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^{1}H AND ^{13}C NMR SPECTRA OF STRYCHNOS ALKALOIDS: SELECTED NMR UPDATES

Abstract. *The PBE0/pcSseg-2//pcseg-2 calculations of ^{1}H and ^{13}C NMR chemical shifts were performed for a classical series of 12 Strychnos alkaloids (except for the earlier studied parent strychnine), namely akuammicine, isostrychnine, rosibiline, tsilanine, spermostrychnine, diaboline, cyclostrychnine, henningsamide, strychnosilidine, strychnobrasiline, holstiine, and icajine. It was found that calculated ^{1}H and ^{13}C NMR chemical shifts demonstrated markedly good correlations with available experimental data characterized by a mean absolute error of 0.22 ppm for the range of 8 ppm for protons and 1.97 ppm for the range of 180 ppm for carbons. Complimentary, present results provide essential NMR update and fill a gap in the NMR data of this distinguished group of the vitally important natural products.*

Keywords: *^{1}H and ^{13}C NMR, DFT, strychnos alkaloids.*

1 INTRODUCTION

It is well known that ^{1}H and ^{13}C NMR chemical shifts provide a powerful tool in structural elucidation of organic molecules, natural compounds, and biochemical species. Theoretical grounds of the calculation of these parameters is well covered in a handbook of molecular electromagnetism[1] and in a number of comprehensive and prospective reviews on computational and theoretical aspects of NMR (see, for example, basic reviews[2,3,4,5,6,7.8,9,10,11,12] and numerous references given therein). In this vein, a representative family of *Strychnos* alkaloids presents a rigorous test and a challenging task for modern NMR computational facilities, used for the calculation of ^{1}H and ^{13}C NMR chemical shifts of large molecules.

The family of *Strychnos* alkaloids involves several dozens of compounds and is represented by thirteen basic structures including the parent strychnine, mostly known toxic terpene indole alkaloid. Our previous paper[13] was devoted to this prominent alkaloid alone, so that in this study we consider the rest of the twelve *Strychnos* alkaloids shown below in Scheme 1. Among those are akuammicine (**1**), isostrychnine (**2**), rosibiline (**3**), tsilanine (**4**), spermostrychnine (**5**), diaboline (**6**), cyclostrychnine (**7**), henningsamide (**8**), strychnosilidine (**9**), strychnobrasiline (**10**), holstiine (**11**), and icajine (**12**) without paying more attention to strychnine itself.

The vivid progress in the total synthesis of *Strychnos* alkaloids was reviewed very recently by He *et al.* [14] Relating to their origin and biological activity, akuammicine (**1**) is a monoterpenoid indole alkaloid, isolated from several plant species including *Alstonia spatulata*, *Catharanthus roseus*, and *Vinca major*. It has a role as a plant metabolite. From a chemical point of view, it combines the structural features of a methyl ester, a tertiary amino compound, being an organic heteropentacyclic compound and a monoterpenoid indole alkaloid. Isostrychnine (**2**) was originally isolated from the seeds of *Strychnos nux-vomica*. It has a role of a plant metabolite and an antineoplastic agent, being the substance that inhibits or prevents the proliferation of neoplasms. Rosibiline (**3**) was extracted from the root bark of *S. variabilis*. The structure of rosibiline was confirmed by its preparation in the reaction of desacetylretuline with formaldehyde in the presence of acetic acid. Tsilanine (**4**) belongs to the stem bark alkaloids of *Strychnos henningsii* showing convulsive, hypotensive, and cardiac depressant activities, due to their effect on the central nervous system. Spermostrychnine (**5**) was isolated from the

leaves, stem, and root barks of Australian *Strychnos psilosperma*. Diaboline (**6**) is a curare alkaloid, extracted from the flowering plant *Strychnos diaboli*. It was synthesized in conjunction with a total synthesis of structurally related strychnine. Diaboline is a glycine receptor antagonist and, like strychnine, is a convulsant. Cyclostrychnine (**7**) and henningsamide (**8**) the effective anti-depressants, have been isolated from the leaves, stem, and root barks of *Strychnos henningsii* collected in Tanzania. Strychnosilidine (**9**) was extracted from the trunk bark of *Strychnos brasiliensis*, growing in the northeast tropical forest of Argentina. Strychnobrasiline (**10**) is a major alkaloid constituent of *S. myrtoïdes*. It has been shown that it lacks both intrinsic antimalarial activity and cytotoxycity effect, but exhibited *in vitro* significant chloroquine potentiating action against a chloroquine-resistant strain of *Plasmodium falciparum*. Holstiine (**11**) was isolated from the plant *Strychnos henningsii* and subjected to a total structural assignment through the concerted application of a number of two-dimensional NMR techniques that included COSY, HC-COSY, HOHAHA, NOESY, and proton-detected long-range HMBC performed by Martin and coworkers. [15] The twelfth representative of this family, icajine (**12**), was found in different species of *Strychnos*, especially in *S. nux vomica* providing some specific biological activity.

However, the most prominent biological activity in this series is exhibited by a parent strychnine (not considered herewith and being the subject of our recent more thorough investigation[13] together with that of a number of the earlier studies[16,17,18,19,20,21,22,23]), a classically known highly toxic terpene indole alkaloid used, in particular, as a pesticide for killing birds and rodents.

Herewith, we use the most effective DFT computational scheme, PBE0/pcSseg-2//pcseg-2, derived in our most recent study of strychnine to perform verification and additional clarification of the earlier structural assignments and report ^{1}H and ^{13}C NMR data of **1-12** missing in world literature.

2 COMPUTATIONAL DETAILS

Geometry optimization of **1-12** together with all their 62 diastereomers was performed with GAUSSIAN 09[24] code at the M06-2X/cc-pVQZ level (for nitrogen and oxygen atoms, the extended aug-cc-pVQZ basis set was used to take into account the effect of the diffused lone pairs). The solvent effect was accounted for in the calculations within the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM).[25,26] Cartesian coordinates of the optimized structures of **1-12** are given in the Supporting Information.

All calculations of ^{1}H and ^{13}C NMR isotropic magnetic shielding constants (and, accordingly, chemical shifts) were carried out at the DFT level for a liquid phase by implying the GAUSSIAN 09 code. In these calculations, we used the PBE0/pcSseg-2//pcseg-2 computational scheme introduced in our previous publication. [13] Namely, the generalized gradient functional of Perdew, Burke, and Ernzerhof[27,28] with a predetermined amount of exact exchange known as PBE0,[29] was employed throughout. This functional was used in combination with the segmented contracted basis sets of Jensen pcSseg-2 and pcseg-2.[30] In these calculations, the locally dense triple-zeta quality pcSseg-2 basis set was used on the atoms of interest (*i.e.* on those, for which chemical shifts were calculated), while the pcseg-2 basis set was employed for the atoms in the rest of the molecules.

Calculated ^{1}H and ^{13}C isotropic magnetic shielding constants were converted into ^{1}H and ^{13}C NMR chemical shifts as recommended by the International Union of Pure and Applied Chemistry (IUPAC).[31] To take into account the systematic error of calculated ^{1}H and ^{13}C NMR chemical shifts, we have established correlations between their calculated and experimental values. These correlations were used further on to find out the linear correlation equations of the $y = ax + b$ type. The slope a and intercept b were then used for recalculating theoretical chemical shifts into experimental δ-scale using the equation $\delta_{recalc} = (\delta_{calc} - b)/a$.

