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Structural revision in the reactions of 3-cyanochromones with primary aromatic amines. Improved synthesis of 2-amino-3-(aryliminomethyl)chromones

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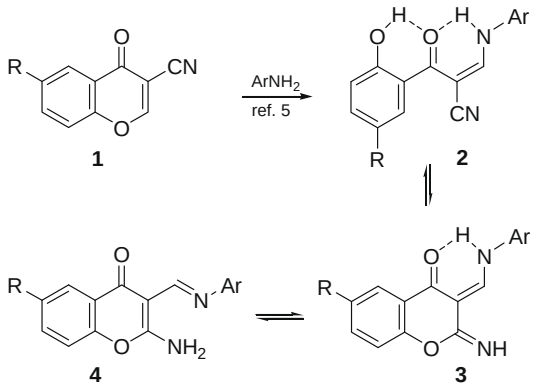
ABSTRACT

3-Cyanochromones react with primary aromatic amines to give 2-amino-3-(aryliminomethyl)chromones as the sole products or as their mixtures with *Z*- and *E*-3-anilino-2-salicyloylacrylonitriles, depending on the reaction conditions. With aliphatic amines, 2-amino-3-(alkyliminomethyl)chromones are obtained in good yields. The reaction of 3-cyanochromone with *o*-phenylenediamine is reinvestigated and proof for the product structure and a possible reaction pathway are presented.

Introduction of the electron-withdrawing CN group at the 3-position of a chromone system significantly changes the reactivity of the pyrone ring with respect to nucleophiles, and provides broad synthetic potential for 3-cyanochromone **1**.[1] Among the diverse transformations of **1**, one of the most important is its conversion, on heating with morpholine in an aqueous DMF,[2] with *n*-propylamine in an aqueous ethanol[3] or in the presence of NaOH in water,[4] into 2-amino-3-formylchromone. On heating at reflux with ethylenediamine in ethanol, chromone **1** gives 2-amino-3-formylchromone together with 2-(salicyloylmethylene)tetrahydroimidazole as a minor product.[3] However, to the best of our knowledge, very little is known about the reaction of **1** with primary aromatic amines. There is only one report on the reaction of 3-cyano- and 3-cyano-6-methylchromones **1** with *p*-toluidine in benzene at reflux.[5] It was claimed that benzene induces the initial 1,4-addition of *p*-toluidine and the product of this reaction, 2-amino-3-(*p*-tolyliminomethyl)chromone **4**, depending on the conditions, can exist solely or partially as its two other tautomeric forms **2** and **3** (Scheme 1). For example, according to the ^{1}H NMR spectrum in $CDCl_3$, the Schiff base **4** (R = Me) has been described as its enamine form **3** ($^3J_{H,NH}$ = 13.0 Hz), while in the solid state it exists as the acrylonitrile **2** (ν_{CN} = 2210 cm^{-1} in KBr).[5] However, structure **3** was not established with certainty and remains open to question, especially since we noted the unusually downfield shifted signal due to the H-5 aromatic proton (δ 8.20 ppm), which is typically manifested in the 6-methylchroman-4-one series at ca. δ 7.7 ppm. It seemed more logical to us that the reaction of **1** with *p*-toluidine would produce a mixture of **4** and open-chain form **2** where the H-6 aromatic proton (H-5 in **3**) is shifted downfield due to the deshielding effect of the cyano group in a planar confor-



R = H (**a**), Me (**b**); Ar = *p*-MeC$_6$H$_4$

Scheme 1.

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mation. The latter should be stabilized in $CDCl_3$ solution by two intramolecular hydrogen bonds involving the NH and OH protons and the carbonyl group.

