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Application of theoretically computed chemical shifts to structure determination of novel heterocyclic compounds

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Abstract

Combined use of 2D NMR correlation methods (^{1}H–^{13}C and ^{1}H–^{15}N 2D HMBC) and the DFT-GIAO chemical shift calculations allows unequivocal determination of structure for novel quinoxaline. Such interplay of experiment and theory is really reliable and convenient way for structure elucidation of complex heterocycles.

Keywords: 2D NMR; ^{1}H, ^{13}C and ^{15}N chemical shifts; DFT-GIAO chemical shifts; Structure elucidation; Quinoxalines

1. Introduction

The developments of NMR equipment and powerful multi-dimensional correlation NMR techniques have opened a direct way for the structure elucidation of organic compounds in solution [1]. Nevertheless, particularly in the field of natural products and heterocyclic chemistry, when there are several non-magnetic nuclei in a molecular skeleton, these methods can be used to establish the structure of the fragments only. In such cases, one needs reliable rules to combine experimentally derived fragments into molecule as whole [2]. Therefore, often NMR spectroscopists undergo an arduous intellectual journey of 'puzzle solving' before they finally find correct structure of an unknown molecule.

An application of theoretically computed chemical shifts to link these fragments ('to solve puzzle') is very challenging although it has not yet become routine in practical applications [3]. It has been recently demonstrated that predicted chemical shifts (i.e. ^{13}C) are accurate within a very few parts per million for molecules in solution that include a wide variety of functional groups and conformations [4]. The predictions also can be achieved at modest computational cost.

Here, we show how combined use of modern 2D NMR methods and non-empirical chemical shift (CS) calculations provides simple and reliable way to recover overall structure of new heterocyclic compound of practical interest.

2. Experimental

2.1. Synthesis of compounds

2.1.1. Preparation of 3-phenylbromeacetylquinoxaline-2(1H) one (2)

To the suspension of 0.2 g (0.75 mmol) of 3-phenylacetylquinoxaline-2(1*H*)one and 0.062 g (0.75 mmol) of sodium acetate in 10 mL acetic acid was added slowly 0.04 mL (0.75 mmol) of bromine in 5 mL acetic acid. The mixture was stirred during 3 h. After cooling, the reaction mixture was poured into water (30 mL). The precipitated product was collected by filtration and washed with H_2O (2× 10 mL), dried to give the yellow crystalline compound (**2**), yield 75%, mp. >310 °C (decom.); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta = 7.96$ (1H, d, $J = 8.2$ Hz, H-5), 7.68 (1H, dd, $J = 8.2$, 7.5 Hz, H-7), 7.59 (2H, d, $J = 6.9$ Hz, H-2′, H-6′), 7.50 (1H, d, $J = 8.2$ Hz, H-8), 7.44 (1H, dd, $J = 7.8$, 7.5 Hz, H-6), 7.35 (3H, m, H-3′, H-4′, H-5′), 6.93 (1H, s, CH); IR, ν, cm^{-1} (potassium bromide) (Vector-22 (Bruker)): 528, 552, 560, 593, 701, 732, 759, 960, 1122, 1130, 1141, 1346, 1465, 1492, 1540, 1607, 1654, 1716, 2725, 3084, 3475, 3611. $C_{16}H_{11}BrN_2O_2$ found, %: C 56.21, H 3.35, Br 23.42, N 8.10. Calculated, %: C 56.00, H 3.23, Br 23.28, N 8.16.

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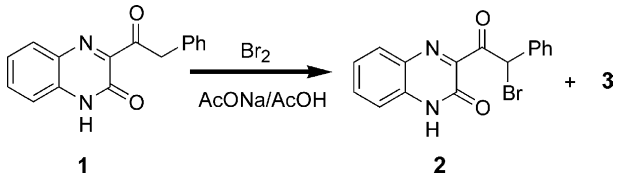

Scheme 1.

