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Synthesis and conformational analysis of naphthylnaphthoxazine derivatives

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ABSTRACT

Four new primary aminonaphthols (**4**, **5**, **9** and **10**) were synthesized from 1- or 2-naphthol and 1- or 2-naphthaldehyde via naphthoxazines in modified Mannich condensations. Simple ring-closure reactions of these aminonaphthols with paraformaldehyde, 4-nitrobenzaldehyde, phosgene or 4-chlorophenyl isothiocyanate led to new heterocyclic derivatives. In these transformations, either an sp^2 or an sp^3 carbon was inserted between the hydroxy and amino groups. The effects of substituents and the naphthyl ring on the conformation were investigated by means of NMR measurements, employing both dipolar and scalar couplings. The structures were confirmed by DFT quantum chemical calculations involving computed coupling constants, intramolecular distances between nuclei and the relative energies of the preferred conformers.

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1. Introduction

The chemistry of the Betti bases dates from the beginning of the 20th century, when Betti reported the synthesis of 1-(α-aminobenzyl)-2-naphthol [1,2]. The three-component modified Mannich reaction involving 2-naphthol, benzaldehyde and ammonia resulted in 1,3-diphenylnaphthoxazine, which was subsequently hydrolysed to 1-(α-aminobenzyl)-2-naphthol.

The reaction can be extended by using chiral amines instead of ammonia, which furnishes non-racemic *N*-substituted aminonaphthol derivatives; this opened up a new area of application of these enantiopure compounds as chiral ligands in asymmetric transformations [3–7]. As a result of an integrated, virtual database screening, 7-[anilino(phenyl)methyl]-2-methyl-8-quinolinol was found to represent a promising new class of non-peptide inhibitors of the MDM2–p53 interaction [8].

Interest in the synthesis of primary aminonaphthols has greatly increased during the past few years following an evaluation of the hypotensive and bradycardiac effects of 1-aminomethyl-2-naphthol derivatives [9], and the synthesis of a wide variety of such compounds were recently achieved through the hydrolysis of 1-amidomethyl-2-naphthols [10–12]. Through the use of aliphatic aldehydes, e.g. formaldehyde [13], acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde and pivalaldehyde, 1-(1-aminoalkyl)-2-naphthols have been synthesized [14,15], while from heteroaromatic aldehydes primary aminonaphthols have been prepared and their ring-chain tautomeric behaviour has been studied [16].

Our present aim was to prepare new primary aminonaphthols from 1- or 2-naphthol and 1- or 2-naphthaldehyde and to extend the applicability of these compounds for the preparation of new heterocyclic derivatives by simple ring-closure reactions with paraformaldehyde, 4-nitrobenzaldehyde, phosgene or 4-chlorophenyl isothiocyanate. We additionally investigated the influence of the substituents at position 3 or 2 and the connecting position of the naphthalene ring on the conformation.

2. Results and discussion

2.1. Syntheses

The aminonaphthols **4**, **5**, **9** and **10** were prepared via the reactions of the corresponding 1- or 2-naphthol with 1- or 2-naphthaldehyde in the presence of methanolic ammonia solution in absolute methanol at room temperature for 24 h. This led to the naphthoxazines **2**, **3**, **7** and **8** (Scheme 1: i), acidic hydrolysis of which gave the desired aminonaphthol hydrochlorides **4**, **5**, **9** and **10** (Scheme 1: ii). Because of the instability of the aminonaphthyl

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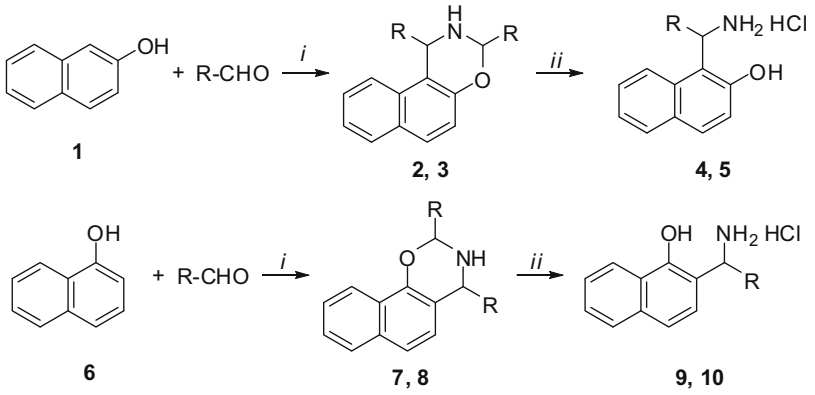


R = 2-naphthyl: **2**, **4** (87%), **7**, **9** (32%)
R = 1-naphthyl: **3**, **5** (28%), **8**, **10** (42%)

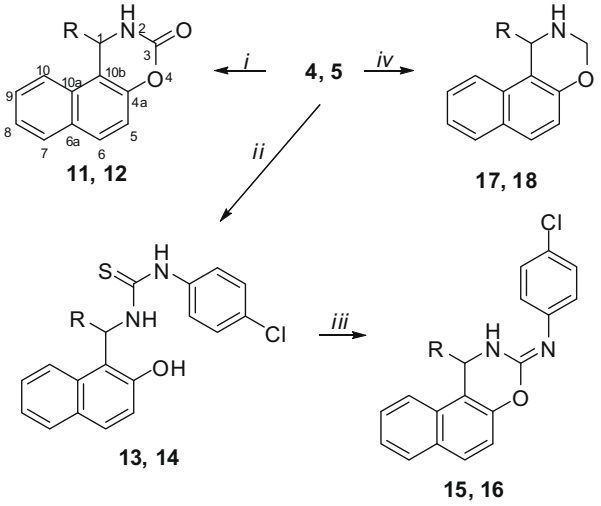
Scheme 1. Reagents and conditions: (i) NH_3/MeOH, r.t.; (ii) 60 °C for 2–3 h, HCl/H_2O.

naphthol derivatives, compounds **4**, **5**, **9** and **10** were isolated as their hydrochlorides, in moderate to good yields (28–87%).

In the first stage of the transformations of **4**, **5**, **9** and **10** to heterocyclic derivatives, an sp^2 carbon (C-3 or C-2) was inserted between the hydroxy and amino groups (Schemes 2 and 3).

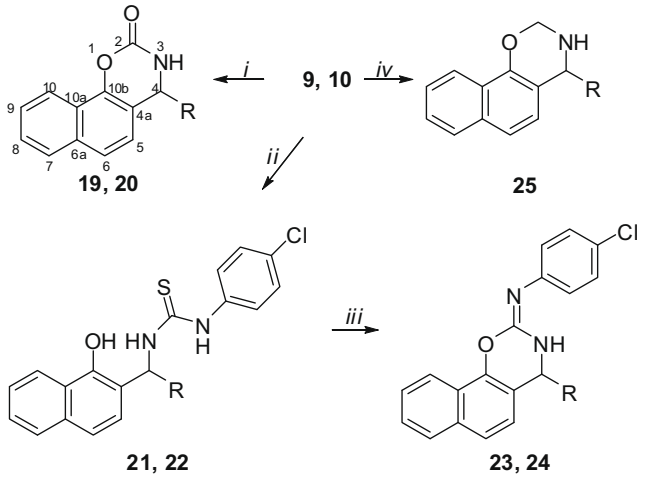
When aminonaphthols **4**, **5**, **9** and **10** were treated with $COCl_2$ in the presence of Na_2CO_3 in toluene/H_2O solution at room temperature for 10 min., the corresponding naphthoxazin-3-ones **11** and **12** and naphthoxazin-2-ones **19** and **20** were formed, in moderate yields (40–86%) in each case (Schemes 2 and 3: i).

For the preparation of 3- and 2-(4-chlorophenylimino)-substituted naphthoxazines **15**, **16**, **23** and **24**, aminonaphthols **4**, **5**, **9** and **10** were reacted with 4-chlorophenyl isothiocyanate (Schemes 2 and 3: ii). Thioureas **13**, **14**, **21** and **22** were converted to the corresponding *S*-methylisothiourea derivatives with methyl iodide, and subsequent treatment with methanolic KOH gave the corresponding 3- or 2-arylimino-substituted naphthoxazines **15**, **16**, **23** and **24**, in good yields (67–82%), via methyl mercaptan elimination (Schemes 2 and 3: iii).



R = 2-naphthyl: **11** (86%), **13** (82%), **15** (76%), **17** (49%)
R = 1-naphthyl: **12** (44%), **14** (80%), **16** (82%), **18** (42%)

Scheme 2. Reagents and conditions: (i) $COCl_2$, toluene/H_2O, Na_2CO_3, 10 min. r.t.; (ii) 4-ClC_6H_5NCS, Et_3N, toluene, r.t.; (iii) MeI, KOH, MeOH, r.t.; (iv) paraformaldehyde, Et_3N, $CHCl_3$, 6 h, r.t.