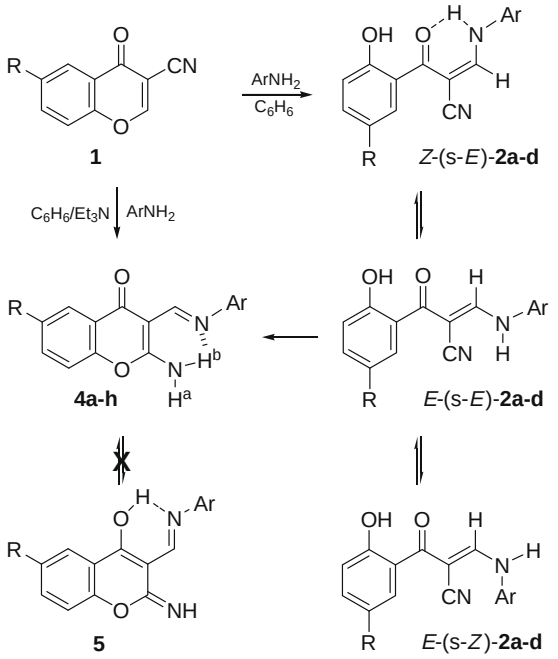
We therefore repeated the reactions of chromones **1** with aniline and *p*-methyl-, *p*-methoxy-, and *p*-bromoanilines following the literature method (reflux, benzene, 4 h).[5] We also used benzyl- and isopropylamines in order to determine whether aliphatic substituents influence the structure of the reaction products. In the case of 3-cyano-6-methylchromone **1** (R = Me) and aniline, we obtained a 77:23 mixture ($CDCl_3$) of isomers *Z*-**2a** and *E*-**2a**,[6] having s-*E* conformation at the C–N bond, and no traces of **4a**. *p*-Methyl- and *p*-methoxyanilines gave similar product mixtures along with a small amount of **4b, c** (6–17%). It is a well-established phenomenon with push–pull alkenes, that the *Z*/*E* equilibrium is dependent on the solvent polarity.[7] Indeed, in DMSO-d_6, the equilibrium was shifted toward the *E*-**2** isomer (Table 1). This result can be explained by considering the fact that the formation of *Z*-**2** is preferred in solvents of low polarity, such as chloroform, due to the presence of the intramolecular hydrogen bond between the NH and carbonyl group, whereas in high polarity solvents, such as DMSO, isomer *E*-**2** may be more favorable due to the strength of the intermolecular hydrogen bond. The structural assignment of compounds **2** as the *Z*- and *E*-isomer of 3-anilino-2-salicyloylacrylonitriles was based on ^1H, ^{13}C, and ^{15}N NMR spectroscopy. In addition, all the signals in the ^1H and ^{13}C NMR spectra of **2a** were assigned on the basis of 2D ^1H–^{13}C HSQC and HMBC experiments. Consequently, structure **3** should be revised to **2** (Scheme 2).

The different isomeric forms of acrylonitriles **2** have characteristic ^1H NMR spectra. Thus, the vicinal coupling constant, $^3J_{H,NH}$ = 13.5 Hz, found for *Z*-**2** is in agreement with the fixed s-*E* conformation around the C–N bond. The signal corresponding to the NH proton appears at ca. 12.5 ppm and is only slightly dependent on the solvent polarity; this provides evidence that the proton is involved in an intramolecular hydrogen bond and is in agreement with the *Z* configuration. The doublet due to the NH proton of *E*-**2** exists at much higher field than that of *Z*-**2** (ca. δ 8.1 ppm in $CDCl_3$) and is shifted downfield with increasing solvent polarity (ca. δ 11.0 ppm in DMSO-d_6). Therefore, it can be concluded that this proton is involved in an intermolecular hydrogen bond. In $CDCl_3$, the large $^3J_{H,NH}$ = 15.2 Hz value allowed us to assign the s-*E* conformation to the C–N bond of *E*-**2**, however, the corresponding coupling was not observed in DMSO-d_6 solution where the NH and =CH protons appeared as slightly broadened singlets. This may be attributed to the s-*Z* conformation in which the coupling constant due to the NH proton (usually $^3J_{H,NH}$ = 7–8 Hz) can be decreased or eliminated, depending on the amount of water present in the solvent and the solute concentration.[7] These spectral data are in line with the structures proposed for isomers **2a–d**.