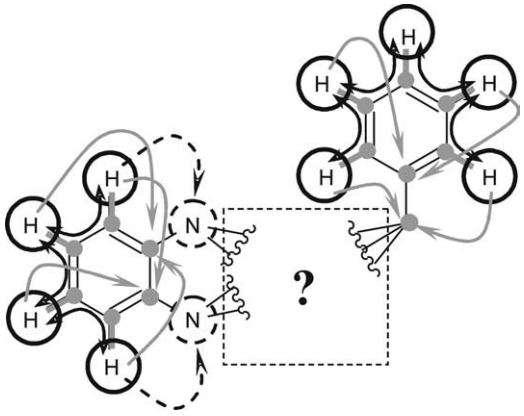

Fig. 1. COSY (black arrows), HSQC (gray) and principal HMBC (^{1}H–^{13}C—gray and ^{1}H–^{15}N—dotted arrows) correlations for 3.

2.1.2. Preparation of 2-phenyl-3-hydroxyfuro[2,3-b] quinoxaline (3)

The filtrate obtained above by dilution with water was kept overnight in at room temperature and the precipitate was collected by filtration and dried to give the white crystalline compound (**3**), yield 20%, mp. = 252–253 °C; ^{1}H NMR (DMSO, 600 MHz, 50 °C): δ = 8.21 (1H, m, H-8), 8.15 (2H, d, J = 6.2 Hz, H-2′, H-6′), 8.09 (1H, m, H-5), 7.83 (2H, m, H-7), 7.82 (2H, m, H-6), 7.59 (2H, dd, J = 6.2, 3.1 Hz, H-3′, H-5′), 7.46 (1H, ddt, J = 6.2, 3.1 Hz, H-4′), 3.29 (br, OH); ^{13}C NMR (DMSO, 150.86 MHz, 50 °C): δ = 151.04 (C-3), 144.42 (C-2), 140.92 (C-8a), 138.29 (C-9a), 138.16 (C-4a), 134.68 (C-1), 128.80 (C-1′), 128.76 (C-4′), 128.73 (C-3′, C-5′), 128.68 (C-6), 128.07 (C-5, C-8), 128.02 (C-7), 124.81 (C-2′, C-6′); m/z = (262)M^{+}; IR, ν, cm^{-1} (neat) (Vector-22 (Bruker)): 656, 684, 758, 769, 1060, 1119, 1133, 1164, 1224, 1289, 1307, 1325, 1410, 1443, 1513, 1566, 1630, 1665, 1720, 2629. $C_{16}H_{10}N_2O_2$ found, %: C 73.04, H 3.64, N 10.42. Calculated, %: C 73.27, H 3.84, N 10.68.

2.2. NMR spectroscopy

All NMR experiments were performed in dilute DMSO solutions at 50 °C with a Bruker AVANCE-600 spectrometer equipped with a 5 mm diameter broad band probehead working at 600,000 MHz in ^{1}H, 150.864 MHz in ^{13}C and 60.796 MHz in ^{15}N experiments. CSs are reported on the δ (ppm) scale and are relative to the residual ^{1}H and ^{13}C signal of DMSO-d6. ^{15}N CSs were referenced to the external of CD_3CN. Assignment of the ^{1}H and ^{13}C NMR spectra of the title compounds was accomplished by DEPT, 2D COSYGP, HSQC, HMBC experiments. Related 1D and 2D NMR spectra can be obtained in supporting materials.

2.3. Computational methods

CSs were determined within the DFT framework using a hybrid exchange-correlation functional, B3LYP, at the 6-31G(d) level as implemented in Gaussian 98 [5]. Full geometry optimizations were done at the ab initio RHF/6-31G level. All data were referred to TMS (^{1}H and ^{13}C) and NH_3 (^{15}N) CSs that were calculated in the same conditions.

