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Unexpected isomerization of new naphth[1,3]oxazino[2,3-*a*] isoquinolines in solution, studied by dynamic NMR and supported by theoretical DFT computations

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ABSTRACT

Through the reactions of 1-aminomethyl-2-naphthol and substituted 1-aminobenzyl-2-naphthols with 3,4-dihydroisoquinoline or 6,7-dimethoxy-3,4-dihydroisoquinoline under microwave conditions, naphth-[1,2-*e*][1,3]oxazino[2,3-*a*]-isoquinoline derivatives were prepared in good yields. The latter reaction was extended by using 2-aminoarylmethyl-1-naphthols, leading to isomeric naphth-[2,1-*e*][1,3]oxazino[2,3-*a*] isoquinolines. Beside the detailed NMR spectroscopic and theoretical study of both stereochemistry and dynamic behaviour of these new conformational flexible heterocyclic ring systems an unexpected dynamic process between two diastereomers was observed in solution, studied by variable temperature ^{1}H NMR spectroscopy and the mechanism proved by theoretical DFT computations.

1. Introduction

The Mannich reaction[1] is an important C–C bond formation reaction that is widely used in the syntheses of secondary and tertiary amine derivatives and as a key step in the syntheses of many bioactive molecules and complex natural products.[2] One of its special variations is the modified Mannich reaction, in which electron-rich aromatic compounds such as 1- or 2-naphthol are applied.[3] In consequence of the two or more functional groups in the structure of the Mannich bases prepared via such modified reactions, one of the most important areas of application of these aminonaphthol derivatives is the synthesis of new heterocycles.[3]

In previous papers, we reported on the synthesis and conformational studies of naphth[1,2-*e*][1,3]oxazino[3,4-*c*][1,3]benzoxazine,[4,5] naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline[6] and naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one.[7] Through the cyclization of 1-hydroxynaphthyl-1,2,3,4-tetrahydroisoquinolines, 8-substituted naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinoline derivatives were prepared and their conformational behaviour was examined.[8]

We recently reported unexpected transformations between 1-α-aminobenzyl-2-naphthol or 1-aminomethyl-2-naphthol and 6,7-dimethoxy-3,4-dihydroisoquinoline to furnish 9,10-dimethoxynaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines under microwave (MW) irradiation.[9] A Russian research group later synthesized this compound and a couple of 15-aryl derivatives from the corresponding 1-dimethylaminomethyl-2-naphthols and 6,7-dimethoxy-3,4-dihydroisoquinoline.[10]

It is the major aim of this paper to extend this recent reaction but starting from 3,4-dihydroisoquinoline, to examine the scope and limitations when starting from 3,4-dihydroisoquinolines and 2-aminomethyl-1-naphthol analogues[11] (reverse Betti bases), and to study the obtained conformationally flexible ring system by means of NMR spectroscopy and accompanying theoretical calculations at the DFT level of theory.

2. Results and discussion

2.1. Syntheses

For the synthesis of the model compounds **3** and **7** (cf. Table 1), the previously published synthetic method[9] was applied, starting from 1-aminomethyl-2-naphthol (**1a**) or 1-aminobenzyl-2-naphthol

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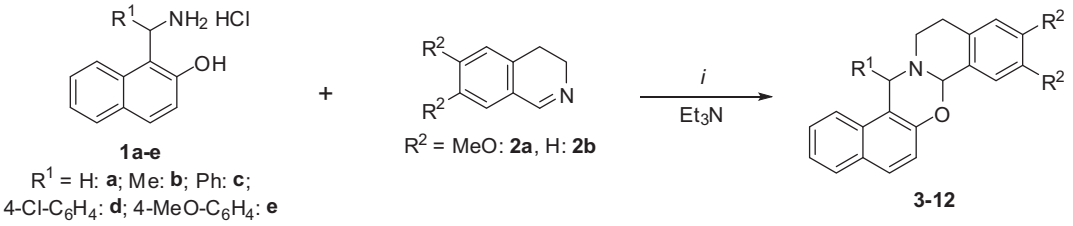
Table 1
Reaction conditions for the preparation of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines **3**–**12**



Entry	Product	R^1	R^2	Conditions (*i*)	Diastereomeric ratio[a] trans/cis	Yield (%)
1	**3**	H	MeO	100 °C, 90 min	—	73
2	**4**	H	H	90 °C, 70 min	—	75
3	**5**	Me	MeO	80 °C, 60 min	[b]	67
4	**6**	Me	H	80 °C, 45 min	98:2	74
5	**7**	Ph	MeO	100 °C, 90 min	99.7:0.3	82
6	**8**	Ph	H	90 °C, 75 min	99.6:0.4	87
7	**9**	4-Cl–C_6H_4	MeO	100 °C, 90 min	99.6:0.4	72
8	**10**	4-Cl–C_6H_4	H	100 °C, 60 min	99.6:0.4	68
9	**11**	4-MeO–C_6H_4	MeO	100 °C, 100 min	99.6:0.4	85
10	**12**	4-MeO–C_6H_4	H	100 °C, 60 min	99.7:0.3	77

[a] Determined from the ^{1}H NMR spectrum of the crude product.
[b] Not detected due to strong overlapping.

(**1c**) and 6,7-dimethoxy-3,4-dihydroisoquinoline (**2a**). To examine the possibility of extending the reaction, **2a** as starting material was replaced by 3,4-dihydroisoquinoline (**2b**). The reaction led to the formation of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline **4** and 15-phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline **8** (Table 1, entries 2 and 6). The scope of the reaction was further tested by using different substituted 1-aminobenzyl-2-naphthol derivatives, such as 1-(1-aminoethyl)-2-naphthol (**1b**), 1-amino-(4-chlorophenyl) methyl-2-naphthol (**1d**) and 1-amino-(4-methoxyphenyl)methyl-2-naphthol (**1e**). Their reaction either with **2a** or with **2b** yielded the desired naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline derivatives in good yields (Table 1). It should be mentioned that the syntheses of 9,10-dimethoxy derivatives **3**, **5**, **7**, **9** and **11** usually required longer reaction times than those for the 9,10-unsubstituted analogues **4**, **6**, **8**, **10** and **12** (Table 1).

Scope and limitations of the reaction were additionally tested by using substituted 2-aminobenzyl-1-naphthol analogues (reverse Betti bases: **13a**–**d**). It could be concluded that somewhat lower temperatures (70 °C) were adequate for the syntheses of 15-alkyl-substituted naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinolines (Table 2, entries 1 and 2) than for their 15-aryl analogues (Table 2, entries 3–10).

2.2. Structural analysis

The comparison of the diastereomeric ratios (trans and cis: as concerns the relative intensity of the H-7a and H-15 proton NMR signals) for the two sets of compounds indicates that the diastereoselectivity of the latter reaction seems to differ depending on the annelation type of the naphthyl ring (**5**–**12** vs **14**–**21**) and the substituent R^1 at position 15. To explain the different ratios in the two naphth[1,3]oxazino[2,3-*a*]isoquinoline ring systems, full geometry optimization of the compounds studied was performed by using *DFT* calculations. The ring systems of **3**–**12** and **14**–**21**, respectively, contain invertible N atoms. As regards both the *R* and the *S* configurations of N-14, C-7a and C-15, all the isomers/enantiomers were considered in the *DFT* calculations; the energy differences (ΔE) obtained for the lowest-energy conformers for each configuration are listed in Tables 3–6.

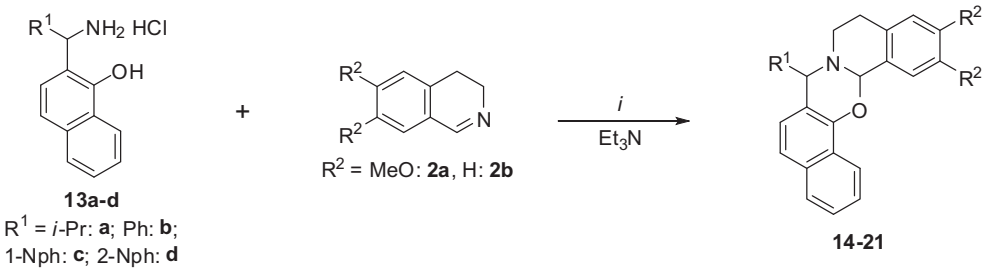
The conformational search protocol involved PM3 geometry minimization, followed by geometry optimization without restrictions. All calculations were carried out by using the Gaussian 09 program package.[12] Different conformations of the studied compounds were preoptimized by using the PM3 Hamiltonian. Density functional theory calculations were carried out at the B3LYP/6-311G** level of theory.[13,14]

For the 15-substituted naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline derivatives (**5**–**12**), the diastereomeric ratios obtained experimentally (Table 1) agreed excellently with the energy differences calculated for the two diastereomers (Tables 3 and 4): the energy difference between the diastereomers was ca. 3.8 kcal/mol and 0–2% of the minor (cis) form was detected experimentally.

For the 15-substituted naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinolines (**14**–**21**), with the exception of the isopropyl derivative (where the presence of the minor diastereomer could not be detected experimentally and the calculated energy differences were found to be 3.88 kcal/mol and 3.91 kcal/mol, respectively), a more significant amount of the minor diastereomer(s) was observed (7–21% for **14**–**17**, **20** and **21**: Table 2) and relative low energy differences (1.33–1.51 kcal/mol: Tables 5 and 6) were computed. The 1-naphthyl substituent in **18** and **19** is restricted in its rotation and, because of this additional chiral axis, atropisomers result. Thus, the latter two compounds are expected to give four diastereomers. Actually, for **18** and for **19** three components were detected by NMR (Table 2). This is in accordance with theoretical calculations, performed for **19**, where four isomers were found to have low energies: (15(*S*),14(*R*),7a(*R*),15(*P*), 15(*R*),14(*S*),7a(*R*),15(*P*), 15(*R*),14(*S*),7a(*R*),15(*M*), and 15(*R*),14(*R*),7a(*R*),15(*P*); see Fig. 1), whereas the latter two differ only in their configuration at the nitrogen atom, which can rapidly invert (see below) to give only one set of signals in the NMR spectrum.

