C. R. Chimie 17 (2014) 1242–1249

Contents lists available at ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Full paper/Mémoire

Synthesis of novel *O*-alkylbenzochromeno-1,5-benzodiazepinones. Study of the N–H····N and C=O····HN hydrogen bonding interactions with 2-aminopyridines

Synthèse de nouvelles O*-alkylbenzochroméno-1,5-benzodiazépinones. Étude des liaisons hydrogène intermoléculaires avec les 2-aminopyridines*

Asma Nsira, Rafik Gharbi *, Moncef Msaddek

Laboratory of Heterocyclic Synthesis and Chemistry of Natural Compounds, Faculty of Sciences of Monastir, route de Kairouan, 5000 Monastir, Tunisia

ARTICLE INFO

Article history:
Received 5 November 2013
Accepted after revision 8 January 2014
Available online 11 August 2014

Keywords:
Benzopyrano-1,5-benzodiazepin-2-one
2-Aminopyridine
O-alkylated-benzochromeno-1,5-benzodiazepin-2-ones
Self-assembled systems
Hydrogen bonding interaction
Crystal structure

ABSTRACT

A series of novel 6-(*O*-alky)lbenzochromeno-1,5-benzodiazepin-2-ones **4a–c** was prepared through the condensation between the [1]benzopyrano[4,3-*c*][1,5]benzodiazepin-7(*8H*)one **1** and a series of alkylalcohols. Scaffold **4** exhibited interesting hydrogen-bonding interaction with 2-aminopyridine derivatives. The so obtained self-assembled systems **5** were fully characterized by 1D/2D-NMR techniques and mass spectrometry. The hydrogen-bonding interaction was supported by IR and Raman spectroscopy and by ^{1}H NMR titration experiments, and was confirmed by an X-ray crystal structure analysis.

RÉSUMÉ

De nouvelles 6-(*O*-alky)lbenzochroméno-1,5-benzodiazépin-2-ones **4a–c** ont été isolées via la condensation de la [1]benzopyrano[4,3-*c*][1,5]benzodiazépin-7(8*H*)one **1** avec une série d'alcools. Les hétérocycles **4** ont montré une capacité particulière à développer de fortes liaisons hydrogène intermoléculaires avec les 2-aminopyridines en donnant naissance à des édifices stables **5**. Les systèmes auto-assemblés **5** ont été caractérisés par spectrométrie de masse et par RMN 1D/2D. D'autre part, l'établissement des liaisons hydrogène a été appuyé par spectroscopie IR et Raman ainsi que par des expériences de titration en RMN ^{1}H, et confirmé par radiocristallographie aux rayons X.

1. Introduction

Compounds possessing the 1,5-benzodiazepine core are well recognized for their broad spectrum of pronounced biological and pharmacological activities [1,2]. Thus, interest in their chemistry continues unabated. Moreover, new insights have recently been found into the development of more efficient and versatile methods for the synthesis of these 1,5-benzodiazepinic scaffolds [3,4]. In a previous work, our research team has explored the condensation between the [1]benzopyrano[4,3-*c*][1,5]benzodiazpin-7(8*H*)one **1** and a series of *N,N*-binucleophiles to give the aforementioned heterocoumarins as a result of a multiple-step sequence involving successive ring-opening and recyclization processes [5,6].

* Corresponding author.
E-mail addresses: asma_nsira@yahoo.fr (A. Nsira), raf_gharbi@yahoo.fr (R. Gharbi), moncef.msaddek@fsm.rnu.tn (M. Msaddek).

1631-0748/$ – see front matter
http://dx.doi.org/10.1016/j.crci.2014.01.007

As a continuation of our ongoing efforts directed towards the synthesis of novel polyheterocycles containing the 1,5-benzodiazepine moiety, especially promising bioactive compounds [7–10], we were prompted to study the behavior of **1** towards 2-aminopyridine derivatives as 1,3-dinitrogenated nucleophile and we report herein our results, which are of particular interest.

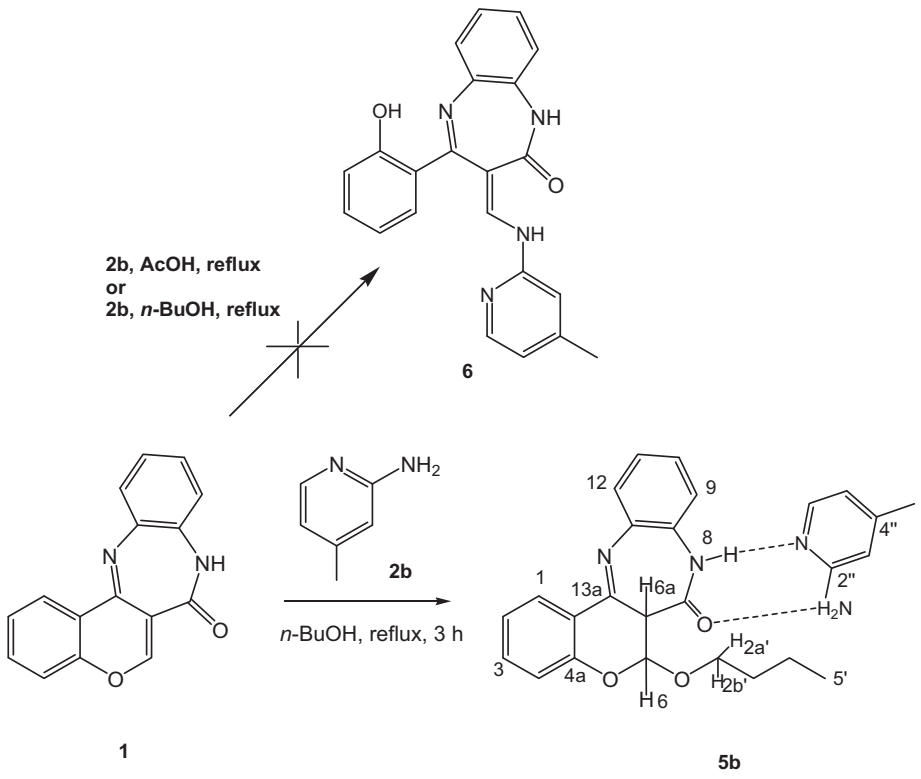
2. Results and discussion

Keeping in mind our previous report on the synthesis of new heterocoumarins [5,6], we firstly carried out the reaction between **1** and 2-aminopyridine under drastic acidic conditions, aiming thereby to achieve the 3(*N*-pyridinylamino)methylene-1,5-benzodiazepinone **6** via a nucleophilic attack of the amino group at the C-2 of the benzopyran ring. The key intermediate **6**, if obtained, would probably undergo a series of rearrangements to afford interesting benzodiazepine derivatives.