3. Results and discussion

The current study was initiated by attempts to find new drug candidates among the derivatives of 3-phenylacetylquinoxalin-2-one (**1**) [6]. In the reaction of **1**, besides the main product—3-phenylbromacetylquinoxalin-2(1H)-ones (**2**)—the novel

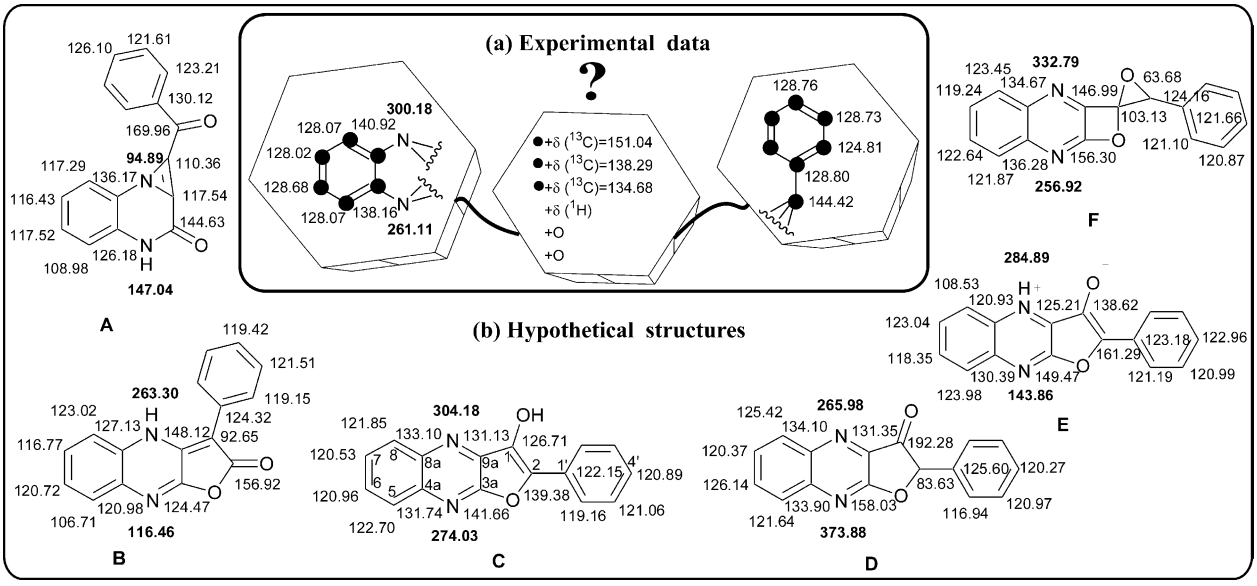

Fig. 2. (a) Experimental data for three with CSs (in ppm) of ^{13}C and ^{15}N (bold); (b) hypothetical structural isomers of three with calculated CSs of ^{13}C and ^{15}N (bold).

product (**3**) was always obtained (Scheme 1). Unfortunately, ^{1}H and ^{13}C NMR spectra could not be directly ascribed to reaction products we expected.

^{1}H spectrum of **3** consists of several signals of aromatic protons and broadened line at δ 3.29. Two groups of protons of benzo moieties and phenyl group uniquely stand out in the 2D COSY spectrum (Fig. 1).

The ^{13}C NMR CSs of all hydrogenated carbons could be assigned unambiguously by the 2D HSQC spectrum. The most important are 2D HMBC correlations, which allow to assign resonance of some quaternary carbons and to establish the structures of two molecular parts (Fig. 1). Namely, there are correlations between the protons of benzo moieties at δ 8.09 and δ 7.83 and the carbon resonance at δ 140.92; the protons at 8.21 and δ 7.82 and the carbon resonance at δ 138.16; the protons at 7.59 (H-3′, H-5′) and the carbon resonance at δ 128.80 (C-1′); the protons at 8.15 (H-2′, H-6′) and the carbon resonance at δ 144.42. In addition, there are three quaternary carbons at δ 151.04, 138.29 and 134.68, which have no HMBC correlations to any protons, and therefore these resonance cannot be assigned and there is no experimental (NMR) ground to link these three carbons to above fragments.