To identify the configurations of the minor components of **19** found by NMR in solution, the chemical shift differences of some selected nuclei between the major trans component (15(*S*),7a(*R*),15(*P*)-**19**) and the minor components were calculated theoretically and compared with the experimental data (see Table 7). The results were in good agreement with the computations, and it could be concluded that the minor component in an amount of 8.2% has the configuration

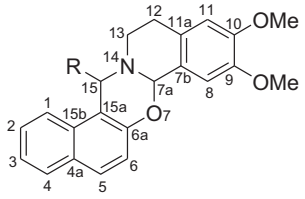
Table 2
Reaction conditions for the preparation of naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinolines **14**–**21**



Entry	Product	R^1	R^2	Conditions (*i*)	Diastereomeric ratio[a] trans/cis	Yield (%)
1	**14**	*i*-Pr	OMe	70 °C, 40 min	100:0	67
2	**15**	*i*-Pr	H	70 °C, 40 min	100:0	72
3	**16**	Ph	OMe	90 °C, 60 min	82:18	75
4	**17**	Ph	H	90 °C, 60 min	79:21	83
5	**18**	1-Nph	OMe	85 °C, 75 min	[b]	65
6	**19**	1-Nph	H	85 °C, 60 min	[b]	77
7	**20**	2-Nph	OMe	85 °C, 75 min	83:17	70
10	**21**	2-Nph	H	85 °C, 60 min	79:21	74

[a] Determined from the ^{1}H NMR spectrum of the crude product.
[b] More than two diastereomers; **18**: 92.9:5.8:1.3; **19**: 89.4:8.2:2.4.

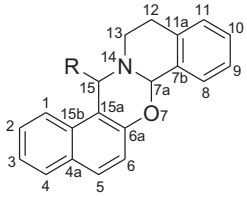
Table 3
Calculated energy differences for **3**, **5**, **7**, **9** and **11** in kcal/mol



3 R=H		**5** R=Me				**7** R=Ph				**9** R=4-Cl−C_6H_4				**11** R=4−MeO−C_6H_4			
—		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)	
G_1^a	G_2^b	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f
0.0	1.26	0.0	3.26	3.84	5.83	0.0	3.44	3.68	4.90	0.0	3.67	3.78	5.11	0.0	3.35	3.58	4.78

Corresponding to the following configurations: [a]14(*R*),7a(*R*), [b]14(*S*),7a(*R*), [c]15(*S*),14(*R*),7a(*R*), [d]15(*S*),14(*S*),7a(*R*), [e]15(*S*),14(*R*),7a(*S*) and [f]15(*S*),14(*S*),7a(*S*).

Table 4
Calculated energy differences for **4**, **6**, **8**, **10**, and **12** in kcal/mol



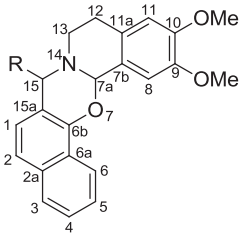
4 R=H		**6** R=Me				**8** R=Ph				**10** R=4-Cl−C_6H_4				**12** R=4-MeO−C_6H_4			
		trans (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)	
G_1^a	G_2^b	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f	G_{t1}^c	G_{t2}^d	G_{c1}^e	G_{c2}^f
0.0	1.42	0.0	3.41	3.87	5.81	0.0	3.51	3.79	4.85	0.0	3.76	3.85	5.11	0.0	3.72	3.98	5.03

Corresponding to the following configurations: [a]14(*R*),7a(*R*), [b]14(*S*),7a(*R*), [c]15(*S*),14(*R*),7a(*R*), [d]15(*S*),14(*S*),7a(*R*), [e]15(*S*),14(*R*),7a(*S*) and [f]15(*S*),14(*S*),7a(*S*).

15(*R*),7a(*R*),15(*P*), while the component in an amount of 2.4% has the configuration 15(*R*),7a(*R*),15(*M*). Thus, both minor components are cis isomers.

In the NMR spectra of **3** and **4**, line broadenings due to dynamic interconversion (mutual exchange of the two diastereotopic protons H-15) were observed. The experimentally estimated free energies of this dynamic process were found to be $\Delta G^{\#}$ (at 343 K)=16.2 kcal/mol for **3** and $\Delta G^{\#}$ (at 368 K)=17.4 kcal/mol for **4**. Our first assumption was that the appropriate dynamic process may have involved combined *N*-inversion/ring inversion processes and the reaction

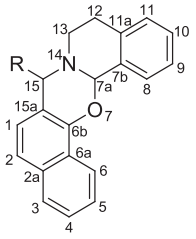
Table 5
Calculated energy differences for **14**, **16**, **18** and **20** in kcal/mol



14 R=*i*-Pr				**16** R=Ph				**18** R=1-Nph				**20** R=2-Nph			
trans (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)	
G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}	G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}	G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}	G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}
0.0	3.89	3.88	4.87	0.0	3.27	1.33	2.84	0.0[e]	4.78[f]	1.46[e]	2.55[f]	0.0	3.90	1.43	3.39

Corresponding to the following configurations: [a]15(*S*),14(*R*),7a(*R*), [b]15(*S*),14(*S*),7a(*R*), [c]15(*S*),14(*R*),7a(*S*) and [d]15(*S*),14(*S*),7a(*S*), [e]15*P* rotamer and [f]15*M* rotamer.

Table 6
Calculated energy differences for **15**, **17**, **19** and **21** in kcal/mol



15 R=*i*-Pr				**17** R=Ph				**19** R=1-Nph				**21** R=2-Nph			
trans (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)		*trans* (**B**)		*cis* (**C**)	
G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}	G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}	G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}	G^a_{t1}	G^b_{t2}	G^c_{c1}	G^d_{c2}
0.0	3.38	3.91	4.86	0.0	3.29	1.42	2.77	0.0[e]	4.85[f]	1.50[e]	2.53[f]	0.0	3.91	1.51	3.25
								4.89[f]	7.01[e]	2.51[f]	4.99[e]				

Corresponding to the following configurations: [a]15(*S*),14(*R*),7a(*R*), [b]15(*S*),14(*S*),7a(*R*), [c]15(*R*),14(*S*),7a(*R*), [d]15(*R*),14(*R*),7a(*R*), [e]15*P* rotamer and [f]15*M* rotamer.

coordinate of this dynamic process was searched for employing theoretical calculations. The transition state energies of **3** and **4** were computed at the MP2/6311G** level,[15] including solvent effects[16] of DMF. For this purpose the Self-Consistent Reaction Field with the Polarized Continuum Model using the Integral Equation Formalism (SCRF IEF-PCM) approach was used. The molecular modelling software package SYBYL 7.3[17] was used to display results and geometries. Theoretical calculations of solely the nitrogen inversion as the dynamic process gave a difference between the ground and transition states of only 8.2 kcal/mol for **3** and 8.1 kcal/mol for **4** (Fig. 2). These values are much too small to explain the dynamic behaviour observed experimentally.

The literature values of $\Delta G^{\#}$ for nitrogen inversion and/or ring inversion are in fact higher than our calculated values, e.g., for *cis*-decalin ($\Delta G^{\#}$ (at 255 K)=12.85 kcal/mol)[18] and azabicycles (quinolizidine derivatives) with a bridgehead nitrogen such as butaclamol ($\Delta G^{\#}$ (at 200 K)=9.6 kcal/mol),[19] or the synthetic alkaloid 14-(*R*)-hydroxymarcfortine A ($\Delta G^{\#}$ (at 228 K)=11.5 kcal/mol),[20] but they are still too small in comparison with the observed dynamic process.

In continuation of our investigations with the naphth[2,1-*e*][1,3]-oxazino[2,3-*a*]isoquinolines **14**–**21**, it was of special interest that the room temperature NOESY spectra showed not only the expected NOE signals, but also several others, probably exchange peaks between the different isomers in **16**–**21**. Especially H-7a and H-15 are involved in this potential dynamic process and this in all of the studied compounds. This led us to further questions: (i) Is there an exchange process between the diastereomers in **5**–**12** as well, (ii) is it the same dynamic process that occurs in **14**–**21** and (iii) what is the mechanism (reaction coordinate) of the exchange process between the diastereomers? As a start, the careful examination of the NOESY spectra of **5**–**12** revealed several exchange peaks. Thus, the diastereomers, though with very different ratios than those for **16**–**21** (see Table 2), should be included in the exchange process as observed for **14**–**21**.

For **16**, **17**, **20** and **21** the dynamic process (mutual exchange of the two isomers) at elevated temperatures could be studied in detail (cf. Table 8). The structures of the exchanging isomers were investigated by stereochemical analysis of two compounds as examples (vide supra). For **15**, which was found to be not a mixture of diastereomers, the NOESY signals were integrated and related. From a comparison of the volume integrals, with the assumption of a distance of 2.5 Å between two neighbouring aromatic protons, rough distances between other protons can be estimated. These were found to be 3.8 Å between H-7a and H-15, 2.3 Å between H-7a and the isopropyl proton H-1′, and 2.2 Å between H-15 and the pseudoequatorial H-13. This is in good agreement with quantum theoretically calculated distances for the trans isomer (3.6, 2.1 and 2.2 Å, respectively). Thus, the trans diastereomer is the preferred configuration for **15** as suggested previously (cf. Table 2). The same procedure was carried out for **17** at low temperature (193 K) to avoid rapid chemical exchange, which can distort the integration.

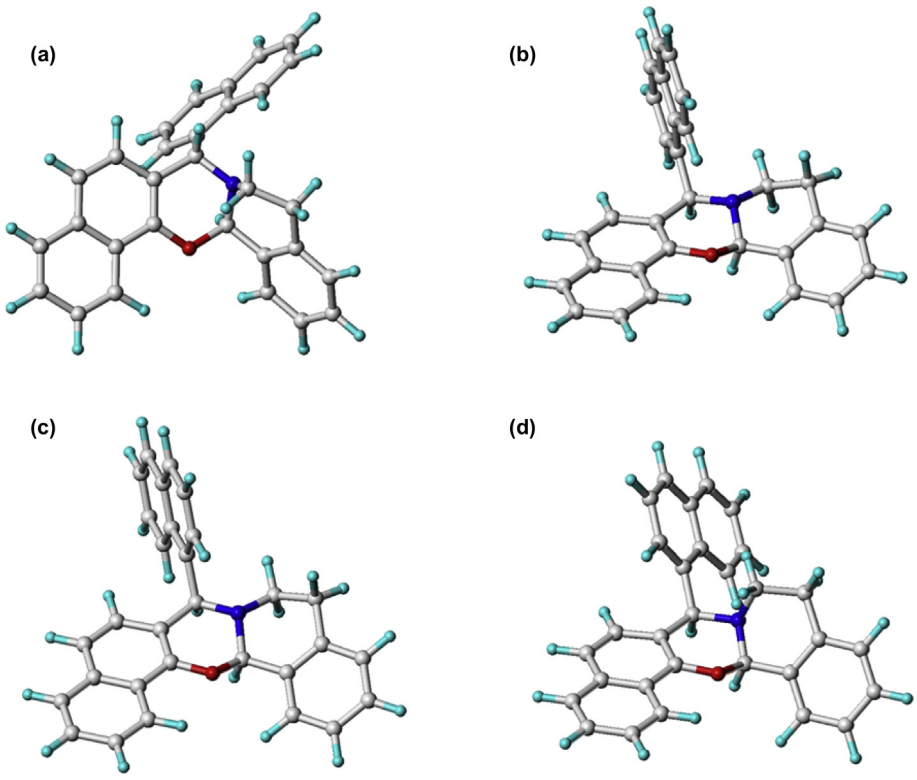


Fig. 1. Four isomers of **19** with lowest energies: (a) 15(*S*),14(*R*),7a(*R*),15(*P*)—0.00 kcal mol^{-1}; (b) 15(*R*),14(*S*),7a(*R*),15(*P*)—1.50 kcal mol^{-1}; (c) 15(*R*),14(*S*),7a(*R*),15(*M*)—2.51 kcal mol^{-1} and (d) 15(*R*),14(*R*),7a(*R*),15(*M*)—2.53 kcal mol^{-1}.