Table 1
^1H NMR analysis of the reaction products in $CDCl_3$ and DMSO-d_6

Product	R	Ar	*Z*-**2**/*E*-**2**/**4**[a] (%)	Yield (%)
2a	Me	Ph	77:23:0[b]	36
2a	Me	Ph	35:65:0[c]	–
2b + **4b**	Me	4-MeC_6H_4	84:10:6[b,d]	51
2b + **4b**	Me	4-MeC_6H_4	35:60:5[c]	–
2c + **4c**	Me	4-$MeOC_6H_4$	76:7:17[b]	81
2c + **4c**	Me	4-$MeOC_6H_4$	30:50:20[c]	–
2d + **4d**	H	4-MeC_6H_4	25:0:75[b,d]	54
4e	H	4-$MeOC_6H_4$	0:0:100[b,c]	64
4f	H	4-BrC_6H_4	0:0:100[c]	80
4g	H	$PhCH_2$[e]	0:0:100[b,c]	57
4h	H	*i*-Pr[e]	0:0:100[c]	65

[a] The ratio of products was determined from the ^1H NMR spectra.
[b] In $CDCl_3$.
[c] In DMSO-d_6.
[d] Previously[5] this product was described as an equilibrium mixture of **2**, **3**, and **4**.
[e] Ar = aliphatic.

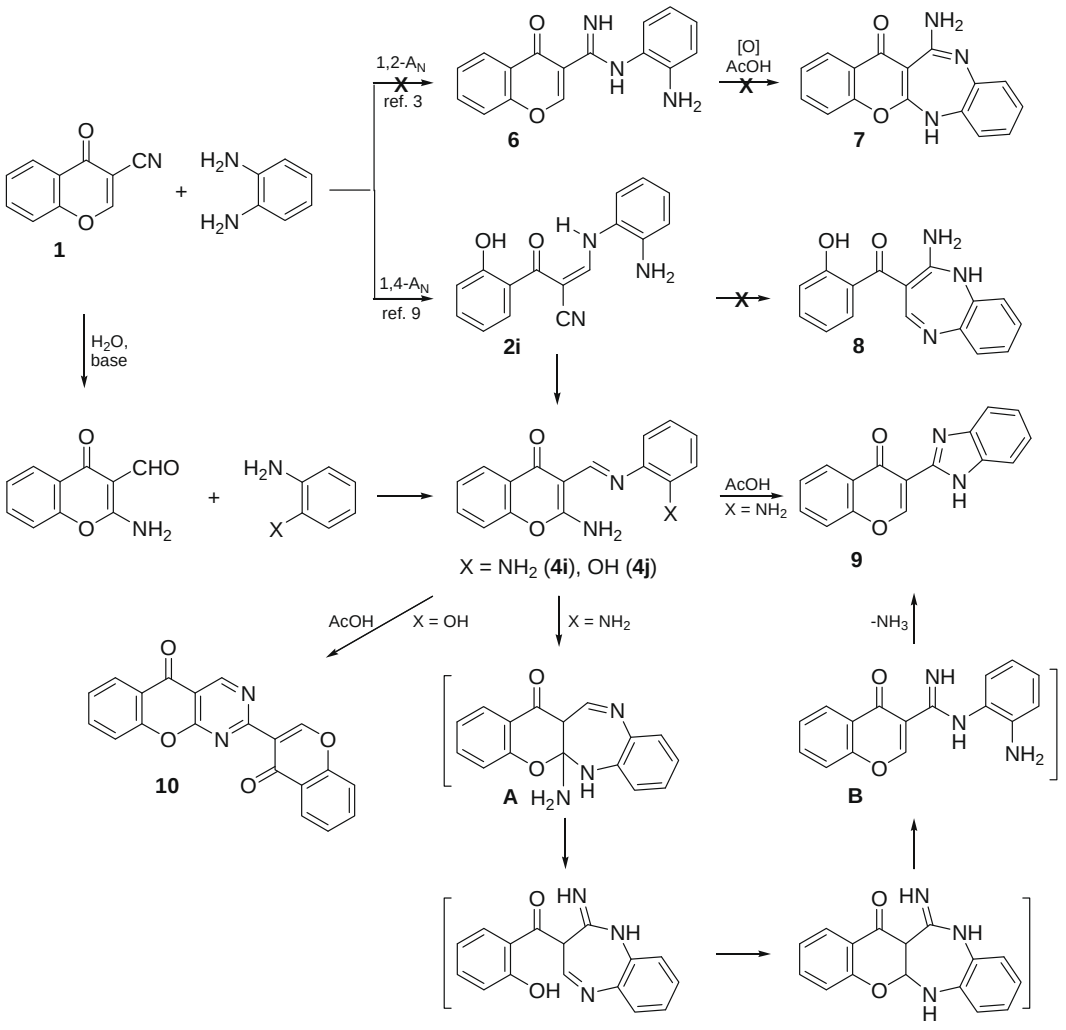


Scheme 2.