Nevertheless, under such vigorous conditions, all attempts led to the formation of complex crudes and directed us to opt for milder conditions using *n*-butanol instead of acetic acid. Thus, when a mixture of benzopyrano-benzodiazepine **1** and 2-aminopyridine **2a** or 2-amino-4-methylpyridine **2b** in *n*-butanol was heated under reflux for 3 h, the attempted 3(*N*-pyridinylamino)-methylene-1,5-benzodiazepinone **6** was not obtained. On the basis of their spectral data, the isolated products were identified as a self-assembled molecular system **5a,b** linked via an intermolecular hydrogen bonding between the 6-(*O*-butyl)benzochromeno-1,5-benzodiazepinone **4a** and the 2-aminopyridine **2** (Scheme 1).

According to this finding, we made a careful review of the literature that revealed a continual growing interest in benzodiazepinic systems for their specificity to recognize and bind through intermolecular hydrogen bonding and π–π stacking to a modulatory site on GABA receptors [11]. In addition, Pavlovsky et al. previously described the arrangement of 3-arylidene-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one in dimers due to the N(1)-H···O(2) hydrogen bonds [12]. On another hand, the 2-aminopyridine also revealed a great tendency to develop intermolecular hydrogen bonding [13,14]. Such self-assembled systems continuously attract the researcher's interest due to their potential to be applied in the field of chemistry, biology and physics [15–17].

Here, one can return to the first spectroscopic evidence that emerged from the mass spectrum (ES + mode) of the self-assembled system **5b** (**4a** + **2b**) chosen as an illustration example which exhibited a molecular ion peak [MH^+] at m/z = 445.3. In fact, this value represents the sum of the molecular weights of diazepine **1**, 2-amino-4-methylpyridine **2b**, and *n*-butanol. On the other hand, the ^{1}H NMR spectrum of **5b** showed a large singlet (4.51 ppm, 1H), which was attributed to the free amino group of the pyridinic ring. This confirmed that the 2-amino-4-methylpyridine **2b** did not participate in the reaction. However, it is worth noting that all the protons of the 2-aminopyridine were easily located in the ^{1}H NMR spectrum. Moreover, the absence of the deshielded phenolic hydrogen singlet



Scheme 1. Synthesis of the self-assembled systems **5b** in one-pot.

usually observed around 15 ppm [18] excluded from the beginning a nucleophilic attack of the amino group at the C-2 of the benzopyran moiety and the consequent ring-opening. Hence, the set of both singlets (5.93 ppm, 1H and 3.29 ppm, 1H) were then assigned to H-6 and H-6a of the dihydrobenzopyrane moiety as a result of an *O*-attack of the butanol [19] at the benzopyran carbon followed by a concomitant proton shift and a subsequent reduction of $C_6 = C_{6a}$. The C_6-linked *n*-butoxy chain was readily assigned on the basis of chemical shifts and multiplicities. Here, the non-coupling between H-6 and H-6a was accidental and undoubtedly due to the non-planarity of the fused heptatomic–hexatomic ring systems.

This finding led us to consider the HMBC 2D-map that did not reveal any spot pointing out a long-range C–H correlation between protons H-6 and carbons of the pyridine moiety, whereas it has been found that protons H-2a′ (3.56 ppm) and H-2b′ (3.76 ppm) correlates with C-6 (96.2 ppm). Consequently, it can be stated that derivative **2b** is not directly attached to the benzodihydropyrane moiety, but more probably linked through an intermolecular hydrogen bonding.

The event of a $H_{(amide)\mathbf{5a}}\cdots N_{(pyridine)\mathbf{2b}}$ hydrogen bonding was deeply supported by an n*O*esy study that showed a correlation between the amidic hydrogen H-8 (8.97 ppm) and the free amino group (4.51 ppm). This observation highlights the proximity between the diazepine **4a** and the 2-aminopyridine ring **2**.

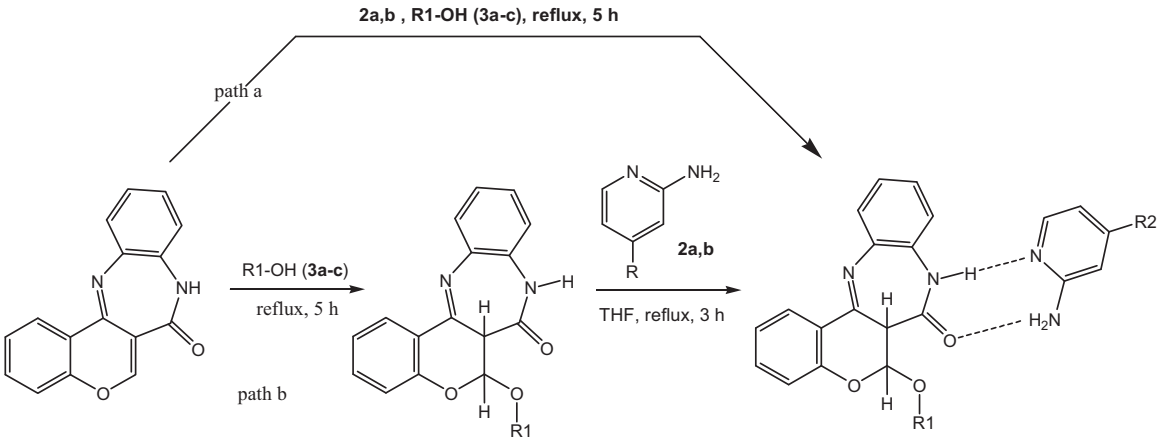
At this stage of the work, the 6-(*O*-butyl) benzochromeno-1,5-benzodiazepinone **4a** was isolated to further study its behavior towards 2-aminopyridines **2a,b**. Indeed, the reaction between the key intermediate **1** and *n*-butanol has been carried out, the corresponding benzodiazepinone **4a** was obtained in good yield. As a second step, the condensation between **4a** and **2a**,**b** under reflux in tetrahydrofuran, led to the expected self-assembled structures **5a,b** (Scheme 2).

In order to get more proofs of the establishment of the intermolecular hydrogen bonding, we have carried out a ^{1}H NMR titration experiment [20,21]. While the concentration of compound **4a** was kept constant, we have progressively increased the concentration of **2b**. Consequently, apparent down field shift of the amidic proton signal of **4a** was observed as a result of a strong $NH_{5a}\cdots N_{2b}$ intermolecular hydrogen bonding between the diazepine **4a** and the 2-amino-4-methylpyridine **2b** (Fig. 1).