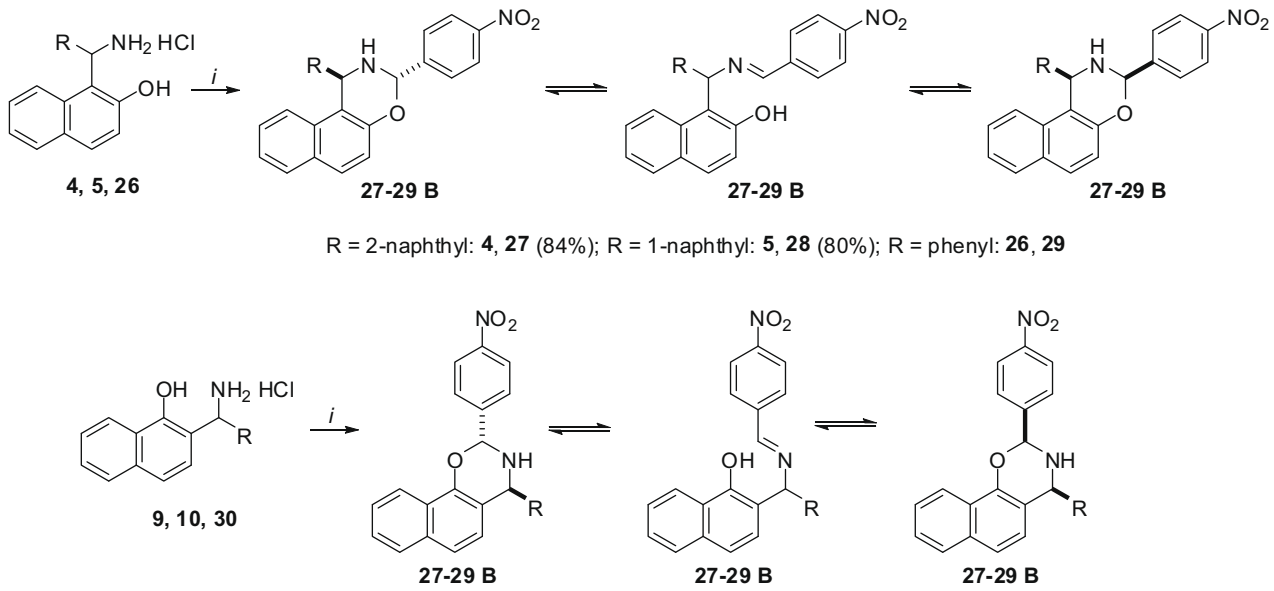
R = 2-naphthyl: **19** (40%), **21** (65%), **23** (67%)
R = 1-naphthyl: **20** (78%), **22** (72%), **24** (74%), **25** (37%)

Scheme 3. Reagents and conditions: (i) $COCl_2$, toluene/H_2O, Na_2CO_3, 10 min; r.t.; (ii) 4-Cl-PhNCS, Et_3N, toluene, r.t.; (iii) MeI, KOH, MeOH, r.t.; (iv) paraformaldehyde, Et_3N, $CHCl_3$, 6 h, r.t

The ring closures of aminonaphthols **4**, **5**, **9** and **10** with oxo compounds (i.e. the insertion of an sp^3 carbon) resulted in naphthoxazines.

The reactions of aminonaphthols **4**, **5** and **10** with paraformaldehyde under mild conditions (at room temperature for 6 h) gave the corresponding 3- and 2-unsubstituted naphthoxazines **17**, **18** and **25** in yields of 37–49% (Schemes 2 and 3: iv). The corresponding reaction of **9** did not lead to the desired naphthoxazine. After a reaction time of 3 h TLC demonstrated that no starting material remained, and the TLC plots observed suggested the rapid decomposition of the expected naphthoxazine derivative.

The analogous reactions of **4**, **5**, **9** and **10** with 4-nitrobenzaldehyde were accomplished under mild conditions. The products **27, 28**, **31** and **32** were separated from the reaction mixture in good yields (78–84%, Scheme 4: i). Compounds **27–29** and **31–33** in solution can participate in three-component ring-chain tautomeric equilibria involving the C-3 (**27–29**) or C-2 (**31–33**) epimeric naphthoxazines (**B** and **C**) and the open tautomer (**A**). The tautomeric behaviour (the tautomeric ratios) of **27–29** and **31–33** depend on substituent R at position 1 or 4, and on the properties of the solvent in question, as revealed in Table 1 [13].



Scheme 4. Reagents and conditions: (i) 4-nitrobenzaldehyde, Et_3N, MeOH, 10 min., r.t.

For **27**–**29**, the predominant form is the *trans* tautomer (**B**). The portion of **B** decreases in the sequence **27** > **28** > **29**, while that of the *cis* form (**C**) displays the opposite tendency (Table 1: entries 1–3). This can be explained in terms of steric hindrance. Relative to $CDCl_3$, the more polar solvent DMSO causes a small increase in the proportion of the open-chain form (**A**) at the expense of form (**C**) for **29** (Table 1: entry 3**)**, but the main tendency was found to be similar with that discussed above.

For **31–33** in $CDCl_3$, the steric hindrance of the aryl substituents at position 4 must exert the most important effect as regards the composition of the tautomeric mixture and, similar as for 1,3-disubstituted naphth[1,2-*e*][1,3]oxazines, the phenyl ring (smaller then the naphthyl ringsystem) resulted in more form (**C**) and less form (**B**) (Table 1: entries 4–6).

The effect of the change of the solvent seems to be somewhat more marked for **31**–**33** (Table 1: entries 4–6) than for **27–29** (Table 1: entries 1–3).

2.2. Conformational analysis

Theoretical calculations were performed on the compounds studied and their global minimum-energy structures were determined. These structures were compared with the relevant NMR spectroscopic data (NOEs and *vicinal* H,H-coupling constants) to check particularly on the conformation of the (unsaturated) oxazine ring moiety. The same procedure was applied in the event of additional substitution at C-3 in the 2-naphthoxazines and at C-2 in the 1-naphthoxazines, of the sp^2 hybridization of C-2 or C-4. The complete agreement of the computed structures (the preferred conformers) and the NMR parameters is strong evidence of the correctness of the calculated geometries of the compounds studied.

Both the 1- and 2-naphthyl substituents at C-1 in the 2-naphthoxazines and at C-4 in the 1-naphthoxazines, respectively, were found to have only marginal influence on the conformational equilibria, whereas in the *trans* isomers of the disubstituted 1- and 2-naphthoxazines **27**, **28**, **31** and **32** they do influence the preference for the corresponding *S*/*R* and *R*/*S* diastereomers, respectively (*vide infra*).

Table 1
Proportions of tautomers (%) in **27–29** and **31–33**.

Entry	Comp.	$CDCl_3$			DMSO		
		A	**B**	**C**	**A**	**B**	**C**
1	**27**	–	100.0[a]	–	–	100.0	–
2	**28**	–	95.4	4.6	–	94.8	5.2
3	**29**[b]	3.1	86.1	10.8	15.0	84.8	0.2
4	**31**	13.8	68.9	17.3	34.3	46.1	19.6
5	**32**	4.5	77.6	17.9	–	82.8	17.2
6	**33**[c]	14.9	50.1	35.0	36.9	42.6	20.5

[a] Either the population of tautomers **A** and **C** is too low to be detected by NMR, or the equilibration is fast on the NMR time scale (see text below).
[b] Data from Ref. [17].
[c] Data from Ref. [18].

2.2.1. Compounds with sp^3 C-2 or C-3 atoms

Compounds which are only mono-substituted with 1- and 2-naphthyl substituents at C-1 and C-4, respectively (**17**, **18** and **25**), prefer *twisted-chair* conformers (cf. the global minimum-energy structure of **17**, for instance, in Fig 1). The analogue of **17** could not be obtained experimentally, but was computed at the DFT level of theory; the same *twisted-chair* conformer as in **17**, **18** and **25** was found to be preferred.

This preferred conformation (cf. **17** in Fig. 1) proves to be in excellent agreement with the experimental NMR data: NOEs were observed between H-1 and NH (the corresponding distance was computed to be only 2.243 Å) and between NH and H-3_{eq} (computed distance −2.360 Å). Moreover, the corresponding scalar vicinal $^3J_{H,H}$ coupling constants were 5.0 Hz ($^3J_{H1,NH}$ computed 4.7 Hz, dihedral angle 43.3°), 3.9 Hz ($^3J_{H\text{-}3eq,NH}$ computed 3.2 Hz, dihedral angle −57.3°), and 13.6 Hz ($^3J_{H\text{-}3ax,NH}$ computed 13.1 Hz, dihedral angle −178.2°). The corresponding NMR data of **18** are given in Table 2 and are likewise seen to be in excellent agreement with the computed values.

A *twisted-chair* conformer was also found for **25** (cf. Fig. 2). As for **17** and **18**, a similar $^3J_{H,H}$ value in the O(2)CH_2—NH–C(4)H coupling fragment and similar NOEs between NH and H-2_{eq} and H-4, respectively, were observed (cf. Table 2).

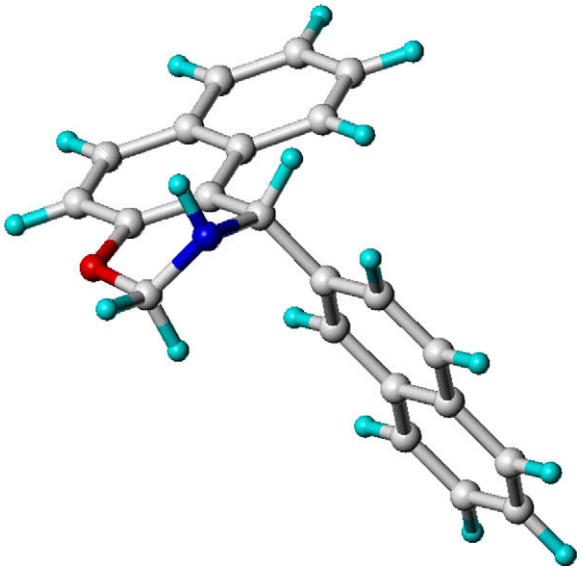


Fig. 1. Energy-minimum structure of (*1S*)-17.

If the compounds are additionally substituted at C-3 (β-naphthoxazines) or C-2 (α-naphthoxazines), tautomeric equilibria result (cf. Scheme 4). The major ring form **B** was isolated and studied by NMR spectroscopy. In contrast with the simple *R*/*S* chirality in **17**, **18** and **25**, which does not influence the NMR spectra in achiral media, in **28**, **29**, **31** and **32** *R*/*S* and *S*/*R* diastereomers have to be considered.