The reaction of 3-cyanochromones with amines turned out to be very sensitive to the nature of the substituent at the 6-position. When **1** (R = H) was allowed to react with *p*-substituted anilines, and benzyl- and isopropylamines in benzene at reflux for 4 h, the initially formed intermediates **2** could not be isolated and underwent rapid cyclization via addition of the phenolic hydroxy to the CN group to give chromone derivatives **4d–h** as the sole products in 54–80% yields (except for **4d**, which was isolated as a 1:3 mixture of **2d** and **4d**). This remarkable change from product **2** to product **4** on changing the C-6 substituent of **1** from methyl to hydrogen possibly results from the electron-donating effect of the 5-Me group of **2**, which decreases the acidity of the OH group. In accordance with this, chromones **4a–d** were obtained in pure form (68–98% yields) under the same reaction conditions in the presence of two drops of triethylamine, which accelerates the cyclization step via deprotonation of the phenolic hydroxy group of intermediate **2**.

The ^1H NMR spectra of compounds **4** in DMSO-d_6 consisted of a characteristic singlet due to the =CH proton at ca. δ 9.0 and two singlets due to the resonances of the non-equivalent NH_2 protons at δ 9.3–9.4 (H^a) and 10.5–10.7 (H^b). Addition of CD_3CO_2D resulted in the disappearance of the two latter signals. All the signals in the ^1H and ^{13}C NMR spectra of compound **4f**[8] were assigned on the basis of 2D ^1H–^{13}C HSQC and HMBC experiments. The choice between the tautomeric forms **4** and **5** was made in favor of the former on the basis of 2D ^1H–^{15}N HMQC and HMBC experiments. Since the ^{15}N chemical shifts relative to ammonia are δ 98.9 (NH_2) and 287.4 (N=C) (for **4f**), the structure **5** with the two imine nitrogen atoms is excluded. It is reasonable to assume that the non-equivalence of the NH_2 protons is connected with an intramolecular hydrogen bond involving H^b and the imine nitrogen atom. This explains the formation of *E*-anils **4**, exclusively.

In the light of these findings, we envisaged that the reaction of 3-cyanochromone with *o*-phenylenediamine would produce the corresponding anil **4i**. However, the reported structures **6** and **8** of the reaction product of **1** with *o*-phenylenediamine, differed from our results. It was claimed that the reaction occurred via 1,2-addition of *o*-phenylenediamine to the cyano group to form amidine **6**, which on further reflux in AcOH gave benzodiazepine



Scheme 3.

7,[3] or via initial attack at the electrophilic C-2 atom (1,4-addition) followed by intramolecular cyclization involving the amino and cyano groups to form benzodiazepine **8**, which was transformed into benzimidazole **9** by treatment with AcOH[9] (Scheme 3).

In order to clarify this discrepancy, we repeated the reaction of **1** with *o*-phenylenediamine at reflux in ethanol (benzene can also be used) and found that the product was, in fact, the expected 2-amino-3-(2-aminophenyliminomethyl)chromone **4i**,[10] instead of the reported compounds **6** and **8**. Close scrutiny of the ^{1}H and ^{13}C NMR spectral data provided in Ref. 9 (unfortunately, in Ref. 3, no spectral data of **6** are given) revealed that the benzodiazepine structure **8** was assigned erroneously to the reaction product. Risitano et al.[9] assigned the signal at δ 179 to the C=O group of the salicyloyl moiety, whereas this carbon usually resonates at about δ 190 in similarly constituted molecules. Moreover, in the ^{1}H NMR spectrum, all the protons of the benzene ring were shifted to a lower field in comparison with those of the salicyloyl fragment. When anil **4i** (this compound was also obtained from 2-amino-3-formylchromone and *o*-phenylenediamine) was refluxed in acetic acid for 3 h, the known benzimidazole **9**[11] was obtained, and not the earlier claimed,[3] on the basis of the incorrect structure **6**, benzodiazepine **7**. Consequently, structures **6** and **8** should be revised to **4i** and structure **7** changed into **9**. A possible route for the transformation of **4i** into **9** occurs via rearrangement of intermediates **A** to **B** through addition–elimination sequences as outlined in Scheme 3. Interestingly, when anil **4j**, prepared from 2-amino-3-formylchromone and *o*-aminophenol, was refluxed in AcOH, the expected 1,3-benzoxazole derivative was not isolated. Instead, the known self-condensation product of 3-cyanochromone, 2-(4-oxo-4*H*-chromen-3-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-5-one **10**,[3] was obtained in 67% yield.

