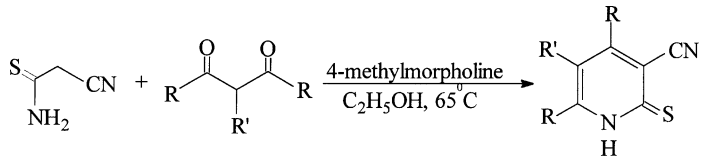
Address correspondence to Mohamed Ali Khalil, Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt. E-mail: deyaakhalil@hotmail.com

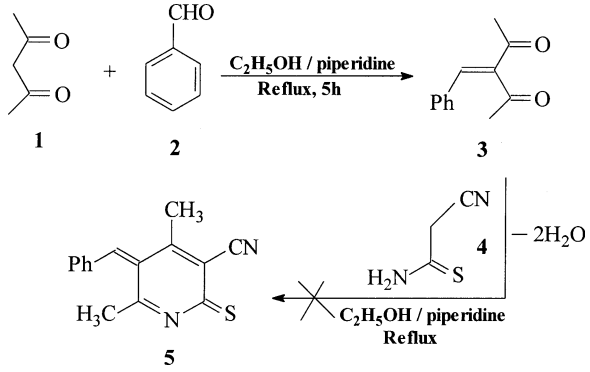


R' = CO_2Me, O-Ph, Me, $(CH_2)_4Me$, F,Cl-C_6H_3-CH_2-

SCHEME 1

RESULTS AND DISCUSSION

Our initial strategy aimed to synthesize 5-benzylidene-4,6-dimethyl-3-cyano-pyridine-2-thione **5** core which assumed to be a good synthon in a further heterocyclic synthesis, as is shown in Scheme 2. The benzylidene acetylacetone **3** easily reacted with cyanothioacetamide **4** in ethanol containing piperidine to yield yellow crystals after about 30 min of reflux. The IR spectrum of that product revealed intense absorption bands at υ 1572, 1698, 2218, 3292, and 3377 cm^{-1}. The mass spectra (70 eV) showed molecular ion at 335 (M + 1, 1), 334 (M^+, 3). The ^1H NMR spectrum (DMSO-d_6) showed signals at δ 13.7 (1H), 7.1–7.3 (5H), 4.9–4.4 (2H), 2.5 (3H), 2.1 (3H). Since our expectation was that product would be 5-benzylidene-3-cyano-4,6-dimethylpyridine-2-thione **5** which has $m/z = 252$ corresponds to molecular formula $C_{15}H_{12}N_2S$. Thus, this assumption is ruled out based on obtained spectral and elemental data, (Scheme 2).



SCHEME 2

The presence of intense absorption bands in the ir spectrum due to carbonyl and amine functions, as well as the presence of two singlet

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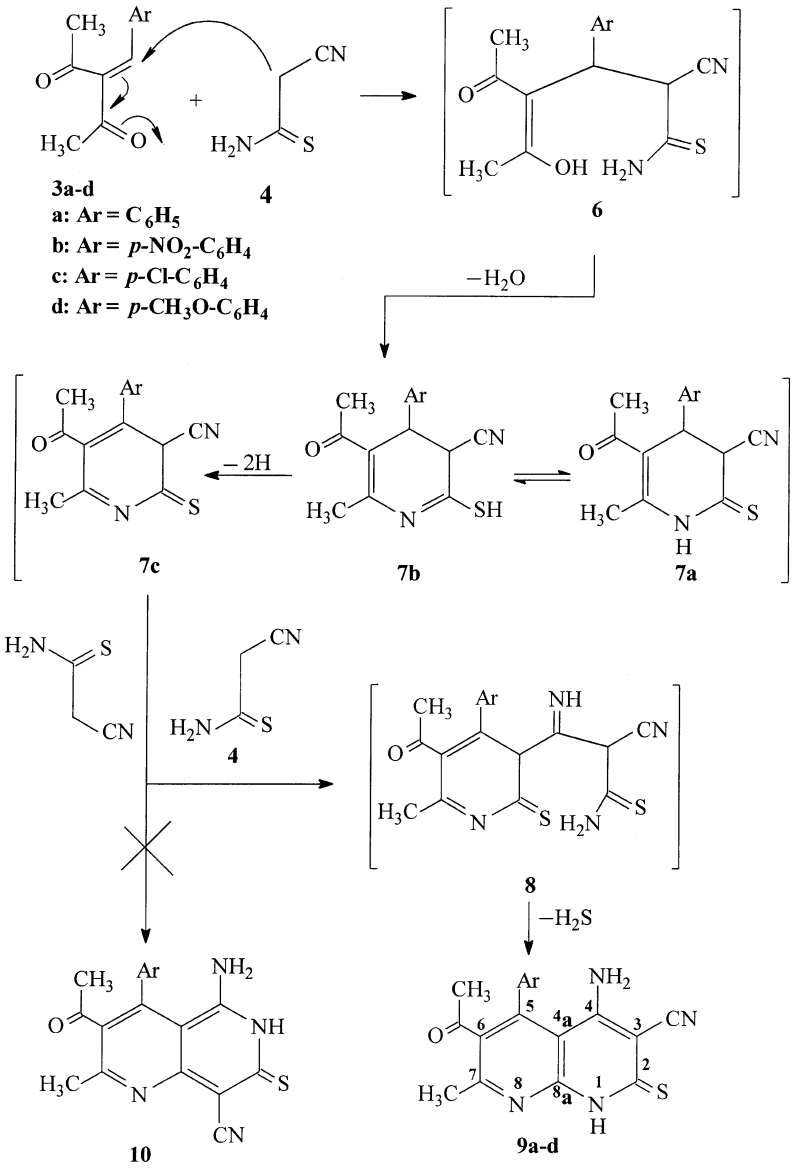
signals in the ^{1}H-NMR each integrating for three protons of two methyl groups, prompted us to suggest a plausible mechanistic pathway as is shown in Scheme 3. The addition of the activated methylene of cyanothioacetamide **4** into the activated double bond of arylidene **3** afforded



