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Synthesis and conformational analysis of naphth[1,2-*e*][1,3]oxazino[4,3-*a*]-[1,3]isoquinoline and naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinoline derivatives

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ABSTRACT

Through the cyclization of 1-(β-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinoline and 1-(α-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinoline with formaldehyde, phosgene, *p*-nitrobenzaldehyde or *p*-chlorophenyl isothiocyanate, 8-substituted 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*]-isoquinolines (**3** and **4**) and 10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinolines (**15** and **16**) were prepared. Conformational analysis of both the piperidine and the 1,3-oxazine moieties of these heterocycles by NMR spectroscopy and an accompanying theoretical study revealed that these two conformationally flexible six-membered ring moieties prefer twisted chair conformers.

1. Introduction

In consequence of their valuable biological activity and wide-ranging potential for synthetic applications, considerable interest has been demonstrated in partially saturated isoquinolines.[1] Recent systematic studies on tricyclic derivatives of saturated isoquinoline derivatives containing another saturated heteroring, bearing different substituents at positions 1, 2, and 4 (1,3-oxazino[4,3-*a*]-,[2] 1,2,3-oxathiazino[4,3-*a*]-,[3] 1,3,2-oxaphosphorino[4,3-*a*]-,[4] 1,3,2-diazaphosphorino[6,1-*a*]-,[5] 1,3,4-diazaphosphino[5,4-*a*]-, and 1,3,4-diazaphosphino[4,5-*b*]isoquinolines[6]), led to the conclusion that the heteroatoms, the substituents on the partly saturated heterocyclic rings, and the configurations of the substituted carbon atoms exert pronounced effects on the conformational equilibria of these compounds.

Our present aims were to investigate the influence of a naphthalene ring annelated to positions 1, 2 of naphth[1,2-*e*]-[1,3]oxazino[4,3-*a*]isoquinoline and naphth[2,1-*e*]oxazino[4,3-*a*]isoquinoline and to study the effects of different substituents (oxo, *p*-nitrophenyl, and phenylimino) at position 8 on the conformations of these conformationally flexible heterocyclic ring systems.

2. Results and discussion

2.1. Syntheses

The ring-closure reaction of 1-substituted 1,2,3,4-tetrahydroisoquinoline 1,3-amino alcohols with one-carbon fragments is a common method for the synthesis of 1,3-oxazino[4,3-*a*]isoquinolines. This transformation is often applied for homocalycotomines, bearing substituents in the side-chain, for the purpose of determining the configuration of the substituted atoms in the rigid ring-closed products.[2e,7]

The starting materials, 1-(β-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinolines (**1** and **2**)[8] and 1-(α-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinolines (**13** and **14**),[8] were prepared by the reaction of 2- or 1-naphthol with the corresponding 3,4-dihydroisoquinoline derivative according to a method published previously.[8a]

Under mild conditions, the treatment of 1-hydroxynaphthyl-tetrahydroisoquinolines **1**, **2**, **13**, and **14** with formaldehyde led to 8-unsubstituted 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]-oxazino[4,3-*a*]isoquinolines (**3** and **4**, Scheme 1) and 10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*]oxazino[4,3-*a*]isoquinolines (**15** and **16**, Scheme 2). An oxo group could be inserted at position 8 by the treatment of **1**, **2**, **13** or **14** with phosgene in the presence of triethylamine at room temperature yielding **5**, **6** (Scheme 1), **17** or **18** (Scheme 2), respectively.

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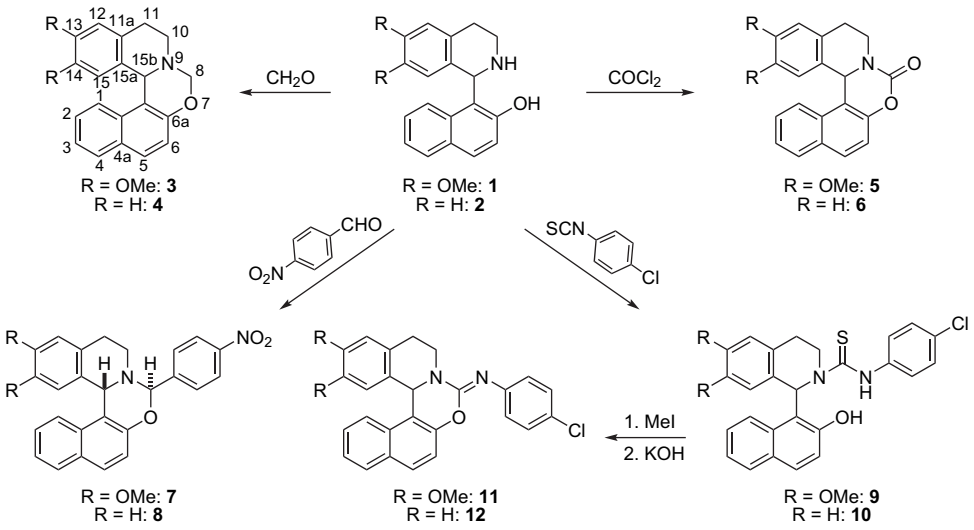


Scheme 1.

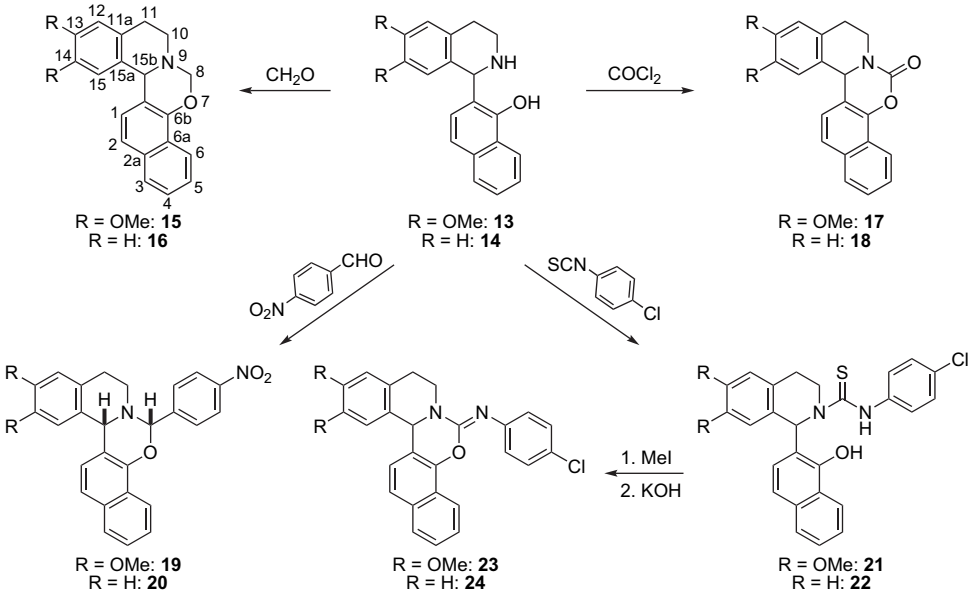
Through the reactions of **1**, **2**, **13**, and **14** with *p*-nitrobenzaldehyde, the *p*-nitrophenyl group could be inserted into position 8 (**7** and **8**, Scheme 1; **19** and **20**, Scheme 2). In the latter reactions, the formation of C-8 epimeric pairs is possible, but the NMR spectra of the crude product revealed the formation of only one diastereomer. Interestingly, the NMR investigations (vide infra) indicated that the corresponding diastereomers contain H-8 and H-15b in the trans position in **7** and **8**, and in the cis position in **19** and **20**. Thus, different diastereoselectivities are involved in the reaction pathways to the new 8-*p*-nitrophenyl-substituted 10,11-dihydro-8*H*,15b*H*-naphth[1,3]oxazino[4,3-*a*]isoquinolines (**7**, **8**, **19**, and **20**, cf. Schemes 1 and 2).

