Pyridopyridazines, Benzimidazolopyrimidines Triazolopyrimidines, 9-Oxo-2,3,6,7-tetraazabicyclo[3.3.1]nona-3,7-diene and Aroylcinnolines from 2-Arylhydrazono-3-oxopropanals

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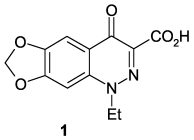
The reaction of the 2-arylhydrazonopropanal **3a** with 2-amino1,1,3-tricyanopropene **4** afforded the pyridopyridazines **6**. On the other hand, reaction of **3b** with **4** afforded **7**. Compounds **3a,b** also condensed with 2-aminobenzimidazole and 3(5)-amino-1,2,4-triazole to yield azolopyrimidines **10** and **13**. Refluxing compounds **3a,b** in acetic acid in the presence of ammonium acetate afforded 2,3,6,7-tetraaza-bicyclo[3.3.1]nona-3,7-diene **14** and aroylcinnoline **15** respectively.

Key words: 2-Arylhydrazonopropanals, Pyridopyridazines, Aminotriazole, Azolopyrimidines, Aroylcinnoline

Introduction

Significant commercial interest in the development of benzopyridazine derivatives, in particular with regard to pharmaceutical applications of pyridazines and cinnolines is shown by the large number of patents filed in this area [1]. For example, cinoxacine **1** [2] is a cinnoline analogue of quinoline antibacterials used for urinary tract infection. ICI-D-7569 **2** [3] is an anxiolytic agent. 2-Arylhydrazono-3-oxopropanals are versatile reagents and their utility in heterocyclic synthesis has recently received considerable interest [4 – 6]. In previous work from our laboratories, we have reported a high yield synthesis of *o*-substituted-2-arylhydrazonopropanals and reported on their potential as building blocks in heterocyclic chemistry [7 – 9].



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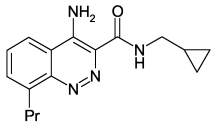

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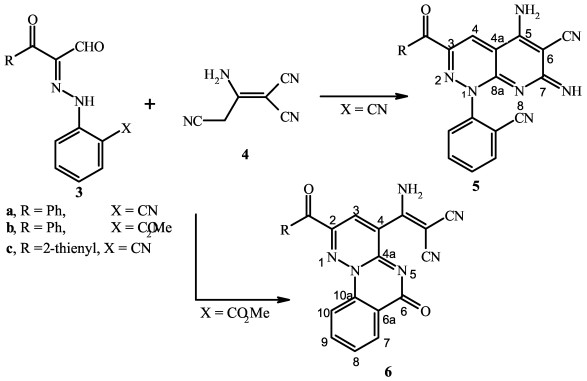
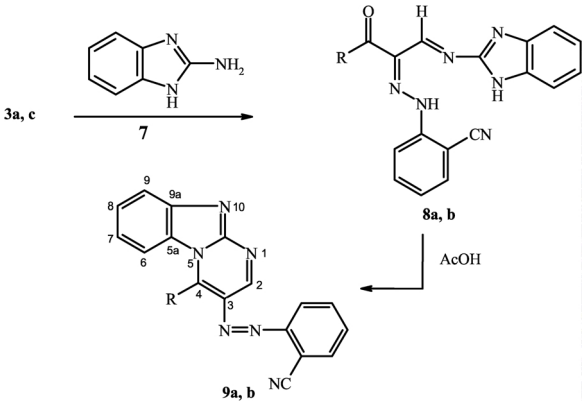
Results and Discussion

In conjunction with this work we report here results of our further investigation aimed at exploring the potential of 2-arylhydrazonopropanals **3a,b**, in heterocyclic synthesis [10, 11]. It has been found that **3a** readily condenses with 2-amino-1,1,3-tricyanopropene (**4**) yielding product of condensation *via* water elimination. Based on spectral data, IR and ^{13}C NMR, compound **5** was established. On the other hand reaction of **3b** with **4** afforded **6** (Scheme 1).



Scheme 1.

The reaction of **3a,c** with 2-aminobenzimidazole (**7**) in refluxing ethanol afforded a condensation product, which was assigned as **8a,b** based on ^{1}H NMR spectral data which revealed the absence of a formyl signal.

