Regioorientation in the Addition Reaction of α-Substituted Cinnamonitrile to Enamines Utilizing Chitosan as a Green Catalyst: Unambiguous Structural Characterization Using 2D-HMBC NMR Spectroscopy

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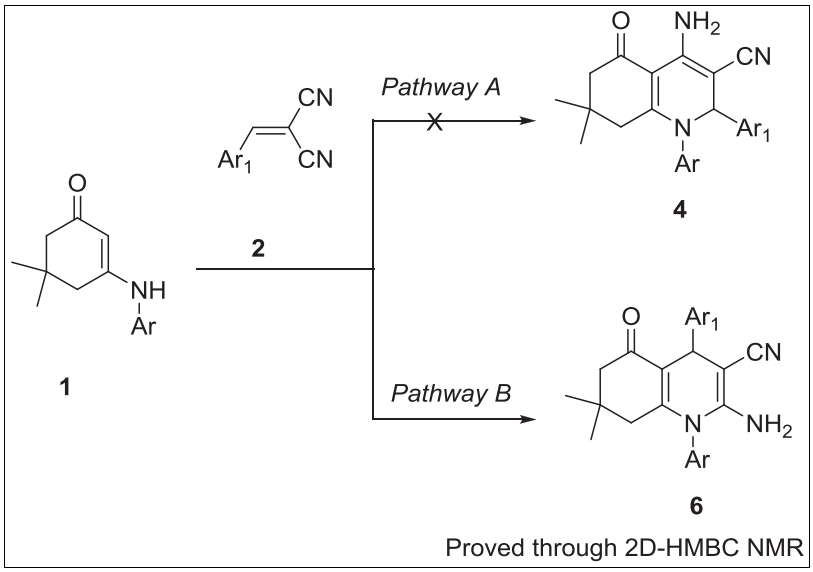
Received June 17, 2014
DOI 10.1002/jhet.2341
Published online 11 June 2015 in Wiley Online Library (wileyonlinelibrary.com).



Hexahydroquinolines and their fused derivatives are obtained in good to excellent yields by proceeding through a simple, mild, and efficient procedure including the reaction of enamines with substituted cinnamonitriles using DABCO, piperidine, or chitosan as catalysts. The regioorientation of Michael addition was established with no doubt using the 2D-HMBC spectroscopy.

J. Heterocyclic Chem., **53**, 817 (2016).

INTRODUCTION

Enamines are versatile reagents, and the nucleophilic character of C-2 has found extensive applications in synthetic organic chemistry [1,2]. Also, it is known that quinoline derivatives are an important class of heterocycles of considerable interest, which have been the subject of extensive research, particularly in the pharmaceutical field, including antibacterial [3–5] and anticancer [6–12] activities, so their synthesis and applications have been comprehensively reviewed [3–7]. Despite the biological importance of quinolones and their fused derivatives, studies on their synthesis are rather limited, which include two- [8a,b], three- [8c], and four-component reactions [8d,e]. This contribution describes the full details of our investigation on the synthesis of hexahydroquinolines and their fused derivatives through the two-component reactions of the cyclic enaminones with the arylidenemalononitrile derivatives.

RESULTS AND DISCUSSIONS

Although the synthesis of biologically interesting hexahydroquinoline derivatives has been investigated in the past [13–20], there is still demand for more concise and efficient elucidation of molecular structure especially using 2D-NMR spectroscopy. In conjunction of this work, we report here the results of our investigations aimed at exploring synthetic potentials of the functionally substituted enamines **1**, **7**, **11**, **14**, and **17**, which were prepared according to the procedure originally reported by Karimi-Jaberi *et al.* [21]. Thus, the Michael addition reaction of the cyclic enaminone **1** toward α,β-unsaturated nitriles was investigated. The reaction of the cyclic enaminone **1** with arylidenemalononitriles **2a–d** affords products for which several isomeric structures seemed possible. The reaction product is either 4-aminohexahydroquinoline-3-carbonitrile **4** that results from initial addition of NH to the activated double bond in **2** (pathway A) or

2-aminohexahydroquinoline-3-carbonitrile **6** that results from initial addition of enamine CH to activated double bond in **2** to yield **5** that readily cyclizes into **6** (pathway B). However, ^{1}H and ^{13}C-NMR simply cannot differentiate the two isomers. In the present study, HMBC experiments unambiguously solved this problem as the decisive difference between the alternative structures **4** and **6** in the HMBC measurement of compound **6d** is due to the fact that in case of compound **6d**, quinoline hydrogen-H4 at $\delta = 4.42$ ppm shows a cross peak which indicates a ^{3}J coupling to CO at $\delta = 195.5$ ppm. (Fig. 1; Scheme 1).

In order to provide chemical evidence for the proposed structure, we investigated the Michael addition reaction of enamine **7** with methyl carboxylate ester on ortho position, where only further cyclization occurred in the case of 2-aminohexahydroquinoline-3-carbonitrile, whereas in the case of 4-aminohexahydroquinoline-3-carbonitrile, no further cyclization occurred. Thus, the reaction results in the formation of product of cyclization with methanol elimination to give compounds **10**.