Table 7
Selected chemical shift differences (calculation vs experiment) between the two observed minor cis components and the major trans component of **19**

	Δδ H7a (ppm)		Δδ H15 (ppm)		Δδ C7a (ppm)		Δδ C15 (ppm)	
	Exp.	Calcd	Exp.	Calcd	Exp.	Calcd	Exp.	Calcd
15*R**,7a*R**,15*P**-**19**	−0.01	−0.13	−0.47	−0.32	7.5	6.6	9.2	8.5
15*R**,7a*R**,15*M**-**19**	0.16	0.12	0.37	0.84	6.7	5.7	−0.8	−2.4

Table 8
Experimental dynamic NMR measurement data for **16**, **17**, **20** and **21**[a]

Compound	Temperature (K)	$\Delta G^{\#}(1)$[b] (kcal/mol)	$\Delta G^{\#}(2)$[c] (kcal/mol)
16	318	17.8	16.8
17	368	20.1	19.1
20	328	17.6	16.7
21	378	20.2	19.5

[a] Solvent: $C_2D_2Cl_4$; mutual exchange of H-15, calculated by iteration with the DNMR module of TopSpin 3.0.
[b] Trans→cis.
[c] Cis→trans.

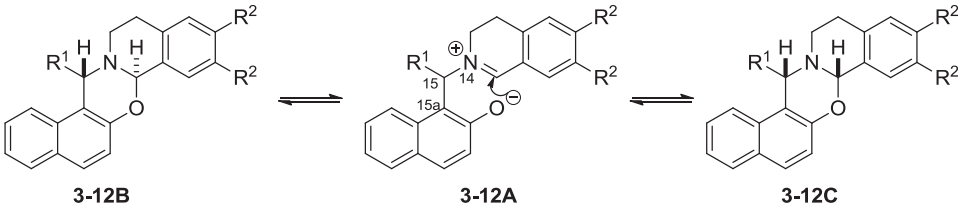
Here, a distance of 3.8 Å (theoretically calculated 3.6 Å) was found between H-7a and H-15 for the major component, and 3.1 Å (calcd 2.6 Å) for the minor component. This is again enough experimental evidence that the major component is the trans and the minor component is the cis isomer (cf. Table 2) and it is in agreement with the theoretical calculations.

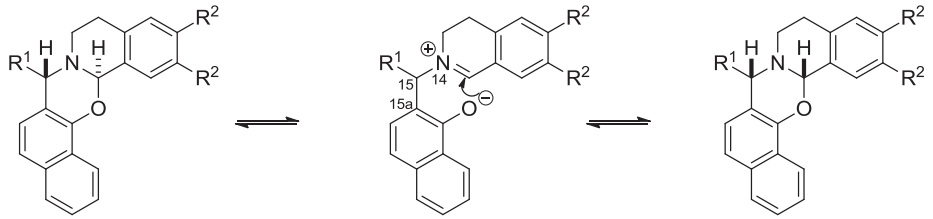
The investigation of the dynamic exchange process for **16**, **17**, **20** and **21** revealed good agreement with the free energy of activation of the already studied dynamic process observed for **3** and **4** (Table 8). Furthermore, the dynamic process ought to involve a configurational isomerization (change of the relative configuration of C-7a and C-15), which can only occur via an open-chain intermediate (**A**) according to Scheme 1.

From the comparison of the experimentally determined diastereomeric ratios for naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines (**5**–**12**: Table 1) and naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinolines (**14**–**21**: Table 2), it can be concluded that the free or hindered rotation around the σ bond C-15a–C-15 in form **A** is crucial for the diastereomeric composition (**B** and **C**) after equilibration during the dynamic process. It should also be noted that the ratios of **B** and **C** differ within the series **14**–**21**, depending on the steric bulkiness of the substituent at position 15 (Table 2). Less hindered rotation occurs with phenyl (**16** and **17**) or 2-naphthyl (**20** and **21**), resulting in the presence of around 20% of form **C**, while for the bulkier isopropyl (**14** and **15**), form **C** cannot be detected (Table 2).

The dynamic process for **17** was computed at the B3LYP/6-311G** level, including SCRF IEF-PCM (dichloromethane) geometry optimization, to find transition states between the ground states (**B** and **C**) and the intermediate chain form **A** (Fig. 2). The transition state search protocol was as follows: set the trans form (**17B** with the geometry G_{t1}), ring opening (breaking bond O–C15), set the CH=N bond in-plane and rotation around C15–N→TS[1] (19.28 kcal/mol); simultaneously, rotation around C15a–C15, C15–Ph and C15–N→metastable chain conformation (**17A**, 14.67 kcal/mol); back-rotation around C15a–C15 and C15–Ph→TS[2] (16.24 kcal/mol); ring closure→cis form (**17C**, 1.46 kcal/mol). The computed free energies of activation ($\Delta G^{\#}$) were found to be slightly lower than the experimental values: 19.3 versus 20.1 kcal/mol for trans→cis, and 17.8 versus 19.1 kcal/mol for cis→trans (Fig. 3).

Finally, it should be mentioned that the *p*-chlorophenyl (**9**) and *p*-methoxyphenyl (**11**) derivatives exhibited another dynamic process (a mutual exchange of the corresponding *o*-protons): a restricted rotation about the aryl–C-15 single bond. $\Delta G^{\#}$ for these





Scheme 1.

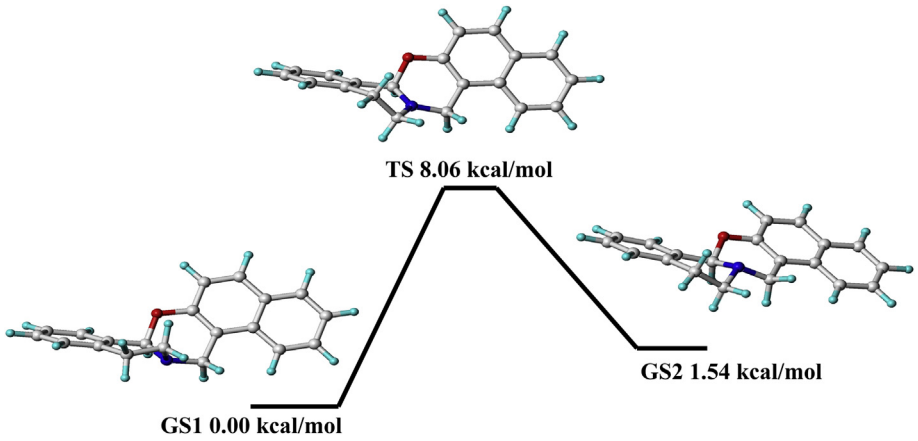


Fig. 2. Ground and transition states of the nitrogen inversion process of **4**.

processes was found to be unusually high for *o*- and *m*-unsubstituted phenyl rings (10.5 kcal/mol at 223 K for **9**, and 11.2 kcal/mol at 238 K for **11**, respectively, Table 9), but in the same range as for sterically hindered bridgehead *p*-chlorophenyl groups in bulky substituted tetrahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6(7*H*)-ones.[21]

3. Conclusions

A series of novel unsubstituted and substituted napth[1,2-*e*][1,3]-oxazino[2,3-*a*]isoquinolines (**3**–**12**) were prepared by the reaction of 1-aminomethyl-2-naphthol or substituted 1-aminobenzyl-2-naphthol derivatives with 3,4-dihydroisoquinolines. This process was extended to the reaction of 2-aminomethyl-1-naphthol analogues with 3,4-dihydroisoquinolines, leading to the annelation analogue, substituted napth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline derivatives (**14**–**21**). The stereochemistry was studied by NMR spectroscopy and accompanying molecular modelling. It was found that for all the compounds the most stable diastereomer displayed the *trans* (**B**) arrangement of H-15 and H-7a, which was also indicated by the DFT geometry optimization. Furthermore, for substituted napth-[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinolines, a dynamic process between the *trans* (**B**) and *cis* (**C**) forms was observed in solution. The latter process was explained with the aid of an isomerization protocol via an open-chain form (**A**). The energies of the transition states for this process were determined through dynamic NMR measurements, and those calculated by theoretical DFT computation were in good agreement.

4. Experimental section

Melting points were determined on a Hinotek-X4 micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser. Merck Kieselgel $60F_{254}$ plates were used for TLC.

The ^{1}H and ^{13}C NMR spectra were recorded in CD_2Cl_2 solutions in 5 mm tubes, at room temperature, on a Bruker Avance III spectrometer at 600.24 (^{1}H) and 150.93 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS (for ^{1}H) or the solvent (53.7 ppm for ^{13}C) as internal standard. All spectra (^{1}H, ^{13}C, gs-H, H–COSY, gs-HMQC, gs-HMBC and NOESY) were acquired and processed with the standard BRUKER[22] software. The PERCH program was used for iterational analysis of some higher-order spin systems.[23]

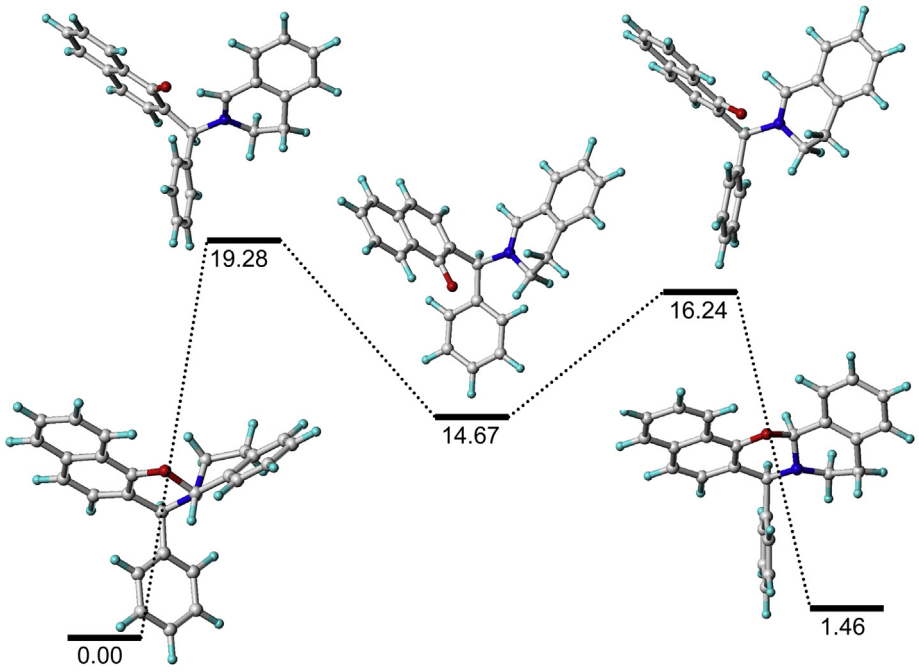


Fig. 3. Ground and transition states of the isomerization process of **17** via the chain form (**17A**).