In addition, the structure of benzo fragment was extended to two nitrogen's from the analysis N–H HMBC correlations [7]: there are cross-peaks between the proton signal of benzo moieties at δ 8.21 and the nitrogen resonance at δ 300.18; the proton signal at δ 8.09 and the nitrogen resonance at δ 261.11 (Fig. 1).

Thus, from extensive spectroscopic investigation two fragments (benzo moiety bonded to nitrogen atoms and phenyl fragment) were surely revealed (Fig. 1) by use of 2D correlation experiments.

Besides, there may be one NH or OH protons, which can be masked (or in exchange) by residual water in DMSO. The mass spectrometry (MS) data indicated that the sample is homogeneous with molecular weight of $m/z=262(M^{+\cdot})$. Taking into account elemental analysis its molecular formula was derived to be $C_{16}H_{10}N_2O_2$.

Chemically meaningful structural isomers were generated by combination of these two experimentally derived fragments bound via moieties possessing two oxygen, one proton and three quaternary carbons and then were used as trial structures for further analysis (Fig. 2). Thus, finally to establish correct structure of **3** one needs a safe and reliable way to choose among the hypothetical ones. Until now, no CS information was used to recover the structure of fragments that were derived from HMBC connectivity only.

It has been shown recently that DFT-GIAO calculations of NMR ^{13}C CSs can provide valid support in interpreting experimental ^{13}C NMR data of unknown species, and hence in resolving structural controversies. Thus, it seems, that having NMR spectra (^{1}H, ^{13}C and ^{15}N), one is able to choose correctly one structure from possible variety of trial structural isomers obtained from a molecular formula [4,8]. Therefore, we applied such approach to establish real structure of **3**. ^{1}H CSs are less sensitive to skeletal structure therefore only ^{13}C and ^{15}N CSs were analyzed in details.

GIAO-calculated CS values of optimized trial structures of **3** (Fig. 2b) were compared versus experimental ^{13}C NMR data. The GIAO method underestimates (^{13}C) CSs, particularly in low field region therefore the shifts might need scaling in order to provide quantitative match with experimental shifts (3m,4b,g). However, in practice, it is important that the relative order of shifts could be predicted accurately which can be characterized by correlation coefficient between theoretical and experimental CS. Therefore, least-squares linear fitting parameters (R^2 or rms) of correlation plots between computed (without scaling) and experimental CS values can be employed to discriminate among the structural hypotheses [9]. As example correlation of ^{13}C CSs is shown in Fig. 3 and the results of the linear regression analysis comparing experimental shifts to GIAO CSs are summarized in Table 1.

Analysis of these data unequivocally demonstrated that only for the **C** isomer predicted ^{13}C CSs correlate well with experimental ones (Fig. 3). Only for the isomer **C** the R^2 values are in the range of 0.93 (for skeletal carbons)—0.97 (for all carbons). On the other hand, with regard to other isomers, the calculated values obviously do not agree with experimental results (Fig. 3), where the correlation coefficients are