For the preparation of 8-(*p*-chlorophenylimino)-substituted 10,11-dihydro-8*H*,15b*H*-naphth[1,3]oxazino[4,3-*a*]isoquinolines **11**, **12** (Scheme 1), **23**, and **24** (Scheme 2), 1-hydroxynaphthyltetrahydroisoquinolines **1**, **2**, **13** or **14** were reacted with *p*-chlorophenyl isothiocyanate. Thioureas **9**, **10**, **21**, and **22** were converted with methyl iodide to the corresponding *S*-methyl isothiourea derivatives, and subsequent treatment with methanolic KOH gave the desired 8-(*p*-chlorophenylimino)-substituted derivatives (**11** and **12**, Scheme 1; **23** and **24**, Scheme 2) via methyl mercaptan elimination.

2.2. Conformational analysis

For the compounds studied, theoretical calculations were performed for all the stereoisomers [the different configurations (*S*/*R*) at C-15 and N-9 (i.e., the cis/trans isomers of the 9-azadecalin moiety), and possible conformations (twisted chair or boat) of the two six-membered heterocyclic ring moieties]; in this way, the global minimum-energy structures were determined.

For **3** and **4**, both the theoretical calculations and the NMR spectroscopic study revealed the conformational equilibria of two conformers each. The energies of the participating conformers were calculated with consideration of the effect of the solvent methylene chloride; this effect, however, proved to be only minor (vide infra). For the other compounds studied, the global minimum-energy structures are energetically so stable relative to the next-following local minimum-energy structure that a consideration of the solvent was neglected.



Scheme 2.

Conformational analyses were carried out by combining these theoretical calculations of the minimum-energy conformations (for both **3** and **4**, a second conformer was found to participate in the conformational equilibria) with the experimental results obtained from NMR measurements. Mainly the coupling constants and the NOEs between H-15b and the other protons of the molecule proved useful for the conformational studies. NOEs were extracted from the 2D-NOESY NMR spectra; and the desired spatial information was extracted from the corresponding theoretically calculated distances of the corresponding protons in the global minimum-energy structures (the two participating conformers for **3** and **4**).

2.2.1. The (unsaturated) piperidine ring moiety

The conformation differs in the various products, depending on the starting material (α- or β-naphthol) and the substituent on the unsaturated oxazine ring.

*2.2.1.1. Compounds **3** and **4**.* In these two compounds, NOEs were found between H-15b and H-10 (*syn*) and H-11 (*syn*), respectively. In the global minimum-energy conformations (**3a** and **4a**, cf. Fig. 1) obtained, the piperidine moiety proved to be in a twisted chair conformation with smaller distances between H-15b and H-10 (*syn*) than between H-15b and H-11 (*syn*) (cf. Table 1). As the corresponding NOEs are similar, this result can be explained only by assuming the participation of the second, low-energy conformer (**3b** and **4b**) in the conformational equilibrium. This theoretically found structure involves a boat conformation of the piperidine ring moiety; it is slightly higher in energy [1.96 kcal/mol for **3** (2.21 kcal/mol in CD_2Cl_2), 0.20 kcal/mol for **4** (both in the gas state and in CD_2Cl_2)] and gives the expected smaller distance between H-15b and the H-11 (*syn*) than that between H-15b and H-10 (*syn*) (cf. Fig. 1).

To prove the assumption of the existence of two conformers in equilibrium in solution if the interconversion process is fast on the NMR time scale, the temperature dependence of any physicochemical property can be studied because the different conformers have different energies. This was proved for the relevant vicinal coupling constants by decreasing the temperature of the solution: the corresponding values were observed to be temperature-dependent changing with decreasing temperature in the direction of the minimum-energy conformation (as shown for **3** in Table 2); a similar dependence was found for **4**. Decrease of the temperature is accompanied by a decrease in the H-10 (*syn*)–H-11 (*anti*) and an increase in the H-10 (*anti*)–H-11 (*syn*) vicinal H,H-coupling constants (cf. Table 2), in line with the changes expected if the global minimum structure is approached.

Table 3 reports the ab intio calculated dihedral angles between the protons H-10 and H-11 for the two minimum-energy structures of **3** (**3a** and **3b**), which were applied to calculate the corresponding vicinal coupling constants between the protons H-10 and H-11 in **3a** and **3b** via the Altona equation.[9] These values, finally, can be employed to calculate the equilibrium constant $K=[J_{exp.}-J_{calcd}(\mathbf{3b})]/[J_{calcd}(\mathbf{3a})-J_{calcd}(\mathbf{3b})]$, the free energy differences $-\Delta G^0=RT\ln K$ for the two participating conformers, and, via $\Delta G^0=\Delta H^0-T\Delta S^0$, the enthalpy difference between the two conformers [the value thus obtained for $\Delta H^0=-2.38$ kcal/mol ($\Delta S^0=6$ cal/mol K) is in good agreement with the theoretically calculated energy difference of the two conformers: −2.21 kcal/mol (in CD_2Cl_2)].

Table 1
Calculated distances (in Å) between H-15b and H-10 (*syn*) and H-11 (*syn*), respectively, in the compounds **3** and **4**

	3a	**3b**	**4a**	**4b**
H-15b–H-10 (*syn*)	2.35	3.29	2.35	3.26
H-15b–H-11 (*syn*)	3.91	2.32	3.91	2.31

Table 2
Temperature dependence of experimentally determined vicinal coupling constants (in Hz) between H-10 and H-11 in compound **3**

^3J(H,H)	Temperature				
	193 K	213 K	233 K	253 K	273 K
H-10 (*syn*)–H-11 (*anti*)[a]	11.6	11.3	10.9	10.5	10.1
H-10 (*anti*)–H-11 (*syn*)[a]	2.0	2.4	3.0	3.4	3.8

[a] Protons (*syn*/*anti*) assigned according to NOEs.

Table 3
Calculated dihedral angles (in °) and vicinal coupling constants (in Hz) between H-10 and H-11 in compound **3**

	3a		**3b**	
	H-10 (*syn*)–H-11 (*anti*)	H-10 (*anti*)–H-11 (*syn*)	H-10 (*syn*)–H-11 (*anti*)	H-10 (*anti*)–H-11 (*syn*)
Dihedral angle (calcd)	155.5	−77.7	64.4	−167.8
^3J(H,H) (calcd)[a]	11.9	1.5	1.8	13.1

[a] Calculated by the method of Altona et al.[9]

*2.2.1.2. Compounds **15** and **16**.* In the NMR spectra of **15** and **16**, no NOEs were found between H-15b and the protons in either position 10 or position 11. This is in excellent accordance with the theoretical results, which indicate only one global minimum-energy structure each, with a twisted chair conformation, as given in Figure 2. In agreement with the experimental findings, the calculated distances between H-15b and H-10 (*syn*) (4.146 Å for **15** and 4.147 Å for **16**) and H-11 (*syn*) (4.187 Å for **15** and 4.180 Å for **16**) were found to be too long to generate NOE enhancements in the NMR spectra.

*2.2.1.3. Compounds **7** and **8**.* A substituent at position 8 obviously prevents the type of equilibrium observed for **3** and **4**. The theoretical study indicated only one minimum-energy structure (H-8 and H-15b in trans position), a twisted chair conformer (cf. Fig. 3 for **8**). However, in contrast with the twisted chair conformer in **15** and **16**, NOEs were obtained and in good agreement with the

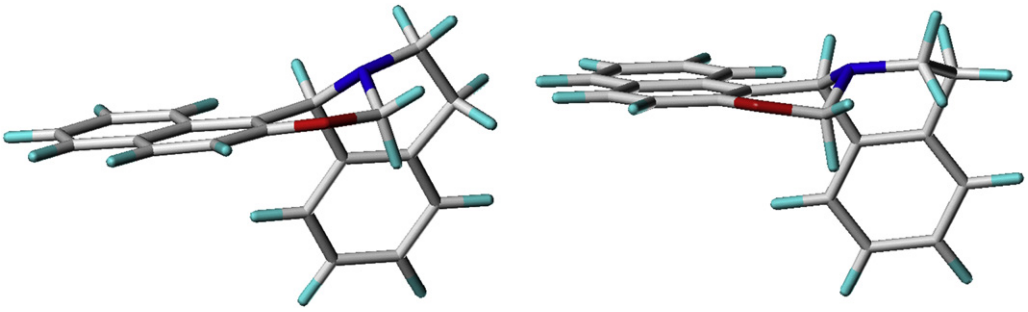


Figure 1. Minimum-energy conformation (left, **4a**) and the conformation next higher in energy (**4b**) for 9*S*,15b*S*-**4**.