Infrared studies gave an additional evidence for the hydrogen bonding between **4a** and **2b**. In fact, the hydrogen bonding interaction has lowered the frequencies of the amino NH bands ($\nu_{N-H} = 3411\ cm^{-1}$). Moreover, the asymmetric and symmetric stretching vibrations of the amino group were weakened and shifted to 3411 cm^{-1} and 3222 cm^{-1} as can be seen when compared with the frequencies of the corresponding mode for the non-interacting 2-aminopyridine [22]. It should be pointed out that the N–H and NH_2 vibrations bands are almost undetectable in the Raman spectrum. Such pattern in the changes of frequencies and intensities in the IR and Raman spectra unambiguously points out the formation of intermolecular H-bonds [23].

As a summary from our experimental results, it is reasonable now to assume that the outcome of the reaction between benzopyrano-1,5-benzodiazepinone **1** and 2-aminopyridines **2a,b** in *n*-butanol is different from what we had previously observed [5] and follows the pathway anticipated and described in Scheme 1.

With this encouraging result in hand, giving the corresponding self-assembled structures in high yield, we decided to extend this study to other alcoholic solvents, such as methanol and ethanol as *O*-nucleophilic agents,



Scheme 2. Synthesis of the self-assembled systems **5a**–**f**, path a: a one-pot synthesis, path b: two-step synthesis.

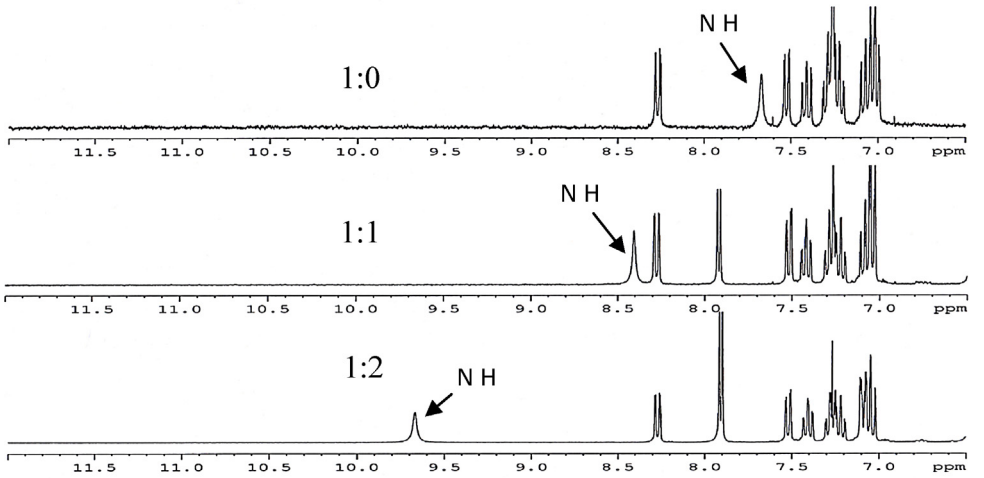


Fig. 1. ^{1}H NMR titration of **4a** ($c = 2.10^{-2}$ M) with **2b** in $CDCl_3$ at room temperature (the molar ratio of **4a**/**2b** is shown in the figure).

and see whether similar H-bonding would link 2-aminopyridine to structure **4** (Scheme 2).

The 1D and 2D-NMR studies enabled the establishment of a whole set of linkages and complete assignment of the self-assembled molecular structures **5c–f** (see Experimental section).

A single cristal suitable for an X-ray diffraction study was obtained for **5e** by recrystallization in EtOH. The ORTEP diagram of the crystal structure of the self-assembly **5e** with the total atomic numbering scheme is shown in Fig. 2.

The molecular structure of the self-assembly **5e** reveals two intermolecular hydrogen bonds. The amidic hydrogen of the *O*-ethylbenzodiazepine, which is bonded to the N(24) of the 2-aminopyridine, represents the first center of hydrogen bonding. This bond is similar in its parameters to the hydrogen bond characteristic of benzodiazepines unsubstituted at N(3) [24–26]. The second interaction is observed between both hydrogens of the amino group H(261) and H(262) and oxygen O(1) of the carbonyle. Hydrogen bonding dimensions for **5e** are listed in Table 1.

It can be observed that the *O*-ethylbenzochromeno-benzodiazepinone **5e** is not planar with the folding of the seven-membered ring, which adopts a boat conformation along the N···N hinge [27]. The loss of the planarity in the pyran moeity as a consequence of the *O*-attack of ethanol is

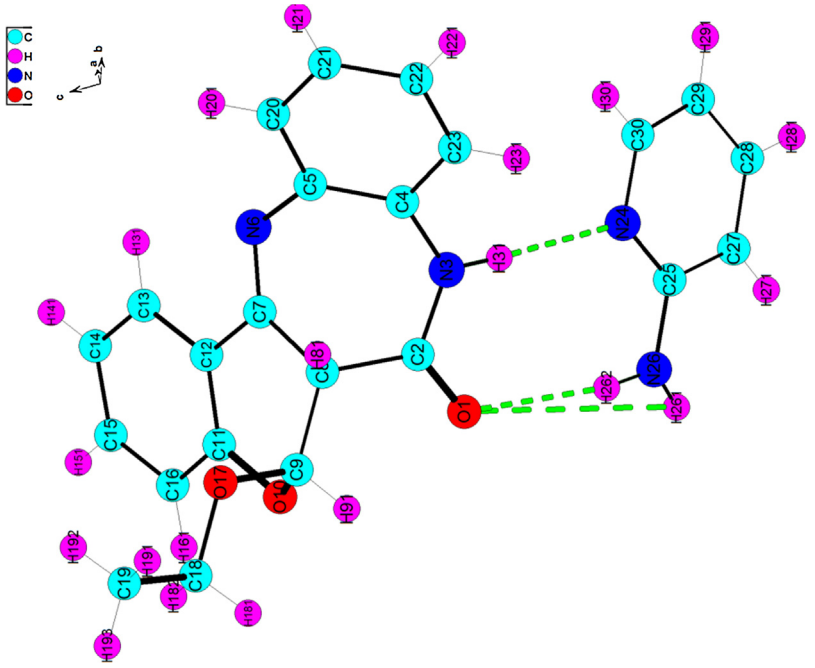


Fig. 2. (Color online.) The structure of the self-assembly **5e** showing the total atomic numbering scheme. Intermolecular hydrogen bonds are shown by dashed lines. For convenience, the numbering of atoms given in the figure does not correspond to the IUPAC nomenclature system.