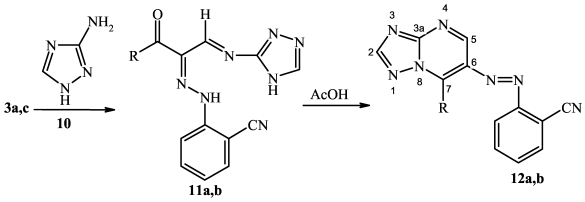


Scheme 2.

When this product was refluxed in AcOH it cyclized smoothly *via* water elimination affording **9a,b** (Scheme 2).

The reaction of **3a,c** with 5-amino-1H-1,2,4-triazole (**10**) afforded the condensation product **11**. ^{1}H NMR data revealed the presence of two singlet at $\delta = 8.5$ trizol NH and $\delta = 15.2$ for hydrazone NH (Scheme 3).

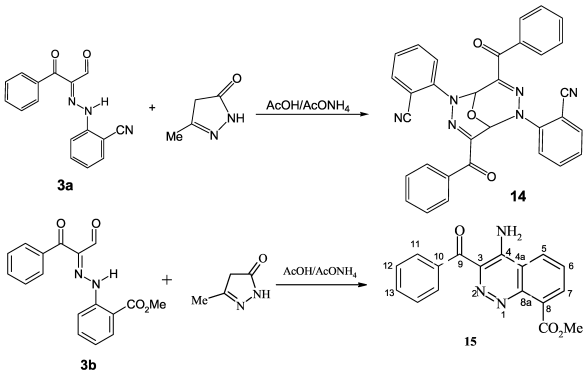
Refluxing **11** in AcOH afforded the 1,2,4-triazolo[1,5-*a*]pyrimidene structure **12**. The ^{1}H NMR spectrum indicated a triazole singlet at δ8.8 ppm shifted to lower field by almost δ1.0 ppm compared to the triazole signal in the parent amino triazole.



Scheme 3.

It could thus be demonstrated that compounds **3a,c** are variable precursors of condensed pyridazines and also of arylazo azolopyrimidines (Scheme 3).

In an attempt to condense **3a** with 5-methyl-2,4-dihydro-pyrazol-3-one **13** in the presence of acetic acid and ammonium acetate a new compound with the molecular formula $C_{32}H_{20}N_6O_2$ was obtained based on mass spectra MS = 536 and X-ray analysis. The reaction takes place *via* condensation of two molecules of **3a**. The hydrazone NH of one molecule attacks the formyl carbonyl carbon of a second molecule, followed by elimination of water to give **14** (Scheme 4). The initial step in this cyclization is the condensation of the formyl group with the amine to yield



Scheme 4.

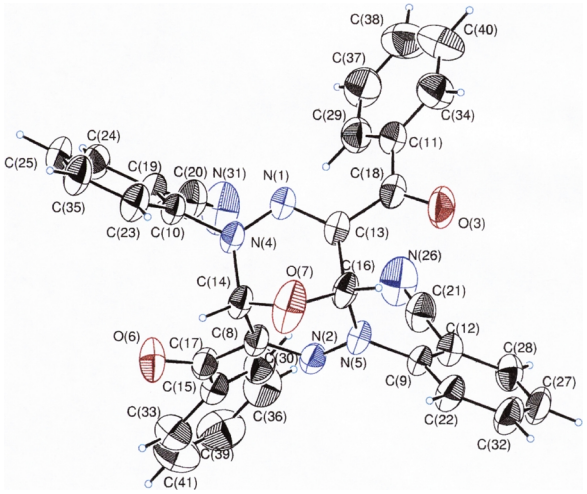


Fig. 1. Molecular structure of **14** with atoms labeling scheme.

an intermediate enaminoazo product which then undergoes 6π-electrocyclization into a dihydcinnoline which in turn aromatizg to the final product. A similar mechanism has been recently established by Al-Awadi *et al*. [12].

In contrast to this behavior compound **3b** cyclized into **15** [12, 13]. The different behavior of **3a** and **3b** may be effected by the nature of the substituent of the aroyl moiety.

To our knowledge, this is first reported example of the formation of 4,8-dibenzoyl-2,6-di(2-cyanophenyl)-9-oxo-2,3,6,7-tetra-azabicyclo[3.3.1]non a-3,7-dienes such as **14**. The reactions took place without involvement of 5-methyl-2,4-dihydro-pyrazol-3-one. When the reactions were repeated in the absence of 5-methyl-2,4-dihydro-pyrazol-3-one, the products obtained were found identical with those obtained before (mp, mix.

mp, and TLC). Product **14** was recrystallized and its structure was solved by X-ray diffraction (Fig. 1).