The global minimum-energy structure of the major ring form **B** is characterized by the *trans* arrangement of H-3 and N—H (as depicted in Fig. 3 for **27B**) and prefers the *twisted-chair* conformation. The experimentally determined vicinal H,H-coupling constants $^3J_{H\text{-}2,H\text{-}3}$ [14.0 Hz in **27B** and 13.6 Hz in **28B**] and $^3J_{H\text{-}1,H\text{-}2}$ [5.2 Hz in **27B** and 4.9 Hz in **28B**] agree well with the computed values [e.g. **27B**: 12.5 Hz ($^3J_{H\text{-}2,H\text{-}3}$) and 4.8 Hz ($^3J_{H\text{-}1,H\text{-}2}$)]. Surprisingly, a strong NOE was found between H-3 and N—H, which are in *trans* position. This dipolar coupling, however, should be near to zero in **27B**, but some **27C** may be present in marginal concentration or in rapid equilibrium with **B** on the NMR time-scale; obviously, the reaction rate allows NOE transfer between the tautomeric species (cf. Table 1).

The main tautomers **31B** and **32B** also occur in a *twisted-chair* conformation, as illustrated for **32B** in Fig. 4. This calculated minimum-energy structure is corroborated by the experimentally determined coupling constants $^3J_{H\text{-}3,H\text{-}4}$ = 5.7 Hz (computed dihedral angle 40.4°) and $^3J_{H\text{-}2,H\text{-}3}$ = 13.5 Hz (computed dihedral angle 177.6°) and the corresponding NOEs, which were found to be strong between N—H and H-4 (computed distance 2.243 Å) and weak between H-2 and N—H (2.902 Å).

Surprisingly, in **27**, **28** and **32** the *S*/*R* diastereomer proved to be more stable than the *R*/*S* analogue; the reverse situation was the case for **31**.

2.2.2. Compounds with sp^2 C-2 or C-3 atoms

Introduction of an sp^2 carbon at position 3 (**11** and **12**) or 2 (**19** and **20**) obviously leads to very similar conformational behaviour; in accordance with this, very similar minimum-energy conformations of all of these compounds were calculated: the oxazine ring is nearly flat with a slight boat conformation (cf. Fig. 5). Only in one case (**11**) could the $^3J_{NH,CH}$ coupling constant be detected; it was 2.9 Hz. The corresponding signals of the other compounds were more or less broadened and the corresponding vicinal coupling constants could not be extracted. The magnitude of $^3J_{NH,CH}$ was in good agreement with the calculated values. These were in the range 0–1.8 Hz, with calculated dihedral angles of 59.6–71.1°, both characteristic of the *syn-clinal* conformation of the NH—CH moiety. The distance between these two hydrogens was computed to be in the range 2.43–2.56 Å, which corresponds to the mean NOEs determined in these compounds.

Table 2
Experimental and computed coupling constants and some calculated dihedral angles and distances for compounds **18** and **25**.

Compound	$^3J_{NCH-NH}$ (exp) (Hz)	$^3J_{NCH-NH}$ (calc) (Hz)	Dihedral angle NC*H*—N*H*	$^3J_{NH-OCHeq}$ (exp) (Hz)	$^3J_{NH-OCHeq}$ (calc) (Hz)	Dihedral angle N*H*–OCH_{eq}	$^3J_{NH-OCHax}$ (exp)	$^3J_{NH-OCHax}$ (calc) (Hz)	Dihedral angle N*H*—OCH_{ax}	Distance NC*H*—N*H* (Å)	Distance N*H*—OCH_{eq} (Å)
18	4.9	4.8	42.8°	3.7	3.1	−57.7°	13.9	13.1	−178.6°	2.241	2.358
25	6.2	4.7	41.6°	5.4	2.0	−58.0°	12.2	13.2	−179.0°	2.242	2.359

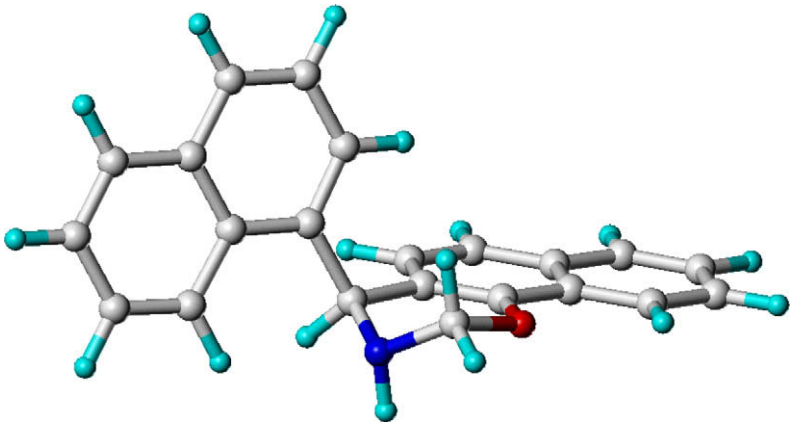


Fig. 2. Minimum-energy structure of (*4S*)-**25**.

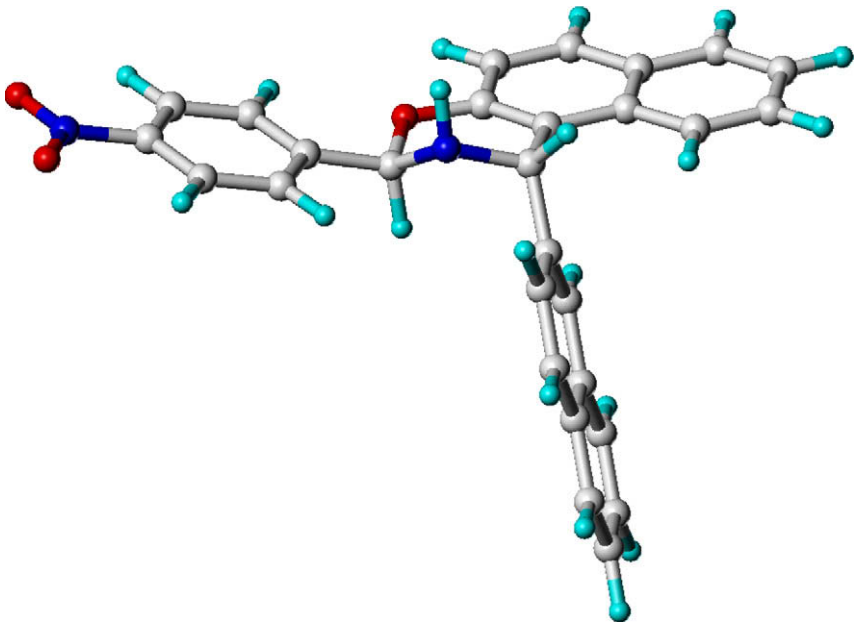


Fig. 3. Minimum-energy structure of (1*S*,3*R*)-**27B**.

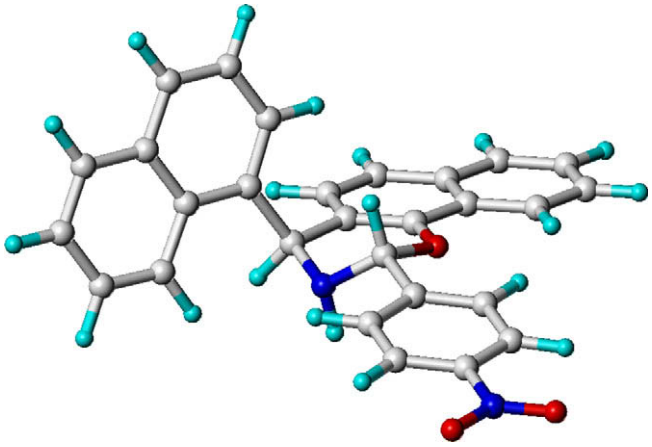


Fig. 4. Minimum-energy structure of (2*R*,4*S*)-**32B**.

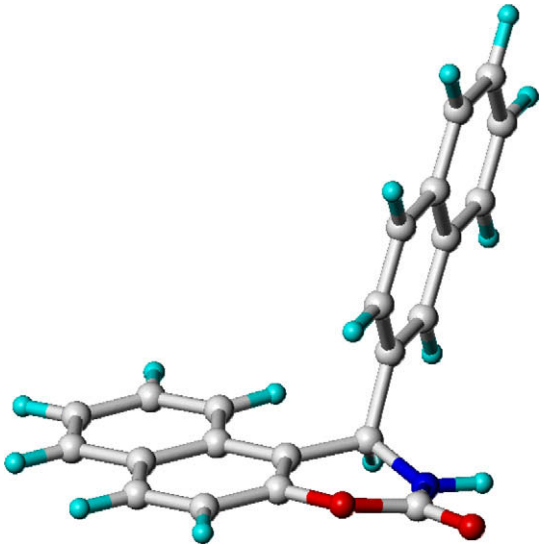


Fig. 5. Minimum-energy structure of (4*R*)-**11**.

For compounds **15**, **16**, **23** and **24** the endocyclic/exocyclic tautomerism of the C=N double bond is possible. The energy levels indicated the presence of the exocyclic form (Schemes 2 and 3). This was supported by the NMR data: NOE interactions were found between N—H and the corresponding C—H at position 1 (**15** and **16**) or 4 (**23** and **24**). *Ab initio* calculations on the title compounds pointed to the presence of the *E* isomers.

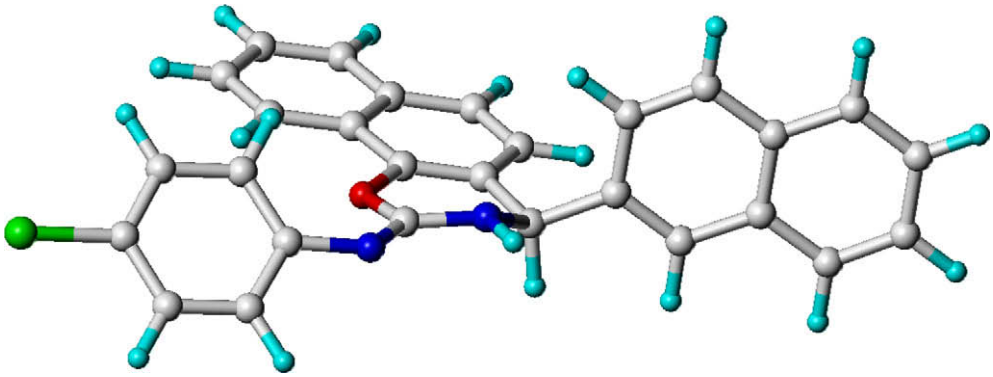


Fig. 6. Minimum-energy structure of (4*R*)-**23**.