SCHEME 3

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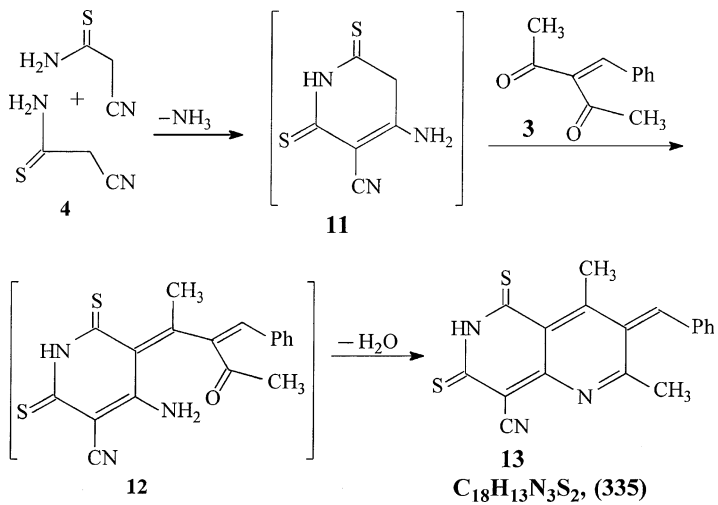
the intermediate **6**, which subsequently loses water to yield the non-isolable intermediates **7a**,**b**, which could be transferred into **7c** under an aerobic oxidation forced by the catalyst, heating and/or oxygen air. Further reaction of **7c** with cyanothioacetamide **4** yields the intermediate **8** upon nucleophilic addition of the activated methylene of **4** to the cyano function, which readily cyclized to the 1,8-naphthyridine-2-thione **9** via losing H_2S. The ^{13}C NMR spectrum (DMSO-d_6) of **9a** showed signals at 209.3 (C=S), 175.0 (C=O), 155.2 (*C-8a*), 152.5 (*C-7*), 143.7 (*C-4*), 128.9–123.9 (aryl-*C*, *C-3*, *C-4a*, *C-5* and *C-6*), 116.5 (*CN*), 27.7 (CH_3—CO), 18.6 (CH_3). For symmetrical and planarity reasons, we believe that the product would be 1,8-naphthyridine **9** not 1,4-naphthyridine **10** which should be obtained if the amine function of cyanothioacetamide **4** adds to the nitrile function of the intermediate **7c**. It is worth noting that the reaction with cyanoacetamide itself was unsuccessful under a variety of reaction conditions.

