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Synthesis and detailed conformational analysis of new naphthoxazino[2,3-*a*]benz[*c*]azepine and naphthoxazino[2,3-*a*]thieno[3,2-*c*]pyridine derivatives

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Abstract

New naphth[1,3]oxazino-benzazepines and -thienopyridines were synthesized using a modified Mannich-type synthetic pathway by the reaction of 4,5-dihydro-3*H*-benz[*c*]azepine or 6,7-dihydrothieno[3,2-*c*]pyridine and different substituted aminonaphthols. Reaction conditions were optimized using microwave irradiation, with relatively short reaction times and a temperature of 80 °C. The formation of undesired naphthoxazine by-products made the separation/purification of the products challenging, therefore the reactions were repeated and systematically studied, starting from secondary and tertiary aminonaphthol derivatives, when the isolation of an ortho-quinonemethide structure occurred unexpectedly. Scope and limitations of its formation were also investigated. Conformational studies including ring inversion of a selection of the novel polyheterocycles were performed using NMR methods and supplementary DFT modelling.

Keywords: aminonaphthol; DFT modelling; Mannich reaction; microwave reaction; *ortho*-quinonemethide

Introduction

The Mannich reaction[1-3] is an important method to form new C–C bonds. This synthetic pathway is widely used in the formation of secondary and tertiary amine derivatives and it is a key step in the syntheses of numerous bioactive molecules and complex natural products.[4,5] In one of the special variations of the modified Mannich reaction (Figure 1), 1- and 2-naphthols are applied as electron-rich aromatic compounds.[6,7]

The synthesis of new heterocycles is one of the most important areas of application of Mannich bases bearing two or more functional groups.[6,7] In previous papers, the synthesis and conformational studies of naphth[1,2-*e*][1,3]oxazino[3,4-*c*][1,3]benzoxazines,[8,9] naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolines,[10] naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones[11] and naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinoline derivatives[12] were published.

In our earlier studies, an unexpected reaction between 1-α-aminobenzyl-2-naphthol or 1-aminomethyl-2-naphthol and 6,7-dimethoxy-3,4-dihydroisoquinoline led to the formation of 9,10-dimethoxy-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines under microwave (MW) irradiation.[13] In the latter syntheses, 1-aminomethyl-2-naphthol and substituted 1-aminobenzyl-2-naphthols were applied to prepare naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline derivatives. Mechanistically, aminonaphthols were proven to be the initiator of the intermediate for the [4+2] cycloaddition forming the desired pentacycles (Figure 1). A detailed NMR spectroscopic and theoretical study on the dynamic behavior of these conformationally flexible heterocyclic ring systems confirmed an unexpected dynamic process between the *trans* and *cis* diastereomers.[14] Maycock *et al.* described an alternative synthesis of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines via the copper-mediated intramolecular α-functionalization of tertiary amines through the oxidative activation of C–H bonds.[15]