3 RESULTS AND DISCUSSION

Interpretation of ^{1}H and ^{13}C NMR spectra of strychnines **1-12**, each having multiple asymmetrical centers, presents a difficult and sometimes even a challenging task. In the series of natural products under study, a large number of hydrogen and carbon atoms has similar stereoelectronic environments and, therefore, very similar, or even equivalent, chemical shifts. As a result, most of their ^{1}H NMR spectra present a superposition of the individual second- or even higher-order multiplets forming complex

unresolved patterns, which are very difficult to analyze and to perform adequate spectral assignments. This is even more so in view of the magnetic nonequivalence of protons in the axial and equatorial positions of the condensed carbocycles forming a general strychnine framework. Indeed, proper resolution and univocal assignments of ^{1}H NMR spectra provide a guiding thread in spectral interpretation of natural products using multinuclear mutipulse techniques. In some cases, certain inconsistencies could occur and would be resolved in ^{13}C NMR spectra of these species by applying the high-level theoretical calculations, which is actually done in the present paper.

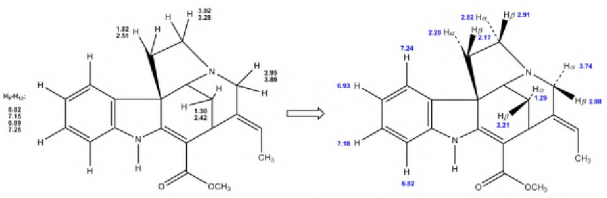
In these difficult cases, of particular importance and of much help are theoretical calculations of ^{1}H and ^{13}C NMR parameters performed at a high theoretical level, which are reported in this paper for the whole family of strychnines **1-12**. Herewith, we performed such calculations for as many as 74 diastereomers of 12 strychnines possessing 62 optical centers in total.

All verified, configurations of **1-12** are shown in Figure 1. In this figure, all asymmetric centers are presented in green, while their calculated and experimental ^{13}C NMR chemical shifts are given accordingly, in blue and in black with "ND" standing for "Not Determined". Interesting to note, that according to the performed calculations, changing configuration at one of the asymmetric centers results in a difference of the ^{13}C NMR chemical shift of a chiral carbon for as much as up to 40 ppm. This is more than enough for the unequivocal configurational assignment of all asymmetric centers in this series, and this was actually done in the present communication for each of the 62 optical centers in the series of **1-12**.

Given in Table 1 are the ^{1}H and ^{13}C NMR chemical shifts of **1-12** calculated at each of the chiral carbon centers, as compared to available experiment. It should be kept in mind that experimental NMR data are given only for one particular configuration at each of all asymmetric centers, while chemical shifts are calculated for both of the two possible configurations. At that, direct comparison of calculated and experimental ^{1}H and/or ^{13}C NMR chemical shifts enables unambiguous assignment at each asymmetric center, which is performed below for all twelve *Strychnos* alkaloids under consideration.

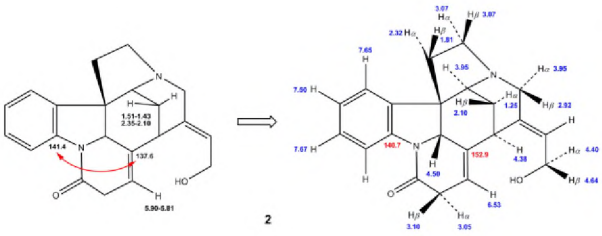
Speaking of computational ^{13}C NMR data, first it should be noted that for all twelve strychnines, the established earlier absolute configurations of all 62 asymmetric centers in all 12 compounds are in a good agreement with the results of the present calculations. The only ambiguity deals with some controversial spectral assignments of C-7 in **1**, C-16 in **3**, C-16 and C-23 in **4**, C-19 and C-20 in **5**, C-19 in **7** and **10**, C-16 in **11**, and C-17 in **12**. Neither calculated chemical shift differences, nor the energetic reasoning based on the calculated ΔE^{0} values could resolve those inconsistences. In those particular cases, all configurations given in Table 1, are retrieved from the original publications and are not verified by the present calculations. Up to date, experimental ^{1}H NMR parameters are not available (not assigned or not determined) in about half of cases, so that the results of the present calculations successfully fill this gap. Complimentary, performed in a number of cases, are the unambiguous assignments of protons in the ^{1}H NMR multiplets representing strongly coupled spin systems, which have not been assigned explicitly in the original publications. In all of these cases, we verified configurational assignments based on computational and energetic reasoning, which is commented on below in more detail for the particular strychnines. A full data set of all calculated and experimental ^{1}H and ^{13}C NMR chemical shifts of **1-12** is given in Tables 2 and 3. In some particular cases we report reassignment of the individual resonances (which are marked in red) and the assignments of the experimentally unresolved signals (mostly those of protons), which are given in blue. Provided below are the comments on each particular compound of this series.

Akuammicine (1). Experimental ^{1}H and ^{13}C data are reported for **1** in a number of papers.[32,33,34] Based on the present calculations, all their performed ^{13}C NMR assignments are correct except for some ambiguity dealing with C-2 and C-17 resonances separated in the experimental spectrum by only 0.2 ppm. This small difference was reproduced in the computed chemical shifts as well. Shown below are the computed ^{1}H NMR chemical shifts of the individual protons of **1** which were not resolved in the original experimental spectrum.

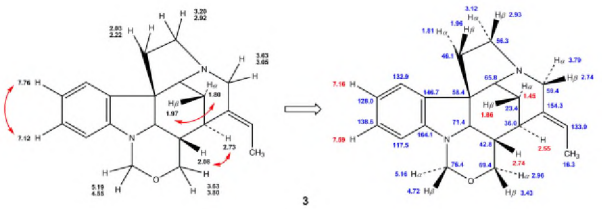


1

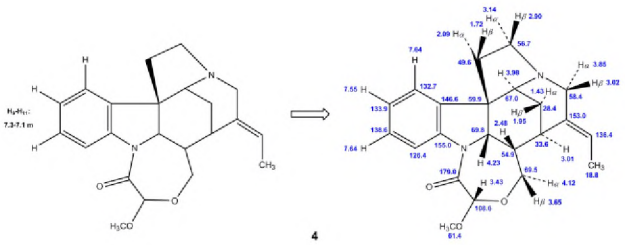
Isostrychnine (2). Based on the performed calculations, we suggest reassignment of C-13 and C-16 in the experimental ^{13}C NMR spectrum of **2** given and assigned in the paper.[35] In addition to the calculations, these reassignments can be confirmed by using the following HMBC correlations: (a) H-9 and H-11 to C-13; (b) H-14, H-15, and H-17 to C-16. For protons, we provide almost full set of calculated shifts (not assigned in the original experimental spectrum) except for H-12 and H-19 measured experimentally and reported in the title publication.