Table 1
Hydrogen bonding distances (Å) and angles [°] in the structure of self-assembled **5e**.

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N3–H31···N24	0.86	2.06	2.920(3)	177
N26–H261···O1^{i}	0.87	2.23	3.024(3)	152(1)
N26–H262···O1	0.87	2.21	3.048(3)	162
C27–H271···O10^{i}	0.93	2.46	3.275(3)	146(1)

presumably the cause of its molecular shape. It is worth mentioning that the addition of ethanol is not enantioselective as it results in the formation of a racemic mixture. Another interesting feature of the compound packing is the π–π interaction. Each self-assembled structure is stacked face to face with the other ones along a crystallographic 0a axis (Fig. 3).

3. Conclusion

In this work, we have successfully developed an efficient and straightforward preparation of novel *O*-alkylatedbenzochromeno-1,5-benzodiazepinones starting from readily available materials. We have demonstrated that these new diazepines revealed a great ability to establish strong NH····N and C=O·····N intermolecular hydrogen bonding with 2-aminopyridines derivatives. A wide range of 1,3-nucleophiles, such as 2-aminobenzothiazole derivatives and 2-aminobenzimidazole could be applied to this process, thereby giving a reliable method for the synthesis of new self-assembled structures with enhanced biological and pharmacological activities.

4. Experimental

All solvents were purified and dried prior to use. ^{1}H and ^{13}C NMR spectra were recorded with an AC-300 Bruker spectrometer with tetramethylsilane as an internal reference. Chemical shifts are reported in parts per million. Two-dimensional NMR experiments were performed with an Avance-500 Bruker spectrometer. High-resolution mass spectra of compounds **4a–c** and the self-assembled **5a–f** were performed within a Hewlett-Packard 5890/5970 GC–mass spectrometer. The $[M]^{+}$ mass for self-assembled **5a–f** were never observed due to their instability in HRMS mode. Low-resolution mass spectra of compound **5a–b** were obtained with a Micromass LCT spectrometer (ESI technique, positive mode).

The FT–IR spectra were measured from KBr pellets using a PerkinElmer 1750 spectrophotometer. To complete the results of the FT–IR spectroscopy, only in case of the self-assembled system **5b**, Raman spectra of samples in sealed glass cell (2 mm in diameter) were obtained at room temperature with a Horibo Jobin Yvon HR800 microcomputer system instrument using a conventional scanning Raman instrument equipped with a Spex 1403 double monochromator (with a pair of 600 grooves/mm gratings) and a Hamamatsu 928.

All the reactions were followed by TLC using aluminum sheets of Merck silica gel 60 F_{254}, 0.2 mm. The starting material **1** was prepared according to the literature [8]. Melting points of benzodiazepines **4a–c** were determined on a Buchi 510 capillary melting point apparatus. However, melting points of the self-assembled systems **5a–f** could not be determined because they decompose on heating.

4.1. General procedure for the synthesis of the self-assembly (5a–f)

To a stirred suspension of compound **1** (262 mg, 1 mmol) in refluxed *n*-alcohol (80 mL) was added the 2-aminopyridine **2a** (94 mg, 1 mmol) or the 4-methyl-2-aminopyridine **2b** (108 mg, 1 mmol), respectively. The solution was allowed to react for 3 to 5 h and its progress was monitored by a TLC control (cyclohexane–ethylacetate 80:20). After the completion of the reaction, the solvents

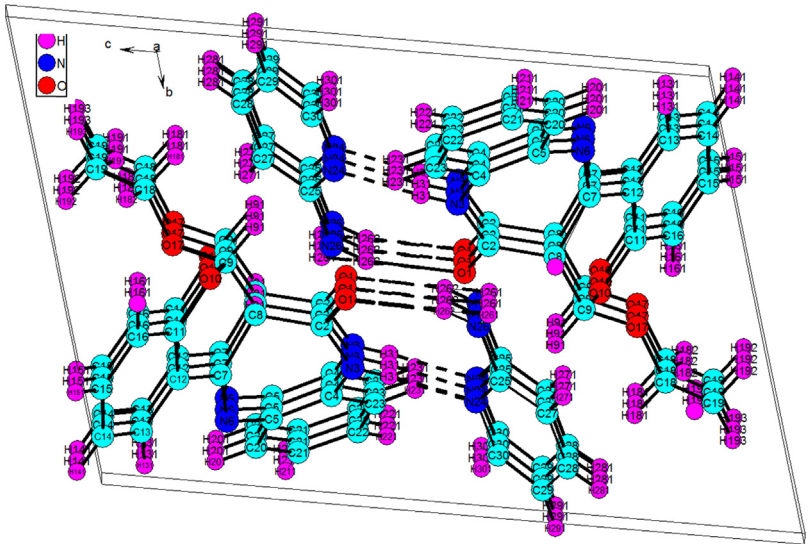


Fig. 3. (Color online.) View along the O*a* axis on the layered supramolecular structure in crystal **5e**.

were removed *in vacuo* and to the resulting yellow crude oil was added the petroleum ether; the so-formed white precipitate was collected and crystallized from a mixture of THF and petroleum ether to give the corresponding products **5a**–**f**, respectively.