To confirm this assumption, possible fragmentation pathways have been proposed for the arylidene **3a** and the product **9a**, as is shown in Charts 1 and 2, respectively. On the other hand, several similar structures, each with $m/z = 335/336$, can be constructed as possible products, however, they are ruled out based on spectral data (Schemes 4 and 5). The cyclic dithione intermediate **11** may result from a self-condensation of cyanothioacetamide **4**, followed by condensation with the benzylidene **3** to yield the intermediate **12**. This intermediate **12** may cyclizes to 1,4-naphthyridine-2,8-dithione **13** via loss of water. Based on the presence



SCHEME 4

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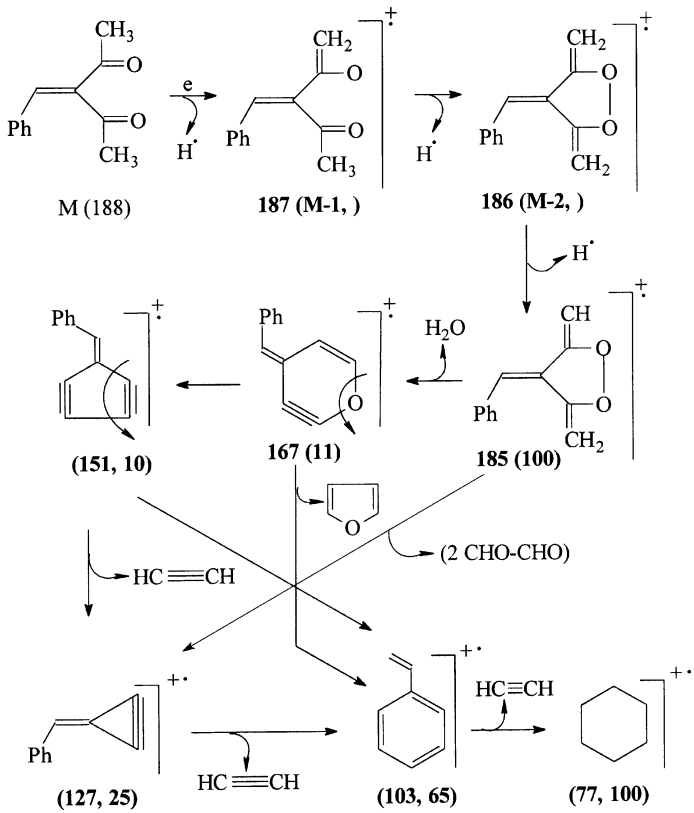

CHART 1

of the carbonyl absorption band at υ 1698 cm^{-1}, and a singlet signal due to NH_2 at δ 4.4 ppm, this assumption is ruled out (Scheme 4).

Similarly, the cyanothioacetamide **4** could react with the pyridine **5** via losing H_2S to yield the proposed 1,8-naphthyridine **14**, which may hydrolyze into its carboamide derivative **15** which has the molecular formula $C_{18}H_{16}ON_4S$ (336). Also, this pathway could safely be excluded since there is an intense absorption band at υ 2218 cm^{-1} assigned for nitrile function, and only one singlet signal due to two protons of amine function (Scheme 5).

EXPERIMENTAL

All melting points were uncorrected. The ^1H-, ^{13}C NMR spectra (DMSO-d_6, δ in ppm) were run on a Varian EM-390 spectrometer using

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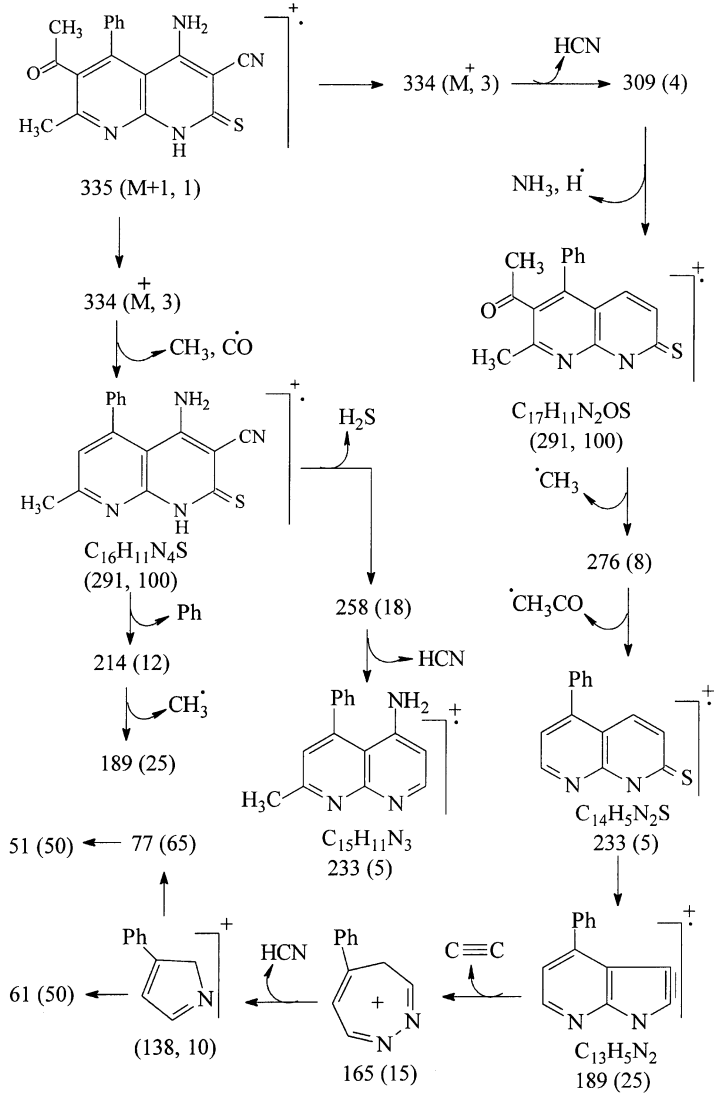