Table 9
Experimental dynamic NMR data for **3**, **4**, **9** and **11**[a]

Compound	Solvent	Position	T_c (K)	$\Delta\nu_c$ (Hz)	k (Hz)	$\Delta G^{\#}$ (kcal/mol)
3	$C_2D_2Cl_4$	H-15	343	122	285	16.2
4	DMF-d_7	H-15	368	106	252	17.4
9	CD_2Cl_2	H-2′	223	641	1423	10.5
11	CD_2Cl_2	H-2′	238	617	1370	11.2

[a] Calculated using the coalescence method.

For dynamic NMR spectroscopy, the probe temperature was calibrated by means of a PT 100 thermocouple inserted into a dummy tube. The temperature measurements were estimated to be accurate to ±2 K. The chemical shift difference $\Delta\nu_c$ (in Hz) was determined by extrapolation from lower temperatures to T_c used to calculate k_c and the $\Delta G^{\#}$ by the Eyring equation at T_c. To calculate $\Delta G^{\#}$ for the dynamic process in **16**, **17**, **20** and **21**, the DNMR module in TopSpin 3.0[22] was used. Variable temperature measurements were made on a Bruker AVANCE spectrometer at 300.13 MHz or on a Bruker AVANCE III spectrometer at 600.24 MHz.

The following starting aminonaphthol derivatives were prepared by literature methods:

1-Aminomethyl-2-naphthol (**1a**),[24] 1-(1-aminoethyl)-2-naphthol (**1b**),[25] 1-aminobenzyl-2-naphthol (**1c**),[24] 1-amino-(4-chlorophenyl) methyl-2-naphthol (**1d**),[22] 1-amino-(4-methoxyphenyl)methyl-2-naphthol (**1e**),[24] 2-amino-(isopropyl)methyl-1-naphthol (**13a**),[26] 2-aminobenzyl-1-naphthol (**13b**),[11] 2-amino-(naphth-1-yl)methyl-1-naphthol (**13c**)[27] and 2-amino-(naphth-2-yl)methyl-1-naphthol (**13d**).[27]

4.1. General procedure for the synthesis of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines and naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinolines

The mixture of the appropriate aminonaphtholhydrochloride (0.44 mmol), 6,7-dimethoxy-3,4-dihydroisoquinoline (**2a**, 0.4 mmol) or 3,4-dihydroisoquinoline (**2b**, 0.4 mmol) and Et_3N (60 mg, 0.6 mmol) in 1,4-dioxane (5 mL) was placed in a 10 mL reaction vial and heated in a CEM LabMate microwave reactor under the microwave conditions given depicted in Tables 1 and 2. The solvent was then evaporated off and the crude product was crystallized with cold EtOH (8–12 mL), filtered off and recrystallized from EtOH (11–15 mL).

4.2. 9,10-Dimethoxynaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (3)

Mp: 191–194 °C (lit.:[10] 186–187 °C). ^{1}H NMR (600 MHz): δ 7.78 (dt, J=8.1, 1.2 Hz, 1H, H-4), 7.67 (dq, J=8.4, 0.9 Hz, 1H, H-1), 7.65 (d, J=8.8 Hz, 1H, H-5), 7.50 (ddd, J=8.3, 6.9, 1.2 Hz, 1H, H-2), 7.36 (ddd, J=8.1, 6.9, 0.9 Hz, 1H, H-3), 7.03 (d, J=8.8 Hz, 1H, H-6), 6.93 (s, 1H, H-8), 6.69 (s, 1H, H-11), 5.70 (s, 1H, H-7a), 4.73 (d, J=15.4 Hz, 1H, H-15), 4.26 (d, J=15.5 Hz, 1H, H-15), 3.86 (s, 3H, 9-OMe), 3.84 (s, 3H, 10-OMe), 3.32 (m, 1H, H-13), 3.03 (m, 1H, H-12), 2.85 (m, 1H, H-13), 2.81 (m, 1H, H-12); ^{13}C NMR (150 MHz): δ 151.8 (C-6a), 149.8 (C-10), 147.9 (C-9), 131.8 (C-15b), 129.1 (C-4a), 128.7 (C-4), 128.2 (C-5), 127.7 (C-11a), 126.7 (C-2), 125.4 (C-7b), 123.6 (C-3), 121.4 (C-1), 118.8 (C-6), 111.5 (C-15a), 111.4 (C-11), 111.3 (C-8), 87.1 (C-7a), 56.2 (9-OMe), 56.0 (10-OMe), 51.5 (C-15), 45.4 (C-13), 28.9 (C-12). Anal. Calcd for $C_{22}H_{21}NO_3$ (347.41): C, 76.06; H, 6.09; N, 4.03. Found: C, 76.15; H, 6.02; N, 4.07.

4.3. Naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (4)

Mp: 176–178 °C. ^{1}H NMR (600 MHz): δ 7.77 (dt, J=8.1, 1.1 Hz, 1H, H-4), 7.67 (dq, J=8.4, 1.1 Hz, 1H, H-1), 7.64 (d, J=8.8 Hz, 1H, H-5), 7.50 (ddd, J=8.3, 6.9, 1.2 Hz, 1H, H-2), 7.43 (dd, J=7.7, 1.2 Hz, 1H, H-8), 7.36 (ddd, J=8.1, 6.9, 1.2 Hz, 1H, H-3), 7.32 (td, J=7.6, 1.3 Hz, 1H, H-10), 7.28 (tt, J=7.6, 0.7 Hz, 1H, H-9), 7.21 (br d, J=7.7 Hz, 1H, H-11), 7.02 (d, J=8.8 Hz, 1H, H-6), 5.77 (s, 1H, H-7a), 4.74 (d, J=14.7 Hz, 1H, H-15), 4.27 (d, J=14.7 Hz, 1H, H-15), 3.35 (m, 1H, H-13), 3.12 (m, 1H, H-12), 2.88 (m, 2H, H-12 and H-13); ^{13}C NMR (150 MHz): δ 151.8 (C-6a), 135.4 (C-11a), 133.4 (C-7b), 131.8 (C-15b), 129.2 (C-4a), 128.9 (C-10), 128.9 (C-11), 128.8 (C-4), 128.5 (C-8), 128.2 (C-5), 126.7 (C-2), 126.3 (C-9), 123.6 (C-3), 121.4 (C-1), 118.9 (C-6), 111.5 (C-15a), 87.1

(C-7a), 51.4 (C-15), 45.3 (C-13), 29.3 (C-12). Anal. Calcd for $C_{20}H_{17}NO$ (287.36): C, 83.59; H, 5.96; N, 4.87. Found: C, 83.65; H, 5.91; N, 4.81.

4.4. (7a*R**,15*S**)-9,10-Dimethoxy-15-methylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (5B)

Mp: 179–181 °C. ^{1}H NMR (600 MHz): δ 7.78 (d, J=8.5 Hz, 1H, H-1), 7.75 (d, J=8.0 Hz, 1H, H-4), 7.62 (d, J=8.9 Hz, 1H, H-5), 7.49 (br t, J=7.9 Hz, 1H, H-2), 7.32 (t, J=7.8 Hz, 1H, H-3), 6.98 (d, J=8.8 Hz, 1H, H-6), 6.95 (s, 1H, H-8), 6.68 (s, 1H, H-11), 5.99 (s, 1H, H-7a), 4.42 (q, J=6.9 Hz, 1H, H-15), 3.88 (s, 3H, 9-OMe), 3.84 (s, 3H, 10-OMe), 3.16 (from PERCH, ddd, J=−11.3, 12.4, 4.1, 1H, H-13ax), 3.08 (from PERCH, ddd, J=−16.1, 12.4, 6.4, 1H, H-12ax), 2.82 (from PERCH, ddd, J=−11.3, 6.4, 1.4, 1H, H-13eq), 2.70 (from PERCH, ddd, J=−16.1, 4.1, 1.4, 1H, H-12eq), 1.73 (d, J=7.0 Hz, 3H, Me); ^{13}C NMR (150 MHz): δ 150.8 (C-6a), 150.0 (C-10), 147.9 (C-9), 132.0 (C-15b), 129.4 (C-4a), 128.9 (C-4), 128.4 (C-5), 127.9 (C-11a), 126.6 (C-2), 125.5 (C-7b), 123.2 (C-3), 122.0 (C-1), 118.9 (C-6), 115.8 (C-15a), 112.0 (C-8), 111.6 (C-11), 82.0 (C-7a), 56.2 (9-OMe), 56.1 (10-OMe), 54.8 (C-15), 45.5 (C-13), 29.1 (C-12), 22.9 (Me). Anal. Calcd for $C_{23}H_{23}NO_3$ (361.43): C, 76.43; H, 6.41; N, 3.88. Found: C, 76.37; H, 6.45; N, 3.92.

4.5. (7a*R**,15*R**)-9,10-Dimethoxy-15-methylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (5C)

^{1}H NMR (600 MHz): δ 5.99 (s, H-7a), 4.27 (from EXSY, H-15).