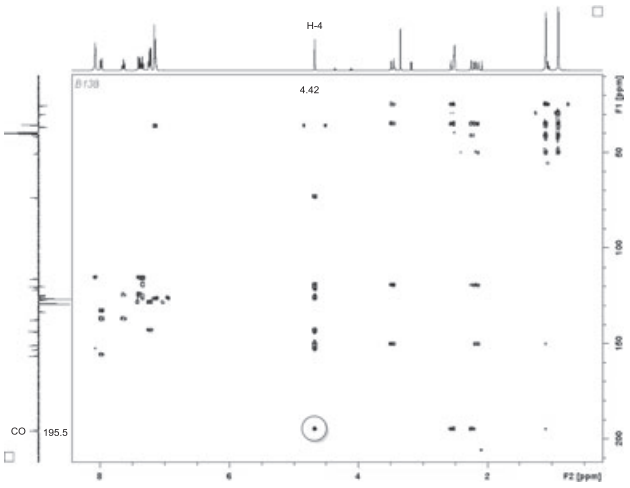


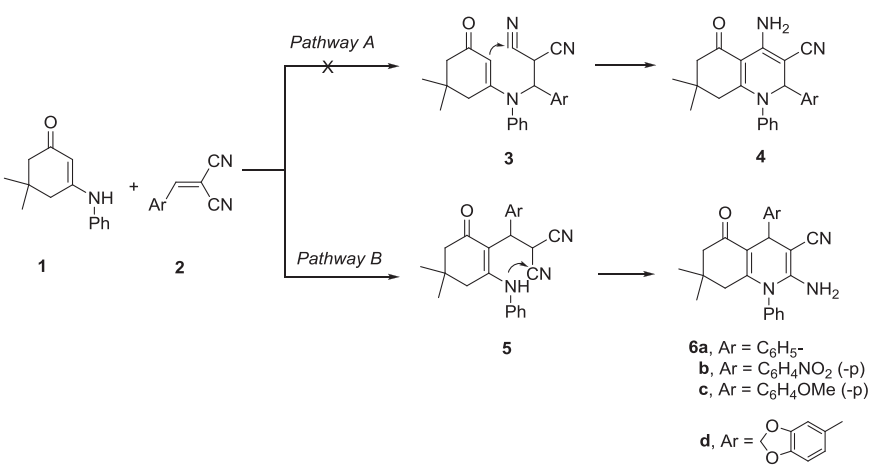
Figure 1. 2D-HMBC NMR spectrum of compound **6d**.

The structure of compound **10a** was confirmed based on the spectroscopic data that revealed the absence of methoxy group. The mass spectrum of **10a** revealed molecular ion peak as a base peak at *m*/*z* 395 corresponding to the loss of methanol. ^{1}H NMR also revealed the absence of OMe protons in the area 3.6–4.0 ppm. In addition, it indicated the presence of a broad singlet signal at 11.69 ppm corresponding to the NH group (cf. Scheme 2).

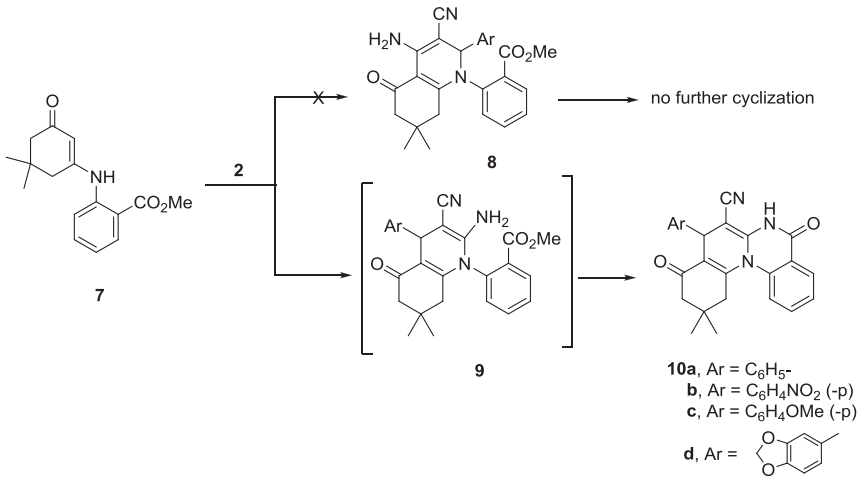
In a similar manner, the reaction of enamine **11** [22] with **2** has resulted in the formation of compounds **13**. Structure **13** was readily established based on IR and ^{13}C NMR that revealed the presence of one CN band and signal. We also managed to establish the structure of the product with certainty through 2D-HMBC measurements of compound **13a**, which revealed H-8 at $\delta = 4.67$ ppm that shows a cross-peak that indicates a ^{3}J coupling to CO at $\delta = 195.8$ ppm (Fig. 2; Scheme 3).