*4.1.1. Intermolecular hydrogen bonded self-assembly 5a (**4a** + **2a**)*

White cottony, yield 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.46 (s, 1H, N–H), 8.26 (dd, 1H, H-1, J = 7,5 Hz), 8.02 (d, 1H, H-6″, J = 4.2 Hz), 7.49 (d, 1H, H-12, J = 7.5 Hz), 7.42 (t, 1H, H-3), 7.40 (t, 1H, H-4″), 7.28–7.20 (m, 2H, H-10,11), 7.10–7.01 (m, 3H, H-2,4,9), 6.59 (t, 1H, H-5″), 6.45 (d, 1H, H-3″, J = 8.1 Hz), 5.93 (s, 1H, H-6), 4.68 (s, 2H, NH_2), 3.78 (m, 1H, H-2b′), 3.58 (m, 1H, H-2a′), 3.29 (s, 1H, H-6a), 1.43 (m, 2H, H-3′), 1.15 (m, 2H, H-4′), 0.77 (t, 3H, H-5′); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.9 (C-7), 158.6 (C-2″), 154.2 (C-4a), 151.1 (C-13a), 147.8 (C-6″), 139.7 (C-12a), 137.8 (C-4″), 133.5 (C-3), 129.0 (C-12), 128.4 (C-8a), 126.5 (C-1), 126.3 (C-10), 125.2 (C-11), 122.2 (C-2), 121.8 (C-9), 120.2 (C-13b), 118.6 (C-4), 113.8 (C-5″), 108.8 (C-3″), 96.3 (C-6), 68.4 (C-2′), 49.2 (C-6a), 31.2 (C-3′), 19.0 (C-4′), 13.6 (C-5′); MS (ES+) m/z 431.2 $[M_{5a} + H]^+$, m/z 337.2 $[M_{4a} + H]^+$, m/z 359.2 $[M_{4a} + Na]^+$ and m/z 695.3 $[2\,M_{4a} + Na]^+$; HRMS (m/z): calcd $[M_{5a(4a+2a)}]^+$ for $C_{25}H_{26}N_4O_3$: 430.2005 was not observed, found: 359.1386 $[M_{4a} + Na]^+$ and 95.0568 $[M_{2a} + H]^+$; ν_{max}(KBr): 3415, 3336, 3221, 1678, 1617, 1459, 1305, 1095, 758 cm^{-1}.

*4.1.2. Intermolecular hydrogen bonded self-assembly **5b** (**4a** + **2b**)*

White cottony, yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.97 (s, 1H, N-H), 8.28 (dd, 1H, H-1, J = 8.1 Hz), 7.91 (d, 1H, H-6″, J = 5.4 Hz), 7.52 (d, 1H, H-12, J = 7.8 Hz), 7.40 (t, 1H, H-3), 7.28–7.18 (m, 2H, H-11, 10), 7.09–7.01 (m, 3H, H-2,4, H9), 6.46 (d, 1H, H-5″, J = 5.1 Hz), 6.31 (s, 1H, H-3″), 5.93 (s, 1H, H-6), 4.51 (s, 2H, NH_2), 3.76 (m, 1H, H-2b′), 3.56 (m, 1H, H-2a′), 3.29 (s, 1H, H-6a), 2.22 (s, 3H, CH_3–4a″), 1.41 (m, 2H, CH_2–3′), 1.13 (m, 2H, CH_2–4′), 0.77 (t, 1H, CH_3–5′), ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.8 (C-7), 158.6 (C-2″), 154.1 (C-4a), 151.1 (C-13a), 148.9 (C-4″), 147.4 (C-6″), 139.6 (C-12a), 133.5 (C-3), 128.9 (C-8a), 128.3 (C-12), 126.5 (C-1), 126.2 (C-10), 125.2 (C-11), 122.2 (C-2), 121.7 (C-9), 120.1 (C-13b), 118.6 (C-4), 115.4 (C-5″), 109.0 (C-3″), 96.3 (C-6), 68.4 (C-2′), 49.1 (C-6a), 31.2 (C-3′), 21.0 (C-4a″), 19.0 (C-4′), 13.6 (C-5′); MS (ES+) m/z 445.3 $[M_{5b} + H]^+$, m/z 337.2 $[M_{4a} + H]^+$, m/z 359.2 $[M_{4a} + Na]^+$ and m/z 695.3 $[2\,M_{4a} + Na]^+$, HRMS (m/z): calcd $[M_{5b(4a+2b)}]^+$ for $C_{26}H_{28}N_4O_3$: 444.2161 was not observed, found: 359.1387 $[M_{4a} + Na]^+$, 695.2849 $[2\,M_{4a} + Na]^+$ and 131.1608 $[M_{2b} + Na]^+$; ν_{max}(KBr): 3417, 3337, 3222, 1679, 1618, 1460, 1306, 1098, 760 cm^{-1}.

*4.1.3. Intermolecular hydrogen bonded self-assembly **5c** (**4b** + **2a**)*

White cottony, yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.27 (dd, 1H, H-1, J = 7.8 Hz), 8.22 (s, 1H, N-H), 8.06 (dd, 1H, H-6″, J = 5.1 Hz), 7.52 (d, 1H, H-12, J = 7.8 Hz), 7.43 (m, 1H, H-4″), 7.42 (t, 1H, H-3), 7.25–7.22 (m, 2H, H-10, 11), 7.07–7.02 (m, 3H, H-2,4,9), 6.62 (m, 1H, H-5″), 6.49 (dd, 1H, H-3″, J = 8.1), 5.85 (s, 1H, H-6), 4.49 (s, 2H, NH_2), 3.48 (s, 1H, OCH_3–2′), 3.34 (s, 1H, H-6a); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.5 (C-7), 158.6 (C-2″), 154.0 (C-4a), 151.0 (C-13a), 147.9 (C-6″), 139.6 (C-12a), 137.7 (C-4″), 133.4 (C-3), 128.4 (C-8a), 128.3 (C-12), 126.5 (C-1), 126.4 (C-10), 125.5 (C-11), 122.2 (C-2), 120.1 (C-13b), 118.6 (C-4), 113.9 (C-5″), 108.9 (C-3″), 97.2 (C-6), 55.9 (C-2′), 49.1 (C-6a); HRMS (m/z): calcd $[M_{5c(4b+2a)}]^+$ for $C_{22}H_{20}N_4O_3$: 388.1535 was not observed, found: 317.0914 $[M_{4b} + Na]^+$ and 95.0567 $[M_{2a} + H]^+$; ν_{max}(KBr): 3410, 3335, 3220, 1677, 1618, 1460, 1302, 1075, 754 cm^{-1}.

*4.1.4. Intermolecular hydrogen bonded self-assembly **5d** (**4b** + **2b**)*

White cottony, yield 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.25 (d, 1H, H-1, J = 7.8 Hz), 8.38 (s, 1H, N-H), 7.84 (d, 1H, H-6″, J = 4.2 Hz), 7.48 (d, 1H, H-12, J = 7.8 Hz), 7.42 (t, 1H, H-3), 7.26–7.22 (m, 2H, H-1110), 7.08–7.02 (m, 3H, H-2, 9, 4), 6.48 (d, 1H, H-5″, J = 5.7 Hz), 6.36 (s, 1H, H-3″), 5.83 (s, 1H, H-6), 5.02 (s, 2H, NH_2), 3.45 (s, 3H, OCH_3). 3.32 (s, 1H, H-6a), 2.25 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.5 (C-7), 157.3 (C-2″), 153.8 (C-4a), 151.0 (C-13a), 150.08 (C-4″), 143.6 (C-6″), 139.5 (C-12a), 133.6 (C-3), 128.6 (C-8a), 128.2 (C-12), 126.5 (C-1), 126.3 (C-10), 125.4 (C-11), 122.3 (C-2), 121.7 (C-9), 120.0 (C-13b), 118.6 (C-4), 115.2 (C-5″), 110.07 (C-3″), 97.3 (C-6), 55.9 (C-2′), 48.9 (C-6a), 21.29 (C-4a″). HRMS (m/z): calcd $[M_{5d(4b+2b)}]^+$ for $C_{23}H_{22}N_4O_3$: 402.1692 was not observed, found: 317.0915 $[M_{4b} + Na]^+$ and 109.0732 $[M_{2b} + H]^+$; ν_{max}(KBr): 3411, 3338, 3223, 1679, 1618, 1461, 1306, 1085, 774 cm^{-1}.