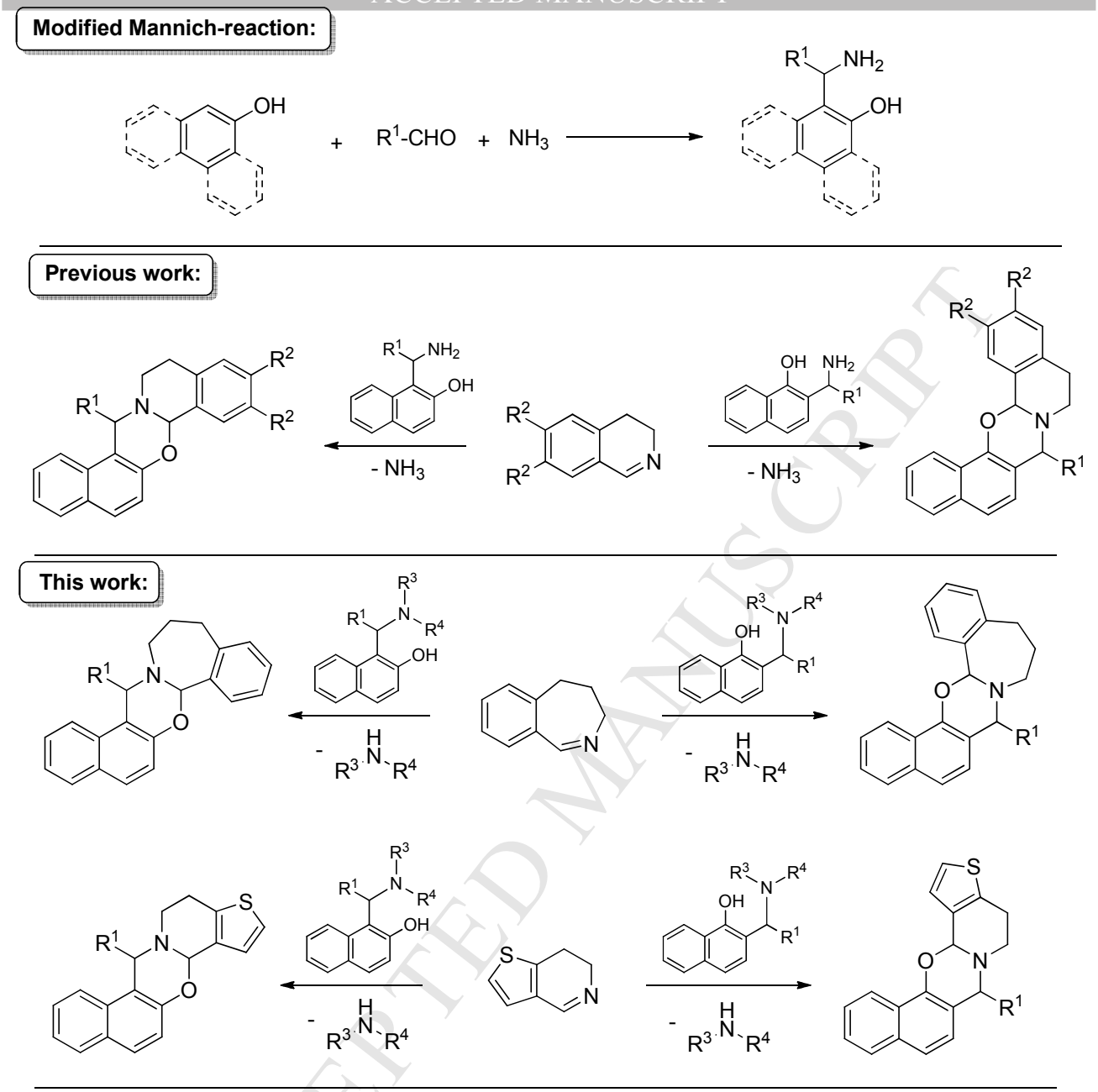
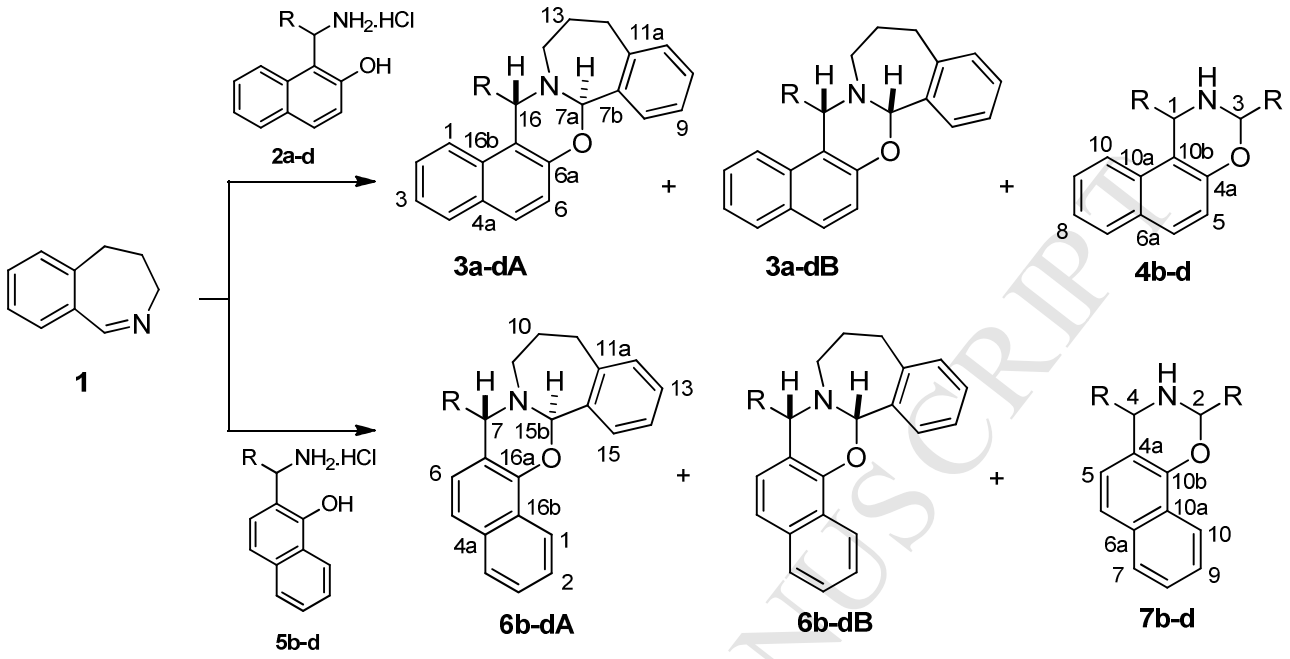