Encouraged by the results acquired from enamines **1**, **7**, and **11**, we attempted to expand the scope of this reaction to prepare pentacyclic structures. Thus, enamines incorporating a tetrahydrothiophene moiety **14** and **17** were prepared. The reaction of enamine **14** with **2** results in the formation of product of cyclization with ethanol elimination to give the benzothienopyrimidoquinoline derivatives **16**. The formation of such pentacyclic product **16** supports our suggestion that the reaction proceeds via initial addition of the enamine CH in compound **14** to the activated double bond in **2** followed by cyclization rather than initial addition of NH in **14** to the double bond in **2**. The structure of compound **16** was established through inspection of their spectroscopic data. The mass spectrum of **16d** revealed molecular ion peak as a base peak at *m*/*z* 499. ^{1}H NMR revealed the disappearance of OEt group and the appearance of NH as a broad singlet at 11.26 ppm. In addition, it revealed a singlet signal at 4.57 ppm corresponding to H-5.

Scheme 1



Scheme 2



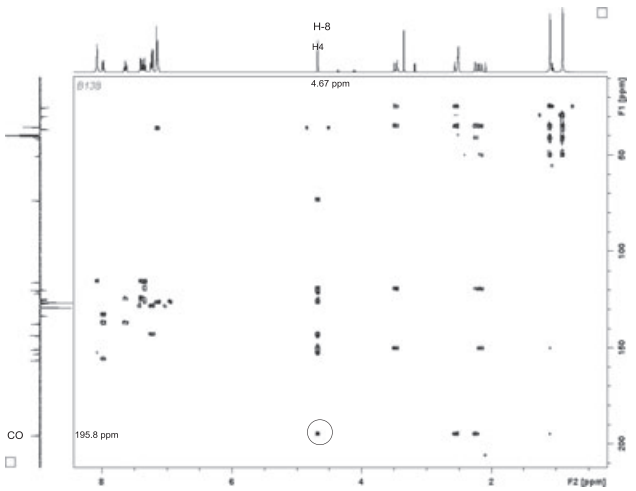


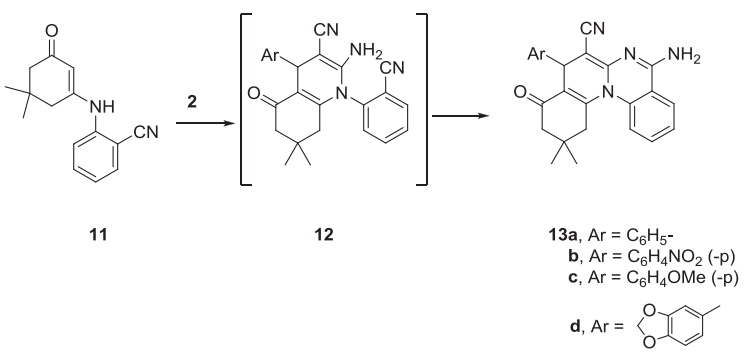
Figure 2. 2D-HMBC NMR spectrum of compound **13a**.

^{13}C NMR was found also to be in agreement with the proposed structure where it showed amidic carbonyl at 157 ppm in addition to the ketonic carbonyl at 195.8 ppm. All other carbon signals appeared at their expected positions (cf. Scheme 4).

In an extension of this reaction, the cyclic enamine **17** carrying CN group on the thiophene ring was prepared. The reaction of enamine **17** with **2** leads to the formation of the pentacyclic structures **19**. The structure of **19a** was established based on spectral data. The ^{1}H NMR spectrum of **19a** indicated two singlet signals at $\delta = 0.96$ and 1.1 ppm for the two methyl groups. It also featured characteristic set of multiplets at $\delta = 1.84$ and 2.64 for the methylene protons. It indicated a singlet signal at $\delta = 4.4$ ppm assigned for H-5. In addition, it indicated a broad singlet at $\delta = 6.17$ ppm for NH_2. It also revealed aromatic protons as multiplets at $\delta = 7.07$ and 7.32. Furthermore, full assignment of the ^{13} C-NMR data confirmed the structure of **19a**, where the key signal at $\delta = 36.6$ was assigned to C-5 and signal at 195.8 ppm assigned to CO group.

In this study, different catalysts were used including piperidine and DABCO. Also, in conjunction with our interest in the utility of green benign approaches in organic synthesis [23,24], we used the green heterogeneous basic catalyst chitosan. The percentage yields were compared in each case, and it was found that chitosan and DABCO were highly effective in most cases (the percentage yields are cited in Table 1; Scheme 5).