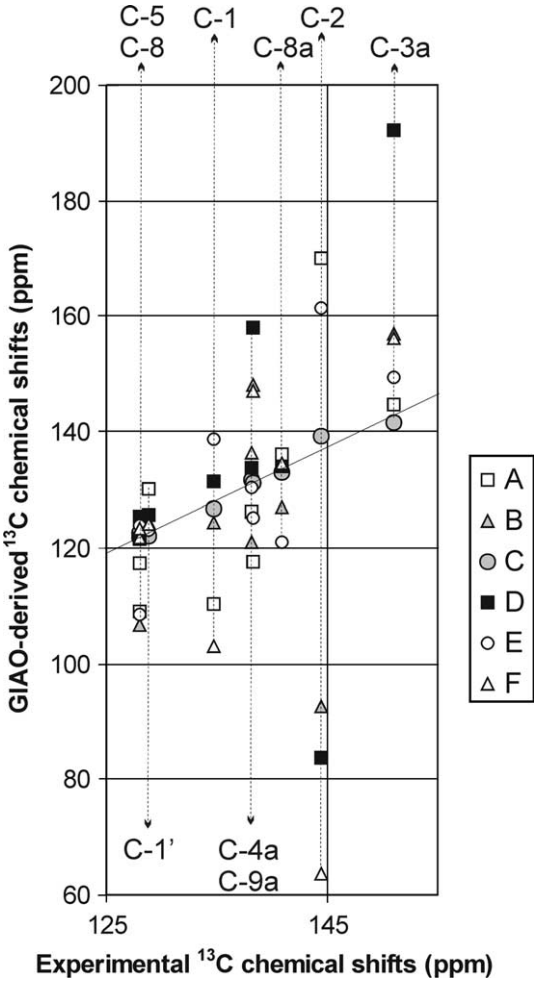

Fig. 3. Correlation of calculated versus experimental ^{13}C CSs (C-1, C-2, C-3a, C-4a, C-5, C-8, C-8a, C-9a, C-1′ atoms) for isomers **A**–**F** (shown on Fig. 2).

Table 1
Linear correlation coefficients of experimental *vs* calculated (GIAO RB3LYP/6-31G(d)//RHF/6-31G) ^{13}C CSs (R^2), root-mean-square errors (rms), slope (a), standard deviations (sd) and mean absolute deviations (MAD $= \sum[|\delta_{exp} - \delta_{calcd}|]/n$) for the isomers A–F

Structure	R^2	rms	a	sd	MAD
A	0.4586[a]	11.62	1.39	12.06	11.39
	0.5150[b]	16.22	2.66	17.77	15.63
	0.5709[c]	19.90	3.37	21.79	15.55
B	0.1458	13.80	0.76	14.32	12.93
	0.0574	20.03	0.94	21.94	18.11
	0.0605	19.17	0.92	21.00	14.28
C	**0.9768**	**1.16**	**0.95**	**1.20**	**7.03**
	0.9345	**1.35**	**0.93**	**1.48**	**7.30**
	0.3628	**10.85**	**1.50**	**11.88**	**8.59**
D	0.2231	20.56	1.45	21.33	13.06
	0.1196	31.17	2.13	34.14	22.70
	0.0548	32.16	1.46	35.23	25.41
E	0.5744	8.89	1.33	9.22	8.92
	0.3122	11.94	1.49	13.08	10.54
	0.5509	13.18	2.33	14.44	16.11
F	0.0115	21.14	0.30	21.94	13.10
	0.0235	31.02	0.91	33.98	22.40
	0.1835	34.28	2.94	37.55	26.84

[a] All ^{13}C.
[b] Only skeletal carbons [9]: C-1, C-2, C-3a, C-4a, C-8a, C-9a.
[c] Estimated according to additive scheme (CambridgeSoft's ChemDraw Program, quaternary ^{13}C: C-1, C-2, C-3a, C-4a, C-8a, C-9a).

essentially less (0.52–0.57) or even worse (Table 1). The rms value for the **C** isomer is also by an order of magnitude smaller than that for other hypotheses.

Moreover, ^{15}N CSs are also in full agreement with this conclusion. As one can see from diagrams of mismatches between experimental and calculated CSs for the hypothetical structures (Fig. 4), only for the **C** isomer reasonably small deviations are observed while for other structures the differences were large.

It is very significant that an attempt to predict ^{1}H NMR and ^{13}C NMR shift values of the **3** based on additivity rules on the ground of tabulated data for typical structural fragments and groups would be totally unsuccessful. For example, estimation of CSs according to additive scheme implemented in 'estimate' utility of CambridgeSoft's ChemDraw Program [10] gives very poor prediction of ^{13}C CSs and correlation coefficients in all cases (for wrong and right structures) do not exceed 0.57 and rms is higher than 10.