The oxazine ring in **15**, **16**, **23** and **24** turned out to be nearly planar; the minimum-energy structure of **23** is shown in Fig. 6.

3. Conclusions

Four new aminomethylnaphthols (**4**, **5**, **9** and **10**) were synthesized by the condensation of 1- or 2-naphthol with 1- or 2-naphthaldehydes in the presence of ammonia, followed by acidic hydrolysis. The condensation of **4**, **5, 9 and 10** with paraformaldehyde, 4-nitrobenzaldehyde, phosgene or 4-chlorophenyl isothiocyanate led to naphthoxazine derivatives. Compounds **27–29** and **31–33** in solution proved to be three-component tautomeric mixtures. The tautomeric ratio influenced by the steric hindrance of the aromatic rings at position 1 or 4 and by the connecting position of the naphthyl rings at the same positions. The conformational analysis revealed that the conformation of the oxazine ring moiety depends on the hybridization of the carbon at position 3 or 2. The compounds containing an sp^3 carbon preferred a twisted-chair conformation, whereas the insertion of an sp^2 carbon led to a nearly flat naphthoxazine ring moiety.

4. Experimental

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Merck Kieselgel $60F_{254}$ plates were used for TLC.

The NMR spectra were recorded in DMSO-d_6 (unless specified as $CDCl_3$) solution in 5 mm tubes, at room temperature, on a BRUKER AVANCE 500 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*-HMBC, and NOESY) were acquired and processed with the standard BRUKER software.

Geometry optimizations were performed without restrictions, using the Gaussian 03 version C.02[19] program package. Different conformation and configurations of all studied compounds were preoptimized by using the PM3 Hamiltonian [20,21]. Density functional theory calculations were carried out at the B3LYP/6-31G** [22,23] level of theory. Stationary points on the potential hypersurface were characterized by force constants. Coupling constants were computed at the same theory level, B3LYP/6-31G** [24,25].

Different starting conformations were created and the results were analysed and displayed by using the molecular modelling program SYBYL 7.3 [26] and the program GaussView 2.0. [27] Different local minimum-energy conformations were selected to analyse the relative stability and the geometrical parameter.

Results were calculated on a SGI and on a Linux cluster.

4.1. General method for the synthesis of aminomethylnaphthylnaphthols (*4*, *5*, *9* and *10*)

To a solution of 1- or 2-naphthol (3.6 g, 25 mmol) in absolute MeOH (30 mL), the appropriate 1- or 2-naphthaldehyde (9.75 g, 62.5 mmol) and 25% methanolic ammonia solution (20 mL) were added. The mixture was allowed to stand at room temperature for 48 h. The solvent was removed under reduced pressure and 10% aq. HCl (210 mL) was added to the residue. The mixture was stirred and heated for 3 h at 60 °C, and the solvent was evaporated off. The crystalline hydrochloride of **4**, **5**, **9** or **10** that separated out from EtOAc (50 mL) was filtered off, washed with $CHCl_3$ and Et_2O, and recrystallized from Et_2O–MeOH (4:1).

4.1.1. 1-[Aminomethyl-(2-naphthyl)]-2-naphthol hydrochloride (*4*)

White crystals, yield 7.29 g (87%), m.p. 193–195 °C. ^{1}H NMR (DMSO-d_6) δ 6.45 (H: C*H*, 1H, s), 7.35 (H: 8, 1H, t, J = 7.5 Hz), 7.46 (H: 3, 1H, d, J = 8.9 Hz), 7.48–7.55 (H: 7′, 1′, 2H, m), 7.59 (H: 6′, 1H, d, J = 7.5 Hz), 7.85–7.91 (H: 4, 4′, 8′, 3′, 5′, 5, 6H, m), 8.07 (H: 7, 1H, s), 8.10 (H: 6, 1H, d, J = 8.6 Hz), 9.05 (H: NH_3, 3H, s), 11.06 (H: O*H*, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 51.0 (C: *C*H), 113.7 (C: 1), 118.7 (C: 3), 121.9 (C: 6), 123.0 (C: 8), 125.2 (C: 6′), 125.9 (C: 7), 126.5 (C: 7′), 126.7 (C: 1′), 127.3 (C: 4′), 127.6 (C: 8′), 127.9 (C: 5′), 128.2 (C: 4a, 3′), 128.9 (C: 5), 130.8 (C: 4), 131.9 (C: 4a′), 132.4 (C: 8a), 132.5 (C: 8a′), 135.1 (C: 2′), 153.9 (C: 2) ppm. $C_{21}H_{18}ClNO$ (335.83): calcd. C 75.11, H 5.40, N 4.17; found C 75.05, H 5.41, N 4.18.

4.1.2. 1-[Aminomethyl-(1-naphthyl)]-2-naphthol hydrochloride (*5*)

White crystals, yield 2.34 g (28%), m.p. 202–204 °C. ^{1}H NMR (DMSO-d_6): δ 6.96 (H: C*H*, 1H, s), 7.25 (H: 2′, 1H, t, J = 7.1 Hz), 7.33 (H: 4′, 1H, t, J = 7.4 (H: 3, 1H, d, J = 16.0 Hz), 7.51–7.55 (H: 3′, 6′, 2H, m), 7.79–7.88 (H: 6, 7′, 8′, 7, 5′, 5H, m), 7.92–7.97 (H: 4, 5, 2H, m), 8.31–8.32 (H: 8, 1H, m), 8.96 (H: NH_3, 3H, s), 11.92 (H: O*H*, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 48.3 (C: *C*H), 113.8 (C: 1), 118.8 (C: 3), 121.8 (C: 6), 122.9 (C: 8), 123.2 (C: 2′), 125.2 (C: 6′), 126.1 (C: 7′), 126.2 (C: 8′), 126.9 (C: 3′), 127.1 (C: 4′), 128.3 (C: 4a), 128.9 (C: 4), 128.9 (C: 5), 129.1 (C: 7), 130.1 (C: 8a′), 130.9 (C: 5′), 131.9 (C: 8a), 133.1 (C: 4a′), 133.5 (C: 1′), 154.2 (C: 2) ppm. $C_{21}H_{18}ClNO$ (335.83): calcd. C 75.11, H 5.40, N 4.17; found C 75.15, H 5.42, N 4.19.

4.1.3. 2-[Aminomethyl-(2-naphthyl)]-1-naphthol hydrochloride (*9*)

White crystals, yield 2.69 g (32%), m.p. 168–171 °C. ^{1}H NMR (DMSO-d_6): δ 6.32 (H: *H*C—NH_3, 1H, s), 7.51–7.57 (H: 7, 6, 3′, 8′, 6′, 5H, m), 7.63–7.56 (H: 5, 4a′, 2H, m), 7.86–7.88 (H: 7′, 1H, m), 7.89–7.95 (H: 4, 5′, 4′, 3H, m), 8.09 (H: 1′, 1H, s), 8.35 (H: 8, 1H, dd, J = 6.20 Hz), 9.27 (H: NH_3, 3H, s), 10.17 (H: O*H*, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 52.1 (C: H*C*—NH_3), 119.5 (C: 2), 120.1 (C: 5′), 122.6 (C: 8), 124.9 (C: 3), 125.3 (C: 8′), 125.3 (C: 8a′), 125.6 (C: 7′), 125.6 (C: 1′), 126.6 (C: 2′), 126.8 (C: 6, 4′), 127.6 (C: 4), 127.8 (C: 6), 127.9 (C: 6′), 128.4 (C: 3′), 132.4 (C: 4a′), 132.5 (C: 8a), 134.0 (C: 4a), 135.7 (C: 2), 150.0 (C: 1) ppm. $C_{21}H_{18}ClNO$ (335.83): calcd. C 75.11, H 5.40, N 4.17; found C 75.12, H 5.39, N 4.16.

4.1.4. 2-[Aminomethyl-(1-naphthyl)]-1-naphthol hydrochloride (*10*)

White crystals, yield 3.52 g (42%), m.p. 161–164 °C. ^{1}H NMR (DMSO-d_6): δ 6.87 (H: *H*C. 1H, s), 7.25 (H: 3, 1H, d, J = 8.7 Hz), 7.34 (H: 4, 1H, d, J = 8.7 Hz), 7.47–7.56 (H: 8′, 6′, 5′, 7, 4H, m), 7.68 (H: 3′, 1H, t, J = 7.7 Hz), 7.78 (H: 6, 1H, d, J = 7.5 Hz), 7.94–7.98 (H: 4′, 7′, 2H, m), 8.03–8.06 (H: 5, 2′, 2H, m), 8.45 (H: 8, 1H, d, J = 8.2 Hz), 9.23 (H: NH_3, 3H, s), 10.54 (H: O*H*, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 48.3 (C: *C*H), 119.0 (C: 2), 120.0 (C: 4), 122.9 (C: 5,8), 123.6 (C: 2′), 125.2 (C:3′), 125.4 (C: 3), 125.4 (C: 8a), 125.6 (C: 8′), 126.2 (C: 5′), 126.9 (C: 6′), 126.9 (C: 7), 127.7 (C: 6), 128.7 (C: 4′), 128.9 (C: 7′), 129.8 (C: 4a′), 133.4 (C: 1′), 133.8 (C: 8a′), 134.2 (C: 4a), 150.0 (C: 1) ppm. $C_{21}H_{18}ClNO$ (335.83): calcd. C 75.11, H 5.40, N 4.17; found C 75.11, H 5.45, N 4.16.