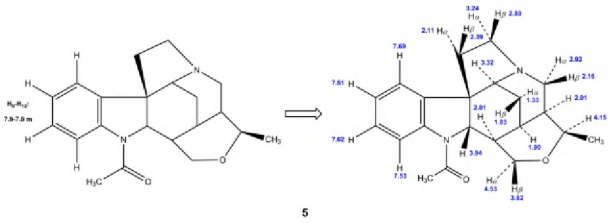
Rosibiline (3). For this compound, proton resonances H-10 and H-11 (7.76 and 7.12 ppm), enantiomeric protons H-15 and H-16 (2.73 and 2.08 ppm), and diastereotopic protons H-14α and H-14β (1.80 and 1.97 ppm) should apparently be reassigned in pairs, as compared to the experimental data.[37] Additionally, unresolved methylenic protons at C-5, C-6, C-17, C-21, and C-22, are now individually assigned, as shown below. A complimentary, calculated ^{13}C NMR spectrum is provided based on the performed calculations (since no experimental ^{13}C NMR spectrum is available in the literature).



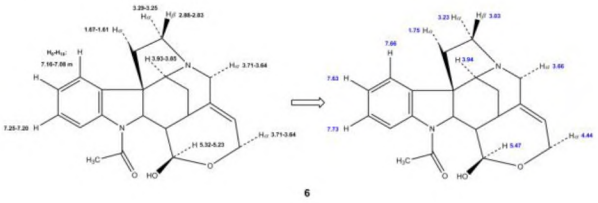
Tsilanine (4). Except for the early practically unassigned ^{1}H NMR spectrum recorded in 1970,[38] almost no spectral information was found for this compound, either for protons or carbons (except for three unresolved aromatic protons H-9, H-10, and H-11, reported in the cited paper). Herewith, we provide calculated ^{1}H as well as ^{13}C NMR chemical shifts of **4** derived in the present study.



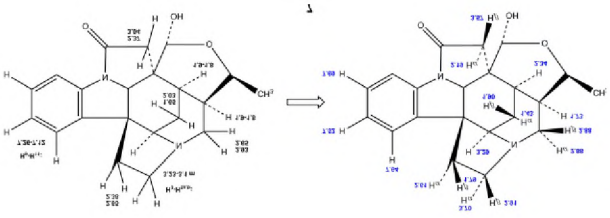
Spermostrychnine (5). No inconsistences are found in the experimental ^{13}C NMR spectrum of **5** given in the basic paper, while very scarce information is available on its ^{1}H NMR spectrum dealing with unassigned aromatic protons H-9, H-10, H-11, and H-12 providing complex unresolved multiplets.[40] Given below are the full set of proton chemical shifts of **5** calculated in the present study.



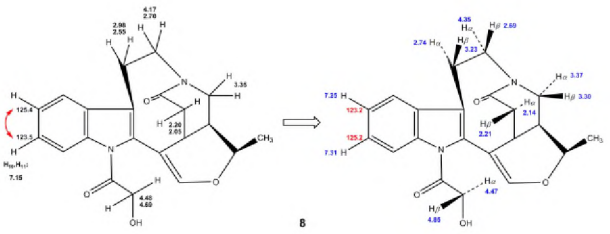
Diaboline (6). A set of the rather recent and reliable experimental ^{1}H and ^{13}C NMR data is available,[41] and present calculations are in a fairly good agreement with experiment, especially those of carbon chemical shifts. Not all of the ^{1}H NMR signals are resolved in the experimental spectrum, so we provide our theoretical values of the individual proton shifts in these difficult cases.



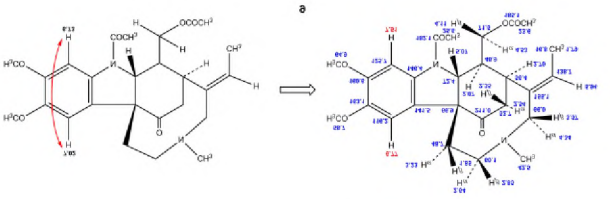
Cyclostrychnine (7). Experimental ^{1}H and ^{13}C NMR spectra of **7** are reported in the original publication.[39] The experimental ^{13}C NMR spectrum is in a very good agreement with present calculations (see Table 3) while most of the protons appeared in the experimental spectrum as strongly coupled unresolved multiplets. Hence, we report here the calculated ^{1}H NMR chemical shifts for all of the superimposed proton signals.



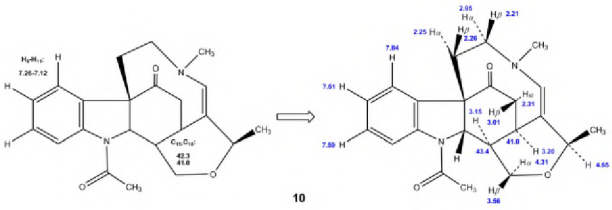
Henningsamide (8). For this compound, both ^{1}H and ^{13}C NMR experimental spectra are known.[39] Based on the performed calculations, we think that signals of C-10 (125.4 ppm) and C-11 (123.5 ppm) are to be reassigned. Indeed, these indole carbons have very close chemical shifts, and they are coupled with very similar protons appearing as poorly resolved doublets of doublets. That is why the former could hardly be distinguished in the spectrum, even with using advanced two-dimensional experiments. On the other hand, we report individual chemical shifts of all the protons, which are unresolved in the experimental spectrum.



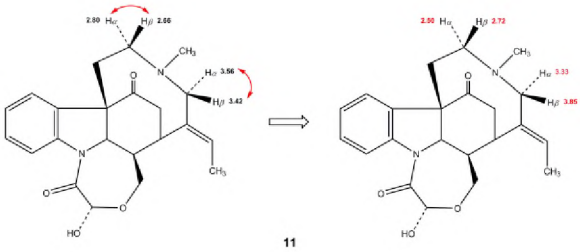
Strychnosilidine (9). All ^{1}H NMR data for this compound were reported in the early paper[40] where the resonances of H-9 (7.02 ppm) and H-12 (6.73 ppm) should apparently be interchanged based on the calculated chemical shifts for H-9 (6.77 ppm) and H-12 (7.51 ppm). We also give our calculated value of the unreported proton chemical shift of the olefinic proton (5.94 ppm) and provide a number of individual methylenic proton shifts unresolved in the experimental spectrum. Also reported herewith is the calculated ^{13}C NMR spectrum of **9**, since no experimental spectrum was found in the literature.



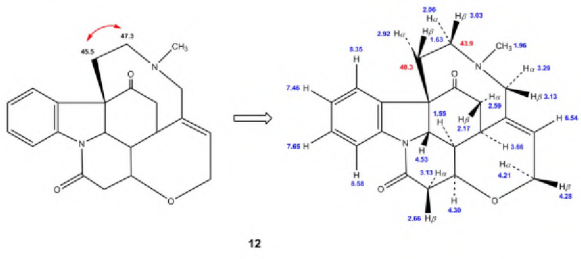
Strychnobrasiline (10). For this compound, both ^{1}H and ^{13}C experimental NMR spectra are known.[42] Our calculations of ^{13}C NMR chemical shifts are in fairly good agreement with those data. While assignments of experimental ^{1}H NMR spectrum of **10** seems to be incomplete,[42] we provide our calculated proton shifts as a more reliable data set. Also, we have assigned C-15 and C-16 (which was not done in the original publication[42]).



Holstiine (11). Our calculated ^{13}C NMR chemical shifts confirm assignment of experimental carbon resonances,[43] while in the proton spectrum both methylenic carbons at C-5 (2.80 and 2.66 ppm) and C-21 (3.56 and 3.42 ppm) must be confidently reassigned in pairs as shown below.