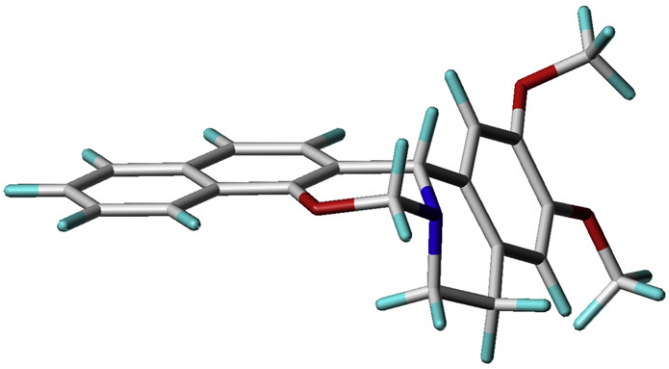


Figure 2. Minimum-energy conformation of 9*S*,15b*S*-**15**.

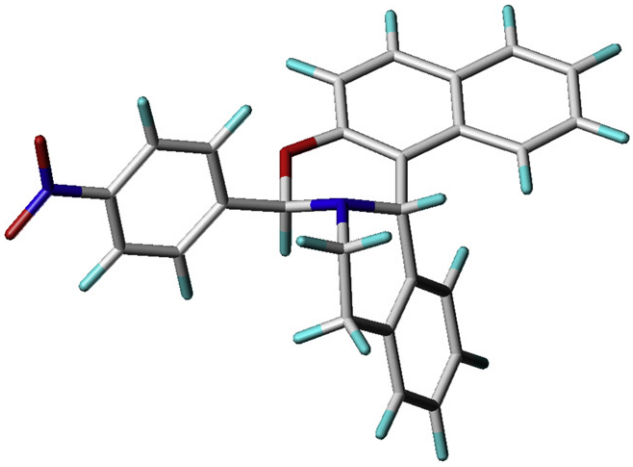


Figure 3. Minimum-energy conformation of 8*R*,9*S*,15b*S*-**8**.

corresponding distances in the calculated structures, e.g., for **7** an H-15b–H-10 (*syn*) distance of 2.266 Å and an H-8–H-11 (*anti*) distance of 2.619 Å.

*2.2.1.4. Compounds **19** and **20**.* For these compounds (H-8 and H-15b in cis position), boat conformations were calculated, as depicted in Figure 4 for **19**. In complete agreement with the calculated distances between H-15b and H-8 (2.323 Å for **19** and 2.320 Å for **20**), and between H-10 (*syn*) and H-2′ of the *p*-nitrophenyl substituent (2.933 Å for **19** and 2.953 Å for **20**), the corresponding significant NOEs detected lend further support to the theoretical

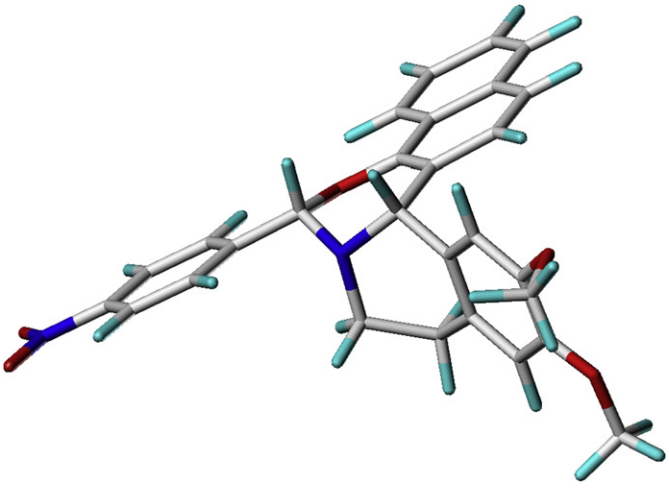


Figure 4. Global minimum-energy conformation of 8*S*,9*S*,15b*S*-**19**.

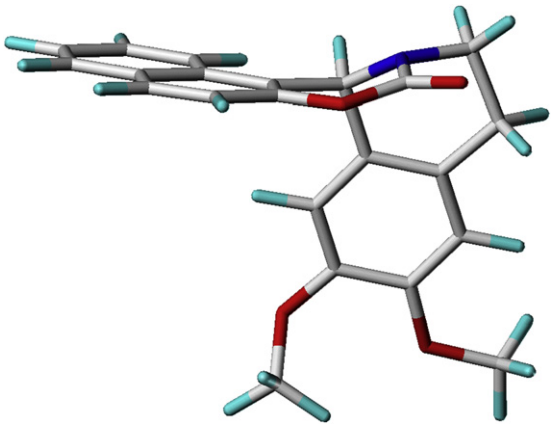


Figure 5. Minimum-energy conformation of 9*S*,15b*S*-**5**.

method, which successfully reproduces the experimental conformation evidence.

*2.2.1.5. Compounds **5**, **6**, **11**, **12**, **17**, **18**, **23**, and **24**.* Introduction of the sp^2 carbon at position 8 obviously leads to very similar conformational behavior of this kind of compounds; in accordance with this, very similar minimum-energy conformations of all of them were calculated theoretically. These structures are characterized by a twisted chair conformation of the piperidine ring moiety, with short distances between H-15b and H-10 (*syn*), corroborated excellently by the experimentally found NOE enhancements. As an example, the global minimum-energy conformation of **5** is given in Figure 5; the distance between H-15b and H-10 (*syn*) in this case proved to be 2.297 Å.

2.2.2. The (unsaturated) oxazine ring moiety

The conformation of the related unsaturated oxazine ring in the compounds studied depends strongly on the hybridization of C-8. In the compounds with an sp^3 C-8, there is likewise a twisted-boat conformation (cf. e.g., Fig. 4), while in compounds with an sp^2-hybridized C-8 the ring is nearly flat, with a slight boat conformation (cf. e.g., Fig. 5). This can be clearly seen from the different bond angles C-8–N-9–C-15b, which have values of ∼111° in the former case and ∼120° in the latter case.

Further, due to conjugation of the N-9 lone pair and the C(8)=O carbonyl group, the carbamate fragments R_2N–C(=O)–OR in these compounds are almost planar; this is clearly demonstrated by the sum of the bond angles C-8–N-9–C-10, C-10–N-9–C-15b, and C-15b–N-9–C-8, which is 349°–351° in **5**, **6**, **11**, **12**, **17**, **18**, **23**, and **24**, but only 335.8°–341.3° in the remaining compounds **3**, **4**, **7**, **8**, **15**, **16**, **19**, and **20**, where the pyramidality of the N-9, for example, the configuration of the fused heterocyclic piperidine and oxazine ring (in other words, the configuration of the substituted 9-azadecaline moiety), can be characterized by the relative position of the lone pair of N-9 and H-15b.[2–6] In all naphthoxazinoisoquinolines containing C-8 in sp^3 hybridization the lone pair of N-9 and H-15b is in the cis position.