4.2. General method for the synthesis of naphthylnaphthoxazinones (*11*, *12*, *19 and 20*)

Aminonaphthol **4**, **5**, **9** or **10** (0.50 g, 1.49 mmol) was dissolved in toluene–H_2O 1:1 (50 mL), phosgene (0.32 mL; 20% in toluene, 1.64 mmol) and sodium carbonate (0.69 g, 1.64 mmol) were added. The mixture was stirred at r.t. for 10 min. and the resulting white precipitate was filtered off and recrystallized from iPr$_2$O (30 mL).

*4.2.1. 1-(2-Naphthyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazin-3-one (**11**)*

White crystals, yield 0.42 g (86%), m.p. 260–264 °C. ^{1}H NMR (DMSO-d_6): δ 7.01 (H: 2′, 1H, d, J = 7.1 Hz), 7.13 (H: 1, 1H, s), 7.31 (H:7′; 1H, s), 7.33 (H: 3′, 1H, d, J = 3.8 Hz), 7.37 (H: 4′, 1H, d, J = 7.2 Hz), 7.41 (H: 6′, 1H, t, J = 8.1 Hz), 7.47 (H: 6, 1H, d, J = 8.9 Hz), 7.65 (H: 8, 1H, t, J = 7.3), 7.74 (H: 9, 1H, t, J = 7.2 Hz), 7.88 (H: 8′, 1H, d, J = 8.1 Hz), 7.96 (H 5′, 1H, d, J = 8.1 Hz), 8.02 (H: 7, 1H, d, J = 8.1 Hz), 8.05 (H: 5, 1H, d, J = 9.0 Hz), 8.95 (H: NH, 1 H, d, J = 2.9 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 49.7 (C: C*H*), 114.0 (C: 10b), 116.9 (C: 6), 122.8 (C: 6′), 123.5 (C: 10), 125.1 (C: 7′), 125.3 (C: 2′), 125.9 (C: 4′), 126.3 (C: 3′), 126.0 (C: 9), 127.4 (C: 3′), 128.7 (C: 7), 128.8 (C: 5′), 128.8 (C: 8′), 129.1 (C: 8a′), 130.0 (C: 1′), 130.4 (C: 10a), 130.5 (C: 4a′), 133.7 (C: 6a), 148.1 (C: 3), 149.3 (C: 4a) ppm. $C_{22}H_{15}NO_2$ (325.36): calcd. C 81.21, H 4.65, N 4.30; found C 81.28, H 4.66, N 4.28.

*4.2.2. 1-(1-Naphthyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazin-3-one (**12**)*

White crystals, yield 0.21 g (44%), m.p. 262–265 °C. ^{1}H NMR (DMSO-d_6) δ 6.38 (H: 1, 1H, s), 7.39–7.49 (H: 3′, 6′, 5′, 6, 4H, m), 7.49–7.53 (H: 8, 8′, 2H, m), 7.85–7.89 (H: 4′, 7, 9, 7′, 4H, m), 7.93 (H: 1′, 1H, s), 7.95 (H: 10, 1H, d, J = 7.6 Hz), 8.03 (H: 5, 1H, d, J = 9.0 Hz), 8.95 (H: 2, 1H, d, J = 2.9 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 55.6 (C: 1), 115.1 (C: 10a), 118.4 (C: 6), 124.5 (C: 7′), 126.1 (C: 3′), 126.5 (C: 5′), 127.3 (C: 1′), 127.9 (C: 8), 128.1 (C: 8′), 128.8 (C: 6′), 128.9 (C: 4′), 129.4 (C: 7), 130.1 (C: 10), 130.4 (C: 9), 130.5 (C: 6a), 131.9 (C: 5), 131.9 (C: 8a′), 133.9 (C: 4a′), 134.1 (C: 2′), 141.3 (C: 10b), 148.6 (C: 4a), 150.8 (C: 3) ppm. $C_{22}H_{15}NO_2$ (325.36): calcd. C 81.21, H 4.65, N 4.30; found C 81.23, H 4.63, N 4.29.

*4.2.3. 4-(2-Naphthyl)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazin-2-one (**19**)*

White crystals, yield 0.19 g (40%), m.p. 227–232 °C. ^{1}H NMR (DMSO-d_6): δ 6.04 (H: 4, 1H, s), 7.20 (H: 5, 1H, d, J = 8.4 Hz), 7.49 (H: 1′, 1H, d, J = 8.4 Hz), 7.51–7.56 (H: 4″, 5′, 2H, m), 7.59–7.68 (H: 9, 7, 6, 3H, m), 7.89–7.96 (H: 8′, 7′, 6′, 8, 3′, 5H, m), 8.24 (H: 10, 1H, d, J = 8.3 Hz), 8.86 (H: 3, 1H, s) ppm, ^{13}C NMR (DMSO-d_6): δ 56.6 (C: 4), 115.9 (C: 2′), 120.6 (C: 10), 122.5 (C: 8a′), 123.8 (C: 8), 124.1 (C: 5), 124.8 (C: 1′), 125.7 (C: 3′), 126.5 (C: 4′), 126.7 (C: 6′), 127.0 (C: 8), 128.0 (C: 9), 128.9 (C: 7′), 132.6 (C: 4a′), 132.8 (C: 10a), 133.1 (C: 6a), 140.5 (C: 4a), 143.5 (C: 10b), 149.2 (C: 2) ppm. $C_{22}H_{15}NO_2$ (325.36): calcd. C 81.21, H 4.65, N 4.30; found C 81.20, H 4.61, N 4.29.

*4.2.4. 4-(1-Naphthyl)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazin-2-one (**20**)*

White crystals, yield 0.38 g (78%), m.p. 234–237 °C. ^{1}H NMR (DMSO-d_6): δ 6.70 (H: 4, 1H, s), 6.94 (H: 5, 1H, d, J = 8.5 Hz), 7.48 (H: 2′, 1H, d, J = 6.8 Hz), 7.53 (H: 3′, 1H, t, J = 7.8 Hz), 7.55–7.575 (H: 6, 6′, 8′, 3H, m), 7.61 (H: 8, 1H, t, J = 7.6 Hz), 7.68 (H: 9, 1H, t, J = 7.3 Hz), 7.89 (H: 5′, 1H, d, J = 8.1 Hz), 7.95 (H: 4′, 1H, d, J = 7.9 Hz), 8.00–8.02 (H: 7′, 1H, m), 8.36 (H: 10, 1H, d, J = 8.3 Hz), 8.33 (H: 7, 1H, d, J = 7.1 Hz), 8.80 (H: 3, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 53.7 (C: 4), 116.4 (C: 1′), 120.6 (H: 10), 122.5 (C: 5), 123.4 (C: 7), 123.5 (C: 4a), 123.8 (C: 6), 125.8 (C: 8′), 126.0 (C: 6′), 126.7 (C: 2′), 126.9 (C: 8), 127.1 (C: 9, 3′), 127.9 (C: 5′), 128.9 (C: 4′, 7′), 130.3 (C: 8a′), 133.2 (C: 6a), 133.9 (C: 10a) ppm. $C_{22}H_{15}NO_2$ (325.36): calcd. C 81.21, H 4.65, N 4.30; found C 81.20, H 4.64, N 4.32.

*4.3. General method for the synthesis of thiourea derivatives (**13**, **14**, 21 and **22**)*

A mixture of aminonaphthol **4**, **5**, **9** or **10** (0.30 g, 0.89 mmol) and 4-chlorophenyl isothiocyanate (0.22 g, 1.29 mmol) in abs. toluene (10 mL) was stirred at room temperature for 6 h. The crystals that separated out were filtered off and washed with toluene (2 × 10 mL). The product was purified by column chromatography (silica gel, eluent: *n*-hexane–EtOAc, 3:1).

*4.3.1. N^1-[α-(1-hydroxynaphth-2-yl)naphth-2-yl-methyl]-N^2-(4-chlorophenyl)thiourea (**21**)*

Light-yellow crystals, yield 0.26 g (65%), m.p. 125–129 °C. 7.32–7.51 (H: 4, 1′, 7′, 8, 8′, 3′, 7, 2″, CH, 10H, m), 7.63 (H: 4′, 6, 2H, d, J = 15.0 Hz), 7.77 (H: 3, 1H, s), 7.83–7.91 (H: 3″, 5′, 5, 4H, m), 8.22–8.25 (H: 6′, 1H, m), 8.78 (H: CHN*H*, 1H, d, J = 13.9 Hz), 9.69 (H: CN*H*, 1H, s), 9.87 (H: O*H*, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 56.4 (C: HC—NH), 119.8 (C: 4), 122.1 (C: 6′), 123.4 (C: 2, 8a), 124.2 (C: 4′), 124.7 (C: 3), 125.1 (C: 6), 125.4 (C: 4a), 125.7 (C: 1′), 125.8 (C: 7′), 126.0 (C: 8), 126.2 (C: 8′, 3′), 126.4 (C: 7), 127.5 (C: 5), 127.7 (C: 3″), 127.9 (C: 5′), 128.4 (C: 2″), 132.0 (C: 4a′, 2′), 132.8 (C: 4″), 133.7 (C: 8a′), 138.7 (C: 4a′), 140.0 (C: 1″), 149.6 (C: 1), 180.2 (C: *C*S) ppm. $C_{28}H_{21}ClN_2OS$ (469.00): calcd. C 71.71, H 4.51, N 5.97; found C 71.78, H 4.50, N 5.98.