*4.1.5. Intermolecular hydrogen bonded self-assembly **5e** (**4c** + **2a**)*

White cottony, yield 41%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.28 (d, 1H, H-1, J = 7.8 Hz), 8.23 (s, 1H, N-H), 8.05 (d, 1H, H-6″, J = 4.2 Hz), 7.49 (d, 1H, H-12, J = 7.8 Hz), 7.43 (m, 1H, H-4″), 7.38 (t, 1H, H-3), 7.30–7.21 (m, 3H, H-2,10, 11), 7.04–7.01 (m, 2H, H-4,9), 6.61 (m, 1H, H-5″), 6.47 (d, 1H, H-3″, J = 8.4 Hz), 5.95 (s, 1H, H-6), 4.47 (s, 2H, NH_2), 3.85 (m, 1H, H-2b′), 3.67 (m, 1H, H-2a′), 3.31 (s, 1H, H-6a), 1.09 (t, 3H, CH_3–3′). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.6 (C-7), 158.6 (C-2″), 154.2 (C-4a), 151.2 (C-13a), 148.0 (C-6″), 139.7 (C-12a), 137.7 (C-4″), 133.6 (C-3), 128.6 (C-8a), 128.4 (C-12), 126.5 (C-1), 126.3 (C-10), 125.4 (C-11), 122.2 (C-2), 121.6 (C-9), 120.1 (C-13b), 118.6 (C-4), 114.0 (C-5″), 108.6 (C-3″), 96.1 (C-6), 64.2 (C-2′), 49.1 (C-6a), 14.8 (C-3′); HRMS (m/z): calcd $[M_{5e(4c+2a)}]^+$ for $C_{23}H_{22}N_4O_3$: 402.1692 was not observed, found: 309.1198 $[M_{4c} + H]^+$ and 95.0569 $[M_{2a} + H]^+$; ν_{max}(KBr): 3410, 3337, 3223, 1679, 1615, 1460, 1305, 1082, 765 cm^{-1}.

*4.1.6. Intermolecular hydrogen bonded self-assembly **5f** (**4c** + **2b**)*

White cottony, yield 55%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.40 (s, 1H, N-H), 8.28 (d, 1H, H-1, J = 7.8 Hz), 7.90 (d, 1H, H-6″, J = 5.4 Hz), 7.50 (dd, 1H, H-12, J = 7.8 Hz), 7.39 (t, 1H, H-3), 7.30–7.24 (m, 3H, H-11, 10, 2), 7.08–7.05 (m, 2H, H-4,9), 6.47 (d, 1H, H-5″, J = 5.4 Hz), 6.32 (s, 1H, H-3″), 5.96 (s, 1H, H-6), 4.44 (s, 2H, NH_2), 3.83 (m, 1H, H-2b′), 3.64 (m, 1H, H-2a′), 3.32 (s, 1H, H-6a), 2.22 (s, 3H, CH_3), 1.09 (t, 3H, H-3′). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.7 (C-7), 158.4 (C-2″), 154.2 (C-4a), 151.1 (C-13a), 150.8 (C-4″), 147.5 (C-6″),

139.6 (C-12a), 133.6 (C-3), 128.7 (C-8a), 128.3 (C-12), 126.5 (C-1), 126.3 (C-10), 125.3 (C-11), 122.2 (C-2), 121.6 (C-9), 120.1 (C-13b), 118.6 (C-4), 115.5 (C-5″), 109.0 (C-3″), 96.0 (C-6), 64.2 (C-2′), 49.1 (C-6a), 21.0 (C-4a″), 14.8 (C-3′); HRMS (*m*/*z*): calcd $[M_{5f(4c+2b)}]^+$ for $C_{24}H_{24}N_4O_3$: 416.1848 was not observed, found: 309.1198 $[M_{4c}+H]^+$ and 109.0729 $[M_{2b}+H]^+$; ν_{max}(KBr): 3411, 3338, 3223, 1679, 1618, 1461, 1306, 1085, 774 cm^{-1}.

4.2. General procedure for the synthesis of the 6(O-alkylated)benzochromeno-1,5-benzodiazepinones (4a–c)

Compounds **4a–c** were synthesized from 262 mg of **1** in 80 mL of *n*-butanol, methanol and ethanol, respectively. The mixture was refluxed under stirring for five hours. The reaction was stopped due to the formation of some decomposition products as evidenced by TLC analysis. Concentration *in vacuo* of the obtained solution gave a pale yellow precipitate. Successive recrystallization using diethyl ether, THF and petroleum ether allowed the isolation of compounds **4a** in good yield, and respectively **4b** and **4c** in lower yield.

4.2.1. 6-(O-butyl) benzochromeno [4,3-c][1,5] benzodiazepin-7(10H)-one (4a)

White cottony, yield 74%. Mp = 147.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.25 (dd, 1H, H-1, *J* = 7.8 Hz), 7.93 (s, 1H, N-H), 7.50 (dd, 1H, H-12, *J* = 7.8 Hz), 7.38 (t, 1H, H-3), 7.28 (t, 1H, H-10), 7.21 (m, 1H, H-9), 7.10–7.00 (m, 3H, H-2, 4, 11), 5.93 (s, 1H, H-6), 3.76 (m, 1H, H-2b′), 3.56 (m, 1H, H-2a′), 3.31 (s, 1H, H-6a), 1.41 (m, 2H, CH_2–3′), 1.16 (m, 2H, CH_2–4′), 0.77 (t, 3H, CH_3–5′). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.6 (C-7), 154.2 (C-4a), 151.2 (C-13a), 139.6 (C-12a), 133.5 (C-3), 128.6 (C-8a), 128.4 (C-12), 126.5 (C-1), 126.3 (C-9), 125.4 (C-10), 122.2 (C-4), 121.6 (C-11), 120.1 (C-13b), 118.6 (C-2), 96.3 (C-6), 68.4 (C-2′), 49.2 (C-6a), 31.2 (C-3′), 19.0 (C-4′), 13.6 (C-5′). ESI (HRMS) *m*/*z* calcd for $C_{20}H_{20}N_2O_3$ 336.1474 found 337.1566 $[M_{4a}+H]^+$ and 359.1387 $[M_{4a}+Na]^+$; ν_{max}(KBr): 3466, 1678 cm^{-1}.