Scheme 3



Scheme 4

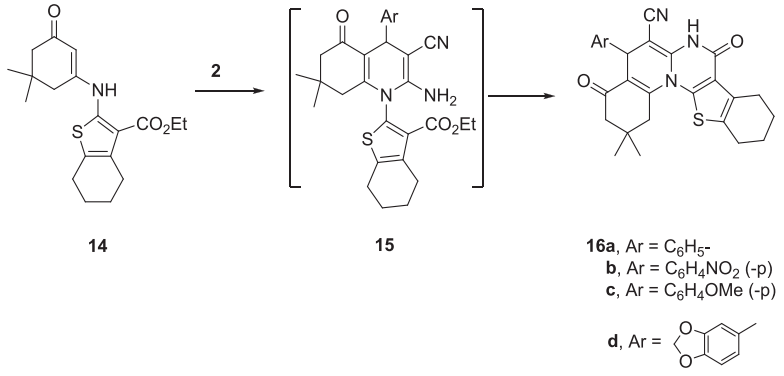
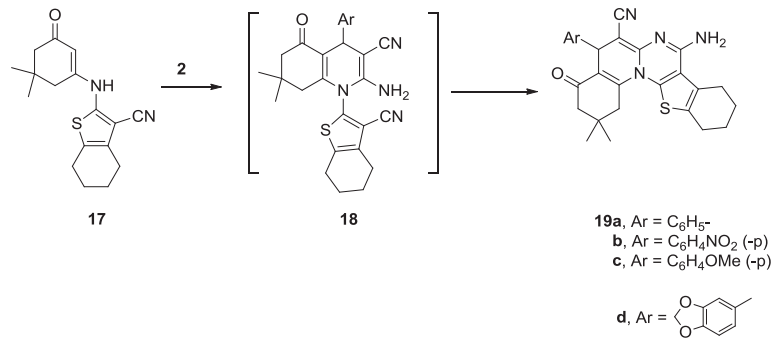


Table 1

Comparison of percentage yield of products obtained from piperidine, chitosan, and DABCO.

	% Yields				% Yields		
Entry	Piperidine	DABCO	Chitosan	Entry	Piperidine	DABCO	Chitosan
6a [25,26]	88	90	95	**13c**	74	92	83
6b	90	90	94	**13d**	72	96	81
6c [26]	85	93	96	**16a**	75	90	78
6d	82	89	94	**16b**	80	88	80
10a [27]	78	92	82	**16c**	69	85	78
10b	70	93	80	**16d**	72	86	82
10c	68	90	78	**19a**	73	93	88
10d	69	92	83	**19b**	72	91	86
13a	76	95	82	**19c**	75	88	82
13b	68	94	76	**19d**	80	93	84

Scheme 5



CONCLUSION

In conclusion, the synthesis of hexahydroquinoline and fused quinolines via reactions of different substituted cyclic enamines with unsaturated nitriles are very efficient. Moreover, DABCO and chitosan were found to be the best catalysts for this type of reactions. Furthermore, 2D-HMBC spectroscopy can be utilized effectively to establish, with certainty, the structures of the reaction products.

EXPERIMENTAL

Melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a Bruker-vector 22 spectrophotometer FTIR. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 300 and 75 MHz, respectively, on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMSS-QP-1000 EX mass spectrometer at 70 eV.

The enaminoketones **1** [21], **7** [21], **11** [22], **14** [28], and **17** [28] were prepared from the corresponding cyclohexa-1, 3-diones and amines according to procedures described in the literature.

General procedures for compounds 6a-d, 10a-d, 13a-d, 16a-d and 19a-d.

Method A. A mixture of 3-arylamino-5,5-dimethylcyclohex-2-enone **1**, **7**, **11**, **14**, or **17** (10 m*M*), and benzylidene derivatives **2a-d** was refluxed in dioxan (20 mL) in the presence of piperidine (0.5 mL) or DABCO (0.5 mL) for 6 h. The solvent was evaporated under vacuum, and the crude product was collected and crystallized from ethanol or ethanol/dioxan.

Method B. A mixture of 3-arylamino-5,5-dimethylcyclohex-2-enone **1**, **7**, **11**, **14**, **17** (10 m*M*), and benzylidene derivatives **2a-d** was refluxed in dioxan (20 mL) in the presence of chitosan (0.2 g) for 6 h. The solvent was evaporated under vacuum, and the crude product was collected and crystallized from ethanol or ethanol/dioxan. The catalyst, chitosan, is removed by filtration prior or during the crystallization process.

2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6b). This compound was obtained as yellow solid (ethanol), mp 264–266°C; ir: 3459, 3320 (NH_2), 2179 (CN) and 1645 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.73, 0.89 (2 s, 6H, $2CH_3$), 1.71–2.20 (m, 4H, $2CH_2$), 4.63 (s, 1H, CH), 5.50 (s, 2H, NH_2, D_2O exchangeable), 7.45–8.24 (m, 9H, Ar–H); MS (EI): *m/z* (%) = 414 (M^+).

Anal. Calcd for $C_{24}H_{22}N_4O_3$ (414.46): C, 69.55; H, 5.35; N, 13.52. Found: C, 69.36; H, 5.45; N, 13.73.