3. Conclusions

A series of napth[1,2-*e*]- and naphth[2,1-*e*][1,3]oxazino[4,3-*a*]-isoquinoline derivatives with both sp^3 (**3**, **4**, **7**, **8**, **15**, **16**, **19**, and **20**) and sp^2 hybridization of C-8 (**5**, **6**, **11**, **12**, **17**, **18**, **23**, and **24**) have been synthesized by the cyclization of 1-(β-hydroxynaphthyl)- or 1-(α-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinoline, respectively, with formaldehyde, phosgene, *p*-nitrobenzaldehyde or *p*-chlorophenyl isothiocyanate. The conformational analyses revealed that (except for **15** and **16**) the compounds exhibit a twisted chair

conformation. Compounds **3** and **4** additionally display the corresponding boat conformation in their conformational equilibria. The twisted chair conformations, however, are not the same in all the compounds studied: the minimum-energy conformations of **15** and **16** are characterized by C-10 being below the virtual ring plane, in contrast with the other compounds, where C-10 is above the same plane. Moreover, the stereochemistry differs in compounds **7**, **8**, **19**, and **20**, with a substituent at position 8; **7** and **8** have the *R** configuration, and **19** and **20** the *S** configuration at this position. This may be due to the differing degrees of steric hindrance encountered during the syntheses.

4. Experimental

4.1. General remarks

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Merck Kieselgel 60 F_{254} plates were used for TLC. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless specified as CD_2Cl_2 or DMSO-d_6) solution in 5 mm tubes, at room temperature, on a 500 MHz NMR spectrometer at 500.17 (^{1}H) and 125.78 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as the internal standard for ^{1}H or the solvent as the internal standard for ^{13}C. All spectra (^{1}H, ^{13}C, gs-H,H-COSY, gs-HMQC, gs-1D-HMQC, gs-HMBC, and NOESY) were acquired and processed with the standard software. In cases involving strong overlapping of the ^{1}H signals, the PERCH[10] software was used to extract the coupling constants. Quantum chemical calculations were carried out with the program package GAUSSIAN 03 version C.02.[11] Different conformations and configurations of the studied compounds were preoptimized with the PM3 Hamiltonian.[12] The B3LYP density functional method was selected for all calculations. The method was based on Becke's three-parameter hybrid functionals[13] and the correlation functional of Lee et al.[14] A moderate split valence basis set 6-31G*[15] was used because of the size of the studied compounds. Polarization functions on H atoms were not used because no H-bonds exist in this series. All optimizations were carried out without any restriction at this B3LYP/6-31G* level of theory. The self-consisted reaction field (SCRF) method and the self-consisted isodensity polarized continuum model (SCIPCM) were used at the B3LYP/6-31G* level of theory to consider the solvent; the dielectric constant ε of $CDCl_3$, 4.18, was used in the calculations.

Visualization was carried out with the modeling software SYBYL 7.3[16] and the program GaussView 2.0.[17] Results were calculated on an SGI and on a Linux cluster.

Compounds **1**, **2**, **13**, and **14** were prepared according to procedures reported in the literature.[8] General procedures for the synthesis of other compounds (**3**–**12** and **15**–**24**) follow.

4.2. General method for the synthesis of 13,14-dimethoxy-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*]-isoquinoline (3), 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*]-[1,3]oxazino[4,3-*a*]isoquinoline (4), 13,14–10,11-dihydro-8*H*,15b*H*-dimethoxynaphth[2,1-*e*][1,3]oxazino[4,3-*a*]-isoquinoline (15), and 10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*]-[1,3]oxazino[4,3-*a*]isoquinoline (16)

To a stirred solution of the 1-hydroxynaphthyltetrahydroisoquinoline **1**, **2**, **13** or **14** (1.82 mmol) in toluene (25 mL), 40% aqueous formaldehyde (0.2 mL, 2.66 mmol) was added. The mixture was stirred at room temperature until TLC indicated the absence of the starting material (the reaction times are shown individually for all compounds). The solution was then dried with Na_2SO_4, the solvent was evaporated off, the crude product was crystallized from Et_2O, and recrystallized from *i*-Pr_2O–EtOAc (3:1).

4.2.1. Compound *3*

Reaction time: 6 h; yield: 0.35 g (55%). Mp 148–150 °C. ^{1}H NMR δ 7.78 (m, 2H, H-1 and H-4), 7.73 (d, J=8.8 Hz, 1H, H-5), 7.45 (t, J=7.5 Hz, 1H, H-2), 7.34 (t, J=7.3 Hz, 1H, H-3), 7.12 (d, J=8.8 Hz, 1H, H-6), 6.67 (s, 1H, H-12), 6.52 (s, 1H, H-15), 5.54 (s, 1H, H-15b), 4.75 (d, J=−6.8 Hz, 1H, H-8), 4.69 (d, J=−6.8 Hz, 1H, H-8), 3.86 (s, 3H, OMe-13), 3.79 (m, 1H, H-10), 3.35 (s, 3H, OMe-14), 3.20 (m, 1H, H-10), and 2.86 (m, 2H, H-11); ^{13}C NMR δ 150.8 (C-6a), 148.0 (C-13), 147.1 (C-14), 132.7 (C-15d), 129.3 (C-5), 128.9 (C-4a), 128.9 (C-15a), 128.6 (C-4), 126.3 (C-2), 123.3 (C-3), 123.1 (C-1), 123.1 (C-11a), 118.9 (C-6), 114.9 (C-15c), 112.6 (C-15), 111.5 (C-12), 78.2 (C-8), 55.9 (OMe-13), 55.6 (OMe-14), 54.3 (C-15b), 47.1 (C-10), and 24.9 (C-11). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.93; H, 6.12; N, 4.09.

4.2.2. Compound *4*

Reaction time: 7 h; yield: 0.43 g (82%). Mp 168–170 °C. ^{1}H NMR δ 7.80 (d, J=7.8 Hz, 1H, H-4), 7.73 (d, J=8.9 Hz, 1H, H-5), 7.67 (d, J=8.4 Hz, 1H, H-1), 7.42 (t, J=8.3 Hz, 1H, H-2), 7.35 (t, J=8.0 Hz, 1H, H-3), 7.20 (m, 3H, H-12, H-13, and H-14), 7.12 (d, J=8.9 Hz, 1H, H-6), 6.87 (d, J=7.7 Hz, 1H, H-15), 5.54 (s, 1H, H-15b), 4.62 (m, 2H, H-8), 3.85 (ddd, J=−13.0, 7.7, and 7.0 Hz, 1H, H-10), 3.03 (ddd, J=−13.0, 6.2, and 6.9 Hz, 1H, H-10), 2.96 (ddd, J=−10.9, 6.2, and 7.0 Hz, 1H, H-11), and 2.96 (ddd, J=−10.9, 7.7, and 6.9 Hz, 1H, H-11); ^{13}C NMR δ 150.9 (C-6a), 137.1 (C-11a), 134.4 (C-15a), 132.8 (C-15d), 129.3 (C-5), 128.9 (C-15), 128.8 (C-4a), 128.5 (C-4), 128.3 (C-12), 127.1 (C-13), 126.6 (C-2), 126.1 (C-14), 123.3 (C-3), 123.0 (C-1), 118.8 (C-6), 114.3 (C-15c), 78.6 (C-8), 54.3 (C-15b), 46.7 (C-10), and 25.8 (C-11). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.48; H, 6.02; N, 5.91.