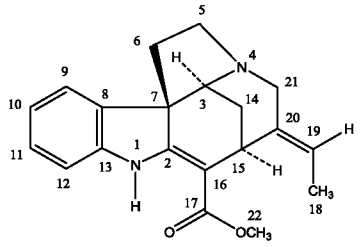


Icajine (12). Based on the performed calculations, we suggest interchanging of carbon resonances of C-5 (47.3 ppm) and C-6 (45.5 ppm) in the experimental spectrumin[44] accord with the calculated ones for C-5 (43.9 ppm) and C-6 (48.3). No experimental ^{1}H NMR spectrum was found in the literature, so we provide here our calculated proton chemical shifts in full.

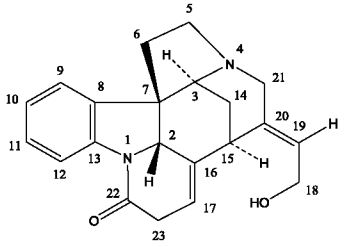


Presented in Figures 2 and 3 are the final correlations of calculated *versus* experimental ^{1}H and ^{13}C NMR chemical shifts of **1-12**, original (left) and reassigned (right), demonstrating an adequate level of theory applied herewith for the calculations of these parameters in the whole

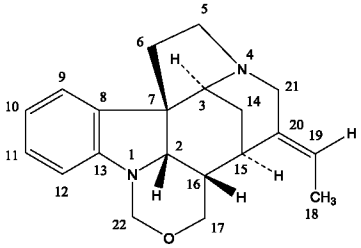
series of strychnines under study. It is seen that taking into account performed reassignments noticeably decreases MAE from 0.23 to 0.22 ppm for protons and from 2.06 to 1.97 ppm for carbons. For the full details, dealing with the reassignments and additional assignments in the proton and carbon NMR spectra of **1-12**, see Tables 2 and 3, respectively.



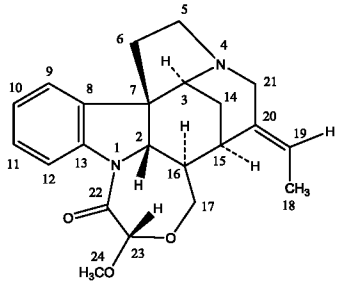
Akuammicine, $C_{20}H_{22}N_2O_2$ (**1**)



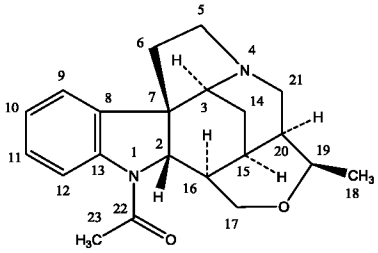
Isostrychnine, $C_{21}H_{22}N_2O_2$ (**2**)



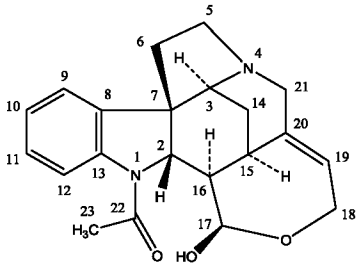
Rosibiline, $C_{20}H_{24}N_2O$ (**3**)



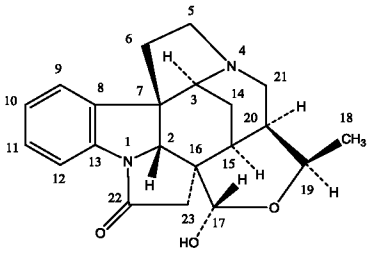
Tsilanine, $C_{22}H_{26}N_2O_3$ (**4**)



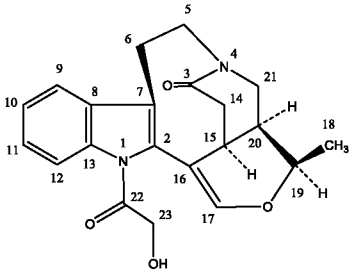
Spermostrychnine, $C_{22}H_{28}N_2O_2$ (**5**)



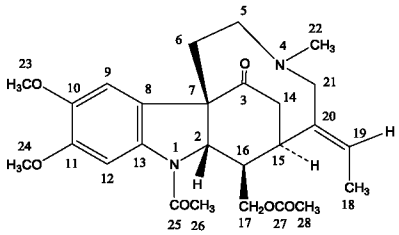
Diaboline, $C_{21}H_{24}N_2O_3$ (**6**)



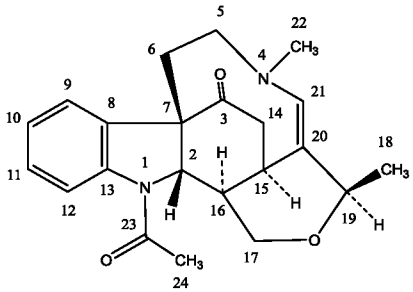
Cyclostrychnine, $C_{21}H_{24}N_2O_3$ (**7**)



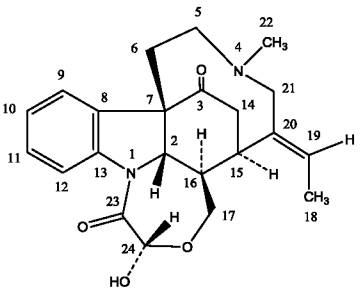
Henningsamide, $C_{21}H_{22}N_2O_4$ (**8**)



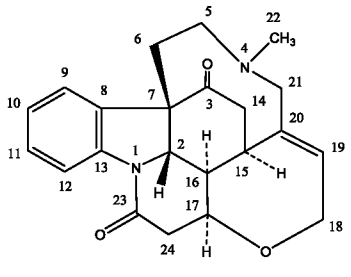
Strychnosilidine, $C_{26}H_{34}N_2O_6$ (**9**)



Strychnobrasiline, $C_{22}H_{26}N_2O_3$ (**10**)

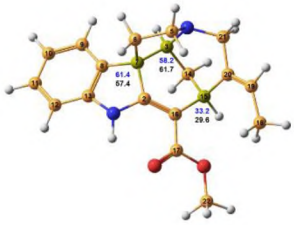


Holstiine, $C_{22}H_{26}N_2O_4$ (**11**)

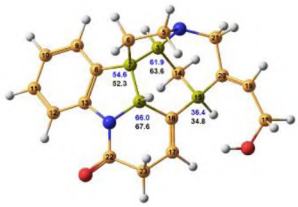


Icajine, $C_{22}H_{24}N_2O_3$ (**12**)

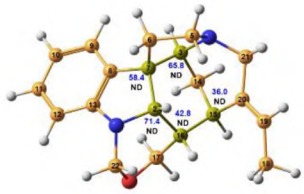
Scheme 1. Chemical structures and enumeration of carbons of twelve basic *Strychnos* alkaloids (excluding parent strychnine).