2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6d). This compound was obtained as yellow solid (ethanol), mp 258–260°C; ir: 3448, 3324 (NH_2), 2180 (CN) and 1655 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.76, 0.89 (2 s, 6H, $2CH_3$), 1.69–2.21 (m, 4H, $2CH_2$), 4.42 (s, 1H, CH), 5.32 (s, 2H, NH_2, D_2O exchangeable), 6.0 (s, 2H, $–OCH_2O–$), 6.74–7.62 (m, 8H, Ar–H); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 26.8, 29.5, 32.4, 36.6, 41.4, 49.8, 61.0, 101.3, 107.6, 108.7, 120.2, 121.9, 130.2, 130.4, 130.7, 136.7, 141.2, 146.1, 147.7, 150.5, 151.5, 195.5; MS (EI): *m/z* (%) = 413 (M^+).

Anal. Calcd for $C_{25}H_{23}N_3O_3$ (413.47): C, 72.62; H, 5.61; N, 10.16. Found: C, 72.58; H, 5.86; N, 10.39.

11,11-Dimethyl-5,9-dioxo-8-phenyl-6,8,9,10,11,12-hexahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile (10a). This compound was obtained as white solid (ethanol-dioxane), mp 290–292°C; ir: 3396 (NH), 2195 (CN), 1714 and 1652 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.91, 1.08 (2 s, 6H, $2CH_3$), 2.14–2.25 (m, 4H, $2CH_2$), 4.68 (s, 1H, CH), 7.19–7.98 (m, 9H, Ar–H), 11.69 (s, 1H, NH, D_2O exchangeable); MS (EI): *m/z* (%) = 395 (M^+).

Anal. Calcd for $C_{25}H_{21}N_3O_2$ (395.45): C, 75.93; H, 5.35; N, 10.63. Found: C, 76.11; H, 5.46; N, 10.96.

11,11-Dimethyl-8-(4-nitrophenyl)-5,9-dioxo-6,8,9,10,11,12-hexahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile (10b). This compound was obtained as yellow solid (ethanol-dioxane), mp 288–290°C; ir: 3438 (NH), 2198 (CN), 1696 and 1656 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.91, 1.08 (2 s, 6H, $2CH_3$), 2.15–2.26 (m, 4H, $2CH_2$), 4.85 (s, 1H, CH), 7.38–8.1 (m, 8H, Ar–H), 11.79 (s, 1H, NH, D_2O exchangeable); MS (EI): *m/z* (%) = 440 (M^+).

Anal. Calcd for $C_{25}H_{20}N_4O_4$ (440.45): C, 68.17; H, 4.58; N, 12.72. Found: C, 68.35; H, 4.72; N, 12.93.

8-(4-Methoxyphenyl)-11,11-dimethyl-5,9-dioxo-6,8,9,10,11,12-hexahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile (10c). This compound was obtained as yellow solid (ethanol-dioxane), mp 292–294°C; ir: 3381 (NH), 2193 (CN), 1690 and 1655 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.91, 1.08 (2 s, 6H, $2CH_3$), 2.06–2.27 (m, 4H, $2CH_2$), 3.67 (s, 3H, OCH_3), 4.61 (s, 1H, CH), 6.80–7.98 (m, 8H, Ar–H), 11.67 (s, 1H, NH, D_2O exchangeable); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 25.7, 32.2, 35.5, 35.9, 50.6, 55.5, 70.3, 114.1, 114.7, 118.3, 119.9, 120.5, 120.8, 125.6, 127.9, 134.4, 134.7, 137.8, 146.1, 150.8, 158.8, 159.6, 195.8; MS (EI): *m/z* (%) = 425 (M^+).

Anal. Calcd for $C_{26}H_{23}N_3O_3$ (425.48): C, 73.39; H, 5.45; N, 9.88. Found: C, 73.53; H, 5.66; N, 9.69.

8-(Benzo[d][1,3]dioxol-5-yl)-11,11-dimethyl-5,9-dioxo-6,8,9,10,11,12-hexahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile (10d). This compound was obtained as yellowish green solid (ethanol-dioxane), mp 293–295°C; ir: 3328 (NH), 2195 (CN), 1681 and 1650 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.90, 1.08 (2 s, 6H, $2CH_3$), 2.12–2.57 (m, 4H, $2CH_2$), 4.60 (s, 1H, CH), 5.93 (s, 2H, $–OCH_2O–$), 6.67–7.98 (m, 7H, Ar–H), 11.65 (s, 1H, NH, D_2O exchangeable); MS (EI): *m/z* (%) = 439 (M^+).

Anal. Calcd for $C_{26}H_{21}N_3O_4$ (439.46): C, 71.06; H, 4.82; N, 9.56. Found: C, 71.17; H, 4.67; N, 9.73.