4.6. (7a*R**,15*S**)-15-Methylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (6B)

Mp: 178–180 °C. ^{1}H NMR (600 MHz): δ 7.70 (d, J=8.5 Hz, 1H, H-1), 7.66 (d, J=8.1 Hz, 1H, H-4), 7.54 (d, J=8.9 Hz, 1H, H-5), 7.40 (dd, J=8.4, 6.9 Hz, 1H, H-2), 7.36 (dd, J=7.4, 1.5 Hz, 1H, H-8), 7.24 (br t, J=7.5 Hz, 1H, H-3), 7.24 (td, J=7.5, 1.4 Hz, 1H, H-10), 7.20 (t, J=7.3 Hz, br, 1H, H-9), 7.12 (d, J=7.4 Hz, 1H, H-11), 6.88 (d, J=8.9 Hz, 1H, H-6), 5.98 (s, 1H, H-7a), 4.34 (q, J=6.9 Hz, 1H, H-15), 3.09 (m, 2H, H-12 and H-13), 2.74 (m, 2H, H-12 and H-13), 1.65 (d, J=6.9 Hz, 3H, Me); ^{13}C NMR (150 MHz): δ 150.7 (C-6a), 135.6 (C-11a), 133.5 (C-7b), 132.0 (C-15b), 129.4 (C-4a), 129.1 (C-8), 129.1 (C-10), 129.0 (2C, C-4 and C-11), 128.5 (C-5), 126.6 (C-2), 126.3 (C-9), 123.3 (C-3), 122.0 (C-1), 119.0 (C-6), 115.9 (C-15a), 82.1 (C-7a), 54.8 (C-15), 45.4 (C-13), 29.4 (C-12), 22.9 (Me). Anal. Calcd for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.75; H, 6.31; N, 4.67.

4.7. (7a*R**,15*R**)-15-Methylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (6C)

^{1}H NMR (600 MHz): δ 5.11 (s, H-7a), 4.25 (from EXSY, H-15).

4.8. (7a*R**,15*S**)-9,10-Dimethoxy-15-phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (7B)

Mp: 182–184 °C (Lit.:[10] 155–156 °C). ^{1}H NMR (600 MHz): δ 7.78 (d, J=7.5 Hz, 1H, H-4), 7.75 (d, J=8.9 Hz, 1H, H-5), 7.40 (d, J=8.0 Hz, 1H, H-1), 7.33–7.22 (m, 7H, H-2, H-3, H-2′, H-3′, and H-4′), 7.09 (d, J=8.9 Hz, 1H, H-6), 6.78 (s, 1H, H-8), 6.67 (s, 1H, H-11), 5.55 (s, 1H, H-7a), 5.44 (s, 1H, H-15), 3.81 (s, 3H, 10-OMe), 3.78 (s, 3H, 9-OMe), 3.28 (m, 1H, H-13ax), 3.18 (ddd, J=15.7, 12.3, 6.2 Hz, 1H, H-12ax), 3.09 (dd, J=10.8, 6.2 Hz, 1H, H-13eq), 2.76 (dd, J=15.8, 3.5 Hz, 1H, H-12eq); ^{13}C NMR (150 MHz): δ 152.3 (C-6a), 149.8 (C-10), 147.8 (C-9), 142.9 (C-1′), 132.6 (C-15b), 129.6 (C-2′), 129.3 (C-5), 129.2 (C-4a), 128.8 (C-4), 128.4 (C-3′), 127.6 (2C, C-11a and C-4′), 126.7 (C-2), 125.2 (C-7b), 123.4 (C-3), 122.8 (C-1), 118.9 (C-6), 111.7 (C-8), 111.5 (C-11), 111.1 (C-15a), 82.3 (C-7a), 62.9 (C-15), 56.1 (9-OMe), 56.0 (10-OMe), 45.6 (C-13), 29.1 (C-12). Anal. Calcd for $C_{28}H_{25}NO_3$ (423.50): C, 79.41; H, 5.95; N, 3.31. Found: C, 79.49; H, 5.91; N, 3.37.

4.9. (7a*R**,15*R**)-9,10-Dimethoxy-15-phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (7C)

^{1}H NMR (600 MHz): δ 5.44 (from EXSY, H-7a), 5.23 (s, H-15).

4.10. (7a*R**,15*S**)-15-Phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (8B)

Mp: 231–234 °C. ^{1}H NMR (600 MHz): δ 7.78 (d, J=7.7 Hz, 1H, H-4), 7.75 (d, J=8.9 Hz, 1H, H-5), 7.41 (d, J=8.9 Hz, 1H, H-1), 7.34–7.18 (m, 10H, H-2, H-3, H-8, H-10, H-11, H-2′, H-3′ and H-4′), 7.20 (t, J=7.9 Hz, 1H, H-9), 7.08 (d, J=8.9 Hz, 1H, H-6), 5.63 (s, 1H, H-7a), 5.45 (s, 1H, H-15), 3.29 (m, 2H, H-12ax and H-13ax), 3.11 (m, 1H, H-13eq), 2.85 (m, 1H, H-12eq); ^{13}C NMR (150 MHz): δ 152.2 (C-6a), 142.8 (C-1′), 135.4 (C-11a), 133.3 (C-7b), 132.6 (C-15b), 129.6 (C-2′), 129.3 (C-5), 129.2 (C-4a), 129.0, 128.9, 128.9 (C-8, C-10 and C-11), 128.8 (C-4), 128.4 (C-3′), 127.7 (C-4′), 126.7 (C-2), 126.2 (C-9), 123.4 (C-3), 122.9 (C-1), 119.0 (C-6), 111.2 (C-15a), 82.4 (C-7a), 62.9 (C-15), 45.6 (C-13), 29.5 (C-12). Anal. Calcd for $C_{26}H_{21}NO$ (363.45): C, 85.92; H, 5.82; N, 3.85. Found: C, 85.88; H, 5.87; N, 3.81.

4.11. (7a*R**,15*S**)-15-Phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (8C)

^{1}H NMR (600 MHz): δ 5.53 (s, H-7a), 5.25 (s, H-15).

4.12. (7a*R**,15*S**)-9,10-Dimethoxy-15-(4-chlorophenyl)naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (9B)

Mp: 154–156 °C. ^{1}H NMR (600 MHz): δ 7.79 (d, J=7.8 Hz, 1H, H-4), 7.76 (d, J=8.9 Hz, 1H, H-5), 7.37 (d, J=8.0 Hz, 1H, H-1), 7.33 (br t, J=7.5 Hz, 1H, H-2), 7.30 (br t, J=7.4 Hz, 1H, H-3), 7.25 (m, 4H, H-2′ and H-3′), 7.08 (d, J=8.9 Hz, 1H, H-6), 6.77 (s, 1H, H-8), 6.67 (s, 1H, H-11), 5.49 (s, 1H, H-7a), 5.40 (s, 1H, H-15), 3.82 (s, 3H, 10-OMe), 3.79 (s, 3H, 9-OMe), 3.27 (m, 1H, H-13ax), 3.18 (ddd, J=15.7, 12.3, 6.1 Hz, 1H, H-12ax), 3.08 (dd, J=10.8, 6.1 Hz, 1H, H-13eq), 2.76 (dd, J=15.8, 3.4 Hz, 1H, H-12eq); ^{13}C NMR (150 MHz): δ 152.3 (C-6a), 149.9 (C-10), 147.8 (C-9), 141.5 (C-1′), 133.3 (C-4′), 132.5 (C-15b), 131.0 (C-2′), 129.6 (C-5), 129.2 (C-4a), 128.8 (C-4), 128.5 (C-3′), 127.6 (C-11a), 126.9 (C-2), 125.1 (C-7b), 123.5 (C-3), 122.7 (C-1), 119.0 (C-6), 111.6 (C-8), 111.5 (C-11), 110.6 (C-15a), 82.3 (C-7a), 62.1 (C-15), 56.1 (9-OMe), 56.0 (10-OMe), 45.5 (C-13), 29.1 (C-12). Anal. Calcd for $C_{28}H_{24}ClNO_3$ (457.95): C, 73.44; H, 5.28; N, 3.06. Found: C, 73.52; H, 5.33; N, 3.08.

4.13. (7a*R**,15*R**)-9,10-Dimethoxy-15-(4-chlorophenyl)naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (9C)

^{1}H NMR (600 MHz): δ 5.39 (from EXSY, H-7a), 5.22 (s, H-15).

4.14. (7a*R**,15*S**)-15-(4-Chlorophenyl)naphth[1,2-*e*][1,3]oxazino[2,3-a]isoquinoline (10B)

Mp: 186–189 °C. ^{1}H NMR (600 MHz): δ 7.79 (d, J=8.0 Hz, 1H, H-4), 7.75 (d, J=8.9 Hz, 1H, H-5), 7.36 (m, 1H, H-1), 7.32 (m, 2H, H-2 and H-3), 7.30–7.22 (m, 7H, H-8, H-10, H-11, H-2′ and H-3′), 7.21 (m, 1H, H-9), 7.07 (d, J=8.9 Hz, 1H, H-6), 5.57 (s, 1H, H-7a), 5.41 (s, 1H, H-15), 3.28 (m, 2H, H-12 and H-13), 3.10 (m, 1H, H-13), 2.85 (m, 1H, H-12); ^{13}C NMR (150 MHz): δ 152.2 (C-6a), 141.4 (C-1′), 135.3 (C-11a), 133.4 (C-7b), 133.1 (C-4′), 132.5 (C-15b), 131.1 (C-2′), 129.6 (C-5), 129.2 (C-4a), 129.1, 129.0, 128.9 (C-8, C-10 and C-11), 128.8 (C-4), 128.5 (C-3′), 126.9 (C-2), 126.3 (C-9), 123.5 (C-3), 122.7 (C-1), 119.0 (C-6), 110.7 (C-15a), 82.3 (C-7a), 62.1 (C-15), 45.5 (C-13), 29.5

(C-12). Anal. Calcd for $C_{26}H_{20}ClNO$ (397.90): C, 78.48; H, 5.07; N, 3.52. Found: C, 78.55; H, 5.13; N, 3.47.

4.15. (7a*R**,15*R**)-15-(4-Chlorophenyl)naphth[1,2-*e*][1,3]oxazino[2,3-a]isoquinoline (10C)

^{1}H NMR (600 MHz): δ 5.23 (s, H-15).