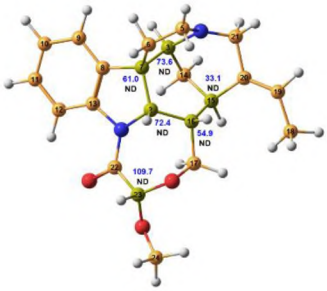
Akuammicine (**1**)



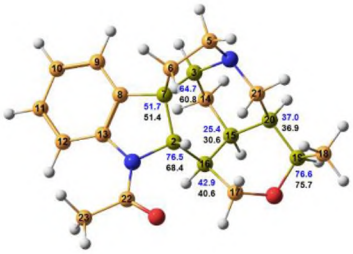
Isostrychnine (**2**)



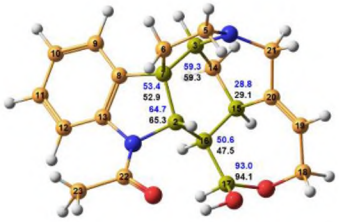
Rosibiline (**3**)



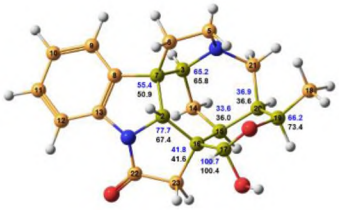
Tsilanine (**4**)



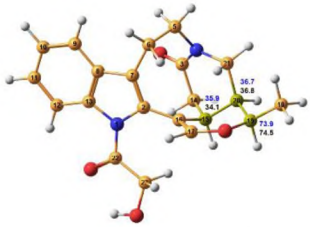
Spermostrychnine (**5**)



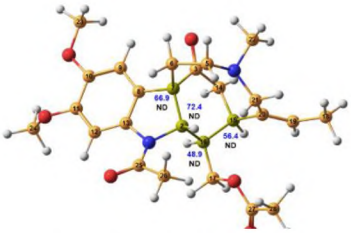
Diaboline (**6**)



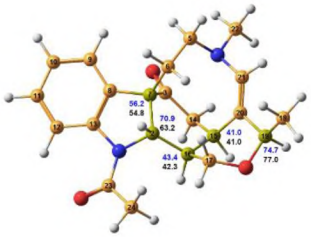
Cyclostrychnine (**7**)



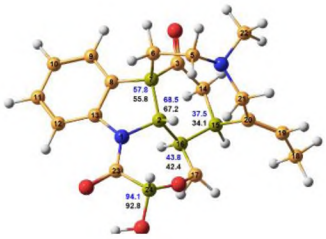
Henningsamide (**8**)



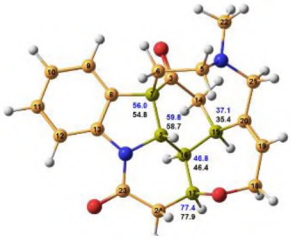
Strychnosilidine (**9**)



Strychnobrasiline (**10**)



Holstiine (**11**)



Icajine (**12**)

Figure 1. The 3D structures of strychnines **1-12** with all asymmetric centers marked in light green. Their calculated and experimental ^{13}C NMR chemical shifts are given accordingly, in blue and black. "ND" stands for "Not Determined".

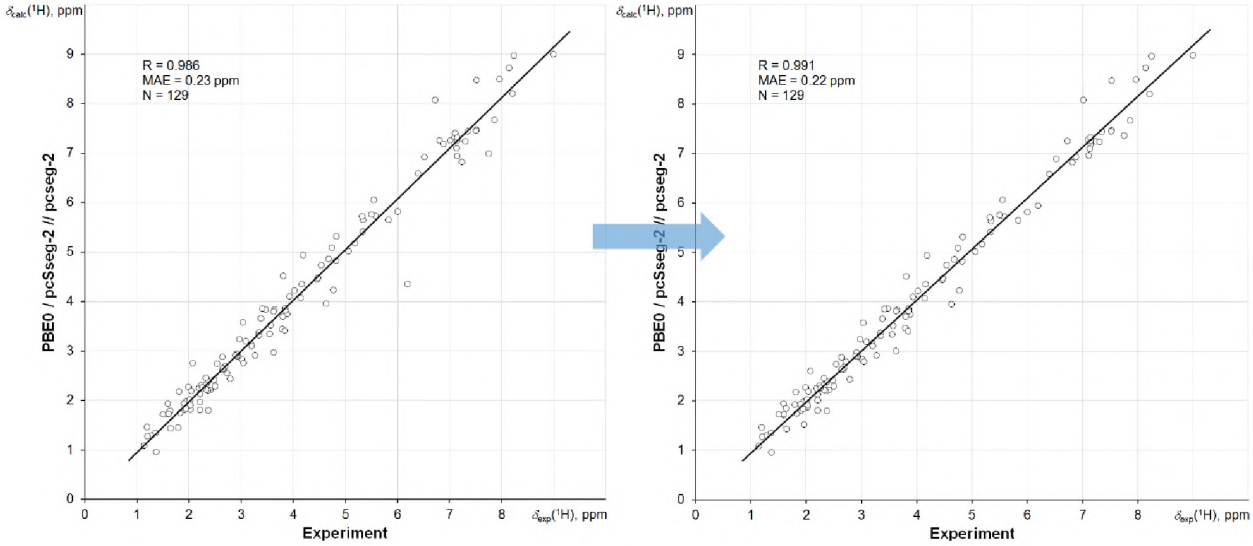


Figure 2. Correlation plots of calculated ^{1}H NMR chemical shifts of strychnines **1-12** *versus* experiment: original (left) and reassigned (right). All calculations are performed by using the PBE0/pcSseg-2//pcseg-2 computational scheme.

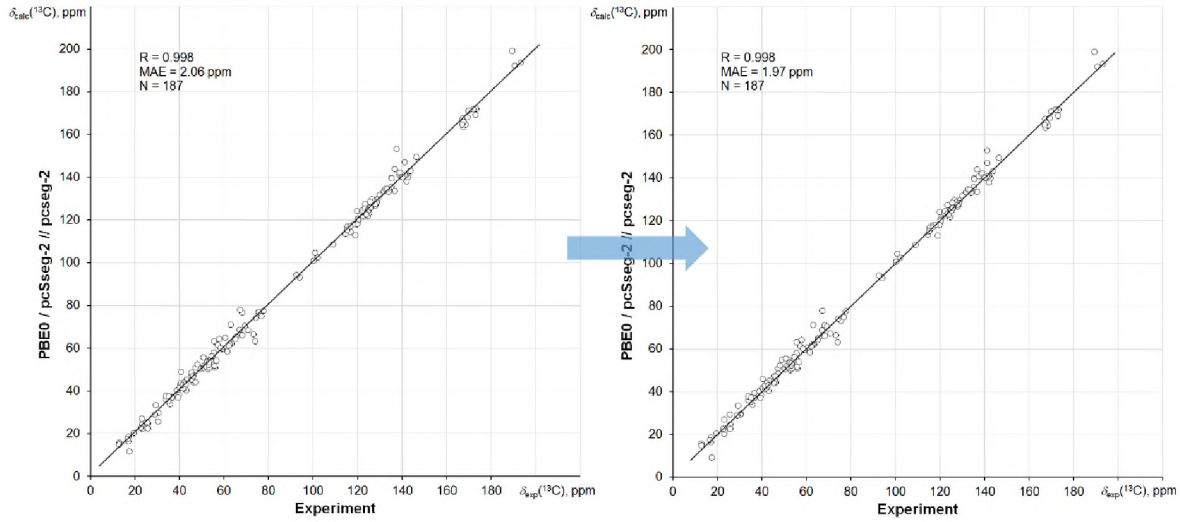


Figure 3. Correlation plots of calculated ^{13}C NMR chemical shifts of strychnines **1-12** *versus* experiment: original (left) and reassigned (right). All calculations are performed by using the PBE0/pcSseg-2//pcseg-2 computational scheme.

Table 1. Calculated and experimental ^{1}H and ^{13}C NMR chemical shifts (ppm) at/of the chiral carbon centers of **1-12** for their alternative configurations (*R* and *S*).