5-Amino-11,11-dimethyl-9-oxo-8-phenyl-9,10,11,12-tetrahydro-8H-quinolino[1,2-a]quinazoline-7-carbonitrile (13a). This compound was obtained as yellowish green solid (ethanol-dioxane), mp > 300°C; ir: 3414, 3335 (NH_2), 2190 (CN) and 1610 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.89, 1.09 (2 s, 6H, $2CH_3$), 2.08–2.25 (m, 2H, CH_2), 3.16–3.34 (m, 2H, CH_2), 4.67 (s, 1H, CH), 7.12–8.07 (m, 11H, Ar–H and NH_2); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 25.5, 30.0, 35.6, 36.7, 49.1, 50.7, 73.9, 116.0, 120.0, 120.1, 121.7, 124.8, 125.4, 126.7, 127.1, 129.1, 133.4, 137.7, 143.7, 151.0, 153.4, 156.6, 195.8; MS (EI): *m/z* (%) = 394 (M^+).

Anal. Calcd for $C_{25}H_{22}N_4O$ (394.47): C, 76.12; H, 5.62; N, 14.20. Found: C, 76.45; H, 5.83; N, 14.05.

5-Amino-11,11-dimethyl-8-(4-nitrophenyl)-9-oxo-9,10,11,12-tetrahydro-8H-quinolino[1,2-a]quinazoline-7-carbonitrile (13b). This compound was obtained as yellow solid (ethanol-dioxane), mp > 300°C; ir: 3456, 3323 (NH_2), 2183 (CN) and 1652 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.78, 0.89 (2 s, 6H, $2CH_3$), 1.79–2.27 (m, 4H, 2 CH_2), 4.64 (s, 1H, CH), 7.58–8.22 (m, 10H, Ar–H + NH_2); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 26.0, 32.2, 37.9, 41.3, 49.5, 60.2, 111.2, 114.1, 116.6, 121.3, 123.8, 129.1, 131.4, 132.8, 135.0, 135.7, 138.4, 146.6, 150.3, 150.5, 151.1, 154.2, 195.2; MS (EI): *m/z* (%) = 439 (M^+).

Anal. Calcd for $C_{25}H_{21}N_5O_3$ (439.47): C, 68.33; H, 4.82; N, 15.94. Found: C, 68.59; H, 4.65; N, 15.67.

5-Amino-8-(4-methoxyphenyl)-11,11-dimethyl-9-oxo-9,10,11,12-tetrahydro-8H-quinolino[1,2-a]quinazoline-7-carbonitrile (13c). This compound was obtained as yellow solid (ethanol-dioxane), mp > 300°C; ir: 3458, 3326 (NH_2), 2181 (CN) and 1644 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.76, 1.03 (2 s, 6H, $2CH_3$), 1.81–2.22 (m, 4H, $2CH_2$), 3.71 (s, 3H, OCH_3), 4.41 (s, 1H, CH), 6.76–8.12 (m, 10H, Ar–H + NH_2); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 26.0, 35.5, 36.9, 41.8, 49.7, 55.4, 61.5, 111.2, 113.7, 114.3, 116.3, 120.5,

127.7, 129.1, 131.2, 132.8, 135.7, 138.7, 139.2, 150.7, 153.3, 158.5, 195.8; MS (EI): *m/z* (%) = 424 (M^+).

Anal. Calcd for $C_{26}H_{24}N_4O_2$ (424.49): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.49; H, 5.95; N, 13.12.

5-Amino-8-(benzo[d][1,3]dioxol-5-yl)-11,11-dimethyl-9-oxo-9,10,11,12-tetrahydro-8H-quinolino[1,2-a]quinazoline-7-carbonitrile (13d). This compound was obtained as yellow solid (ethanol-dioxane), mp > 300°C; ir: 3446, 3335 (NH_2), 2178 (CN) and 1652 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.79, 0.90 (2 s, 6H, $2CH_3$), 2.02–2.21 (m, 4H, 2 CH_2), 4.41 (s, 1H, CH), 5.9 (s, 2H, –OCH_2O–), 6.73–8.12 (m, 9H, Ar–H + NH_2).; ^{13}C nmr (100 MHz, DMSO-d6): δ, ppm: 26.1, 32.3, 37.5, 41.3, 49.7, 62.1, 101.1, 108.0, 108.5, 112.1, 114.3, 116.4, 121.2, 121.6, 131.3, 132.7, 134.9, 135.6, 138.6, 141.1, 146.1, 147.6, 149.3, 150.4, 195.2; MS (EI): *m/z* (%) = 438 (M^+).

Anal. Calcd for $C_{26}H_{22}N_4O_3$ (438.48): C, 71.22; H, 5.06; N, 12.78. Found: C, 71.37; H, 5.19; N, 12.96.