4.16. (7a*R**,15*S**)-9,10-Dimethoxy-15-(4-methoxyphenyl) naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (11B)

Mp: 137–140 °C (Lit.:[10] 182–184 °C). ^{1}H NMR (600 MHz): δ 7.78 (dd, *J*=8.1, 1.3 Hz, 1H, H-4), 7.73 (d, *J*=8.9 Hz, 1H, H-5), 7.42 (d, *J*=8.2 Hz, 1H, H-1), 7.32 (ddd, *J*=8.3, 6.8, 1.4 Hz, 1H, H-2), 7.28 (dd, *J*=8.0, 6.8 Hz, 1H, H-3), 7.20 (br, 2H, H-2′), 7.08 (d, *J*=8.9 Hz, 1H, H-6), 6.80 (d, *J*=8.8 Hz, 2H, H-3′), 6.78 (s, 1H, H-8), 6.67 (s, 1H, H-11), 5.56 (s, 1H, H-7a), 5.38 (s, 1H, H-15), 3.81 (s, 3H, 10-OMe), 3.79 (s, 3H, 9-OMe), 3.73 (s, 3H, 4′-OMe), 3.25 (from PERCH, ddd, *J*=−11.3, 12.5, 4.1 Hz, 1H, H-13ax), 3.16 (from PERCH, ddd, *J*=−16.1, 12.5, 6.4 Hz, 1H, H-12ax), 3.07 (from PERCH, ddd, *J*=−11.3, 6.4, 1.3 Hz, 1H, H-13eq), 2.75 (from PERCH, ddd, *J*=−16.1, 4.1, 1.3 Hz, 1H, H-12eq); ^{13}C NMR (150 MHz): δ 159.2 (C-4′), 152.2 (C-6a), 149.8 (C-10), 147.8 (C-9), 135.1 (C-1′), 132.6 (C-15b), 130.6 (C-2′), 129.2 (C-4), 129.2 (C-4a), 128.7 (C-5), 127.7 (C-11a), 126.7 (C-2), 125.3 (C-7b), 123.3 (C-3), 122.9 (C-1), 118.9 (C-6), 113.7 (C-3′), 111.7 (C-8), 111.5 (C-11), 111.4 (C-15a), 82.2 (C-7a), 62.3 (C-15), 56.1, 56.0 (9- and 10-OMe), 55.4 (4′OMe), 45.4 (C-13), 29.1 (C-12). Anal. Calcd for $C_{29}H_{27}NO_4$ (453.53): C, 76.80; H, 6.00; N, 3.09. Found: C, 76.87; H, 5.92; N, 3.13.

4.17. (7a*R**,15*R**)-9,10-Dimethoxy-15-(4-methoxyphenyl) naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (11C)

^{1}H NMR (600 MHz): δ 5.44 (s, H-7a), 5.19 (s, H-15).

4.18. (7a*R**,15*S**)-15-(4-Methoxyphenyl)naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (12B)

Mp: 169–172 °C. ^{1}H NMR (600 MHz): δ 7.78 (d, *J*=7.7 Hz, 1H, H-4), 7.73 (d, *J*=8.9 Hz, 1H, H-5), 7.42 (d, *J*=8.2 Hz, 1H, H-1), 7.32 (br t, *J*=7.6 Hz, 1H, H-2), 7.28 (m, 3H, H-3, H-8 and H-10), 7.20 (m, 4H, H-9, H-11 and H-2′), 7.06 (d, *J*=8.9 Hz, 1H, H-6), 6.79 (d, *J*=8.7 Hz, 2H, H-3′), 5.63 (s, 1H, H-7a), 5.39 (s, 1H, H-15), 3.73 (s, 3H, OMe), 3.28 (m, 1H, H-13), 3.24 (m, 1H, H-12), 3.08 (m, 1H, H-13), 2.85 (m, 1H, H-12); ^{13}C NMR (150 MHz): δ 159.2 (C-4′), 152.1 (C-6a), 135.4 (C-11a), 135.0 (C-1′), 133.3 (C-7b), 132.6 (C-15b), 130.7 (C-2′), 129.2 (C-4), 129.2 (C-4a), 129.0, 128.9, 128.8 (C-8, C-10 and C-11), 128.8 (C-5), 126.7 (C-2), 126.2 (C-9), 123.4 (C-3), 122.9 (C-1), 118.9 (C-6), 113.7 (C-3′), 111.5 (C-15a), 82.3 (C-7a), 62.3 (C-15), 55.4 (OMe), 45.4 (C-13), 29.5 (C-12). Anal. Calcd for $C_{27}H_{23}NO_2$ (393.48): C, 82.42; H, 5.89; N, 3.56. Found: C, 82.57; H, 5.81; N, 3.59.

4.19. (7a*R**,15*R**)-15-(4-Methoxyphenyl)naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline (12C)

^{1}H NMR (600 MHz): δ 5.52 (s, H-7a), 5.21 (s, H-15).

4.20. (7a*R**,15*S**)-9,10-Dimethoxy-15-isopropylnaphth[2,1-*e*] [1,3]oxazino[2,3-*a*]isoquinoline (14B)

Mp: 134–136 °C. ^{1}H NMR (600 MHz): δ 8.11 (d, *J*=8.2 Hz, 1H, H-6), 7.75 (d, *J*=8.1 Hz, 1H, H-3), 7.43 (br t, *J*=7.6 Hz, 1H, H-4), 7.40 (br t, *J*=7.7 Hz, 1H, H-5), 7.35 (d, *J*=8.5 Hz, 1H, H-2), 7.24 (d, *J*=8.5 Hz, 1H, H-1), 7.04 (s, 1H, H-8), 6.70 (s, 1H, H-11), 5.86 (s, 1H, H-7a), 3.43 (d, *J*=7.4 Hz, 1H, H-15), 3.90 (s, 3H, 9-OMe), 3.85 (s, 3H, 10-OMe), 3.13 (m, 1H, H-13), 3.13 (m, 1H, H-12), 2.72 (m, 2H, H-12, H-13), 2.20 (m, 1H, H-1′), 1.14 (d, *J*=6.7 Hz, 3H, H-2′), 1.05 (d, *J*=6.7 Hz, 3H, H-2′); ^{13}C NMR (150 MHz):δ 149.8 (C-10), 149.4 (C-6b), 147.9 (C-9), 133.5 (C-2a), 128.3 (C-11a), 127.5 (C-3), 127.1 (C-1), 126.0 (C-4), 125.7 (C-7b), 125.2 (C-5), 125.0 (C-6a), 121.9 (C-6), 118.6 (C-2), 116.2 (C-15a), 112.2 (C-8), 111.3 (C-11), 84.5 (C-7a), 67.8 (C-15), 56.3 (9-OMe), 56.0 (10-OMe), 46.2 (C-13), 34.4 (C-1′), 29.2 (C-12), 20.2 (C-2′), 19.3 (C-2′). Anal. Calcd for $C_{25}H_{27}NO_3$ (389.49): C, 77.09; H, 6.99; N, 3.60. Found: C, 77.17; H, 6.91; N, 3.62.

4.21. (7a*R**,15*S**)-15-Isopropylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*] isoquinoline (15B)

Mp: 119–120 °C. ^{1}H NMR (600 MHz): δ 8.08 (d, *J*=8.2 Hz, 1H, H-6), 7.75 (d, *J*=8.0 Hz, 1H, H-3), 7.54 (d, *J*=6.6 Hz, 1H, H-8), 7.42 (br t, *J*=7.6 Hz, 1H, H-4), 7.35 (m, 4H, H-2, H-5, H-9, H-10), 7.25 (d, *J*=8.5 Hz, 1H, H-1), 7.22 (d, *J*=6.9 Hz, 1H, H-11), 5.93 (s, 1H, H-7a), 3.43 (d, *J*=7.4 Hz, 1H, H-15), 3.19 (m, 2H, H-12, H-13), 2.75 (m, 2H, H-12, H-13), 2.20 (m, 1H, H-1′), 1.14 (d, *J*=6.7 Hz, 3H, H-2′), 1.06 (d, *J*=6.7 Hz, 3H, H-2′); ^{13}C NMR (150 MHz): δ 128.9 (C-10 or C-11), 128.8 (C-10 or C-11), 149.4 (C-6b), 136.0 (C-11a), 133.7 (C-7b), 133.5 (C-2a), 129.4 (C-8), 127.5 (C-3), 127.2 (C-1), 126.3 (C-9), 126.1 (C-4), 125.2 (C-5), 125.0 (C-6a), 121.9 (C-6), 118.7 (C-2), 116.2 (C-15a), 84.5 (C-7a), 67.8 (C-15), 46.1 (C-13), 34.4 (C-1′), 29.6 (C-12), 20.2 (C-2′), 19.3 (C-2′). Anal. Calcd for $C_{23}H_{23}NO$ (329.43): C, 83.85; H, 7.04; N, 4.25. Found: C, 83.67; H, 7.09; N, 4.27.

4.22. (7a*R**,15*S**)-9,10-Dimethoxy-15-phenylnaphth[2,1-*e*][1,3] oxazino[2,3-*a*]isoquinoline (16B)

Mp: 138–140 °C. ^{1}H NMR (600 MHz): δ 8.13 (d, *J*=8.2 Hz, 1H, H-6), 7.79 (d, *J*=8.0 Hz, 1H, H-3), 7.47 (br t, *J*=7.8 Hz, 1H, H-5), 7.43 (br t, *J*=7.7 Hz, 1H, H-4), 7.39 (d, *J*=8.4 Hz, 1H, H-2), 7.30 (m, 5H, H-2′, H-3′, H-4′), 7.13 (d, *J*=8.4 Hz, 1H, H-1), 6.89 (s, 1H, H-8), 6.68 (s, 1H, H-11), 5.61 (s, 1H, H-7a), 5.05 (s, 1H, H-15), 3.82 (s, 3H, 10-OMe), 3.81 (s, 3H, 9-OMe), 3.30 (ddd, *J*=12.4, 11.3, 3.3 Hz, 1H, H-13), 3.17 (ddd, *J*=14.8, 12.3, 6.1 Hz, 1H, H-12), 3.09 (dd, *J*=12.4, 6.2 Hz, 1H, H-13), 2.76 (dd, *J*=14.7, 3.2 Hz, 1H, H-12); ^{13}C NMR (150 MHz):δ 150.0 (C-10), 149.7 (C-6b), 147.9 (C-9), 143.8 (C-1′), 134.0 (C-2a), 129.5 (C-2′), 128.4 (C-3′), 127.9 (C-11a), 127.8 (C-3), 127.8 (C-4′), 127.3 (C-1), 126.5 (C-5), 125.5 (C-7b), 125.4 (C-4), 125.1 (C-6a), 122.0 (C-6), 119.3 (C-2), 113.3 (C-15a), 112.1 (C-8), 111.6 (C-11), 83.0 (C-7a), 65.2 (C-15), 56.2 (9-OMe), 56.1 (10-OMe), 45.7 (C-13), 29.3 (C-12). Anal. Calcd for $C_{28}H_{25}NO_3$ (423.50): C, 79.41; H, 5.95; N, 3.31. Found: C, 79.37; H, 5.92; N, 3.36.