Cmpd	Asymmetric center	^{13}C NMR			^{1}H NMR			ΔE^{0}, kcal/mol [b]
		Calc.	Exp. [a]	Configuration	Calc.	Exp. [a]	Configuration	
1	C-3	92.9 (*R*) 58.2 (*S*)	61.7	*S*	4.21 (α) 5.37 (β)	4.03	α	87.3
	C-7	61.3 (*R*) 61.4 (*S*)	57.4	*S*				3.9
	C-15	48.4 (*R*) 33.2 (*S*)	29.6	*S*	4.09 (α) 3.05 (β)	3.94	α	64.3
2	C-2	73.8 (*R*) 66.0 (*S*)	67.6	*S*	4.93 (α) 4.50 (β)	NA [c]	β	18.6
	C-3	103.3 (*R*) 61.9 (*S*)	63.6	*S*	3.95 (α) 4.23 (β)	NA	α	77.1
	C-7	54.6 (*R*) 65.8 (*S*)	52.3	*R*				18.5
	C-15	49.8 (*R*) 36.4 (*S*)	34.8	*S*	4.38 (α) 3.24 (β)	NA	α	60.0
3	C-2	67.3 (*R*) 71.4 (*S*)	ND [d]	*S*	3.57 (α) 3.80 (β)	3.65	β	24.4
	C-3	104.0 (*R*) 65.8 (*S*)	ND	*S*	3.83 (α) 3.84 (β)	3.48	α	78.0
	C-7	58.4 (*R*) 65.2 (*S*)	ND	*R*				30.8
	C-15	36.0 (*R*) 50.1 (*S*)	ND	*R*	2.55 (α) 3.01 (β)	2.08 [e]	α	61.7
	C-16	49.8 (*R*) 42.8 (*S*)	ND	*S*	1.86 (α) 2.74 (β)	2.73 [e]	β	2.7
4	C-2	75.0 (*R*) 72.4 (*S*)	ND	*S*	4.04 (α) 4.66 (β)	ND	β	15.6
	C-3	104.4 (*R*) 73.6 (*S*)	ND	*S*	3.42 (α) 4.12 (β)	ND	α	77.3
	C-7	61.0 (*R*)	ND	*R*				26.1

		60.5 (*S*)						
	C-15	33.1 (*R*) 49.1 (*S*)	ND	*R*	2.41 (α) 2.82 (β)	ND	α	65.3
	C-16	54.9 (*R*) 52.7 (*S*)	ND	R^f	2.48 (α) 2.41 (β)	ND	α	3.0
	C-23	109.7 (*R*) 111.6 (*S*)	ND	*R*	4.92 (α) 4.97 (β)	5.07	β	4.3
5	C-2	76.9 (*R*) 76.5 (*S*)	68.4	*S*	4.12 (α) 3.94 (β)	ND	β	20.3
	C-3	97.4 (*R*) 64.7 (*S*)	60.8	*S*	3.32 (α) 4.54 (β)	ND	α	81.2
	C-7	51.7 (*R*) 68.4 (*S*)	51.4	*R*				60.2
	C-15	51.2 (*R*) 25.4 (*S*)	30.6	*S*	1.90 (α) 2.60 (β)	ND	α	62.2
	C-16	37.6 (*R*) 42.9 (*S*)	40.6	*S*	2.01 (α) 2.31 (β)	ND	α	19.9
	C-19	76.6 (*R*) 81.1 (*S*)	75.7	R^f	4.15 (α) 3.07 (β)	ND	α	2.5
	C-20	37.0 (*R*) 49.7 (*S*)	36.9	*R*	2.01 (α) 1.55 (β)	ND	α	11.3
6	C-2	77.4 (*R*) 64.7 (*S*)	65.3	*S*	3.98 (α) 4.93 (β)	4.20	β	35.3
	C-3	98.4 (*R*) 59.3 (*S*)	59.3	*S*	3.94 (α) 3.89 (β)	3.93- 3.85 m	α	82.9
	C-7	53.4 (*R*) 59.3 (*S*)	52.9	*R*				30.1
	C-15	28.8 (*R*) 47.6 (*S*)	29.1	*R*	3.65 (α) 2.29 (β)	3.39	α	67.9
	C-16	50.6 (*R*) 63.9 (*S*)	47.5	*R*	1.71 (α) 2.44 (β)	1.51	α	18.8
	C-17	93.0 (*R*) 110.2 (*S*)	94.1	*R*	5.48 (α) 5.63 (β)	5.32- 5.23	α	8.4

7	C-2	77.7 (*R*) 81.6 (*S*)	67.4	*R*	4.10 (α) 4.22 (β)	4.78	β	42.3
	C-3	99.5 (*R*) 65.2 (*S*)	65.8	*S*	3.29 (α) 3.67 (β)	3.23-3.1	α	75.1
	C-7	55.4 (*R*) 76.9 (*S*)	50.9	*R*				98.1
	C-15	46.4 (*R*) 33.6 (*S*)	36.0	*S*	2.34 (α) 2.46 (β)	1.9-1.8 m	α	59.4
	C-16	41.8 (*R*) 57.0 (*S*)	41.6	*R*				54.5
	C-17	108.0 (*R*) 100.7 (*S*)	100.4	*S*	4.88 (α) 5.08 (β)	4.75	β	5.7
	C-19	66.2 (*R*) 81.4 (*S*)	73.4	*R*	4.51 (α) 3.81 (β)	3.82	α	6.6
	C-20	36.9 (*R*) 52.1 (*S*)	36.6	*R*	1.73 (α) 1.85 (β)	1.9-1.8 m	α	14.0
8	C-15	40.7 (*R*) [g] 35.9 (*S*)	34.1	*S*	2.90 (α) 2.81 (β)	2.90	α	51.9
	C-15	48.2 (*R*) [h] 35.9 (*S*)	34.1	*S*	2.90 (α) 3.80 (β)	2.90	α	74.8
	C-19	73.9 (*R*) 79.7 (*S*)	74.5	*R*	4.44 (α) 4.43 (β)	4.47	α	9.4
	C-20	36.7 (*R*) 63.3 (*S*)	36.8	*R*	2.30 (α) 2.77 (β)	2.25	α	39.5
9	C-2	74.0 (*R*) 72.4 (*S*)	ND	*S*	4.73 (α) 5.07 (β)	ND	β	47.7
	C-7	66.9 (*R*) 59.3 (*S*)	ND	*R*				35.3
	C-15	56.4 (*R*) 36.6 (*S*)	ND	*R*	2.70 (α) 3.13 (β)	ND	α	50.2
	C-16	48.9 (*R*) 43.6 (*S*)	ND	*R*	2.07 (α) 2.92 (β)	ND	α	10.7