*4.3.2. N^1-[α-(1-hydroxynaphth-2-yl)naphth-1-yl-methyl]-N^2-(4-chlorophenyl)thiourea (**22**)*

Light-yellow crystals: yield 0.29 g (72%), m. p. 158–160 °C. ^{1}H NMR (DMSO-d_6): δ 7.30–7.34 (C: 2″, 2, 5, 4H, m), 7.43–7.56 (C: 6, 7′, 8′, 3′, 4′, 8, 6H, m), 7.63 (C: H: 3″, 2H, d, J = 8.5 Hz), 7.82–7.89 (C: C*H*, 3, 6′, 3H, m), 7.95 (H: 2, 1H, d, J = 7.9 Hz), 8.23–8.26 (H: 2, 7, 2H, m), 8.67 (H: HC—NH, 1H, d, J = 7.7 Hz), 9.63 (H: O*H*, 1H, s), 9.75 (H: *H*N—SC, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 52.7 (C: *C*H), 119.6 (C: 4), 122.1 (C: 7), 123.0 (C: 2), 123.8 (C: 3″), 124.3 (C: 2′), 125.1 (C: 6), 125.2 (C: 4a), 125.3 (C: 5), 125.8 (C: 7′, 8′), 125.9 (C: 3′), 126.3 (C: 4′), 127.4 (C: 8a), 127.7 (C: 3, 6′), 128.2 (C: 2″), 128.6 (C: 8), 131.0 (C: 4a′), 133.5 (C: 8a′), 133.7 (C: 1′), 138.2 (C: 4″), 138.8 (C: 1″), 149.4 (C: 1), 179.8 (C: *C*S) ppm. $C_{28}H_{21}ClN_2OS$ (469.00): calcd. C 71.71, H 4.51, N 5.97; found C 71.74, H 4.51, N 5.97.

*4.3.3. N^1-[α-(2-hydroxynaphth-1-yl)naphth-2-yl-methyl]-N^2-(4-chlorophenyl)thiourea (**13**)*

Light-yellow crystals: yield 0.342 g (82%), m.p. 193–197 °C. ^{1}H NMR (DMSO-d_6): δ 7.26–7.44 (H: 1′, 8′, 7, 6′, 7′, 3, 6H, m), 7.50–7.61 (H: 3′, 3″, 4, 4H, m), 7.81–7.87 (H: 5′, 5, 2″, 4H, m), 7.94–8.03 (H: 8, 6, 2H, m), 8.30 (H: C*H*, 1H, d, J = 8.6 Hz), 8.36–8.39 (H: 4′, 1H, m), 8.65 (H: HC—N*H*, 1H, d, J = 5.7 Hz), 9.96 (H: OH, 1H, s), 10.21 (H: *H*NC, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 52.32 (C: *H*C—NH), 117.7 (C: 1), 118.8 (C: 3), 122.6 (C:8) 123.8 (C: 3″, 3′), 125.2 (C:6), 125.7 (C: 6′, 7′), 126.4 (C: 7), 126.7 (C: 8′), 127.9 (C: 1′), 128.3 (C: 2″), 128.4 (C: 4′), 128.6 (C: 4), 128.8 (C: 5),,129.5 (C: 8a, 5′), 131.2 (C: 4a′), 132.6 (C: 4a′), 132.6 (C: 8a′), 133.6 (C: 4″), 136.1 (C: 1″), 138.6 (C: 2′), 153.8 (C: 2), 179.2 (C: *C*S) ppm. $C_{28}H_{21}ClN_2OS$ (469.00): calcd. C 71.71, H 4.51, N 5.97; found C 71.69, H 4.49, N 5.93.

*4.3.4. N^1-[α-(2-hydroxynaphth-1-yl)naphth-1-yl-methyl]-N^2-(4-chlorophenyl)thiourea (**14**)*

Light-yellow crystals: yield 0.33 g (80%), m.p. 88–92 °C. ^{1}H NMR (DMSO-d_6): δ 12.01–12.27 (H: 3, 4, 5, 8′, 6′, 7, 7′, 4′, 2″, C*H*, 11H, m), 12.39 (H: 2′, d, J = 8.8 Hz), 12.53 (H: 6, 1H, s), 12.60–12.64 (H: 3′, 3″, 5′, 4H, m), 12.98–13.01 (H: 8, 1H, m), 13.55 (H: N*H*CH, 1H, d, J = 8.4 Hz), 14.45 (H: SCN*H*, 1H, s), 14.63 (H: O*H*, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 56.4 (C: *C*H), 119.8 (C: 3), 122.1 (C: 8), 123.4 (C: 1), 124.2 (C: 2′), 124.7 (C: 6), 125.2 (C: 8′), 125.4 (C: 8a′), 125.7 (C: 4,5), 125.8 (C: 6′), 126.0 (C: 7), 126.2 (C: 7′), 126.4 (C: 4′), 127.5 (C: 3′), 127.7 (C: 3″), 127.9 (C: 5′), 128.3 (C: 2″), 132.0 (C: 4a), 132.8 (C: 8a), 133.7 (C: 4a′), 138.7 (C: 1′), 140.0 (C: 1″), 149.6 (C: 4″, 2), 180.3 (C: *C*S) ppm. $C_{28}H_{21}ClN_2OS$ (469.00): calcd. C 71.71, H 4.51, N 5.97; found C 71.68, H 4.49, N 6.00.

*4.4. General method for the synthesis of naphthyl-(4-chlorophenylimino)naphthoxazine (**15**, **16**, 23 and **24**)*

To a solution of thiourea **13**, **14**, **21** or **22** (0.10 g, 0.23 mmol) in MeOH (6 mL), MeI (0.10 mL, 6.43 mmol) was added and the solution was stirred for 4 h. After evaporation of the solvent, the residue was stirred in 3 M methanolic KOH (10 mL) for 4 h, after which the resultant white precipitate was filtered off and recrystallized from *n*-hexane–iPr$_2$O (5:1, 36 mL).

*4.4.1. 1-(2-Naphthyl)-3-(4-chlorophenylimino)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**15**)*

Yellow crystals, yield 0.07 g (76%), m.p. 102–105 °C. ^{1}H NMR (DMSO-d_6): δ 6.61 (H: 6′, 1H, d, J = 7.0 Hz), 7.13 (H: 1, 1H, s), 7,15–7.23 (H: 3″, 7′, 3H, m), 7.32–7.45 (H: 5, 1′, 5′, 3′, 4H, m), 7.56–7.64 (H: 8, 2″, 2H, m), 7.75–7.82 (H: 10, 8′, 2H, m), 7.96–7.99 (H: 7, 1H, m), 8.06–8.07 (H: 6, 1H, d, J = 9.0 Hz), 7.88–8.89 (H: 9, 1H, d, J = 8.5 Hz), 9.43 (H: 2, 1H, s) ppm. ^{13}C NMR (DMSO-d_6): δ 51.3 (C: 1), 114.8 (C: 10a), 116.2 (C: 5), 119.3 (C: 1′), 122.9 (C: 3′), 123.9 (H: 6′), 124.7 (C: 9), 124.8 (C: 4′), 124.9 (C: 8a′), 125.5 (C: 7′), 126.0 (C: 8), 126.4 (C: 4a′), 127.2 (C: 8′), 127.8 (C: 7), 128.2 (C: 3″), 128.4 (C: 10a), 128.5 (C: 6a), 128.7 (C: 2″), 129.7 (C: 6), 129.8 (C: 10), 130.7 (C: 10b), 130.9 (C: 2′), 133.8 (C: 1″), 139.6 (C: 4″), 144.6 (C: 3), 147.7 (C: 4a) ppm. $C_{28}H_{19}ClN_2O$ (434.92): calcd. C 77.33, H 4.40, N 6.44; found: C 77.30, H 4.42, N 6.48.

*4.4.2. 1-(1-Naphthyl)-3-(4-chlorophenylimino)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**16**)*

Yellow crystals, yield 0.075 g (82%), m.p. 115–119 °C. ^{1}H NMR (DMSO-d_6): δ 7.20 (H: 5, 1H, d, J = 7.6 Hz), 7.32–7.51 (H: 10, 9, 6′, 4′, 7, 7′, 7″, 1′, 8, 9H, m), 7.61 (H: 2″, 2H, d, J = 7.4), 7.70 (H: 2′, 1H, s), 7.79–7.84 (H: 3″, 5′, 6, 3, 4, 6H, m), 8.09 (H: C*H*, 1H, s), 8.19 (H: N*H*, 1H, s), ^{13}C NMR (DMSO-d_6): δ 53.7 (C: 1), 119.7 (C: 10b), 120.3 (C: 5), 123.9 (C: 10), 125.2 (C: 8), 125.9 (C: 2″), 126.4 (C: 9), 127.0 (C: 4′), 127.6 (C: 6′), 128.4 (C: 2′), 128.8 (C: 3″), 129.1 (C: 6, 7), 129.4 (C: 6a), 130.1 (C: 7′), 130.2 (C: 3′), 133.3 (C: 8a′, 4″), 134.0 (C: 1′), 134.1 (C: 10a, 4a′), 139.8 (C: 1″), 141.5 (C: 4a), 181.7 (C: 3) ppm. $C_{28}H_{19}ClN_2O$ (434.92): calcd. C 77.33, H 4.40, N 6.44; found C 77.31, H 4.38, N 6.48.

*4.4.3. 4-(2-Naphthyl)-2-(4-chlorophenylimino)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazine (**23**)*

Yellow crystals, yield 0.062 g (67%), m.p. 185–188 °C. ^{1}H NMR (DMSO-d_6): δ 6.06 (H: NH—C*H*, 1H, s), 7.19 (H: 4′, 1H, d, J = 8.4 Hz), 7.31 (H: 2″, 2H, d, J = 8.8 Hz), 7.43–7.52 (H: 3′, 8, 5, 3 H, m), 7.56–7.63 (H: 10, 7′, 2H, m), 7.67 (H: 9, 1H, t, J = 7.3 Hz), 7.74(7, 6, 2H, d, J = 8.3 Hz), 7.86–7.93 (H: 3″, 5′, 8′, 1′, 5H, m), 8.30 (H: 6′, 1H, d, J = 8.3 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.7 (C: 4), 118.2 (C: 4a), 119.8 (C: 6), 120.6 (C: 6′), 122.4 (C: 10a), 123.6 (C: 7′), 124.5 (C: 4′), 124.9 (C: 1′), 125.4 (C: 5), 125.7 (C: 8), 126.0 (C: 3′), 126.4 (C: 9). 126.6 (C: 7), 126.8 (C: 10), 127.6 (C: 5′), 127.9 (C: 2″), 128.5 (C: 3″), 128.6 (C: 4a′, 8′), 132.3 (C: 6a), 132.9 (C: 8a′, 4″) ppm. $C_{28}H_{19}ClN_2O$ (434.92): calcd. C 77.33, H 4.40, N 6.44; found C 77.35, H 4.43, N 6.45.