4.2.3. Compound *15*

Reaction time: 8 h; yield: 0.30 g (68%). Mp 218–219 °C. ^{1}H NMR δ 8.17 (d, J=7.3 Hz, 1H, H-6), 7.70 (d, J=7.1 Hz, 1H, H-3), 7.44 (m, 2H, H-4 and H-5), 7.25 (d, J=8.8 Hz, 1H, H-2), 7.22 (d, J=8.6 Hz, 1H, H-1), 6.90 (s, 1H, H-5), 6.66 (s, 1H, H-12), 5.48 (s, 1H, H-15b), 5.47 (d, J=10.0 Hz, 1H, H-8), 5.18 (d, J=9.5 Hz, 1H, H-8), 3.98 (s, 3H, OMe-14), 3.87 (s, 3H, OMe-13), 3.25 (ddd, J=−11.9, 11.8, and 4.5 Hz, 1H, H-10), 3.14 (ddd, J=−11.9, 6.6, and 1.7 Hz, 1H, H-10), 3.08 (ddd, J=−16.2, 11.8, and 6.6 Hz, 1H, H-11), and 2.66 (ddd, J=−16.2, 4.5, and 1.7 Hz, 1H, H-11); ^{13}C NMR δ 148.3 (C-13), 147.5 (C-6b), 146.7 (C-14), 133.4 (C-2a), 127.4 (C-3), 126.3 (C-11a or C-15a), 126.2 (C-15a or C-11a), 126.0 (C-4), 125.2 (C-5), 125.1 (C-1), 124.4 (C-6a), 121.7 (C-6), 119.3 (C-2), 116.0 (C-15c), 112.8 (C-15), 111.8 (C-12), 84.7 (C-8), 57.2 (C-15b), 56.2 (OMe-14), 55.8 (OMe-13), 43.2 (C-10), and 28.6 (C-11). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.13; H, 6.03; N, 4.11.

4.2.4. Compound *16*

Reaction time: 7 h; yield: 0.38 g (73%). Mp 186–188 °C. ^{1}H NMR δ 8.17 (d, J=7.4 Hz, 1H, H-6), 7.59 (d, J=7.2 Hz, 1H, H-3), 7.43 (m, 2H, H-4 and H-5), 7.40 (d, J=7.3 Hz, 1H, H-15), 7.30 (t, J=7.0 Hz, 1H, H-14), 7.26 (t, J=7.5 Hz, 1H, H-13), 7.24 (m, 1H, H-2), 7.18 (m, 2H, H-1 and H-12), 5.57 (s, 1H, H-15b), 5.47 (d, J=−9.9 Hz, 1H, H-8), 5.19 (d, J=−9.9 Hz, 1H, H-8), 3.30 (m, 1H, H-10), 3.15 (m, 2H, H-10 and H-11), and 2.75 (m, 1H, H-11); ^{13}C NMR δ 147.7 (C-6b), 134.2 (C-11a), 133.4 (2C, C-2a and C-15a), 129.8 (C-15), 129.5 (C-12), 127.4 (C-3 or C-13), 127.3 (C-13 or C-3), 126.1 (C-4), 125.2 (3C, C-1, C-5, and C-14), 124.4 (C-6a), 121.7 (C-6), 119.2 (C-2), 115.8 (C-15C), 84.7 (C-8), 57.6 (C-15b), 43.3 (C-10), and 29.0 (C-11). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.73; H, 5.88; N, 4.91.

4.3. General method for the synthesis of 13,14-dimethoxy-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*]-isoquinolin-8-one (5), 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*]-[1,3]oxazino[4,3-*a*]isoquinolin-8-one (6), 13,14-dimethoxy-

10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*]-isoquinolin-8-one (17), and 10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinolin-8-one (18)

1-Hydroxynaphthyltetrahydroisoquinoline **1**, **2**, **13** or **14** (1.82 mmol) was suspended in toluene–H_2O (20:20 mL), and Et_3N (0.74 g, 7.3 mmol) and phosgene (2.5 mL, 20% in toluene, 2.73 mmol) were added. The mixture was stirred at room temperature until TLC showed no more starting material, and EtOAc (40 mL) and H_2O (40 mL) were then added. The organic layer was separated, dried (Na_2SO_4), and evaporated. The oily residue crystallized on treatment with *n*-hexane (20 mL). The crystalline product was filtered off and recrystallized from *n*-hexane–*i*-Pr_2O (1:1).

*4.3.1. Compound **5***

Reaction time: 25 h; yield: 0.33 g (51%). Mp 183–185 °C. ^{1}H NMR δ 7.91 (d, J=8.2 Hz, 1H, H-4), 7.89 (d, J=8.9 Hz, 1H, H-5), 7.76 (d, J=8.4 Hz, 1H, H-1), 7.57 (t, J=7.6 Hz, 1H, H-2), 7.50 (t, J=7.5 Hz, 1H, H-3), 7.28 (d, J=8.9 Hz, 1H, H-6), 6.73 (s, 1H, H-12), 6.18 (s, 1H, H-15), 6.12 (s, 1H, H-15b), 4.47 (ddd, J=−12.8, 7.6, and 4.8 Hz, 1H, H-10), 3.85 (s, 3H, OMe-13), 3.61 (ddd, J=−13.1, 9.1, and 6.4 Hz, 1H, H-10), 3.38 (ddd, J=−16.5, 8.2, and 8.2 Hz, 1H, H-11), 3.30 (s, 3H, OMe-14), and 2.95 (ddd, J=−16.1, 5.7, and 5.1 Hz, 1H, H-11); ^{13}C NMR δ 150.7 (C-8), 148.7 (C-13), 147.8 (C-6a), 147.1 (C-14), 130.6 (C-15d or C-4a), 130.5 (C-4a or C-15d), 130.5 (C-5), 128.9 (C-4), 128.3 (C-15a), 127.4 (C-2), 126.8 (C-11a), 125.2 (C-3), 123.1 (C-1), 117.2 (C-6), 112.0 (C-12), 111.9 (C-15c), 109.3 (C-15), 56.0 (OMe-13), 55.7 (OMe-14), 54.7 (C-15b), 44.6 (C-10), and 26.1 (C-11). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.25; H, 5.27; N, 3.91.

*4.3.2. Compound **6***

Reaction time: 25 h; yield: 0.34 g (62%). Mp 248–250 °C. ^{1}H NMR (CD_2Cl_2) δ 7.93 (d, J=7.6 Hz, 1H, H-4), 7.92 (d, J=9.4 Hz, 1H, H-5), 7.69 (d, J=8.4 Hz, 1H, H-1), 7.56 (td, J=7.2 and 1.2 Hz, 1H, H-2), 7.52 (td, J=7.8 and 1.0 Hz, 1H, H-3), 7.26 (d, J=7.9 Hz, 1H, H-12), 7.25 (d, J=9.0 Hz, 1H, H-6), 7.21 (t, J=7.4 Hz, 1H, H-13), 6.93 (t, J=7.5 Hz, 1H, H-14), 6.55 (d, J=7.8 Hz, 1H, H-15), 5.31 (s, 1H, H-15b), 4.31 (ddd, J=−13.1, 7.3, and 6.1 Hz, 1H, H-10), 3.68 (ddd, J=−13.1, 7.8, and 6.9 Hz, 1H, H-10), 3.36 (ddd, J=−16.6, 7.8, and 7.3 Hz, 1H, H-11), and 3.08 (ddd, J=−16.6, 6.1, and 6.9 Hz, 1H, H-11); ^{13}C NMR (CD_2Cl_2) δ 150.5 (C-8), 148.2 (C-6a), 137.0 (C-15a), 135.3 (C-11a), 131.0 (C-15d), 130.8 (2C, C-4a and C-5), 129.2 (C-12), 129.0 (C-4), 128.3 (C-13), 127.9 (C-2), 126.3 (C-14), 125.4 (C-15), 125.2 (C-3), 123.4 (C-1), 117.3 (C-6), 112.0 (C-15c), 54.9 (C-15b), 44.4 (C-10), and 26.8 (C-11). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.85; H, 5.07; N, 4.71.