10	C-2	71.8 (*R*) 70.9 (*S*)	63.2	*S*	4.11 (α) 3.95 (β)	4.64	β	14.5
	C-7	56.2 (*R*) 66.5 (*S*)	54.8	*R*				34.5
	C-15	41.0 (*R*) 36.3 (*S*)	41.0 [e]	*R*	3.20 (α) 4.78 (β)	ND	α	51.8
	C-16	43.4 (*R*) 49.6 (*S*)	42.3 [e]	*R*	3.15 (α) 3.72 (β)	ND	α	33.7
	C-19	74.7 (*R*) 83.5 (*S*)	77.0	*R*	4.65 (α) 4.51 (β)	ND	α	6.5
11	C-2	72.3 (*R*) 68.5 (*S*)	67.2	*S*	5.62 (α) 5.31 (β)	4.84	β	30.7
	C-7	57.8 (*R*) 61.2 (*S*)	55.8	*R*				13.8
	C-15	37.5 (*R*) 38.4 (*S*)	34.1	*R*	3.09 (α) 3.77 (β)	3.21	α	34.6
	C-16	43.8 (*R*) 43.1 (*S*)	42.4	*R*	2.45 (α) 3.26 (β)	2.33	α	4.1
	C-24	109.3 (*R*) 94.1 (*S*)	92.8	*S*	5.53 (α) 5.41 (β)	5.34	β	4.2
12	C-2	69.9 (*R*) 59.8 (*S*)	58.7	*S*	4.44 (α) 4.53 (β)	ND	β	28.6
	C-7	56.0 (*R*) 57.4 (*S*)	54.8	*R*				23.5
	C-15	37.1 (*R*) 42.3 (*S*)	35.4	*R*	3.66 (α) 3.44 (β)	ND	α	42.1
	C-16	46.8 (*R*) 57.2 (*S*)	46.4	*R*	1.55 (α) 3.00 (β)	ND	α	17.3
	C-17	76.5 (*R*) 77.4 (*S*)	77.9	*S*	4.30 (α) 4.15 (β)	ND	α	5.1

[a] See text for references. [b] Energetic preference of the predominant (original) diastereomer. [c] Not assigned. [d] No data or not determined. [e] Reassigned in the present paper. [f] Original assignment suggested by the authors. [g] C^3,C^{14}-α-configuration. [h] C^3,C^{14}-β-configuration.

Table 2. Calculated versus experimental (given in parenthesis) ^{1}H NMR chemical shifts (ppm) of *Strychnos* alkaloids **1-12**.

Nucleus	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
2		4.50	3.83 (3.65)	4.23	3.94	4.93 (4.20)	4.22 (4.78)		5.07	3.95 (4.64)	5.31 (4.84)	4.53
3	4.21 (4.03)	3.95	3.83 (3.48)	3.98	3.32	3.94 (3.93-3.85)	3.29 (3.23-3.1)					
5_α	2.82 (3.02)	3.07	3.12 (3.20)	3.14	3.24	3.23 (3.29-3.25)	2.91 (3.23-3.1)	4.35 (4.17)	2.64	2.95	2.50 (2.80)	2.06
5_β	2.91 (3.28)	3.07	2.93 (2.92)	2.90	2.89	3.03 (2.88-2.83)	3.70 (3.23-3.1)	2.69 (2.70)	2.85	2.21	2.72 (2.66)	3.03
6_α	2.28 (2.51)	2.32	1.81 (2.03)	2.09	2.11	1.75 (1.67-1.61)	2.61 (2.65)	2.74 (2.55)	3.23	2.25	3.19 (3.10)	2.92
6_β	2.17 (1.82)	1.81	1.96 (2.22)	1.72	2.39	1.80 (1.92)	1.79 (2.38)	3.23 (2.98)	1.85	2.26	1.83 (1.95)	1.63
9	7.24 (6.82)	7.65	7.31 (7.11)	7.64 (7.3-7.1)	7.69 (7.9-7.0)	7.66 (7.16-7.08)	7.64 (7.26-7.12)	7.44 (7.36)	6.77 (7.02)	7.84 (7.32-6.97)	7.45 (7.52)	8.35
10	6.93 (7.15)	7.50	6.98 (7.76)	7.55 (7.3-7.1)	7.51 (7.9-7.0)	7.63 (7.16-7.08)	7.52 (7.26-7.12)	7.25 (7.15)		7.51 (7.32-6.97)	7.09 (7.14)	7.46
11	7.18 (6.89)	7.67	7.40 (7.12)	7.64 (7.3-7.1)	7.62 (7.9-7.0)	7.73 (7.25-7.20)	7.69 (7.26-7.12)	7.31 (7.15)		7.59 (7.32-6.97)	7.23 (7.31)	7.65
12	6.82 (7.25)	8.72 (8.15)	6.92 (6.53)	8.96 (8.25)	7.53 (7.9-7.0)	7.66 (7.87)	7.47 (7.53)	8.49 (7.97)	7.51 (6.73)	8.47 (7.53)	8.19 (8.22)	8.58
14_α	1.29 (1.30)	1.25 (1.51-1.43)	1.45 (1.80)	1.43	1.33	0.95 (1.38)	1.43 (1.65)	2.14 (2.05)	2.54	2.31	2.41 (2.49)	2.59
14_β	2.21 (2.42)	2.10 (2.35-2.10)	1.86 (1.97)	1.95	1.83	1.80 (2.22)	1.90 (2.03)	2.21 (2.20)	2.35	3.01	2.25 (2.27)	2.17
15	4.09 (3.94)	4.38	2.55 (2.73)	3.01	1.90	3.65 (3.39)	2.34 (1.9-1.8)	2.90 (2.90)	2.70	3.20	3.09 (3.21)	3.66
16			2.74 (2.08)	2.48	2.01	1.71 (1.51)			2.07	3.15	2.45 (2.33)	1.55
17		6.53				5.47	5.08	6.57				4.30

		(5.90-5.81)				(5.32-5.23)	(4.75)	(6.41)				
17_{α}			2.96 (3.63)	4.12	4.53				4.53	4.31	4.06 (4.15)	
17_{β}			3.43 (3.80)	3.65	3.62				4.11	3.56	3.41 (3.85)	
18	1.93 (1.60)		1.78 (1.64)	1.71 (1.60)	1.08 (1.15)		1.16 (1.21)	1.45 (1.20)	1.79	1.34 (1.37)	1.72 (1.61)	
18_{α}		4.40				4.44 (3.71-3.64)						4.21
18_{β}		4.64				4.81 (4.83)						4.28
19	5.64 (5.35)	5.72 (5.59)	5.71 (5.33)	6.05 (5.56)	4.15	5.64 (5.84)	4.51 (3.82)	4.44 (4.47)	5.94	4.65	5.75 (5.51)	6.54
20					2.01		1.73 (1.9-1.8)	2.30 (2.25)				
21										5.81 (6.01)		
21_{α}	3.74 (3.89)	3.95	3.79 (3.63)	3.85	2.92	3.66 (3.71-3.64)	2.88 (2.93)	3.37 (3.35)	4.34 (6.20)		3.33 (3.56)	3.29
21_{β}	2.88 (2.95)	2.92	2.74 (3.05)	3.02	2.16	2.62 (2.68)	2.88 (2.65)	3.30 (3.35)	3.57 (6.20)		3.85 (3.42)	3.13
22	3.70 (3.81)								1.98 (1.96)	2.12 (2.22)	1.92 (1.91)	1.96
22_{α}			5.16 (5.19)									
22_{β}			4.72 (4.55)									
23				5.01 (5.07)	2.38 (2.38)	2.26 (2.00)			3.86 (3.86)			
23_{α}		3.05					2.19 (2.37)	4.47 (4.48)				
23_{β}		3.10					3.57 (3.04)	4.85 (4.69)				
24				3.51 (3.58)					3.81 (3.86)	2.21 (2.34)	5.41 (5.34)	

24_{α}												3.13
24_{β}												2.66
26									2.31 (2.33)			
28									2.01 (2.02)			
OH		1.74 (1.84)				8.06					4.93	
NH	8.99 (9.00)											

Table 3. Calculated versus experimental (given in parenthesis) ^{13}C NMR chemical shifts (ppm) of *Strychnos* alkaloids **1-12**.