Experimental Section

All melting points were measured on Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye Unicam SP 3-300 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-d6) at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) *as an* internal reference and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University. The crystal and molecular structure was determined by X-ray diffraction from a single crystal.

General procedure for the preparation of **5**, **6**

A solution of compound **3a,b** (0.1 mol) in ethanol (30 ml) was treated with 2-amino-l-propene-1,1,3-tricarbonitrile **4** (0.1 mol) in the presence of few drops of piperidine. The reaction mixture was refluxed for 3 h. The solid products were isolated by filtration, washed with ethanol and dried. Products were recrystallized from ethanol.

*5-Amino-3-benzoyl-1-(2-cyanophenyl)-7-imino-l,7-dihydropyrido[2,3-c]pyrimidine-6-carbonitrile (***5***)*

Compound **5** was obtained as dark red crystals (85%), m. p. $>$ 300 °C. IR: $\tilde{\nu}_{max}$(KBr) 3460(NH_2), 3377(NH), 3174 (CH aromatic), 2215, 2203 $\equiv$ C) and 1632 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 5.29 (br, 2H, NH_2), 6.81 – 7.87 (m, 10H, arom-H and NH), 8.42 ppm. (s, 1H, H-4); ^{13}C NMR (200 MHz, DMSO-d_6): 116.0, 117.2 (2C $\equiv$ N), 99.6; 115.8, 119.2, 132.8, 133.6, 150.2 (C_6H_4-CN), 128.0, 130.1, 134.3, 136.7 (phenylcarbons); 155.0 (C-3), 123.5 (C-4), 138.0 (C-4a), 172 (C-5), 87 (C-6), 164.0 (C-7), 166.1 (C-8a); and 189.64 ppm (*C*=O); MS [EI, 70 eV]: $m/z = [M^+ + 2]$ (393)[77(45.4%), 105(30.8%), 118(13.9%), 222(28.0%), 313(100%), 393(49.4%)]; Analysis for $C_{22}H_{13}N_7O$: calcd. C 67.52, H 3.34, N 25.05; found C 67.60, H 3.5, N 25.3.

*3-Amino-1-cyano-2-(2-benzoyl-6-oxopyridazino[2,3-c]-quinazoline-4-yl)acrylo-nitrile(***6***)*

Compound **6** was obtained as beige crystals (80%), m. p. $>$ 300 °C. IR: $\tilde{\nu}_{max}$(KBr) 3344 (NH_2), 2218, 2202 (2CN), 1640 (C=O) and 1615 cm^{-1} (C=O ring), ^{1}H NMR (DMSO-d_6): δ = 5.49 (s,2H, NH_2), 7.64 – 8.29 (m, 9H, arom-H), 8.51 ppm (s, 1H, H-3); ^{13}C NMR (200 MHz, DMSO-d_6): 117.2(C $\equiv$ N), 54.1 (C=*C*-CN), 186.3 (NH_2-*C*=C), 129.0, 130.1, 134.4, 136.7 (phenyl carbons); 155.0 (C-2), 123 (C-3), 138.0 (C-4), 164.0 (C-4a), 123.3 (C-6a), 130.5 (C-7), 119.0 (C-8), 135.1 (C-9), 115.6 (C-10), 147.9 (C-10a), 177.64 (ring C=O) and 190.0 ppm (*C*=O): MS [EI, 70 eV]: $m/z = [M^+]$(392). Analysis for $C_{22}H_{12}N_6O_2$: calcd. C 67.29, H 3.08, N 21.49; found C 67.40, H 3.21, N 21.60.

General procedure for the preparation of **8a**, **b**

A mixture of compound **3a,c** (0.1 mol) and 2-aminobenzimidazol (0.1 mol) was refluxed in ethanol or dioxan (30 ml) for 2 h. The solvent was then removed *in vacuo* and the residue cooled to deposit a solid, which was crystallized from ethanol.