CHART 2

TMS as internal standard at Dusiburg-Essen University, Germany. Their spectra (KBr, ν in cm^{-1}) were recorded on a Pye-Unicam SP-1100 Spectrophotometer. Mass spectra were recorded on a Varian MAT 311 A spectrometer at 70 eV, and the elemental analysis were determined at the Microanalytical Center, Cairo University, Egypt.

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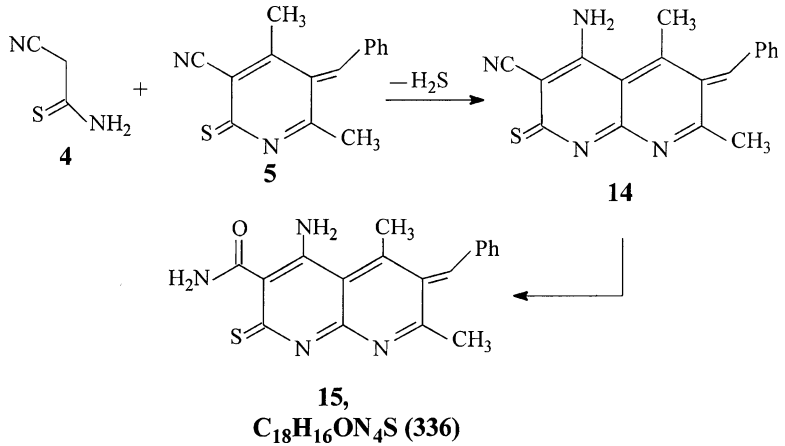

SCHEME 5

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3-Arylideneacetylacetone derivatives **3a–d** were synthesized according to the method of Horning et al.[18]

Preparation of 6-Acetyl-4-amino-5-aryl-3-cyano-7-methyl-1,8-naphthyridin-2-thiones (9a–d)

To 50 ml of ethanol containg 3.8 g (2 mmol) of **3a** and 2.0 g (2 mmol) of cyanothioacetamide **4** an 0.2 ml of piperidine was added, and the mixture was refluxed. The yellow needles formed after 15 minutes was filtered from the solution after one hour and recrystallized from a mixture of ethanol-dimethyl-formamide (3:1) into yellow needles. In analogy, compounds **3b–d** reacted with cyanothioacetamide **4** to give the products **9b–d**, respectively.

6-Acetyl-4-amino-3-cyano-7-methyl-5-phenyl-1,8-naphthyridin-2-thione (9a)

The yield in this mixture is 4.0 g (59%); mp: 310–312 °C; IR: 1572 (C=S), 1698 (C=O), 2218 (CN), 3292 and 3377 (NH and NH_2); ^{1}H NMR: 13.7 (*s*, 1H, NH), 7.07–7.30 (*m*, 5H, Ar-H), 4.9–4.4 (*br*, 2H, NH_2), 2.5 (*s*, 3H, CH_3), 2.1 (*s*, 3H, CH_3); ^{13}C NMR: 209.3 (C=S), 175.0 (C=O), 155.2 (*C-8a*), 152.5 (*C-7*), 143.7 (*C-4*), 128.9–123.9 (phenyl-*C*, *C-3*, *C-4a*, *C-5* and *C-6*), 116.5 (CN), 27.7 (CH_3—CO), 18.6 (CH_3). MS, *m/z* (%): 335 (M + 1, 1), 334 (M^+, 2), 309 (2), 291 (100), 276 (8), 233 (3), 189 (3), 165 (4), 151 (3). Anal. Calcd. for $C_{18}H_{14}N_4OS$ (334.40): C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.46; H, 4.10; N, 16.56; S, 9.44.