2,2-Dimethyl-4,8-dioxo-5-phenyl-2,3,4,5,7,8,9,10,11,12-decahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (16a). This compound was obtained as yellow solid (ethanol-dioxane), mp >300°C; ir: 3429 (NH), 2185 (CN), 1707 and 1652 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.81, 1.11 (2 s, 6H, $2CH_3$), 1.74–2.10 (m, 6H, $3CH_2$), 2.60–2.81 (m, 6H, $3CH_2$), 4.64 (s, 1H, CH), 7.44–8.22 (m, 5H, Ar–H), 11.40 (br s., 1H, NH); MS (EI): *m/z* (%) = 455 (M^+).

Anal. Calcd for $C_{27}H_{25}N_3O_2S$ (455.57): C, 71.18; H, 5.53; N, 9.22; S, 7.04. Found: C, 71.44; H, 5.75; N, 9.32; S, 7.11.

2,2-Dimethyl-5-(4-nitrophenyl)-4,8-dioxo-2,3,4,5,7,8,9,10,11,12-decahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (16b). This compound was obtained as yellow solid (ethanol-dioxane), mp 280–282°C; ir: 3403 (NH), 2185 (CN), 1705 and 1649 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.81, 0.92 (2 s, 6H, $2CH_3$), 1.20–1.27 (m, 2H, CH_2), 1.80–1.81 (m, 4H, $2CH_2$), 2.09–2.16 (m, 2H, CH_2), 2.78–2.81 (m, 4H, $2CH_2$), 4.59 (s, 1H, CH), 7.44–7.66 (dd, 2H, Ar–H, *J* = 8.4 Hz), 8.16–8.22 (dd, 2H, Ar–H, *J* = 8.4 Hz), 11.53 (br s., 1H, NH); MS (EI): *m/z* (%) = 500 (M^+).

Anal. Calcd for $C_{27}H_{24}N_4O_4S$ (500.57): C, 64.78; H, 4.83; N, 11.19; S, 12.78. Found: C, 64.67; H, 4.91; N, 11.32; S, 12.67.

5-(4-Methoxyphenyl)-2,2-dimethyl-4,8-dioxo-2,3,4,5,7,8,9,10,11,12-decahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (16c). This compound was obtained as yellow solid (ethanol-dioxane), mp 290–292°C; ir: 3434 (NH), 2200 (CN), 1704 and 1657 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.94, 1.11 (2 s, 6H, $2CH_3$), 1.76–2.18 (m, 6H, $3CH_2$), 2.63–2.81 (m, 6H, $3CH_2$), 3.68 (s, 3H, OCH_3), 4.57 (s, 1H, CH), 6.82 (d, 2H, Ar–H, *J* = 8.0 Hz), 7.06 (d, 2H, Ar–H, *J* = 8.0 Hz), 11.23 (br s., 1H, NH); MS (EI): *m/z* (%) = 484 (M^+).

Anal. Calcd for $C_{28}H_{27}N_3O_3S$ (485.60): C, 69.25; H, 5.60; N, 8.65; S, 6.60. Found: C, 69.43; H, 5.71; N, 8.76; S, 6.71.

5-(Benzo[d][1,3]dioxol-5-yl)-2,2-dimethyl-4,8-dioxo-2,3,4,5,7,8,9,10,11,12-decahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (16d). This compound was obtained as yellow solid (ethanol-dioxane), mp >300°C; ir: 3424 (NH), 2188 (CN), 1704 and 1650 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.94, 1.11 (2 s, 6H, $2CH_3$), 1.73–2.17 (m, 6H, $3CH_2$), 2.62–2.80 (m, 6H, $3CH_2$), 4.57 (s, 1H, CH), 5.9 (s, 2H, –OCH_2O–), 6.62–6.82 (m, 3H, Ar–H), 11.26 (br s., 1H, NH); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 22.0, 22.8, 24.1, 25.3, 25.4, 30.3, 32.6, 35.3, 36.3, 49.9, 60.8, 69.2, 101.5, 107.3, 108.8, 117.9, 118.7, 120.1, 129.5, 132.1, 136.7, 144.5, 146.8, 148.0, 148.6, 157.0, 195.8; MS (EI): *m/z* (%) = 499 (M^+).

Anal. Calcd for $C_{28}H_{25}N_3O_4S$ (499.16): C, 67.32; H, 5.04; N, 8.41; S, 6.42. Found: C, 67.18; H, 5.17; N, 8.62; S, 6.64.

8-Amino-2,2-dimethyl-4-oxo-5-phenyl-2,3,4,5,9,10,11,12-octahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (19a). This compound was obtained as yellow solid (ethanol-dioxane), mp >300°C; ir: 3466 (NH), 2183 (CN), 1647 and 1579 (2CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.96 and 1.1 (2 s, 6H, $2CH_3$), 1.84–2.32 (m, 6H, $3CH_2$), 2.64–2.78 (m, 6H, $3CH_2$), 4.4 (s, 1H, CH), 6.17 (br s., 2H, NH_2), 7.07–7.32 (m, 5H, Ar–H); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 21.8, 22.8, 24.3, 25.1, 26.9, 32.5, 36.6, 49.7, 114.8, 118.5, 121.2, 126.6, 127.0, 127.7, 128.6, 128.9, 129.1, 144.3, 148.5, 149.9, 150.0, 153.3, 154.8, 195.8; MS (EI): *m/z* (%) = 454 (M^+).