*2-(2-Cyanophenylhydrazono)-3-(benzoimidazol-2-ylimino)-l-phenyl-l-propanone (***8a***)*

Compound **8a** was obtained as orange crystals (84%), m. p. 193 °C. IR: $\tilde{\nu}_{max}$(KBr) (show complex spectra due to H-bond between O and NH), 3354 (NH imidazole), 2220 (CN), 1640 cm^{-1} (C=O ketone); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 6.97 – 8.03 (m, 13H, arom-H); 9.4 (s, 1H, CH olefinic),12.13 (s, 1H, NH imidazole) and 15.9 ppm; (s, H, NH) ^{13}C NMR (200 MHz, DMSO-d_6): 116.5 (C$\equiv$N), 99.1, 116.88, 119.18, 131.98, 133.96, 150.2 (C_6H_4-CN), 128.0, 130.3, 134.3, 136.5 (phenyl carbons); 115.4, 122.9, 137.9, 141.5(imidazole carbons), 146.80(*C*=N-N), 155.64(N=*C*H-C) and 187.64 ppm (*C*=O); MS [EI, 70 eV]: $m/z = [M^+]$(392). Analysis for $C_{23}H_{16}N_6O$: calcd. C 70.40, H 4.11, N 21.42; found C 70.50, H 4.09, N 21.56.

*2-(2-Cyanophenylhydrazono)-3-(benzoimidazol-2-ylimino)-l-(2-thienyl)-l-propanone (***8b***)*

Compound **8b** was obtained as yellow crystals (84%), m.p. 200 °C. IR: $\tilde{\nu}_{max}$(KBr) (show complex spectra due to H-bond between O and NH), 3354 (NH imidazole), 1640 (C=O ketone) and 2220 cm^{-1} (C$\equiv$N); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.23 – 7.97 (m, 9H, thienyl, H-5 and 8H, arom-H), 8.18 – 8.20 (m, 2H, thienyl, H-3, H-4), 9.4 (s, 1H, CH olefinic), 12.11(s, 1H, NH imidazole) and 15.8 ppm (s, 1H, NH); ^{13}C NMR (200 MHz, DMSO-d_6): 116.5 (C$\equiv$N), 99.1, 116.88, 119.18, 131.98, 133.96, 150.2 (C_6H_4-CN); 122.8, 125.3, 127.5, 142.6 (thienyl carbons), 115.4, 122.9, 137.9, 141.5 (imidazole carbons), 146.80 (*C*=N-N), 155.64 (N=*C*H-C) and 177.54 ppm (*C*=O) MS [EI, 70 eV]: $m/z = [M^+]$ (398). Analysis for $C_{21}H_{14}N_6OS$: calcd. C 63.30, H 3.54, N 21.09; found C 63.50, H 3.56, N 20.94.

General procedure for the preparation of **9a**, **b**

A solution of **8a** or **8b** (0.1 mol) in acetic acid (10 ml) was refluxed for 2 h, then left cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol.

*3-(2-Cyanophenylazo)-4-phenylpyrimido[1,2-a]benzimidazole (**9a**)*

Compound **9a** was obtained as orange crystals (78%), m. p. 148 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$): $\delta = 7.15-7.94$ (m, 13H, arom-H), 9.36 ppm (s, 1H, H-2); ^{13}C NMR (200 MHz, DMSO-d$_6$): $\delta = 151.8$ (C-2), 144.2 (C-3), 142.6 (C-4), 137.9 (C-5a), 127.0 (C-6), 122.9 (C-7), 118.4 (C-9), 143.7 (C-10a), 116.5 (C≡N), 129.0, 130.1, 134.3, 136.7 (phenyl carbons); 129.09, 134.06, 135.48, 139.69, 139.83, 148.12 ppm (*C*$_6$H$_4$CN); MS [EI, 70 eV] $m/z = [M^+]$ (374). Analysis for $C_{23}H_{14}N_6$: calcd. C 73.72, H 3.76, N 22.52; found C 73.60, H 3.50, N 22.40.