6-Acetyl-4-amino-3-cyano-7-methyl-5-(4-nitrophenyl)-1,8-naphthyridin-2-thione (9b)

The yield for this mixture is 2.5 g (66%); mp: 190–192°C (MeOH); IR: 1575 (C=S), 1695 (C=O), 2215 (CN), 3290 and 3372 (NH and NH_2); ^{1}H NMR: 13.2 (s, 1H, NH), 7.1–7.7 (*m*, 4H, Ar-H), 4.5 (*s*, 2H, NH_2), 2.4 (*s*, 3H, CH_3), 1.9 (*s*, 3H, CH_3); ^{13}C NMR: 208.5 (C=S), 176.1 (C=O), 152.4 (*C-8a*), 150.5 (*C-7*), 144.2 (*C-4*), 138.2 (phenyl-4-NO_2), 131.2–123.7 (phenyl-C, *C-3*, *C-4a*, *C-5* and *C-6*), 117.3 (CN), 27.3 (CH_3—CO), 18.4 (CH_3). MS, *m/z* (%): 381 (M + 2, 2), 380 (M + 1, 4), 379 (M^+, 55). Anal. Calcd. for $C_{18}H_{13}N_5O_3S$ (379.40): C, 56.98; H, 3.45; N, 18.46; S, 8.45. Found: C, 56.81; H, 3.26; N, 18.28; S, 8.27.

6-Acetyl-4-amino-3-cyano-7-methyl-5-(4-chloro)phenyl-1,8-naphthyridin-2-thione (9c)

The yield for this mixture is 2.0 g (54%); mp: 240–242°C (MeOH); IR: 1570 (C=S), 1694 (C=O), 2218 (CN), 3291 and 3375 (NH and NH_2); ^{1}H NMR: 12.8 (*s*, 1H, NH), 7.1–7.5 (*m*, 4H, Ar-H), 4.7 (*s*, 2H, NH_2), 2.3 (*s*, 3H, CH_3), 2.2 (*s*, 3H, CH_3); ^{13}C NMR: 207.8 (C=S), 175.6 (C=O), 154.5 (*C-8a*), 151.3 (*C-7*), 141.5 (*C-4*), 135.2 (Phenyl-4-Cl), 128.9–122.9 (phenyl-C, *C-3*, *C-4a*, *C-5* and *C-6*), 118.1 (CN), 27.1 (CH_3—CO), 16.3 (CH_3). MS, *m/z* (%): 370 (M + 2, 3), 369 (M + 1, 2), 368 (M^+, 65). Anal. Calcd. for $C_{18}H_{13}N_4OSCl$ (368.84): C, 58.62; H, 3.55; N, 15.19; S, 8.69; Cl, 9.61. Found: C, 58.47; H, 3.38; N, 15.01; S, 8.52; Cl, 9.45.

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6-Acetyl-4-amino-3-cyano-7-methyl-5-(4-methoxy)-phenyl-1,8-naphthyridin-2-thione (9d)

This mixture was precipitated after 20 min of reflux as yellow crystals. The yield is 2.8 g (76%); mp: 295–296°C (DMF/EtOH); IR: 1570 (C=S), 1694 (C=O), 2218 (CN), 3291 and 3375 (NH and NH_2); ^{1}H NMR: 13.6 (*s*, 1H, NH), 7.1–7.7 (*m*, 4H, Ar-H), 4.7 (*s*, 2H, NH_2), 3.6 (s, 3H, OCH_3), 2.4 (*s*, 3H, CH_3), 2.2 (*s*, 3H, CH_3); ^{13}C NMR: 208.5 (C=S), 175.3 (C=O), 154.8 (*C-8a*), 153.9 (*C-7*), 142.1 (*C-4*), 132.9–123.4 (phenyl-C, *C-3*, *C-4a*, *C-5* and *C-6*), 117.3 (CN), 55.4 (OCH_3) 26.8 (CH_3—CO), 17.4 (CH_3). MS, *m/z* (%): 366 (+2, 2), 365 (M + 1,1), 364 (M^+, 75). Anal Calcd. for $C_{19}H_{16}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.47; H, 4.28; N, 15.21; S, 8.62.

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