4.2.2. 6-(O-methyl) benzochromeno [4,3-c][1,5] benzodiazepin-7(10H)-one (4b)

White cottony, yield 45%. Mp = 167.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.26 (dd, 1H, H-1, *J* = 7.8 Hz), 7.83 (s, 1H, N-H), 7.49 (d, 1H, H-12, *J* = 7.8 Hz), 7.39 (t, 1H, H-3), 7.27 (t, 1H, H-10), 7.18 (m, 1H, H-9), 7.11–6.99 (m, 3H, H-2, 4, 11), 5.83 (s, 1H, H-6), 3.45 (s, 3H, OCH_3), 3.32 (s, 1H, H-6a), ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 166.4 (C-7), 153.9 (C-4a), 150.9 (C-13a), 139.6 (C-12a), 133.7 (C-3), 128.5 (C-8a), 128.4 (C-12), 126.6 (C-1), 126.3 (C-9), 125.5 (C-10), 122.4 (C-2), 121.6 (C-11), 120.1 (C-13b), 118.6 (C-4), 97.4 (C-6), 55.9 (C-2′). 49.0 (C-6a); ESI (HRMS) *m*/*z* calcd for $C_{17}H_{14}N_2O_3$ 294.1004 found 295.1078 $[M_{4b}+H]^+$ and 317.0914 $[M_{4b}+Na]^+$; ν_{max}(KBr): 3469, 1674.

4.2.3. 6-(O-ethyl) benzochromeno [4,3-c][1,5] benzodiazepin-7(10H)-one (4c)

White cottony, yield 49%. Mp = 154.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.26 (d, 1H, H1, *J* = 7.8 Hz), 7.79 (s, 1H, N-H), 7.49 (d, 1H, H-12, *J* = 7.8 Hz), 7.39 (t, 1H, H-3), 7.27 (t, 1H, H-10), 7.21 (m, 1H, H-9), 7.05–7.09 (m, 3H, H-2, 4, 11), 5.93 (s, 1H, H-6), 3.82 (m, 1H, H-2b′), 3.63 (m, 1H, H-2a′), 3.32 (s, 1H, H-6a), 1.10 (t, 3H, H-3′). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ(ppm) 166.6 (C-7), 153.9 (C-4a), 150.9 (C-13a), 139.7 (C-12a), 133.7 (C-3), 128.7 (C-8a), 128.4 (C-12), 126.4 (C-1), 126.3 (C-9), 125.4 (C-10), 122.2 (C-2), 121.6 (C-11), 120.1 (C-13b), 118.6 (C-4), 96.1 (C-6), 64.2 (C-2′), 49.1 (C-6a), 14.8 (C-3′); ESI (HRMS) *m*/*z*: calcd for $C_{18}H_{16}N_2O_3$ 308.1161 found 309.1198 $[M_{4c}+H]^+$ and 331.0978 $[M_{4c}+Na]^+$; ν_{max}(KBr): 3467, 1678.

4.3. Reaction of the 6-(O-alkyl)benzochromeno-1,5-benzodiazepinones (4a–c) with 2-aminopyridine (2a,b)

A mixture of compounds **4a–c** respectively with 1 equiv of 2-aminopyridine **2a** and 1 equiv of 2-amino-4-méthylpyridine **2b** respectively in 50 mL of dry THF was heated at 40 °C for 3 h. The resulting mixture was allowed to stand at room temperature and then kept under stirring for 12 h. Then the mixture was evaporated to dryness under reduced pressure to give a pale yellow oil residue, which solidified after adding petroleum ether. Recrystallization from THF/petroleum ether (1:3) afforded the corresponding self-assembled **5a–f**.

4.4. Crystallography

Single-crystal diffraction data were collected on an Xcalibur, Atlas, Gemini ultra diffractometer, Cu Kα radiation (λ = 1.5418 Å) for compound **5e**. The structure was solved by direct methods using the SIR97 program and then refined with the aid of the WINGX program.

Cristal data for compound **5e** ($C_{18}H_{16}N_2O_3{\cdot}C_5H_6N_2$); *M* = 402.45, *T* = 150 K; triclinic $P\bar{1}$, *a* = 6.849 (5) Å, *b* = 10.387 Å, *c* = 15.298 Å, α = 106.251 (5)°, β = 91.102 (5)°, γ = 97.942 (5)°, *v* = 1032.9 (10) A^3, *Z* = 2, *d* = 1.294 Mg m^{-3}, μ = 0.71 mm^{-1}, A final refinement on F^2 with unique intensities and parameters converged at $\omega R(F^2) = 0.085$.

5. Supplementary material

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, No. 948433, for self-assembly **5e**. Copies of this information may be obtained free of charge from the CCDC, 12 Union Road, Cambridge CB2, IEZ, UK (e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.ac.uk).

Acknowledgements

We gratefully acknowledge Dr. Marie-Thérèse Martin for 2D-NMR experiments. The authors acknowledge Dr. Sébastien Vidal and Dr. Erwann Jeanneau (University Claude-Bernard Lyon-1) for X-ray crystallographic analysis.

References

[1] (a) A. Zellou, Y. Cherrah, M. Hassar, E.-M. Essassi, Ann. Pharm. Fr. 56 (1998) 169;
(b) F. Savelli, F.A. Boido, A. Mule, L. Pui, M.C. Alamanni, G. Pirisino, M.