*3-(2-Cyanophenylazo)-4-(2-thienyl)-pyrimido[1,2-a]benzimidazole (**9b**)*

Compound **9a** was obtained as orange crystals (78%), m. p. 160 °C. ^{1}H NMR (200 MHz, d$_6$-DMSO): $\delta = 7.15-7.97$ (m, 9H, thienyl, H-5 and 8H, arom-H), 8.18 – 8.20 (m, 2H, thienyl, H-3, H-4), 9.36 ppm (s, 1H, H-2); MS [EI, 70 eV]: ^{13}C NMR (200 MHz, DMSO-d$_6$): $\delta = 151.8$ (C-2), 144.2 (C-3), 142.6 (C-4), 137.9 (C-5a), 127.0 (C-6), 122.9 (C-7), 118.4 (C-9), 143.7 (C-10a), 116.5 (C≡N), 122.8, 125.4, 127.5, 142.6 (thienyl carbons); 129.09, 134.06, 135.48, 139.69, 139.83, 148.12 ppm (*C*$_6$H$_4$CN); $m/z = [M^+]$ (380). Analysis for $C_{21}H_{12}N_6S$: calcd. C 66.30, H 3.18, N 22.09; found C 66.39, H 3.22, N 22.21.

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

A mixture of compounds **3a,c** (0.1 mol) and 3-amino-l,2,4-trizole (0.1 mol) was refluxed in ethanol or dioxan (30 ml) for 2 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from ethanol.

*2-(2-Cyanophenylhydrazono)-3-(l,2,4-trizol-3-ylimino)-l-phenylpropanone (**11a**)*

Compound **11a** was obtained as yellow crystals (87%), m.p. 235 °C. IR: $\tilde{\nu}_{max}$(KBr) (show complex spectra due to keto-enol forms with H-bond between O and NH), 3290 (NH triazole), 2220 (C≡N) and 1640 cm^{-1} (C=O ketone); ^{1}H NMR (200 MHz, DMSO-d$_6$): $\delta = 6.97-8.03$ (m, 9H, arom-H); 8.12 (s, 1H, CH olefinic), 8.54 (s, 1H, 1,2,4-trizole NH), 9.35 (s, 1H, 1,2,4-triazole H-5) and 15.26 ppm (s, 1H, NH hydrazone); ^{13}C NMR (200 MHz, DMSO-d$_6$): 116.0 (C≡N), 116.90, 117.18, 124.86, 131.98, 133.96, 135.41 (*C*$_6$H$_4$-CN), 128.0, 130.1, 134.3, 136.7 (phenyl carbons); 143.80 (*C*=N-N), 147.5 (1,2,4 trizole-carbon),155.64 (N=CH-C), and 187.64 ppm (*C*=O): MS [EI, 70 eV]: $m/z = [M^+]$ (343). Analysis for $C_{18}H_{13}N_7O$: calcd. C 62.97, H 3.82, N 28.56, found C 63.10, H 3.70, N 28.40.

*2-(2-Cyanophenylhydrazono)-3-(1,2,4-trizol-3-ylimino)-l-(2-thienyl)-l-propanone (**11b**)*

Compound **11b** was obtained as orange crystals (85%), m.p. 252 °C. IR: $\tilde{\nu}_{max}$(KBr) (show complex spectra due to keto-enol forms with H-bond between O and NH), 3290 (NH triazole), 2220 (C≡N) and 1640 cm^{-1} (C=O ketone); ^{1}H NMR (200 MHz, DMSO-d$_6$): $\delta = 7.23-7.97$ (m, 5H, thienyl H-5 and 4H, arom-H), 8.18 – 8.20 (m, 2H, thienyl H-3, H-4), 8.42 (s,1H, CH olefinic), 8.74 (s, 1H, 1,2,4-triazole NH), 9.35 (s, 1H, 1,2,4-trizol H-5) and 15.26 ppm (s, 1H, NH hydrazone).; ^{13}C NMR (200 MHz, DMSO-d$_6$): 116.0 (C≡N), 116.80, 117.18, 124.87, 131.98, 133.96, 135.41 (*C*$_6$H$_4$-CN), 122.8, 125.3, 127.5, 142.6 (thienyl carbons), 143.90 (*C*=N-N), 147.0 (1,2,4 trizol-carbon), 155.64 (N=*C*H-C), and 178.0 ppm. (C=O) MS [EI, 70 eV]: $m/z = [M^+]$ (349). Analysis for $C_{16}H_{11}N_7OS$: calcd. C 55.01, H 3.17, N 28.06; found C 54.90, H 3.20, N 28.20.