*4.4.4. 4-(1-Naphthyl)-2-(4-chlorophenylimino)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazine (**24**)*

Yellow crystals, yield 0.068 g (74%), m.p. 195–196 °C. ^{1}H NMR (DMSO-d_6): δ 6.68 (H: 4, 1H, s), 7.03 (H: 8′, 1H, d, J = 8.3 Hz), 7.09 (H: 7′, 1H, d, J = 15.0 Hz), 7.23 (H: 2″, 2H, d, J = 8.4 Hz), 7.41 (H: 6′, 1H, t, J = 7.6 Hz), 7.57–7.72 (H: 4′, 9, 3″, 6, 5, 8, 7H, m), 7.86 (H: 5′, 1H, d, J = 8.0 Hz), 7.95 (H: 2′, 7, 2H, dd, J = 8.0, 19.8 Hz), 8.33 (H: 3′, 1H, d, J = 8.2 Hz), 8.55 (H: 10, 1H, d, J = 8.1 Hz), 9.54 (H: 3, 1H, br) ppm. ^{13}C NMR (DMSO-d_6): δ 54.3 (C: 4), 117.9 (C: 4a, 1′), 119.5 (C: 9), 120.5 (C: 3′), 122.4 (C: 10a), 123.5 (C: 5), 124.3 (C: 8′), 124.4 (C: 6), 124.8 (C: 4″), 125.4 (C: 7′), 125.6 (C: 10), 125.8 (C: 6′), 126.2 (C: 4′), 126.6 (C: 3″), 126.7 (C: 3″), 127.8 (C: 9, 5′), 128.3 (C: 2″), 128.6 (2′), 130.9 (C: 8a′), 132.9 (C: 4a′), 133.7 (C: 6a), 140.4 (C: 10b), 143.8 (C: 1″), 144.8 (C: 2) ppm. $C_{28}H_{19}ClN_2O$ (434.92): calcd. C 77.33, H 4.40, N 6.44; found C 77.35, H 4.37, N 6.42.

*4.5. General method for the synthesis of naphthylnaphth[1,3]oxazines (**17**, 18 and **25**)*

Aminonaphthol **4**, **5** or **10** (0.15 g, 0.45 mmol), 3 equivalents of paraformaldehyde, 1.1 equivalent of Et$_3$N and chloroform (8 mL) were mixed in room temperature for 6 h and the solvent was then evaporated off. The product was purified by column chromatography (silica gel, eluent: *n*-hexane–EtOAc).

*4.5.1. 1-(2-Naphthyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**17**)*

Eluent for column chromatography: hexane–EtOAc (4:1), white crystals, yield 0.067 g (49%), m.p. 157–160 °C. ^{1}H NMR (DMSO-d_6): δ 4.35–4.39 (H: 2, 1H, m), 4.60 (H: 3, 1H, dd, J = 10.2, 13.65 Hz), 4.89 (H: 3, 1H, dd, J = 3.8, 9.8 Hz), 5.675 (H: 1, 1H, d, J = 5.0 Hz), 7.14 (H: 1, 1H, d, J = 12.9 Hz), 7.22–7,29 (H: 10, 1′, 2H, m), 7.34–7.36 (H: 5, 1H, m), 7.39–7.41 (H: 9, 1′, 2H, m), 7.46 (H: 6′, 1H, t, J = 7.1 Hz), 7.61 (H: 7, 1H, d, J = 8.1 Hz), 7,67 (H: 8′, 1H, d, J = 8.0 Hz), 7.83–7.94 (H: 6, 5′, 7′, 4′, 4H, m) ppm. ^{13}C NMR (DMSO-d_6): δ 51.9 (C: 1), 73.2 (C: 3), 114.8 (C: 10b), 119.1 (C: 5), 122.5 (C: 10), 122.9 (C: 8), 125.9 (C: 6′), 126.1 (C: 7), 126.4 (C: 9), 127.4 (C: 1′), 127.5 (C: 3′), 127.6 (C: 4′), 127.8 (C: 8′), 127.9 (C: 7′), 128.3 (C: 6a), 128.5 (C: 5′), 128.9 (C: 6), 131.4 (C: 10′), 132.2 (C: 4a′), 132.5 (C: 8a′), 140.8 (C: 10a), 152.0 (C:4a) ppm. $C_{22}H_{17}NO$ (311.38): calcd. C 84.86, H 5.50, N 4.50; found C 84.87, H 5.49, N 4.51.

*4.5.2. 1-(1-Naphthyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**18**)*

Eluent for column chromatography: *n*-hexane–EtOAc (3:1), white crystals, yield 0.057 g (42%), m.p. 135–140 °C. ^{1}H NMR (DMSO-d_6): δ 4.31–4.34 (H: 2, 1H, m), 4.63 (H: 3, 1H, dd, J =10.4, 13.8 Hz), 4.86 (H: 3, 1H, dd, J = 3.6, 9.8 Hz), 6.33 (H: 1, 1H, d, J = 4.9 Hz), 6.81 (H: 2′, 1H, d, J = 6.7 Hz), 7.08 (H: 10, 1H, d, J = 8.3 Hz), 7.16–7.25 (H: 5′, 5, 3′, 9, 4H, m), 7.60 (H: 6′, 1H, t, J = 7.5 Hz), 7.67 (H: 8, 1H, t, J = 7.6 Hz), 7.81–7.84 (H: 4′, 6, 8′, 3H, m), 7.98 (H: 7′, 1H, d, J = 8.0 Hz), 8.63 (H: 7, 1H, d, J = 8.3 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 48.4 (C: 1), 73.2 (C: 3), 114.8 (C: 10b), 119.0 (C: 5), 122.3 (C: 10), 122.9 (C: 9), 124.5 (C: 7), 124.7 (C: 3′), 125.8 (C: 8), 126.2 (C: 6′), 126.4 (C: 6), 127.4 (C:2′), 127.8 (C: 4′), 128.3 (C: 6a), 128.5 (C: 8′), 128.6 (C: 5′), 128.8 (C: 7′), 131.0 (C: 8a′), 131.3 (C: 1′), 133.9 (C: 4a′), 138.0 (C: 10a), 152.3 (C: 4a) ppm. $C_{22}H_{17}NO$ (311.38): calcd. C 84.86, H 5.50, N 4.50; found C 84.81, H 5.51, N 4.53.

*4.5.3. 4-(1-Naphthyl)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazine (**25**)*

Eluent for column chromatography: hexane–EtOAc (3:1), white crystals, yield 0.052 g (37%), m.p. 141–145 °C. ^{1}H NMR (DMSO-d_6) δ 4.34 (H: 3, 1H, ddd, J = 5.4; 6.2, 12.2 Hz), 4.75 (H: 2, 1H, dd, J = −10.3, 12.2 Hz), 5.06 (H: 2, 1H, dd, J = 5.4, −10.0 Hz), 6.03 (H: 4, 1H, d, J = 6.2 Hz), 6.93 (1H, d, J = 7.0 Hz), 6.96 (1H, d, J = 8.4 Hz), 7.36 (1H, t, J = 7.7 Hz), 7.38 (1H, d, J = 8.5 Hz), 7.59 (4H, m), 7.86 (2H, d, J = 8.8 Hz), 7.98 (1H, d, J = 8.0 Hz), 8.14 (1H, m), 6.47 (1H, d, J = 8.4 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 52.9 (C: 4), 75.3 (C: 2), 117.4 (C: 7), 119.6 (C: 2′), 121.4 (C: 6′), 123.7 (C: 8′), 124.9 (C: 6), 125.3 (C: 1′), 125.6 (C: 10), 125.8 (C: 8), 126.3 (C: 7′), 126.5 (C: 6′), 126.6 (C: 5), 127.6 (C: 3′), 128.2 (C: 4′), 128.6 (C: 5′), 128.9 (C: 9), 129.3 (C: 10a), 131.7 (C: 8a′), 133.6 (C: 6a), 134.2 (C: 4a′), 138.1 (C: 6a), 150.3 (C: 10b) ppm. $C_{22}H_{17}NO$ (311.38): calcd. C 84.86, H 5.50, N 4.50; found C 84.82, H 5.53, N 4.50.

*4.6. General method for the synthesis of naphthyl-(4-nitrophenyl)-2,3-dihydro-1H-naphth[1,3]oxazines (**27**, **28**, 31 and **32**)*

Aminonaphthol **4**, **5**, **9** or **10** (0.15 g, 0.45 mmol), 1 equivalent amount of 4-nitrobenzaldehyde, 1.1 equivalent of Et_3N and methanol (2 mL) were mixed at room temperature for 10 min, and the resulting crystals were filtered off and recrystallized from iPr_2O (30 mL).