Nucleus	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
2	167.3 (167.5)	66.0 (67.6)	71.4	69.8	76.5 (68.4)	64.7 (65.3)	77.7 (67.4)	133.1 (132.1)	72.4	70.9 (63.2)	68.5 (67.2)	59.8 (58.7)
3	58.2 (61.7)	61.9 (63.6)	65.8	67.0	64.7 (60.8)	59.3 (59.3)	65.2 (65.8)	168.9 (173.3)	211.0	198.9 (189.6)	192.0 (191.0)	193.2 (193.5)
5	50.7 (56.1)	49.9 (53.0)	56.3	56.7	54.3 (54.2)	51.3 (51.9)	51.5 (55.9)	45.1 (45.9)	60.1	51.9 (53.5)	52.9 (53.5)	43.9 (47.3)
6	44.3 (46.1)	44.0 (46.4)	46.1	49.6	48.6 (41.0)	40.0 (39.1)	40.1 (43.2)	20.2 (19.8)	48.7	41.6 (41.0)	47.1 (45.8)	48.3 (45.5)
7	61.3 (57.4)	54.6 (52.3)	58.4	59.9	51.7 (51.4)	53.4 (52.9)	55.4 (50.9)	127.1 (123.6)	66.9	56.2 (54.8)	57.8 (55.8)	56.0 (54.8)
8	133.5 (136.8)	134.0 (134.8)	146.7	146.6	153.2	139.6 (135.4)	141.9 (139.1)	129.7 (129.3)	141.5	134.1 (134.1)	134.4 (132.7)	134.3 (133.4)
9	120.4 (120.4)	121.6 (122.6)	132.9	132.7	123.9 (122.4)	123.4 (122.1)	124.3 (122.4)	117.7 (118.3)	116.2	124.2 (124.7)	124.8 (124.9)	125.7 (126.1)
10	119.2 (120.3)	121.9 (124.4)	128.0	133.9	123.3 (124.9)	124.9 (125.0)	125.2 (125.7)	123.2 (125.4)	163.1	121.6 (124.8)	124.6 (125.4)	122.5 (124.1)
11	126.7 (127.4)	126.8 (128.4)	138.6	138.6	127.7 (127.8)	127.1 (127.9)	128.7 (127.8)	125.2 (123.5)	160.6	126.5 (128.0)	128.0 (128.8)	127.2 (128.0)

12	108.4 (109.1)	113.2 (114.7)	117.5	126.4	114.1 (117.0)	117.9 (119.9)	116.6 (115.7)	116.8 (115.7)	125.7	112.7 (119.1)	116.8 (116.9)	115.0 (115.5)
13	143.7 (136.8)	140.7 (141.4)	164.1	155.0	153.0	142.8 (143.9)	140.5 (142.1)	135.5 (135.4)	146.4	140.7 (141.4)	140.1 (139.9)	139.8 (140.3)
14	29.4 (30.8)	24.4 (26.0)	23.4	28.4	25.1 (25.8)	22.3 (25.9)	22.4 (22.8)	35.0 (35.2)	52.7	41.4 (40.4)	45.0 (43.5)	42.6 (41.5)
15	33.2 (29.6)	36.4 (34.8)	36.0	33.6	25.4 (30.6)	28.8 (29.1)	33.6 (36.0)	35.9 (34.1)	56.4	41.0 (42.3)	37.5 (34.1)	37.1 (35.4)
16	104.3 (101.1)	152.9 (137.6)	42.8	54.9	42.9 (40.6)	50.6 (47.5)	41.8 (41.6)	102.3 (102.4)	48.9	43.4 (41.0)	43.8 (42.4)	46.8 (46.4)
17	163.4 (167.7)	119.9 (120.5)	69.4	69.5	68.2 (71.0)	93.0 (94.1)	100.7 (100.4)	149.2 (146.7)	71.5	65.9 (68.4)	63.0 (74.3)	77.4 (77.9)
18	15.5 (13.1)	64.1 (58.0)	16.3	18.8	11.3 (17.6)	63.0 (55.7)	18.4 (17.2)	16.1 (17.3)	16.8	17.3 (16.8)	14.6 (13.0)	64.0 (65.3)
19	123.9 (120.0)	129.5 (126.6)	133.9	136.4	76.6 (75.7)	125.9 (126.2)	66.2 (73.4)	73.9 (74.5)	138.7	74.7 (77.0)	128.3 (125.8)	131.5 (130.2)
20	140.8 (139.2)	137.8 (142.2)	154.3	153.0	37.0 (36.9)	139.7 (142.8)	36.9 (36.6)	36.7 (36.8)	155.1	158.8	139.3 (135.6)	146.9 (141.5)
21	53.9 (56.8)	54.1 (54.1)	59.4	58.4	50.3 (49.0)	50.6 (53.7)	41.7 (41.6)	41.5 (42.3)	66.0	133.1 (134.1)	70.2 (69.4)	61.1 (62.4)
22	50.4 (50.6)	164.5 (168.7)	76.4	179.0	179.9	170.9 (170.2)	171.7 (173.5)	171.7 (172.2)	42.5	41.2 (41.8)	38.0 (40.0)	36.8 (39.4)
23		36.6 (36.9)		108.6	24.0 (23.3)	22.0 (23.4)	52.1 (48.3)	61.6 (62.7)	58.7	167.9 (169.5)	165.7 (167.9)	164.6 (167.2)
24				61.4					64.9	26.7 (23.3)	94.1 (92.8)	42.8 (43.0)
25									182.1			
26									25.6			
27									185.1			
28									23.6			

4 CONCLUSIONS

The PBE0/pcSseg-2//pcseg-2 calculations of ^{1}H and ^{13}C NMR chemical shifts were performed in a series of classically known twelve *Strychnos* alkaloids (except for the studied earlier parent strychnine), namely akuammicine, isostrychnine, rosibiline, tsilanine, spermostrychnine, diaboline, cyclostrychnine, henningsamide, strychnosilidine, strychnobrasiline, holstiine, and icajine. It was found that calculated ^{1}H and ^{13}C NMR chemical shifts provided a markedly good correlation with experiment characterized by a mean absolute error of 0.22 ppm in the range of 8 ppm for protons and 1.97 ppm in the range of 180 ppm for carbons.

Speaking about computational ^{13}C NMR data, first it should be noted that for all twelve strychnines, established earlier absolute configurations of all 62 asymmetric centers in all 12 compounds are in a good agreement with the results of the present calculations. Further, in some particular cases we report reassignment of the individual resonances, while the assignments of the unresolved signals and/or computed experimentally unknown ^{13}C NMR chemical shifts are also provided.

Up to date, experimental ^{1}H NMR parameters are not available (not assigned or not determined) in about half of the cases, so that the results of the present calculations successfully filled this gap. Complimentary, performed in a number of cases are the unambiguous assignments of protons in the ^{1}H NMR multiplets representing strongly-coupled spin systems, which have not been assigned explicitly in the original publications.

In general, present results provide a solid NMR database for this group of the vitally important natural products.

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