*6-(2-Cyanophenylazo)-7-phenyltrizolo[1,5-a]pyrimidine (**12a**)*

Compound **12a** was obtained as orange crystals (87%), m. p. 220 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$): $\delta = 7.30-7.93$ (m, 9H, arom-H), 8.61, 8.80 ppm (2s, 1H, H-2, H-5); ^{13}C NMR (200 MHz, DMSO-d$_6$): $\delta = 116.5$ (C≡N), 129.0, 130.1, 134.3, 136.7 (phenyl carbons); 129.09, 134.06, 135.48, 139.69, 139.83, 148.12 (*C*$_6$H$_4$CN); 147.9 (C-2), 150.1 (C-3a), 151.8 (C-5), 144.2 (C-6), 158.2 ppm (C-7); MS [EI, 70 eV]: $m/z = [M^+]$ (325). Analysis for $C_{18}H_{11}N_7$: calcd. C 66.46, H 3.40, N 30.14; found C 66.50, H 3.50, N 30.0.

*6-(2-Cyanophenylazo)-7-(2-thienyl)-trizolo[1,5-a]pyrimidine (**12b**)*

Compound **12b** was obtained as green crystals (85%), m. p. 203 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$): $\delta = 7.66-7.94$ (m, 9H, thienyl, H-5 and 8H, arom-H), 8.14 – 8.21 (m, 2H, thienyl, H-3, H-4), 8.66 – 8.84 ppm (2s, 1H, H-3, H-7); ^{13}C NMR (200 MHz, DMSO-d$_6$): $\delta = 116.5$ (C≡N), 122.8, 125.3, 127.5, 142.6 (thienyl carbons), 129.09, 134.06, 135.48, 139.69, 139.83, 148.12 (*C*$_6$H$_4$CN); 148.9 (C-2), 150.9 (C-3a), 153.8 (C-5), 143.2 (C-6), 159.2 ppm (C-7); MS [EI, 70 eV]: $m/z = [M^+]$ (331). Analysis for $C_{16}H_9N_7S$: calcd. C 57.99, H 2.73, N 29.59; found C 57.80, H 2.90, N 29.40.

General Procedure for the preparation of **14**, **15**

A mixture of compounds **3a,b** (0.1 mol) and 5-methyl-2,4-dihydro-pyrazol-3-one (0.1 mol) in glacial acetic (30 ml) and (0.1 mol) of ammonium acetate, was refluxed for 3 h. The precipitated material was isolated by filtration and recrystallized from ethanol.

*4,8-Dibenzoyl-2,6-di(2-Cyanophenyl)-9-oxo-2,3,6,7-tetra-azabicyclo[3.3.1]nona-3,7-diene (**14**)*

Compound **14** was obtained as dark yellow crystals (87%), m.p. 260 °C. ^{1}H NMR (200 MHz, DMSO-d_6): $\delta =$ 4.01 (2s, 2H, CH); 6.41 – 8.03 ppm (m, 18H, arom-H); ^{13}C NMR (200 MHz, DMSO-d_6): $\delta = 190.0$ (CO), 77.8 (C-1), 154.0 (C-4), 117.8 (C≡N), 96.3, 113.0, 117.0, 132.8, 134.8, 147.0 (C_6H_4CN); 129.0, 130.1, 134.3, 136.7 ppm (phenyl carbons); MS [EI, 70 eV]: $m/z = [M^+]$ (536). Analysis for $C_{32}H_{20}N_6O_3$: calcd. C 71.89, H 3.81, N 15.71; found C 71.63, H 3.76, N 15.66.

*4-Amino-3-benzoyl-cinnoline-8-carboxylic acid methyl ester (**15**)*

Compound **15** was obtained as pale brown crystals (85%), m. p. 210 °C. ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 4.2$ (s, 3H, CH_3), 5.21 (b, s, 2H, NH_2), 7.53 – 8.60 ppm (m, 8H, arom-H); ^{13}C NMR (200 MHz, DMSO-d_6): $\delta = 50.0$ (CH_3), 168.0 (CO), 137.4 (C-3), 141.0 (C-4), 118 (C-4a), 127.6 (C-5), 130.4 (C-6), 138.4 (C-7), 128.8 (C-8), 151.4 (C-8a), 193.6 (C-9), 137.0 (C-10), 131.8 (C-11), 129.3 (C-12), 134.3 ppm (C-13); MS [EI, 70 eV]: $m/z = [M^+]$ (307). Analysis for $C_{17}H_{13}N_3O_3$: calcd. C 66.23, H 4.27, N 13.70; found C 66.44, H 4.26, N 13.67.

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