Figure 1

Our major aim in this study was to extend this recent reaction, starting from 4,5-dihydro-3*H*-benz[*c*]azepine and 6,7-dihydrothieno[3,2-*c*]pyridine as cyclic imines and 1-aminobenzyl-2-naphthols and 2-aminomethyl-1-naphthols (Figure 1).[16] In addititon, we also studied the obtained conformationally flexible ring systems by means of NMR spectroscopy and complementary theoretical calculations carried out at the B3LYP/6-31 G(d) level of DFT.

In our first experiments, 4,5-dihydro-3*H*-benz[*c*]azepine (**1**) was reacted with aminonaphthol derivative **2a**. The precursor cyclic imine **1** was synthesized using literature methods in four steps starting from α-tetralone.[17,18] The reaction between **1** and **2a** was performed in 1,4-dioxane under

microwave irradiation at 80 °C. Crystallization of the product in MeOH resulted in formation of **3a** in a good yield (Table 1).



Scheme 1. Synthesis of benz[*c*]azepine derivatives **3a-d** and **6b-d**

The reaction of **1** and primary aminonaphthol **2b**, gave undesired compound **4b**. It was presumed to be a side product[19] formed by the reaction of **2b** and benzaldehyde (the decomposition product of **2b**). *Trans*-**4b** and its acyclic imine form were detected by TLC and by NMR spectroscopy using the characteristic H-3 chemical shift at 5.64 ppm and at 8.77 ppm. Purification by column chromatography gave new pentacycle **3b** identified as the *trans* diastereomer **3bA** (Scheme 1) by the NOE interaction between H-7a and the *ortho* H-2'6' protons of the phenyl group attached to position 16. These conditions were then applied to the reactions starting from **2c** and **2d**. In these two cases, the NMR spectra recorded for the crude products indicated the presence of the desired pentacycles **3c** and **3d** contaminated by naphthoxazines **4c** and **4d**, respectively. The protocol based on column chromatography proved to be successful in the separation of **3c** and **4c**, but failed for the mixture of **3d** and **4d**. Since further attempts (*e.g.* recrystallization) were found to be ineffecient to separate the desired naphthoxazine, the development of a new synthetic strategy was needed to isolate **3d** in pure form.

To examine the possibility of the extension of the reaction, 2-aminobenzyl-1-naphthols (**5b-d**) were also applied as reactants in the annulation reactions. Related results and conditions are

summarized in Table 1. By-products **7b-d**[20,21] were also detected but the separation process with **7b-d** was successful and new derivatives **6b-d** were isolated in pure form (Scheme 1).