4.23. (7a*R**,15*R**)-9,10-Dimethoxy-15-phenylnaphth[2,1-*e*][1,3] oxazino[2,3-*a*]isoquinoline (16C)

^{1}H NMR (600 MHz): δ 8.29 (br, 1H, H-6), 7.73 (br, 1H, H-3), 7.52 (m, 1H, H-4), 7.47 (m, 1H, H-5), 7.30 (m, 7H, H-2, H-8, H-2′, H-3′, H-4′), 6.76 (d, *J*=8.4 Hz, 1H, H-1), 6.64 (br, 1H, H-11), 5.62 (s, 1H, H-7a), 4.90 (s, 1H, H-15), 3.94 (s, 3H, 9-OMe), 3.82 (s, 3H, 10-OMe), 3.01 (m, 1H, H-13), 2.93 (m, 1H, H-12), 2.63 (m, 1H, H-13), 2.57 (m, 1H, H-12); ^{13}C NMR (150 MHz): δ 150.0 (C-10), 149.0 (C-6b), 148.3 (C-9), 142.7 (C-1′), 133.4 (C-2a), 129.9 (C-2′), 128.9 (C-3′), 128.2 (C-4′), 127.7 (C-11a), 119.7 (C-15a), 127.8 (C-3), 126.2 (C-1), 125.9 (C-5), 125.9 (C-7b), 125.9 (C-4), 125.1 (C-6a), 121.7 (C-6), 120.5 (C-2), 111.2 (C-11), 110.4 (C-8), 89.4 (C-7a), 68.7 (C-15), 56.4 (9-OMe), 56.1 (10-OMe), 46.3 (C-13), 28.6 (C-12).

4.24. (7a*R**,15*S**)-15-Phenylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*] isoquinoline (17B)

Mp: 151–153 °C. ^{1}H NMR (600 MHz): δ 8.10 (d, *J*=8.3 Hz, 1H, H-6), 7.80 (d, *J*=8.1 Hz, 1H, H-3), 7.47 (br t, *J*=7.7 Hz, 1H, H-4), 7.40 (m, 4H, H-2, H-5, H-8, H-9), 7.31 (m, 5H, H-10, H-2′, H-3′), 7.25

(m, 1H, H-4′), 7.21 (d, *J*=7.6 Hz, 1H, H-11), 7.14 (d, *J*=8.3 Hz, 1H, H-1), 5.68 (s, 1H, H-7a), 5.06 (s, 1H, H-15), 3.34 (m, 1H, H-13), 3.25 (m, 1H, H-12), 3.11 (m, 1H, H-13), 2.87 (m, 1H, H-12); ^{13}C NMR (150 MHz): δ 149.6 (C-6b), 142.5 (C-1′), 135.6 (C-11a), 134.0 (C-2a), 133.4 (C-7b), 129.5 (C-2′), 129.1, 129.0, 128.9 (C-8, C-10, C-11), 128.4 (C-3′), 127.7 (C-9), 127.6 (C-3), 127.2 (C-1), 126.4 (C-4), 126.4 (C-4′), 125.4 (C-5), 125.1 (C-6a), 121.9 (C-6), 119.4 (C-2), 113.3 (C-15a), 83.0 (C-7a), 65.1 (C-15), 45.5 (C-13), 29.6 (C-12). Anal. Calcd for $C_{26}H_{21}NO$ (363.45): C, 85.92; H, 5.82; N, 3.85. Found: C, 85.96; H, 5.81; N, 3.82.

4.25. (7a*R**,15*R**)-15-Phenylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*] isoquinoline (17C)

^{1}H NMR (600 MHz): δ 8.32 (d, *J*=8.2 Hz, 1H, H-6), 7.84 (d, *J*=7.6 Hz, 1H, H-8), 7.74 (d, *J*=7.9 Hz, 1H, H-3), 7.52 (br t, *J*=7.8 Hz, 1H, H-5), 7.47 (m, 1H, H-4), 7.38 (m, 1H, H-9), 7.31 (m, 5H, H-10, H-2′, H-3′), 7.26 (m, 2H, H-2, H-4′), 7.17 (d, *J*=7.5 Hz, 1H, H-11), 6.77 (d, *J*=8.6 Hz, 1H, H-1), 5.70 (s, 1H, H-7a), 4.91 (s, 1H, H-15), 3.02 (m, 1H, H-13), 3.02 (m, 1H, H-12), 2.66 (m, 1H, H-13), 2.66 (m, 1H, H-12); ^{13}C NMR (150 MHz): δ 148.9 (C-6b), 143.6 (C-1′), 135.9 (C-11a), 133.8 (C-7b), 133.3 (C-2a), 129.9 (C-2′), 128.8 (C-10), 128.6 (C-11), 128.4 (C-3′), 128.1 (C-9), 127.6 (C-3), 127.4 (C-8), 126.5 (C-4), 126.5 (C-4′), 126.1 (C-1), 125.8 (C-5), 125.1 (C-6a), 121.8 (C-6), 120.5 (C-2), 119.6 (C-15a), 89.4 (C-7a), 68.7 (C-15), 46.1 (C-13), 28.9 (C-12).

4.26. (7a*R**,15*S**,15*P**)-9,10-Dimethoxy-15-(naphth-1-yl) naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (18B)

Mp: 194–196 °C. ^{1}H NMR (600 MHz): δ 8.33 (d, *J*=8.5 Hz, 1H, H-8′), 8.17 (d, *J*=8.2 Hz, 1H, H-6), 7.89 (d, *J*=7.9 Hz, 1H, H-5′), 7.82 (d, *J*=8.0 Hz, 1H, H-3), 7.77 (d, *J*=8.2 Hz, 1H, H-4′), 7.62 (br t, *J*=7.9, Hz, 1H, H-7′), 7.52 (m, 2H, H-4, H-6′), 7.46 (dd, *J*=8.3, 7.0, Hz, 1H, H-5), 7.41 (d, *J*=8.3 Hz, 1H, H-2), 7.30 (dd, *J*=8.1, 7.3 Hz, 1H, H-3′), 7.10 (d, *J*=8.4 Hz, 1H, H-1), 6.94 (d, *J*=7.2 Hz, 1H, H-2′), 6.84 (s, 1H, H-8), 6.64 (s, 1H, H-11), 5.76 (s, 1H, H-15), 5.72 (s, 1H, H-7a), 3.79 (s, 3H, 10-OMe), 3.78 (s, 3H, 9-OMe), 3.44 (ddd, *J*=12.1, 11.5, 3.7 Hz, 1H, H-13), 3.34 (dd, *J*=11.4, 6.3 Hz, 1H, H-13), 3.17 (ddd, *J*=16.1, 12.2, 6.3 Hz, 1H, H-12), 2.80 (dd, *J*=16.1, 3.5 Hz, 1H, H-12); ^{13}C NMR (150 MHz): δ 150.1 (C-6b), 149.8 (C-10), 147.8 (C-9), 139.0 (C-1′), 134.4 (C-4a′), 134.1 (C-2a), 132.2 (C-8a′), 129.0 (C-5′), 128.8 (C-2′), 128.6 (C-4′), 127.8 (C-3), 127.7 (C-11a), 127.3 (C-1), 126.5 (C-4), 126.5 (C-7′), 126.0 (C-6′), 125.5 (C-5), 125.3 (C-7b), 124.9 (C-6a), 124.9 (C-3′), 124.4 (C-8′), 121.9 (C-6), 119.5 (C-2), 113.0 (C-15a), 111.9 (C-8), 111.4 (C-11), 82.9 (C-7a), 62.3 (C-15), 56.1 (9-OMe), 56.0 (10-OMe), 45.3 (C-13), 29.2 (C-12). Anal. Calcd for $C_{32}H_{27}NO_3$ (473.56): C, 81.16; H, 5.75; N, 2.96. Found: C, 81.27; H, 5.77; N, 2.92.

4.27. (7a*R**,15*R**,15*P**)-9,10-Dimethoxy-15-(naphth-1-yl) naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (18C$_1$)

^{1}H NMR (600 MHz): δ 8.44 (d, *J*=8.5 Hz, 1H, H-8′), 8.38 (d, *J*=8.4 Hz, 1H, H-6), 7.69 (d, *J*=8.1 Hz, 1H, H-3), 7.65 (m, 1H, H-2′), 7.39 (m, 1H, H-8), 7.08 (m, 1H, H-7′), 6.68 (d, *J*=8.7 Hz, 1H, H-1), 5.72 (s, 1H, H-7a), 5.30 (s, 1H, H-15); ^{13}C NMR (150 MHz): δ 130.6 (C-2′), 127.6 (C-3), 126.8 (C-8′9), 125.4 (C-7′), 125.0 (C-1), 121.7 (C-6), 110.1 (C-8), 90.5 (C-7a), 71.4 (C-15).

4.28. (7a*R**,15*R**,15*M**)-9,10-Dimethoxy-15-(naphth-1-yl) naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (18C$_2$)

^{1}H NMR (600 MHz): δ 8.48 (d, *J*=8.4 Hz, 1H, H-8′), 8.30 (d, *J*=8.5 Hz, 1H, H-6), 7.72 (d, *J*=8.1 Hz, 1H, H-3), 6.71 (m, 1H, H-1), 6.13 (s, 1H, H-15), 5.89 (s, 1H, H-7a); ^{13}C NMR (150 MHz): δ 127.5 (C-3), 126.5 (C-1), 123.0 (C-8′), 121.7 (C-6), 89.5 (C-7a), 61.4 (C-15).

4.29. (7a*R**,15*S**,15*P**)-15-(Naphth-1-yl)naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (19B)

Mp: 162–164 °C. ^{1}H NMR (600 MHz): δ 8.33 (d, *J*=8.5 Hz, 1H, H-8′), 8.14 (d, *J*=8.3 Hz, 1H, H-6), 7.88 (d, *J*=8.1 Hz, 1H, H-5′), 7.82 (d, *J*=8.1 Hz, 1H, H-3), 7.77 (d, *J*=8.2 Hz, 1H, H-4′), 7.61 (dd, *J*=8.4, 7.0 Hz, 1H, H-7′), 7.51 (m, 2H, H-4, H-6′), 7.45 (dd, *J*=8.2, 6.9 Hz, 1H, H-5), 7.42 (d, *J*=8.3 Hz, 1H, H-2), 7.34 (d, *J*=7.4 Hz, 1H, H-8), 7.30 (br t, *J*=7.9 Hz, 1H, H-3′), 7.27 (t, *J*=7.5 Hz, 1H, H-10), 7.20 (t, *J*=7.5 Hz, 1H, H-9), 7.17 (d, *J*=7.6 Hz, 1H, H-11), 7.10 (d, *J*=8.3 Hz, 1H, H-1), 6.96 (d, *J*=7.8 Hz, 1H, H-2′), 5.79 (s, 1H, H-7a), 5.77 (s, 1H, H-15), 3.48 (dt, *J*=12.3, 3.8 Hz, 1H, H-13), 3.36 (dd, *J*=12.2, 6.4 Hz, 1H, H-13), 3.25 (ddd, *J*=16.3, 12.4, 6.3 Hz, 1H, H-12), 2.90 (dd, *J*=16.3, 3.7 Hz, 1H, H-12); ^{13}C NMR (150 MHz):δ 150.1 (C-6b), 138.9 (C-1′), 135.4 (C-11a), 134.4 (C-4a′), 134.1 (C-2a), 133.3 (C-7b), 132.2 (C-8a′), 130.0 (C-5′), 129.1 (C-8), 129.0 (C-10), 128.9 (C-2′), 128.8 (C-11), 128.6 (C-4′), 127.8 (C-3), 127.3 (C-1), 126.5 (C-4), 126.5 (C-7′), 126.2 (C-9), 125.9 (C-6′), 125.5 (C-5), 125.0 (C-6a), 124.9 (C-3′), 124.4 (C-8′), 121.9 (C-6), 119.6 (C-2), 113.1 (C-15a), 83.0 (C-7a), 62.3 (C-159), 45.2 (C-13), 29.6 (C-12). Anal. Calcd for $C_{30}H_{23}NO$ (413.51): C, 87.14; H, 5.61; N, 3.39. Found: C, 87.22; H, 5.65; N, 3.42.