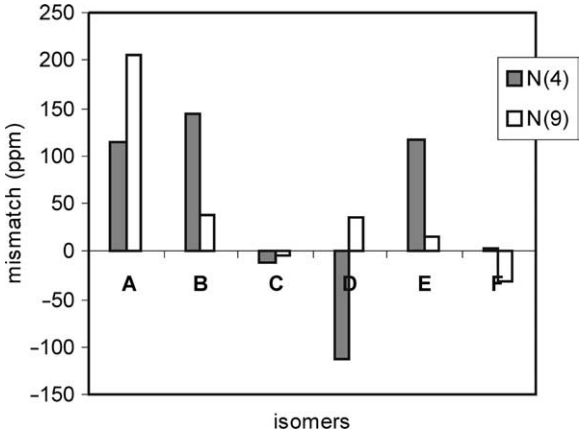

Fig. 4. Mismatch of experimental and calculated ^{15}N CSs for isomers A–F.

It is worth mentioning that above used non-empirical calculations of CS are very cheap in the sense of computational costs and most of the researchers can run them easily on their desk computers (3–5 h per one isomer on Pentium 4 CPU 2.80 GHz 512 Mb RAM).

4. Conclusion

The structure of furo[2,3-*b*]quinoxaline (**3**) obtained in the reaction of 3-phenylacetylquinoxaline-2(1H)one and bromine in acetic acid in the presence of sodium acetate was unambiguously determined.

Combined use of modern multi-dimensional NMR techniques and non-empirical calculations of CSs was shown to be a very efficient and reliable way to elucidate chemical structure of novel compounds in reasonable time.

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2006.01.008

References

[1] (a) W.R. Croasmun, R.M.K. Carlson, Two-Dimensional NMR Spectroscopy, VCH, Weinheim, 1987;
(b) A.E. Derome, Modern NMR Techniques for Chemistry Research, Pergamon Press, Cambridge, 1988;
(c) T.I. Atta-ur-Rahman, One and Two Dimensional NMR Spectroscopy, Elsevier, Amsterdam, 1989;
(d) T. Lindel, J. Junker, M. Kock, J. Mol. Model., 3364.
[2] (a) G.C. Levy, Topics in Carbon-13 NMR Spectroscopy, Wiley–Interscience, New York, 1979;
(b) M. Shamma, D.M. Hindenlang, Carbon-13 NMR Shift Assignment of Amines and Alkaloids, Plenum Press, New York, 1979;
(c) E. Breitmaier, W. Voelter, Carbon-13 NMR Spectroscopy: High Resolution Methods and Applications in Organic Chemistry and Biochemistry, VCH, Weinheim, 1987.
[3] (a) A. De Dios, D.D. Laws, E. Oldfield, J. Am. Chem. Soc. 116 (1994) 7784;
(b) H.M. Sulzbach, Pv.R. Schleyer, H.F. Schaefer III, J. Am. Chem. Soc. 116 (1994) 3967;
(c) A. De Dios, Prog. Nucl. Magn. Reson. Spectrosc. 29 (1996) 229;
(d) J.R. Cheeseman, G.W. Trucks, T.A. Keith, J. Frisch, J. Chem. Phys. 104 (1996) 5497;
(e) H. Lampert, W. Mikenda, A. Karpfen, H. Kalhlig, J. Phys. Chem. A 101 (1997) 9610;
(f) M. Barfield, P. Fagerness, J. Am. Chem. Soc. 119 (1997) 8699;
(g) G.K.S. Prakash, G. Rasul, G.A. Olah, J. Phys. Chem. A 102 (1998) 2579;

(h) I. Alkorta, J. Elguero, New J. Chem. (1998) 381;
(i) P. Cmoch, J.W. Wiench, L. Stefaniak, G.A. Webb, J. Mol. Struct. 510 (1999) 165;
(j) T. Kupka, G. Pasterna, P. Lodowski, W. Szeja, Magn. Reson. Chem. 37 (1999) 421;
(k) E. Kolehmainen, J. Koivisto, V. Nikiforov, M. Perakyla, K. Tuppurainen, K. Laihia, R. Kauppinen, S. Miltsov, V. Karavan, Magn. Reson. Chem. 37 (1999) 743;
(l) R.M. Gomila, D. Quinonero, C. Rotger, C. Garau, A. Frontera, P. Ballester, A. Costa, P.M. Deya, Org. Lett. 4 (2002) 399;
(m) A.B. Sebag, R.N. Hanson, D.A. Forsyth, C.Y. Lee, Magn. Reson. Chem. 41 (2003) 246.