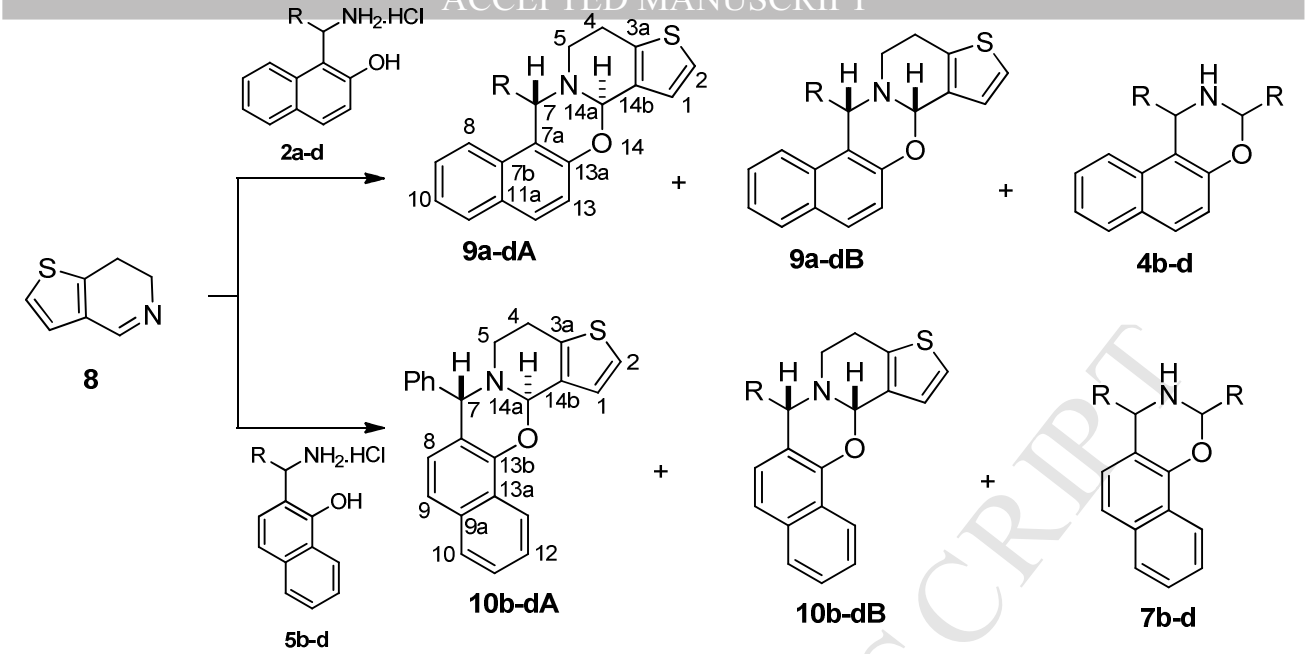
Table 1. Reaction conditions for the preparation of naphthoxazino-benzazepines (**3a-d**, **6b-d**)

Aminonaphthol	Reaction time (min)[a]	Product(s)			D.r.[b]	Conversion[d] (%)	Yield[e] (%)
2a	30	**3aA**			-	91	77
2b	80	**3bA** (48%)	**3bB** (0%)	**4b** (52%)	-[c]	92	37
2c	80	**3cA** (44%)	**3cB** (0%)	**4c** (56%)	-[c]	91	34
2d	40	**3dA** (45%)	**3dB** (0%)	**4d** (55%)	-[c]	88	-[f]
5b	40	**6bA** (44%)	**6bB** (7%)	**7b** (49%)	1:0.16	93	-[g]
5c	20	**6cA** (48%)	**6cB** (0%)	**7c** (52%)	-[c]	88	32
5d	40	**6dA** (39%)	**6dB** (10%)	**7d** (51%)	1:0.25	90	-[g]