In conclusion, 3-cyanochromones are very reactive systems and are useful synthetic building blocks in medicinal chemistry. Since the identity of some of their reaction products with primary aromatic amines was in doubt, we have reinvestigated these reactions and found that the mixtures of 2-amino-3-(aryliminomethyl)chromones and their open forms, *Z*- and *E*-3-anilino-2-salicyloylacrylonitriles, were obtained in variable proportions depending on the nature of the substituents and the conditions used. When the reaction was carried out at reflux in benzene in the presence of triethylamine, 2-amino-3-(aryliminomethyl)chromones were formed as the sole products.

Acknowledgment

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6. *3-Anilino-2-(2-hydroxy-5-methylbenzoyl)acrylonitrile* **2a**. This compound was prepared from chromone **1** (R = Me) and aniline according to the procedure described previously for **3**.[5] Yield 36%, mp 226–228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (*Z*-**2a**, 77%) δ 2.34 (s, 3H, Me), 6.91 (d, 1H, H-3, *J* = 8.4 Hz), 7.22–7.32 (m, 4H, H-2′, H-6′, H-4′, H-4), 7.46 (t, 2H, H-3′, H-5′, *J* = 7.9 Hz), 8.05 (d, 1H, =CH, *J* = 13.4 Hz), 8.19 (br d, 1H, H-6, *J* = 1.5 Hz), 11.17 (s, 1H, OH), 12.45 (br d, 1H, NH, *J* = 13.4 Hz); (*E*-**2a**, 23%) δ 2.35 (s, 3H, Me), 6.92 (d, 1H, H-3, *J* = 8.4 Hz), 7.21–7.50 (m, 6H, H-4, Ar), 8.10 (br d, 1H, H-6, *J* = 1.7 Hz), 8.18 (br d, 1H, NH, *J* = 15.2 Hz), 8.80 (d, 1H, =CH, *J* = 15.2 Hz), 11.68 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*-**2a**) δ 20.60 (Me), 82.38 (C2), 118.05 (C2″, C6″), 118.15 (C3′), 119.35 (C1′), 120.34 (CN), 126.92 (C4″), 128.17 (C5′), 129.08 (C6′), 130.22 (C3″, C5″), 136.78 (C4′), 137.84 (C1″), 155.03 (C3), 159.26 (C2′), 193.14 (C1); (*E*-**2a**) δ 84.02 (C2), 129.44 (C6′), 137.98 (C1″), 154.45 (C3), 160.06 (C2′), 188.90 (C1) (the remaining carbon atoms were not observed due to their intensities being too low); ^{1}H NMR (400 MHz, DMSO-d_6) (*Z*-**2a**, 35%) δ 2.23 (s, 3H, Me), 6.81 (d, 1H, H-3, *J* = 8.2 Hz), 7.10–7.16 (m, 2H, H-4, H-6), 7.24 (tt, 1H, H-4′, *J* = 7.4, 1.0 Hz), 7.41–7.46 (m, 2H, H-3′, H-5′), 7.55–7.59 (m, 2H, H-2′, H-6′), 8.54 (d, 1H,=CH, *J* = 13.5 Hz), 9.93 (s, 1H, OH), 12.31 (br d, 1H, NH, *J* = 13.5 Hz); (*E*-**2a**, 65%) δ 2.23 (s, 3H, Me), 6.82 (d, 1H, H-3, *J* = 8.2 Hz), 7.10–7.16 (m, 2H, H-4, H-6), 7.18 (tt, 1H, H-4′, *J* = 7.4, 1.0 Hz), 7.28–7.32 (m, 2H, H-2′, H-6′), 7.36–7.41 (m, 2H, H-3′, H-5′), 8.13 (br s, 1H, =CH), 9.95 (br s, 1H, OH), 10.99 