[4] (a) D. Colombo, P. Ferraboschi, F. Ronchetti, L. Toma, Magn. Reson. Chem. 40 (2002) 581;
(b) G. Barone, L. Gomez-Paloma, D. Duca, A. Silvestri, R. Riccio, G. Bifulco, Chem. Eur. J. 8 (2002) 3233;
(c) D. Tahmassebi, Magn. Reson. Chem. 41 (2003) 273;
(d) C. Bassarello, P. Cimino, L. Gomez-Paloma, R. Riccio, G. Bifulco, Tetrahedron 59 (2003) 9555;
(e) I. Alkorta, J. Elguero, A. Fruchier, N. Jagerovic, G.P.A. Yap, J. Mol. Struct. 689 (2004) 251;
(f) I. Alkorta, J. Elguero, Magn. Reson. Chem. 42 (2004) 955;
(g) P. Cimino, L. Gomez-Paloma, D. Duca, R. Riccio, G. Bifulco, Magn. Reson. Chem. 42 (2004) S26.

[5] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A., Montgomery Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B.G. Johnson, W. Chen, M.W. Wong, J.L. Andres, M. Head-Gordon, E.S. Replogle, J.A. Pople, GAUSSIAN 98 (Revision A.6), Gaussian Inc., Pittsburgh, PA, 1998.

[6] (a) Y. Blache, A. Gueiffier, A. Elhakmaoui, J. Heterocycl. Chem. 32 (1995) 1317;
(b) H. Prunier, S. Rault, J.C. Lancelot, J. Med. Chem. 40 (1997) 1808;
(c) G. Campiani, A. Cappelli, V. Nacci, J. Med. Chem. 40 (1997) 3670;
(d) E.L. Jacobsen, L.S. Stelzer, K.L. Belonga, J. Med. Chem. 39 (1996) 3820;
(e) E.J. Jacobsen, L.S. Stelzer, K.L. Belonga, J. Med. Chem. 42 (1999) 1123;
(f) J.W. Mickelson, E.L. Jacobsen, D.B. Carter, J. Med. Chem. 39 (1996) 4654;
(g) J. Ohmori, M. Shimizu-Sasamata, M. Okada, J. Med. Chem. 40 (1997) 2053;
(h) D. Korakas, A. Kimbaris, G. Varvounis, Tetrahedron 32 (1996) 1751;
(i) R.G. Glushkov, L.N. Dronova, A.S. Yelina, Zh. Org. Chem. (Russ.) 3 (1985) 336.

[7] M. Kline, S. Cheatham, Magn. Reson. Chem. 41 (2003) 307.

[8] (a) A. Balandina, V. Mamedov, X. Franck, B. Figadere, Sh. Latypov, Tetrahedron Lett. 45 (2004) 4003;
(b) Sh.K. Latypov, M.A. Fakhfakh, J.-Ch. Jullian, X. Franck, R. Hocquemiller, B. Figadere, Bull. Chem. Soc. Jpn 78 (2005) 1296;
(c) A.A. Balandina, A.A. Kalinin, V.A. Mamedov, B. Figadere, Sh.K. Latypov, Magn. Reson. Chem. 43 (2005) 816.

[9] Basically we stressed our attention on the analyses of CSs of only 'skeletal' nuclei because: on the one hand the CSs of substituents have basically to reflect particularities of substituents themselves and, therefore their correlation can hardly be characteristic of the backbone structure; on the other hand, it is cross linking of backbone nuclei that determine structure and properties of the compound as a class and therefore their correlation (calculation vs experiment) may be used to validate structures.

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