Anal. Calcd for $C_{27}H_{26}N_4OS$ (454.59): C, 71.34; H, 5.76; N, 12.32; S, 7.05. Found: C, 71.52; H, 5.92; N, 12.11; S, 7.35.

8-Amino-2,2-dimethyl-5-(4-nitrophenyl)-4-oxo-2,3,4,5,9,10,11,12-octahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (19b). This compound was obtained as yellow solid (ethanol-dioxane), mp >300°C; ir: 3461, 3366 (NH_2), 2191 (CN) and 1657 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6DMSO-d_6): δ, ppm: 0.81 and 0.98 (2 s, 6H, $2CH_3$), 1.84–2.32 (m, 8H, $4CH_2$), 2.64–2.78 (m, 4H, $2CH_2$), 4.6 (s, 1H, CH), 6.3 (br s., 2H, NH_2), 7.44–7.60 (dd, 2H, Ar–H, *J* = 8.0 Hz), 8.11–8.23 (dd, 2H, Ar–H, *J* = 8.0 Hz); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 21.8, 22.7, 24.9, 26.2, 32.6, 37.4, 49.5, 60.4, 113.6, 113.7, 120.8, 123.9, 124.4, 128.4, 128.8, 134.9, 135.7, 142.2, 146.7, 150.7, 150.9, 151.6, 153.8, 195.4; MS (EI): *m/z* (%) = 499 (M^+).

Anal. Calcd for $C_{27}H_{25}N_5O_3S$ (499.58): C, 64.91; H, 5.04; N, 14.02; S, 6.42. Found: C, 65.11; H, 5.23; N, 14.35; S, 6.77.

8-Amino-5-(4-methoxyphenyl)-2,2-dimethyl-4-oxo-2,3,4,5,9,10,11,12-octahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (19c). This compound was obtained as yellow solid (ethanol-dioxane), mp 275–278°C; ir: 3449, 3355 (NH_2), 2185 (CN) and 1657 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.81 and 0.97 (2 s, 6H, $2CH_3$), 1.84–2.31 (m, 8H, $4CH_2$), 2.64–2.78 (m, 4H, $2CH_2$), 3.72 (s, 3H, OCH_3), 4.35 (s, 1H, CH), 6.13 (br s., 2H, NH_2), 6.80–6.96 (dd, 2H, Ar–H, *J* = 8.0 Hz), 7.04–7.23 (dd, 2H, Ar–H, *J* = 8.0 Hz); ^{13}C nmr (100 MHz, DMSO-d_6): δ, ppm: 21.7, 22.8, 24.4, 24.8, 27.2, 32.6, 36.4, 49.7, 55.5, 59.0, 113.4, 114.1, 115.2, 121.3, 128.0, 128.7, 135.6, 137.3, 138.2, 142.6, 149.5, 150.9, 158.9, 162.6, 195.3; MS (EI): *m/z* (%) = 484 (M^+).

Anal. Calcd for $C_{28}H_{28}N_4O_2S$ (484.61): C, 69.40; H, 5.82; N, 11.56; S, 6.62. Found: C, 69.53; H, 5.63; N, 11.56; S, 6.74.

8-Amino-5-(benzo[d][1,3]dioxol-5-yl)-2,2-dimethyl-4-oxo-2,3,4,5,9,10,11,12-octahydro-1H-benzo[4′,5′]thieno[3′,2′:5,6]pyrimido[1,2-a]quinoline-6-carbonitrile (19d). This compound was obtained as yellow solid (ethanol-dioxane), mp >300°C; ir: 3585, 3352 (NH_2), 2189 (CN) and 1650 (CO) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ, ppm: 0.83 and 0.96 (2 s, 6H, $2CH_3$), 1.84–2.24 (m, 8H, $4CH_2$), 2.65–2.78 (m, 4H, $2CH_2$), 4.34 (s, 1H, CH), 5.96 (s, 2H, –OCH_2O–), 6.10 (br s., 2H, NH_2), 6.66–6.78 (m, 3H, Ar–H); MS (EI): *m/z* (%) = 498 (M^+).

Anal. Calcd for $C_{28}H_{26}N_4O_3S$ (498.60): C, 67.45; H, 5.26; N, 11.24; S, 6.43. Found: C, 67.67; H, 5.12; N, 11.13; S, 6.79.

Acknowledgments. Ismail A. Abdelhamid is deeply indebted to the Alexander von Humboldt Foundation, Germany, for granting him a postdoctoral fellowship. He is also very thankful to Prof. Dr Holger Butenschön, Institut für Organische Chemie, Leibniz Universität, Hannover, for kind hospitality.

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