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) (*Z*-**2a**) δ 19.91 (Me), 85.48 (C2), 116.27 (C3′), 118.19 (C2″, C6″), 119.92 (CN), 125.77 (C4″), 126.59 (C1′), 127.24 (C5′), 128.24 (C6′), 129.62 (C3″, C5″), 132.45 (C4′), 138.46 (C1″), 152.67 (C2′), 153.59 (C3), 193.05 (C1); (*E*-**2a**) δ 19.91 (Me), 86.75 (C2), 116.17 (C3′), 116.73 (CN), 118.33 (C2″, C6″), 125.20 (C4″), 125.63 (C1′), 127.70 (C5′), 129.19 (C6′), 129.62 (C3″, C5″), 132.56 (C4″), 139.78 (C1″), 152.83 (C2′), 154.23 (C3), 189.69 (C1); ^{15}N NMR (40 MHz, DMSO-d_6) (*Z*-**2a**) δ 137.6 (NH), (*E*-**2a**) 132.1 (NH). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.56; H, 5.33; N, 10.28.
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8. *2-Amino-3-(p-bromophenyliminomethyl)chromone* **4f**. This compound was prepared according to the procedure described previously.[5] Yield 80%, mp 253–254 °C; IR (KBr) 3211, 3075, 1655, 1605, 1564, 1519 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 (d, 2H, H-2′, H-6′, *J* = 8.7 Hz), 7.42–7.46 (m, 2H, H-6, H-8), 7.56 (d, 2H, H-3′, H-5′, *J* = 8.7 Hz), 7.72 (ddd, 1H, H-7, *J* = 8.5, 7.2, 1.7 Hz), 8.05 (dd, 1H, H-5, *J* = 7.8, 1.7 Hz), 8.97 (s, 1H, =CH), 9.47 (br s, 1H, NH^a), 10.52 (br s, 1H, NH^b); ^{13}C NMR (100 MHz, DMSO-d_6) δ 95.05 (C3), 116.73 (C8), 117.64 (C4′), 121.83 (C4a), 123.15 (C2′, C6′), 125.09 (C6), 125.22 (C5), 132.03 (C3′, C5′), 133.50 (C7), 150.27 (C1′), 152.86 (C8a), 156.46 (C=N), 164.25 (C2), 173.89 (C4); ^{15}N NMR (40 MHz, DMSO-d_6) δ 98.9 (NH_2), 287.4 (N=C). Anal. Calcd for $C_{16}H_{11}BrN_2O_2$: C, 56.00; H, 3.23; N, 8.16. Found: C, 55.86; H, 3.35; N, 7.98.
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10. *2-Amino-3-(2-aminophenyliminomethyl)chromone* **4i**. This compound was prepared from 3-cyanochromone and *o*-phenylenediamine according to the procedure described previously for **6**.[3] Yield 46%, mp 217–218 °C (lit.[3] mp 210 °C, lit.[7] mp 217 °C); IR (KBr) 3330, 3180, 1664, 1601, 1559, 1521, 1498, 1462 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.02 (s, 2H, NH_2), 6.59 (ddd, 1H, H-5′, *J* = 7.8, 7.3, 1.0 Hz), 6.73 (dd, 1H, H-3′, *J* = 7.8, 0.8 Hz), 6.87 (dd, 1H, H-6′, *J* = 7.8, 0.8 Hz), 6.93 (ddd, 1H, H-4′, *J* = 7.8, 7.3, 1.0 Hz), 7.41–7.47 (m, 2H, H-6, H-8), 7.71 (ddd, 1H, H-7, *J* = 8.2, 7.4, 1.6 Hz), 8.06 (dd, 1H, H-5, *J* = 7.7, 1.6 Hz), 8.91 (s, 1H, =CH), 9.30 (s, 1H, NH^a), 10.39 (s, 1H, NH^b). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 69.04; H, 4.67; N, 15.09.
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