Satta, A.A. Peana, Farmaco 44 (1989) 125;
(c) A.A. Failli, J.S. Shumsky, R.J. Steffan, T.J. Caggiano, D.K. Williams, E.J. Trybulski, X. Ning, Y. Lock, T. Tanikella, D. Hartmann, P.S. Chan, C.H. Park, Bioorg. Med. Chem. Lett. 16 (2006) 954.
[2] (a) S.D. Gatzonis, E.K. Angelopoulos, E.G. Daskalopoulou, V. Mantouvalos, A. Chioni, C. Zorrunas, A. Siafakas, Drug Alcohol Depend. 59 (2000) 95;
(b) M. Zappala, A. Pellicano, N. Micale, F.S. Menniti, G. Ferreri, G. Dessaro, S. Grasso, C. De Micheli, Bioorg. Med. Chem. 16 (2006) 167;
(c) P. Ohiger, S. Leutwyler, H. Koeppel, J. Chem. Phys. 17 (2012) 136.
[3] (a) M. Pozarentzi, J.S. Stephanatou, A.C. Tsoleridis, C. Zika, V. Demopoulos, Tetrahedron 65 (2009) 7741;
(b) E.M. Hadac, E.S. Dawson, J.W. Darrow, E.E. Sugg, T.P.L. Lybrand, J.-J. Miller, Bioorg. Med. Chem. 49 (2006) 850;
(c) K. Murai, R. Nakatani, Y. Kita, H. Fujioka, Tetrahedron 64 (2008) 11034.
[4] (a) A. Khodairy, A.M. El-Sayed, H. Salah, H. Abdel-Ghany, Synth. Commun. 37 (2007) 3245;
(b) G. Shyamaprosad, J. Hazra, J. Subrata, J. Heterocyl. Chem. 46 (2009) 861;
(c) Y. Jiang, J.J. Cai, J.P. Zou, W. Zhang, Tetrahedron Lett. 51 (2010) 471.
[5] B. Trimeche, R.R. Gharbi, S. El-Houla, M.-T. Martin, J.M. Nuzillard, Z. Mighri, J. Chem. Res. 5 (2004) 170.
[6] R. Gharbi, A. Romdhane, M.-T. Martin, Z. Mighri, J. Heterocyl. Chem. 42 (2005) 169.
[7] A. Nsira, A. Karoui, R. Gharbi, M. Msaddek, J. Chem. Res. (2012) 152.
[8] B. Trimèche, R. Gharbi, Z. Mighri, M.-T. Martin, Heterocycl. Commun. 8 (2002) 473.
[9] R. Gharbi, M. Ben-Youssef, M.-T. Martin, J. Chem. Res. (2005) 257.
[10] W. Ben-cherif, R. Gharbi, H. Sebai, D. Dridi, N.A. Boughattas, M. Ben-Attia, C. R. Biol. 333 (2010) 214.
[11] (a) D. Hadjipavlou-Litina, R. Garg, C. Hansch, Chem. Rev. 104 (2004) 3751;
(b) M.N. Morshed, M.M. Neaz, M. Muddassar, F.A. Pasha, S. Cho, J. Med. Chem. Res. 18 (2009) 98.
[12] V.I. Pavlovsky, Y.S. Bachinskii, N.A. Tkachuk, Y.S. Makan, S.A. Andronati, Y.A. Simonov, I.G. Filippova, M. Gdaniec, Chem. Heterocycl. Compd. 43 (2007) 1029.
[13] (a) Y. Yuji, O. Hiroumi, N. Yusuke, D. Shigeyuki, N. Yoshinori, J. Phys. Chem. 116 (2012) 9271;
(b) I. Laura, N. Sonia, P. Julio, R. Lucia, R. Victor, D. Jesus, L. Ramon, M.A. Kirsty, W.S. Jonathan, Inorg. Chem. 50 (2011) 8524.
[14] (a) K.M. Al-Ahmary, M.M. Habeeb, E.A. Al-Solmy, J. Mol. Liq. 162 (2011) 129;
(b) S.F. Alshahateet, N.M. Alghezawi, J. Chem. Crystallogr. 41 (2011) 708.
[15] (a) Y. Umebayashi, J.-C. Jiang, Y.-L. Shan, K.-H. Lin, K. Fujii, S. Seki, S.-I. Ishiguro, S.H. Lin, H.-C. Chang, J. Phys. Chem. 130 (2009) 124503;
(b) H.-C. Chang, J.-C. Jiang, W.-C. Tsai, G.-C. Chen, S.H. Lin, J. Phys. Chem. 110 (2006) 3302.
[16] (a) Y. Liu, J. Ding, R. Liu, D. Shi, J. Sun, J. Photochem. Photobiol. A: Chem. 201 (2009) 203;
(b) S. Tardioli, C. Gooijer, G. van der Zwan, J. Phys. Chem. 113 (2009) 6949.
[17] H. Zhang, S.-C. Smith, J. Theor. Comput. Chem. 6 (2007) 789.
[18] M. Hamdi, O. Grech, R. Sakellariou, V. Speziale, J. Heterocycl. Chem. 31 (1994) 509.
[19] (a) R. Varala, S.-R. Adapa, Can. J. Chem. 84 (2006) 1174;
(b) B. Wang, L.-M. Yang, J.-S. Suo, Synth. Commun. 33 (2003) 3929;
(c) J. Singh, N. Gupta, G.-L. Kad, J. Kaur, Synth. Commun. 36 (2006) 2893.
[20] (a) D.B. Davies, D.A. Veselkov, V.V. Kodintsev, M.P. Evstigneev, A.N. Veselkov, Mol. Phys. 98 (2000) 1961;
(b) M.P. Evstigneev, Y.V. Mukhina, D.B. Davies, Mol. Phys. 100 (2006) 647.
[21] J. Zhuang, S. Xiao, Y. Li, H. Li, N. Liu, F. Lu, H. Liu, D. Zhu, Synth. Met. 155 (2005) 643.
[22] Y. Buyukmurat, E. Akalin, A.E. Ozel, S. Akyuz, J. Mol. Struct. (1999) 579.
[23] M. Semenov, I.N. Blyzniuk, T.V. Bolbukh, A.V. Shestopalova, M.P. Evstigneev, V.Y. Maleev, Spectrochim. Acta, Part A 95 (2012) 224.
[24] G. Gilli, V. Bertolasi, M. Sacerdoti, P.A. Borea, Acta Crystallogr. 33 (1977) 2664.
[25] J. Rambaud, J.L. Delarbre, B. Pauvert, L. Maury, A. Dubourg, J.-P. Declercq, Acta Crystallogr. 43 (1987) 2195.
[26] A.A. Karapetyan, V.G. Andrianov, Y.T. Struchkov, A.V. Bogatsky, S.A. Andronati, T.I. Korotenko, Bioorg. Khim. 5 (1979) 1684.
[27] A. Jebani, H. Zouihri, A. El Hakmaoui, S. Lazar, M. Akssira, Acta Crystallogr. 67 (2011) 2003.