*4.3.3. Compound **17***

Reaction time: 20 h; yield: 0.37 g (56%). Mp 199–201 °C. ^{1}H NMR δ 8.31 (m, 1H, H-6), 7.86 (m, 1H, H-3), 7.70 (d, J=8.2 Hz, 1H, H-2), 7.56 (m, 2H, H-4 and H-5), 7.38 (d, J=8.2 Hz, 1H, H-1), 6.70 (s, 1H, H-12), 6.61 (s, 1H, H-15), 5.72 (s, 1H, H-15b), 4.46 (ddd, J=−13.0, 6.6, and 4.0 Hz, 1H, H-10), 3.86 (s, 3H, OMe-13), 3.68 (s, 3H, OMe-14), 3.51 (ddd, J=−13.0, 9.8, and 5.6 Hz, 1H, H-10), 3.31 (ddd, J=−16.3, 9.8, and 6.6 Hz, 1H, H-11), and 2.87 (ddd, J=−16.3, 5.6, and 4.0 Hz, 1H, H-11); ^{13}C NMR δ 150.7 (C-8), 148.6 (C-13), 147.3 (C-14), 145.0 (C-6b), 133.7 (C-2a), 127.9 (C-15a), 127.5 (C-3), 127.1 (C-4 or C-5), 126.9 (C-11a), 126.8 (C-5 or C-4), 123.8 (C-1), 123.5 (C-2), 123.4 (C-6a), 121.5 (C-6), 113.5 (C-15c), 112.0 (C-12), 108.6 (C-15), 56.6 (C-15b), 55.9 (OMe-13), 55.9 (OMe-14), 44.2 (C-10), and 26.5 (C-11). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.17; H, 5.32; N, 3.91.

*4.3.4. Compound **18***

Reaction time: 30 h; yield: 0.38 g (70%). Mp 188–190 °C. ^{1}H NMR δ 8.31 (m, 1H, H-6), 7.87 (m, 1H, H-3), 7.71 (d, J=8.4 Hz, 1H, H-2), 7.56 (m, 2H, H-4 and H-5), 7.38 (d, J=8.4 Hz, 1H, H-1), 7.24 (m, 2H, H-12 and H-13), 7.13 (td, J=7.1 and 1.9 Hz, 1H, H-14), 7.06 (d, J=7.7 Hz, 1H, H-15), 5.79 (s, 1H, H-15b), 4.40 (ddd, J=−12.7, 6.8, and 5.7 Hz, H-10), 3.58 (ddd, J=−13.0, 8.6, and 6.0 Hz, 1H, H-10), 3.32 (ddd, J=−16.1, 8.0, and 7.9 Hz, 1H, H-11), and 2.97 (dt, J=−16.4 and 5.6 Hz, 1H, H-11); ^{13}C NMR δ 150.6 (C-8), 145.0 (C-6b), 136.3 (C-15a), 134.8 (C-11a), 133.8 (C-2a), 129.0 (C-12), 127.9 (C-13), 127.5 (C-3), 127.2 (C-4), 126.7 (C-5), 126.3 (C-14), 124.6 (C-15), 124.1 (C-1), 123.5 (C-2), 123.3 (C-6a), 121.5 (C-6), 112.9 (C-15c), 56.7 (C-15b), 43.9 (C-10), and 26.9 (C-11). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.67; H, 5.05; N, 4.67.

4.4. General method for the synthesis of (8*R,15b*S**)-8-(4-nitrophenyl)-13,14-dimethoxy-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinoline (7), (8*R**,15b*S**)-8-(4-nitrophenyl)-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*]-[1,3]oxazino[4,3-*a*]isoquinoline (8), (8*S**,15b*S**)-8-(4-nitrophenyl)-13,14-dimethoxy-10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinoline (19), and (8*S**,15b*S**)-8-(4-nitrophenyl)-10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinoline (20)**

1-Hydroxynaphthyltetrahydroisoquinoline **1**, **2**, **13** or **14** (1.82 mmol) was heated at 55 °C with an equimolar amount of *p*-nitrobenzaldehyde (0.28 g, 1.28 mmol) in dry toluene (30 mL). When no more starting material could be detected on TLC, the solvent was evaporated off; the residual oil crystallized on treatment with Et_2O. The crystalline product was filtered off and recrystallized from *i*-Pr_2O–EtOAc.

*4.4.1. Compound **7***

Reaction time: 75 h; yield: 0.58 g (68%). Mp 207–209 °C. ^{1}H NMR δ 8.31 (d, J=8.7 Hz, 2H, H-3′), 7.81 (d, J=8.6 Hz, 2H, H-2′), 7.79 (m, 2H, H-1 and H-4), 7.76 (d, J=8.9 Hz, 1H, H-5), 7.51 (td, J=7.7 and 0.7 Hz, 1H, H-2), 7.40 (t, J=7.6 Hz, 1H, H-3), 7.08 (d, J=8.9 Hz, 1H, H-6), 6.69 (s, 1H, H-12), 6.55 (s, 1H, H-15), 5.79 (s, 1H, H-8), 5.77 (s, 1H, H-15b), 3.88 (s, 3H, OMe-13), 3.52 (ddd, J=−14.3, 11.4, and 6.4 Hz, 1H, H-10), 3.35 (s, 3H, OMe-14), 2.85 (ddd, J=−14.3, 7.0, and 2.4 Hz, 1H, H-10), 2.81 (ddd, J=−17.2, 11.4, and 7.0 Hz, 1H, H-11), and 2.64 (ddd, J=−17.2, 6.4, and 2.4 Hz, 1H, H-11); ^{13}C NMR δ 150.4 (C-6a), 148.7 (C-4′), 148.1 (C-13), 147.3 (C-14), 145.0 (C-1′), 132.4 (C-15d), 129.5 (C-2′), 128.9 (C-4 or C-5), 128.6 (C-5 or C-4), 128.6 (C-4a), 128.3 (C-15a), 126.4 (C-2), 125.3 (C-11a), 123.8 (C-3′), 123.5 (C-3), 122.9 (C-1), 118.4 (C-6), 114.7 (C-15c), 112.4 (C-15), 111.7 (C-12), 86.6 (C-8), 55.9 (OMe-13), 55.6 (C-15b), 55.6 (OMe-14), 46.4 (C-10), and 23.8 (C-11). Anal. Calcd for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98. Found: C, 71.59; H, 5.20; N, 5.91.

*4.4.2. Compound **8***

Reaction time: 50 h; yield: 0.48 g (64%). Mp 204–206 °C. ^{1}H NMR δ 8.29 (d, J=8.7 Hz, 2H, H-3′), 7.83 (d, J=8.1 Hz, 1H, H-4), 7.75 (m, 4H, H-1, H-5, and H-2′), 7.48 (t, J=7.7 Hz, 1H, H-2), 7.38 (t, J=7.5 Hz, 1H, H-3), 7.21 (m, 2H, H-12 and H-13), 7.07 (d, J=8.9 Hz, 1H, H-6), 7.03 (t, J=7.2 Hz, 1H, H-14), 6.94 (d, J=7.8 Hz, 1H, H-15), 5.78 (s, 1H, H-15b), 5.70 (s, 1H, H-8), 3.53 (J=−14.1, 10.3, and 6.6 Hz, 1H, H-10), 2.86 (J=−17.2, 10.3, and 7.0 Hz, 1H, H-11), 2.78 (J=−14.1, 7.0, and 3.6 Hz, 1H, H-10), and 2.77 (J=−17.2, 6.6, and 3.6 Hz, 1H, H-11); ^{13}C NMR δ 150.4 (C-6a), 148.7 (C-4′), 145.0 (C-1′), 136.5 (C-15a), 133.8 (C-11a), 132.5 (C-15d), 129.5 (C-2′), 129.0 (C-15), 128.9 (3C, C-4a, C-5, and C-12), 128.6 (C-4), 127.3 (C-13), 126.9 (C-2), 126.4 (C-14), 123.8 (C-3′), 123.5 (C-3), 122.9 (C-1), 118.4 (C-6), 114.4 (C-15c), 86.9 (C-8), 55.6 (C-15b), 46.4 (C-10), and 24.5 (C-11). Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 76.46; H, 4.94; N, 6.86. Found: C, 76.64; H, 4.87; N, 6.81.