4.30. (7a*R**,15*R**,15*P**)-15-(Naphth-1-yl)naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (19C$_1$)

^{1}H NMR (600 MHz): δ 8.46 (d, *J*=8.7 Hz, 1H, H-8′), 8.40 (d, *J*=8.4 Hz, 1H, H-6), 7.81 (m, 1H, H-8), 7.65 (m, 1H, H-2′), 7.19 (m, 1H, H-2), 6.68 (d, *J*=8.6 Hz, 1H, H-1), 5.78 (s, H-7a), 5.30 (s, 1H, H-15); ^{13}C NMR (150 MHz): δ 130.7 (C-2′), 128.9 (C-8), 126.9 (C-8′), 124.9 (C-1), 121.9 (C-6), 120.2 (C-2), 90.5 (C-7a), 71.5 (C-15).

4.31. (7a*R**,15*R**,15*M**)-15-(Naphth-1-yl)naphth[2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (19C$_2$)

^{1}H NMR (600 MHz): δ 8.48 (d, *J*=8.7 Hz, 1H, H-8′), 8.31 (m, 1H, H-6), 6.75 (d, *J*=8.6 Hz, 1H, H-1), 6.14 (s, 1H, H-15), 5.95 (s, 1H, H-7a); ^{13}C NMR (150 MHz): δ 125.9 (C-1), 122.9 (C-8′), 121.9 (C-6), 89.7 (C-7a), 61.5 (C-15).

4.32. (7a*R**,15*S**)-9,10-Dimethoxy-15-(naphth-2-yl)naphth [2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (20B)

Mp: 183–184 °C. ^{1}H NMR (600 MHz): δ 8.16 (d, *J*=8.2 Hz, 1H, H-6), 7.83 (m, 3H, H-3, H-4′, H-5′), 7.69 (d, *J*=8.6 Hz, 1H, H-3′), 7.66 (d, *J*=8.0 Hz, 1H, H-8′), 7.50 (t, *J*=7.3 Hz, 1H, H-4), 7.44 (m, 5H, H-2, H-5, H-1′, H-6′, H-7′), 7.21 (d, *J*=8.3 Hz, 1H, H-1), 6.83 (s, 1H, H-8), 6.69 (s, 1H, H-11), 5.63 (s, 1H, H-7a), 5.19 (s, 1H, H-15), 3.82 (s, 3H, 10-OMe), 3.77 (s, 3H, 9-OMe), 3.35 (ddd, *J*=11.3, 10.6, 3.4 Hz, 1H, H-13), 3.21 (m, 1H, H-12), 3.15 (dd, *J*=10.5, 6.4 Hz, 1H, H-13), 2.79 (dd, *J*=15.8, 3.2 Hz, 1H, H-12); ^{13}C NMR (150 MHz): δ 149.9, 149.8 (C-6b, C-10), 147.8 (C-9), 141.3 (C-2′), 134.1 (C-2a), 133.1 (C-8a′), 133.0 (C-4a′), 128.5 (C-1′), 128.2 (C-8′), 127.8 (3C, C-3′, C-4′, C-5′), 127.7 (2C, C-3, C-11a), 127.3 (C-1), 126.5 (C-4), 126.3 (2C, C-6′, C-7′), 125.4 (2C, C-5, C-7b), 125.1 (C-6a), 122.0 (C-6), 119.3 (C-2), 113.0 (C-15a), 111.9 (C-8), 111.4 (C-11), 82.9 (C-7a), 65.2 (C-15), 56.1 (9-OMe), 56.0 (10-OMe), 45.6 (C-13), 29.2 (C-12).

4.33. (7a*R**,15*R**)-9,10-Dimethoxy-15-(naphth-2-yl)naphth [2,1-*e*][1,3]oxazino[2,3-*a*]isoquinoline (20C)

^{1}H NMR (600 MHz): δ 8.33 (br, 1H, H-6), 7.95 (br, 1H, H-1′), 7.88 (br, 1H, H-8′), 7.83 (m, 2H, H-4′, H-5′), 7.73 (d, *J*=8.0 Hz, 1H, H-3),

7.53 (m, 1H, H-5), 7.48 (m, 1H, H-4), 7.42 (m, 3H, H-3′, H-6′, H-7′), 7.33 (s, 1H, H-8), 7.23 (br, 1H, H-2), 6.79 (br, 1H, H-1), 6.63 (s, 1H, H-11), 5.68 (s, 1H, H-7a), 5.05 (s, 1H, H-15), 3.96 (s, 3H, 9-OMe), 3.82 (s, 3H, 10-OMe), 3.05 (br d, J=10.0 Hz, H-13), 2.92 (br t, J=15.3 Hz, H-12), 2.68 (t, J=10.1 Hz, H-13), 2.55 (d, J=15.5 Hz, H-12); ^{13}C NMR (150 MHz): δ 149.2, 149.1 (C-6b, C-10), 148.1 (C-9), 142.4 (C-2′), 133.4 (C-8a′), 133.4 (C-4a′), 133.0 (C-2a), 129.3 (C-1′), 127.9 (C-8′), 127.8 (C-4′), 127.7 (C-3), 127.3 (C-11a), 126.3 (C-3′),126.3 (C-1), 126.3 (C-4), 125.8 (C-5), 125.8 (C-7b), 125.1 (C-6a), 121.7 (C-6), 120.5 (C-2), 119.8 (C-15a), 111.0 (C-11), 110.2 (C-8), 89.3 (C-7a), 68.8 (C-15), 56.3 (9-OMe), 56.0 (10-OMe), 46.4 (C-13), 28.5 (C-12). Anal. Calcd for $C_{32}H_{27}NO_3$ (473.56): C, 81.16; H, 5.75; N, 2.96. Found: C, 81.21; H, 5.73; N, 2.95.

4.34. (7a*R**,15*S**)-15-(Naphth-2-yl)naphth[2,1-*e*][1,3]oxazino [2,3-*a*]isoquinoline (21B)

Mp: 166–168 °C. ^{1}H NMR (600 MHz): δ 8.13 (d, J=8.2 Hz, 1H, H-6), 7.83 (m, 3H, H-3, H-4′, H-5′), 7.69 (d, J=8.6 Hz, 1H, H-3′), 7.67 (d, J=8.0 Hz, 1H, H-8′), 7.50 (m, 2H, H-4, H-6′), 7.45 (m, 5H, H-2, H-5, H-8, H-1′, H-7′), 7.31 (m, 2H, H-9, H-10), 7.23 (m, 2H, H-1, H-11), 5.71 (s, 1H, H-7a), 5.21 (s, 1H, H-15), 3.40 (ddd, J=11.5, 10.4, 3.0 Hz, 1H, H-13), 3.30 (ddd, J=16.3, 11.6, 5.9 Hz, 1H, H-12), 3.18 (dd, J=10.5, 6.0 Hz, 1H, H-13), 2.90 (dd, J=16.4, 2.9 Hz, 1H, H-12); ^{13}C NMR (150 MHz): δ 149.8 (C-6b), 141.2 (C-2′), 135.6 (C-11a), 134.1 (C-2a), 133.4 (C-7b), 133.1 (C-8a′), 133.0 (C-4a′), 129.1 (C-10), 129.0 (C-9), 128.9 (C-11), 128.5 (C-8), 128.3 (C-8′), 128.2 (C-1′), 127.7 (C-3), 127.7 (C-3′), 127.6 (C-4′), 127.3 (C-5′), 126.5 (C-6′), 126.3 (C-1), 126.3 (C-4), 126.2 (C-7′), 125.5 (C-5), 125.1 (C-6a), 121.9 (C-6), 119.4 (C-2), 113.1 (C-15a), 83.0 (C-7a), 65.2 (C-15), 45.6 (C-13), 29.6 (C-12). Anal. Calcd for $C_{30}H_{23}NO$ (413.51): C, 87.14; H, 5.61; N, 3.39. Found: C, 87.18; H, 5.65; N, 3.41.

4.35. (7a*R**,15*R**)-15-(Naphth-2-yl)naphth[2,1-*e*][1,3]oxazino [2,3-*a*]isoquinoline (21C)

^{1}H NMR (600 MHz): δ 8.35 (d, J=8.2 Hz, 1H, H-6), 7.97 (s, 1H, H-1′), 7.88 (m, 2H, H-8, H-8′), 7.79 (m, 2H, H-4′, H-5′), 7.73 (d, J=8.0 Hz, 1H, H-3), 7.53–7.41 (m, 5H, H-4, H-5, H-3′, H-6′, H-7′), 7.31 (m, 2H, H-9, H-10), 7.24 (m, 1H, H-2), 7.17 (d, J=7.3 Hz, 1H, H-11), 6.80 (d, J=8.5 Hz, 1H, H-1), 5.75 (s, 1H, H-7a), 5.07 (s, 1H, H-15), 3.08 (dd, J=11.0, 4.2 Hz, 1H, H-13), 3.01 (ddd, J=15.9, 11.1, 4.4 Hz, 1H, H-12), 2.71 (dt, J=11.1, 3.1 Hz, 1H, H-13), 2.65 (br d, J=16.0 Hz, 1H, H-12); ^{13}C NMR (150 MHz): δ 149.0 (C-6b), 139.9 (C-2′), 136.0 (C-11a), 133.5 (C-8a′), 133.4 (C-7b), 133.4 (C-4a′), 133.1 (C-2a), 129.3 (C-1′), 128.8 (C-4′), 128.6 (C-11), 128.4 (C-9), 128.3 (C-10), 128.0 (C-8′), 127.7 (C-3), 127.6 (C-8), 127.4 (C-5′), 127.3 (C-3′), 126.4 (C-6′), 126.3 (C-1), 126.3 (C-4), 126.2 (C-7′), 125.9 (C-5), 125.1 (C-6a), 121.8 (C-6), 120.6 (C-2), 119.3 (C-15a), 89.4 (C-7a), 68.8 (C-15), 46.2 (C-13), 28.9 (C-12).

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