*4.6.1. 1-(2-Naphthyl)-3-(4-nitrophenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**27**)*

Yellow crystals, yield 0.162 g (84%), m.p. 232–235 °C. ^{1}H NMR (DMSO-d_6): δ 4.72 (H: 2, 1H, dd, J = 5.3, 13.9 Hz), 5.82 (H: 3, 1H, d, J = 13.9 Hz), 6.47 (H: 1, 1H, d, J = 5.2 Hz), 6.93 (H: 3′, 1H, d, J = 7.0 Hz), 7.13 (H: 6′, 1H, d, J = 8.3 Hz), 7.22 (H: 1′, 1H, t, J = 6.9 Hz), 7.27–7.31 (H: 5, 7′, 2H, m), 7.62 (H: 8, 1H, t, J = 7.3 Hz), 7.70 (H: 2″, 2H, s), 7.72 (H: 9, 1H, s), 7.85–7.92 (H: 8′, 5′, 6, 3H, m), 8.01 (H: 7, 1H, d, J = 8.1 Hz), 8.22 (H: 8′, 1H, d, J = 8.8 Hz), 8.68 (H: 10, 1H, d, J = 8.5 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 49.9 (C: 1), 81.9 (C: 3), 114.6 (C: 10b), 119.0 (C: 5), 122.6 (C: 6′), 123.3 (C: 4′), 123.5 (C: 3″), 124.4 (C: 10), 124.9 (C: 7′), 126.0 (C: 8), 126.5 (C: 9), 126.7(C: 1′), 127.8 (C: 3′), 127.9 (C: 2″), 128.2 (C: 8′), 128.6 (C: 7), 128.7 (C: 8a′), 128.8 (C: 5′), 129.2 (C: 6), 131.0 (C: 10a), 131.1 (C: 4a′), 134.0 (C: 6a), 137.8 (C: 2′), 145.8 (C: 4″), 147.4 (C: 1″), 152.5 (C: 4a) ppm. $C_{28}H_{20}N_2O_3$ (432.47): calcd. C 77.76, H 4.66, N 6.48; found C 77.69, H 4.68, N 6.52.

*4.6.2. 1-(1-Naphthyl)-3-(4-nitrophenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**28**)*

White crystals, yield 0.153 g (80%), m.p. 170–173 °C. ^{1}H NMR (DMSO-d_6): δ 4.74 (H: 2, 1H, dd, J = 5.0, 13.6 Hz), 5.76 (H: 3, 1H, d, J = 13.6 Hz), 5.84 (H: 1, 1H, d, J = 4.9 Hz), 7.29–7.33 (H: 2″, 9′, 2H, m), 7.4–7.53 (H: 10, 2′, 5′, 6′, 8′, 5H, m), 7.69–7.74 (H: 3′, 7′, 2H, m), 7.80 (H: 3″, 2H, d, J = 8.7 Hz), 7.89–7.98 (H: 4′, 7, 6, 6′, 4H, m), 8.25–8.26 (H: 8, 5, 2H, m). ^{13}C NMR (DMSO-d_6): δ 54.6 (C: 1), 83.2 (C: 3), 114.6 (C: 10b), 119.1 (C: 5), 123.3 (C: 8), 123.4 (C: 2″), 124.0 (C: 2′), 124.4 (C: 10), 125.4 (C: 8′), 126.0 (C: 6′), 126.1 (C: 9), 126.7 (C: 3′), 127.5 (C: 4′, 7′), 127.8 (C: 5′), 127.9 (C: 3″), 128.1 (C: 6), 128.5 (C: 6a), 128.7 (C: 6′), 129.4 (C: 7), 131.3 (C: 8a′), 132.3 (C: 10a), 132.5 (C: 4a′), 140.6 (C: 1′), 145.7 (C: 1″), 147.2 (C: 4″), 152.1 (C:4a) ppm. $C_{28}H_{20}N_2O_3$ (432.47): calcd. C 77.76, H 4.66, N 6.48; found C 77.82, H 4.68, N 6.44.

*4.6.3. 4-(2-Naphthyl)-2-(4-nitrophenyl)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazine (**31**)*

Light-brown crystals, yield 0.151 g (78%), m.p. 190–192 °C. ^{1}H NMR ($CDCl_3$): δ 5.45 (H: 4, 1H, s), 5.92 (H: 2, 1H, d, J = 8.4 Hz), 7.14 (H: 5. 1H, d, J = 8.4 Hz), 7.33–7.36 (H: 6′, 1H, m), 7.44–7.51 (H: 10, 5, 2H, m), 7.57–7.59 (1′, 9, 7, 3H, m), 7.76–7.83 (H: 8′, 7′, 2H, m), 7.85–7.87 (H: 2″, 2H, d, J = 7.8 Hz), 7.91 (H: 4′, 1H, d, J = 8.5 Hz), 8.01 (H: 5′, 1H, d, J = 8.2 Hz), 8.25 (H: 3″, 2H, d, J = 8.7 Hz), 8.32–8.38 (H: 10, 8, 2H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 56.0 (C: 4), 82.2 (C: 2), 116.4 (C: 4a), 120.1 (C: 6), 121.3 (C: 8), 123.6 (C: 3″), 125.3 (C: 7), 125.9 (C: 6′), 126.1 (C: 5),126.3 (C: 10), 126.6 (7′), 127.0 (C: 1′) 127.5 (C: 2″), 127.9 (C: 4′), 128.1 (C: 3′), 128.5 (C: 8′), 128.6 (C: 9), 129.5 (C: 5′), 132.9 (C: 4a′), 133.0 (C: 8a′), 133.9 (C: 6a), 140.3 (C: 2′), 146.2 (C: 1″), 147.9 (C: 4″), 149.1 (C: 10b) ppm. $C_{28}H_{20}N_2O_3$ (432.47): calcd. C 77.76, H 4.66, N 6.48; found C 77.78, H 4.64, N 6.50.

*4.6.4. 4-(1-Naphthyl)-2-(4-nitrophenyl)-2,3-dihydro-1H-naphth[2,1-e][1,3]oxazine (**32**)*

Yellow crystals, yield 0.156 g (80%), m.p. 197–200 °C. ^{1}H NMR ($CDCl_3$): δ 2.87 (H: 3, 1H, s), 5.96 (H: 2, 1H, s), 6.05 (H: 4, 1H, s), 7.02–7.07 (H: 5, 8, 2H, m), 7.32 (H: 3′, 1H, t, J = 8.1 Hz), 7.42 (H: 6, 1H, d, J = 8.5 Hz), 7.55–7.61 (H: 6′, 8, 9, 3H, m), 7.77 (H: 3″, 2H, J = 8.5 Hz), 8.37 (H: 10, 1H, d, J = 7.5 Hz), 8.48 (H: 2′, 1H, d, J = 8.5 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 53.1 (C: 4), 82.2 (C: 2), 116.6 (C: 4a), 120.2 (C: 6), 121.3 (C: 2″), 124.1 (C: 2′), 124.8 (C: 3′), 125.2 (C: 10a), 125.9 (C: 8, 5), 126.1 (C: 8′), 126.5 (C: 6′), 126.6 (C: 6′), 126.5 (C: 3″), 127.7 (C: 7′), 127.8 (C: 7), 128.8 (C: 5′, 9), 128.9 (C:4′) ppm. $C_{28}H_{20}N_2O_3$ (432.47): calcd. C 77.76, H 4.66, N 6.48; found C 77.80, H 4.69, N 6.45.

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References

[1] M. Betti, Gazz. Chim. Ital. 30 II (1900) 310.
[2] M. Betti, Org. Synth. Coll. I (1941) 381.
[3] C. Cardellicchio, G. Ciccarella, F. Naso, E. Schingaro, F. Scordari, Tetrahedron: Asymmetry 9 (1998) 3667.
[4] C. Cimarelli, A. Mazzanti, G. Palmieri, E. Volpini, J. Org. Chem. 66 (2001) 4759.
[5] C. Cimarelli, G. Palmieri, E. Volpini, Tetrahedron: Asymmetry 13 (2002) 2417.
[6] J.-X. Ji, L.-Q. Qiu, C.W. Yip, A.S.C. Chan, J. Org. Chem. 68 (2003) 1589.
[7] J.-X. Ji, J. Wu, T.T.-L. Au-Yeung, C.-W. Yip, R.K. Haynes, A.S.C. Chan, J. Org. Chem. 70 (2005) 1093.
[8] Y. Lu, Z. Nikolovska-Coleska, X. Fang, W. Gao, S. Shangary, S. Qiu, D. Qin, S. Wang, J. Med. Chem. 49 (2006) 3759.
[9] A.Y. Shen, C.T. Tsai, C.L. Chen, Eur. J. Med. Chem. 34 (1999) 877.
[10] H.R. Shaterian, H. Yarahmadi, M. Ghashang, Bioorg. Med. Chem. Lett. 18 (2008) 788.
[11] H.R. Shaterian, H. Yarahmadi, M. Ghashang, Tetrahedron 64 (2008) 1263.
[12] H.R. Shaterian, H. Yarahmadi, Tetrahedron Lett. 49 (2008) 1297.
[13] C. Duff, J.E. Bills, J. Chem. Soc. (1934) 1305.
[14] D. Tóth, I. Szatmári, F. Fülöp, Eur. J. Org. Chem. (2006) 4664.
[15] I. Szatmári, D. Tóth, A. Koch, M. Heydenreich, E. Kleinpeter, F. Fülöp, Eur. J. Org. Chem. (2006) 4670.
[16] Z. Turgut, E. Pelit, A. Köycü, Molecules 12 (2007) 345.
[17] I. Szatmári, T.A. Martinek, L. Lázár, F. Fülöp, Tetrahedron 59 (2003) 2877.
[18] I. Szatmári, T.A. Martinek, L. Lázár, F. Fülöp, Eur. J. Org. Chem. (2004) 2231.
[19] Gaussian 03, Revision C.02, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S.A. Dapprich, D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian, Inc., Wallingford, CT, 2004.
[20] J.J.P. Stewart, Comp. Chem. 10 (1989) 209.
[21] J.J.P. Stewart, Comp. Chem. 10 (1989) 221.
[22] W.J. Hehre, L. Radom, P.v.R. Schleyer, J.A. Pople, *Ab Initio* Molecular Orbital Theory, Wiley, New York, 1986.
[23] A.D. Becke, J. Chem. Phys. 98 (1993) 1372.
[24] T. Helgaker, M. Watson, N.C. Handy, J. Chem. Phys. 113 (2000) 9402.
[25] V. Barone, J.E. Peralta, R.H. Contreras, J.P. Snyder, J. Phys. Chem. A 106 (2002) 5607.
[26] SYBYL 7.3, Tripos Inc., 1699 South Hanley Rd. St. Louis, MO 63144, USA, 2006.
[27] GaussView 2.0, Gaussian Inc., Carnegie Office Park, Building 6, Pittsburgh, PA 15106, USA.