*4.4.3. Compound **19***

Reaction time: 24 h; yield: 0.63 g (74%). Mp 231–232 °C. ^{1}H NMR δ 8.36 (d, J=8.2 Hz, 1H, H-6), 8.35 (d, J=8.3 Hz, 2H, H-3′), 8.05 (d,

J=8.4 Hz, 2H, H-2′), 7.77 (d, J=8.0 Hz, 1H, H-3), 7.55 (ddd, J=8.3, 7.0, and 0.8 Hz, 1H, H-5), 7.50 (ddd, J=8.1, 6.8, and 1.2 Hz, 1H, H-4), 7.37 (d, J=8.6 Hz, 1H, H-2), 7.33 (d, J=8.6 Hz, 1H, H-1), 6.98 (s, 1H, H-15), 6.65 (s, 1H, H-12), 6.51 (s, 1H, H-8), 5.76 (s, 1H, H-15b), 4.01 (s, 3H, OMe-14), 3.87 (s, 3H, OMe-13), 2.89 (ddd, J=−16.2, 12.0, and 6.3 Hz, 1H, H-11), 2.85 (ddd, J=−12.0, 12.0, and 4.3 Hz, 1H, H-10), 2.71 (ddd, J=−12.0, 6.3, and 1.7 Hz, 1H, H-10), and 2.54 (ddd, J=−16.2, 4.3, and 1.7 Hz, 1H, H-11); ^{13}C NMR δ 148.5 (C-13), 147.9 (C-4′), 147.4 (C-6b), 146.9 (C-14), 144.8 (C-1′), 133.5 (C-2a), 127.7 (C-2′), 127.5 (C-3), 126.8 (C-11a), 126.3 (C-5), 126.1 (C-15a), 125.6 (C-4), 124.9 (C-1), 124.4 (C-6a), 123.5 (C-3′), 121.5 (C-6), 120.3 (C-2), 116.5 (C-15c), 112.8 (C-15), 111.9 (C-12), 90.5 (C-8), 59.9 (C-15b), 56.3 (OMe-14), 55.8 (OMe-13), 37.2 (C-10), and 28.3 (C-11). Anal. Calcd for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98. Found: C, 71.67; H, 5.15; N, 5.95.

4.4.4. Compound **20**

Reaction time: 24 h; yield: 0.52 g (70%). Mp 219–222 °C. ^{1}H NMR δ 8.36 (d, J=8.4 Hz, 1H, H-6), 8.34 (d, J=8.8 Hz, 2H, H-3′), 8.03 (d, J=8.5 Hz, 2H, H-3′), 7.74 (d, J=8.1 Hz, 1H, H-3), 7.54 (ddd, J=8.3, 6.8, and 1.4 Hz, 1H, H-5), 7.48 (m, 2H, H-4 and H-15), 7.34 (t, J=7.4 Hz, 1H, H-14), 7.33 (d, J=8.7 Hz, 1H, H-2), 7.28 (m, 2H, H-1 and H-13), 7.16 (d, J=7.6 Hz, 1H, H-12), 6.48 (s, 1H, H-8), 5.82 (s, 1H, H-15b), 2.94 (ddd, J=−16.5, 11.8, and 6.4 Hz, 1H, H-11), 2.88 (ddd, J=−12.1, 11.8, and 4.3 Hz, 1H, H-10), 2.71 (ddd, J=−12.1, 6.4, and 1.7 Hz, 1H, H-10), and 2.61 (ddd, J=−16.5, 4.3, and 1.7 Hz, 1H, H-11); ^{13}C NMR δ 147.9 (C-4′), 147.5 (C-6b), 144.8 (C-1′), 134.6 (C-11a), 134.1 (C-15a), 133.5 (C-2a), 129.7 (C-15), 129.5 (C-12), 127.7 (C-2′), 127.5 (2C, C-3 and C-13), 126.3 (C-4), 125.5 (C-5), 125.3 (C-14), 125.1 (C-1), 124.4 (C-6a), 123.5 (C-3′), 121.5 (C-6), 120.3 (C-2), 116.2 (C-15c), 90.4 (C-8), 60.2 (C-15b), 37.3 (C-10), and 28.6 (C-11). Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 76.46; H, 4.94; N, 6.86. Found: C, 76.32; H, 4.96; N, 6.90.

4.5. General method for the synthesis of N^1-[1-(2-hydroxy-1-naphthyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]-N^2-*p*-chlorophenylthiourea (9), N^1-[1-(2-hydroxy-1-naphthyl)-1,2,3,4-tetrahydroisoquinoline]-N^2-*p*-chlorophenylthiourea (10), N^1-[1-(1-hydroxy-2-naphthyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]-N^2-*p*-chlorophenylthiourea (21), and N^1-[1-(1-hydroxy-2-naphthyl)-1,2,3,4-tetrahydroisoquinoline]-N^2-*p*-chlorophenylthiourea (22)

A mixture of 1-hydroxynaphthyltetrahydroisoquinoline **1**, **2**, **13** or **14** (1.82 mmol) and phenyl isothiocyanate (0.30 mL, 2.00 mmol) in abs toluene (50 mL) was stirred at room temperature for 24 h. The crystals that separated out were filtered off, washed with toluene (2×20 mL), and used in the next step without further purification.

4.5.1. Compound **9**

Yield: 0.87 g (95%). Mp 154–155 °C. ^{1}H NMR δ 8.01 (br s, 1H), 7.81 (m, 3H), 7.41 (s, 1H), 7.32 (m, 2H), 7.11 (m, 2H), 7.05 (d, J=8.6 Hz, 2H), 6.92 (d, J=8.6 Hz, 2H), 6.76 (s, 1H), 6.38 (s, 1H), 4.72 (m, 1H), 3.91 (s, 3H), 3.87 (m, 2H), 3.55 (s, 3H), 3.31 (m, 1H), and 2.92 (m, 1H). Anal. Calcd for $C_{28}H_{25}ClN_2O_3S$: C, 66.59; H, 4.99; N, 5.55. Found: C, 66.72; H, 5.02; N, 5.61.

4.5.2. Compound **10**

Yield: 0.78 g (97%). Mp 149–151 °C. ^{1}H NMR δ 8.06 (br s, 1H), 7.87 (m, 2H), 7.68 (m, 1H), 7.29 (m, 4H), 7.12 (m, 3H), 7.04 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.79 (d, J=7.9 Hz, 1H), 5.04 (m, 1H), 3.88 (m, 1H), 3.32 (m, 2H), and 3.04 (m, 1H). Anal. Calcd for $C_{26}H_{21}ClN_2OS$: C, 70.18; H, 4.76; N, 6.30. Found: C, 70.27; H, 4.72; N, 6.32.

4.5.3. Compound **21**

Yield: 0.83 g (90%). Mp 135–137 °C. ^{1}H NMR (DMSO-d_6) δ 10.27 (br s, 1H), 9.85 (br s, 1H), 8.30 (m, 1H), 7.81 (m, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.34 (d, J=8.5 Hz, 1H), 7.25 (t, J=7.5 Hz, 1H), 7.17 (d, J=7.7 Hz, 1H), 6.91 (s, 1H), 6.86 (d, J=8.6 Hz, 1H), 6.54 (s, 1H), 4.54 (m, 1H), 3.80 (s, 3H), 3.57 (s, 3H), 3.50 (m, 1H), 3.18 (m, 1H), and 2.88 (m, 1H). Anal. Calcd for $C_{28}H_{25}ClN_2O_3S$: C, 66.59; H, 4.99; N, 5.55. Found: C, 66.61; H, 4.95; N, 5.57.

4.5.4. Compound **22**

Yield: 0.74 g (92%). Mp 204–206 °C. ^{1}H NMR (DMSO-d_6) δ 10.31 (br s, 1H), 9.84 (br s, 1H), 8.31 (m, 1H), 7.81 (m, 1H), 7.52 (m, 2H), 7.40 (m, 3H), 7.34 (m, 2H), 7.29 (t, J=7.5 Hz, 1H), 7.25 (t, J=7.6 Hz, 1H), 7.18 (m, 2H), 7.01 (d, J=7.7 Hz, 1H), 6.85 (d, J=8.6 Hz, 1H), 4.62 (m, 1H), 3.60 (m, 1H), 3.23 (m, 1H), and 2.99 (m, 1H). Anal. Calcd for $C_{26}H_{21}ClN_2OS$: C, 70.18; H, 4.76; N, 6.30. Found: C, 70.23; H, 4.74; N, 6.28.

4.6. General method for the synthesis of 8-(4-chlorophenylimino)-13,14-dimethoxy-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinoline (11), 8-(4-chlorophenylimino)-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*]-[1,3]oxazino[4,3-*a*]isoquinoline (12), 8-(4-chlorophenylimino)-13,14-dimethoxy-10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinoline (23), and 8-(4-chlorophenylimino)-10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*]-[1,3]oxazino[4,3-*a*]isoquinoline (24)

To a solution of thiourea **9**, **10**, **21** or **22** (1.00 mmol) in MeOH (30 mL), MeI (0.60 mL, 10.00 mmol) was added and the solution was stirred for 20 h. After evaporation of the solvent, the residue was stirred in 3 M methanolic KOH (30 mL) for 4 h. Following evaporation, H_2O (30 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (3×30 mL). After drying (Na_2SO_4) and evaporation of the solvent, the crystalline oxazine was obtained on treatment with *n*-hexane (20 mL); it was filtered off and recrystallized from *n*-hexane–*i*-Pr_2O (3:1).

4.6.1. Compound **11**

Yield: 0.26 g (55%). Mp 158–160 °C. ^{1}H NMR δ 7.89 (d, J=8.1 Hz, 1H, H-4), 7.84 (d, J=8.7 Hz, 1H, H-1), 7.83 (d, J=8.5 Hz, 1H, H-5), 7.59 (t, J=7.7 Hz, 1H, H-2), 7.49 (t, J=7.5 Hz, 1H, H-3), 7.21 (d, J=8.6 Hz, 2H, H-3′), 7.11 (d, J=8.9 Hz, 1H, H-6), 6.99 (d, J=8.6 Hz, 2H, H-2′), 6.72 (s, 1H, H-12), 6.21 (s, 1H, H-15), 6.08 (s, 1H, H-15b), 4.68 (ddd, J=12.8, 6.6, and 2.1 Hz, 1H, H-10), 3.86 (s, 3H, OMe-13), 3.70 (ddd, J=16.4, 10.4, and 6.3 Hz, 1H, H-11), 3.60 (ddd, J=12.4, 11.4, and 5.1 Hz, 1H, H-10), 3.29 (s, 3H, OMe-14), and 2.81 (m, 1H, H-11); ^{13}C NMR δ 148.6 (C-13), 146.9 (C-6a), 146.9 (C-14), 145.7 (C-1′), 145.5 (C-8), 130.9 (C-15d), 130.3 (C-4a), 130.1 (C-5), 128.9 (C-4), 128.4 (C-3′), 127.8 (C-15a), 127.4 (C-2), 127.2 (C-11a or C-4′), 127.1 (C-4′ or C-11a), 124.9 (C-3), 124.9 (C-2′), 122.8 (C-1), 116.8 (C-6), 113.9 (C-15c), 112.2 (C-12), 109.5 (C-15), 55.9 (OMe-13), 55.6 (OMe-14), 54.1 (C-15b), 45.7 (C-10), and 24.5 (C-11). Anal. Calcd for $C_{28}H_{23}ClN_2O_3$: C, 71.41; H, 4.92; N, 5.95. Found: C, 71.57; H, 4.93; N, 5.93.

4.6.2. Compound **12**

Yield: 0.25 g (61%). Mp 223–225 °C. ^{1}H NMR δ 7.89 (d, J=8.1 Hz, 1H, H-4), 7.83 (d, J=8.9 Hz, 1H, H-5), 7.77 (d, J=8.4 Hz, 1H, H-1), 7.57 (t, J=7.5 Hz, 1H, H-2), 7.49 (t, J=7.4 Hz, 1H, H-3), 7.21 (m, 4H, H-12, H-13, and H-3′), 7.10 (d, J=8.9 Hz, 1H, H-6), 6.97 (d, J=8.6 Hz, 2H, H-2′), 6.93 (t, J=7.5 Hz, 1H, H-14), 6.63 (d, J=7.8 Hz, 1H, H-15), 6.10 (s, 1H, H-15b), 4.66 (m, 1H, H-10), 3.69 (m, 2H, H-10 and H-11), and 2.94 (m, 1H, H-11); ^{13}C NMR δ 146.9 (C-6a), 145.7 (C-1′), 145.4 (C-8), 136.1 (C-15a), 135.1 (C-11a), 131.0 (C-15d), 130.3 (C-4a), 130.2 (C-5), 129.3 (C-12), 128.8 (C-4), 128.4 (C-3′), 127.6 (C-2), 127.1 (C-4′), 126.0 (C-14), 125.6 (C-15), 125.0 (C-3), 124.9 (C-2′), 122.8 (2C, C-1 and C-13), 116.7 (C-6), 113.7 (C-15c), 54.2 (C-15b), 45.4 (C-10), and 25.1 (C-11). Anal. Calcd for $C_{26}H_{19}ClN_2O$: C, 76.00; H, 4.66; N, 6.82. Found: C, 76.18; H, 4.62; N, 6.84.

4.6.3. Compound ***23***

Yield: 0.31 g (65%). Mp 238–240 °C. ^{1}H NMR δ 7.83 (d, J=8.0 Hz, 1H, H-3), 7.80 (d, J=8.2 Hz, 1H, H-6), 7.66 (d, J=8.4 Hz, 1H, H-2), 7.51 (t, J=7.9 Hz, 1H, H-4), 7.47 (t, J=8.3 Hz, 1H, H-5), 7.37 (d, J=8.4 Hz, 1H, H-1), 7.29 (d, J=8.6 Hz, 2H, H-3′), 7.08 (d, J=8.6 Hz, 2H, H-2′), 6.72 (s, 1H, H-12), 6.61 (s, 1H, H-15), 5.67 (s, 1H, H-15b), 4.65 (m, 1H, H-10), 3.88 (s, 3H, OMe-13), 3.69 (s, 3H, OMe-14), 3.51 (m, 2H, H-10 and H-11), and 2.75 (m, 1H, H-11); ^{13}C NMR δ 148.5 (C-13), 147.2 (C-14), 146.0 (C-8), 145.8 (C-1′), 144.3 (C-6b), 133.8 (C-2a), 128.4 (C-3′), 127.6 (C-3), 127.3 (C-11a or C-4′), 127.2 (C-4′ or C-11a), 127.1 (C-15a), 126.9 (C-4 or C-5), 126.8 (C-5 or C-4), 124.9 (C-2′), 123.9 (C-1), 123.5 (C-6a), 123.1 (C-2), 121.1 (C-6), 116.0 (C-15c), 112.1 (C-12), 109.0 (C-15), 56.1 (C-15b), 55.9 (OMe-13), 55.9 (OMe-14), 44.8 (C-10), and 25.4 (C-11). Anal. Calcd for $C_{28}H_{23}ClN_2O_3$: C, 71.41; H, 4.92; N, 5.95. Found: C, 71.61; H, 4.95; N, 5.97.

4.6.4. Compound ***24***

Yield: 0.24 g (58%). Mp 224–227 °C. ^{1}H NMR δ 8.27 (d, J=7.1 Hz, 1H), 7.66 (d, J=7.9 Hz, 1H), 7.11–7.39 (m, 9H), 6.98 (d, J=8.6 Hz, 1H), 6.86 (d, J=7.5 Hz, 1H), 6.72 (d, J=8.4 Hz, 1H), 4.63 (m, 1H), 3.35 (m, 3H), and 2.87 (d, J=15.1 Hz, 1H); this compound decomposes very rapidly in solution, and therefore no ^{13}C NMR data are available. Anal. Calcd for $C_{26}H_{19}ClN_2O$: C, 76.00; H, 4.66; N, 6.82. Found: C, 76.11; H, 4.68; N, 6.81.

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