[a] syntheses were achieved at 80 °C using microwave irradiation
[b] diastereomeric ratio (*trans*:*cis*), determined from the ^{1}HNMR spectra of the crude reaction mixtures
[c] the minor distereomer could not be detected
[d] conversion, calculated from the ^{1}HNMR spectra of the crude reaction mixtures
[e] isolated yields, obtained for the major (**A**) products
[f] the desired (**A** and **B**) and the by-product (**C**) could not be separated
[g] the diastereomers (**A** and **B**) could not be separated

Next, 6,7-dihydrothieno[3,2-*c*]pyridine (**8**) was chosen as a new representative cyclic imine. Its synthesis was achieved *via* a Bischler-Napieralski cyclization starting from 2-thiophen-2-yl-ethylamine.[22] Through the reaction of **8** and **2a**, the formation of the desired unsubstituted naphthoxazine **9a** was obtained in good yield (74%, Table 2).

When the synthesis started from aminoarylnaphthols (**2b-d** or **5b-d**; Scheme 2) the results of the separation process of the pentacycles **9b-d** or **10b-d** from the naphthoxazines **4b-d** or **7b-d** depended on the structure of the initial compound. With the exception of **9c** and **9d** column chromatography proved to be successful to provide the desired pentacycles **9b**, **10b-d** (Table 2) in pure form. Because of the difficulty with **9c** and **9d**, an alternative synthetic pathway was needed.



R: H (**a**), Ph (**b**), 1-Nph (**c**), 2-Nph (**d**)

The presented numbering of atoms corresponding the IUPAC rules is used for assignment of the ^{1}H- and ^{13}C NMR data.

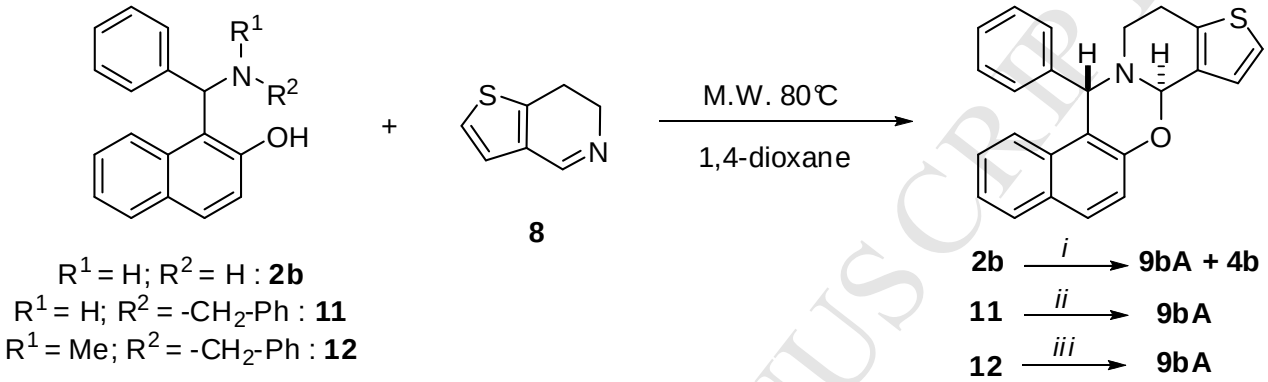
Scheme 2. Synthesis of thieno[3,2-*c*]pyridine derivatives **9a-d** and **10b-d**

Table 2. Reaction conditions for the preparation of naphthoxazino-thienopyridines (**9a-d**, **10b-d**)

Aminonaphthol	Reaction time (min)[a]	Product(s)			D.r.[b]	Conversion[d] (%)	Yield[e] (%)
2a	20	**9aA**			-	92	74
2b	60	**9bA** (42%)	**9bB** (0%)	**4b** (58%)	-[c]	93	38
2c	40	**9cA** (44%)	**9cB** (0%)	**4c** (56%)	-[c]	90	-[f]
2d	40	**9dA** (46%)	**9dB** (0%)	**4d** (54%)	-[c]	91	-[f]
5b	20	**10bA** (34%)	**10bB** (10%)	**7b** (56%)	1:0.30	88	-[g]
5c	20	**10cA** (49%)	**10cB** (0%)	**7c** (51%)	-[c]	92	34
5d	20	**10dA** (36%)	**10dB** (12%)	**7d** (52%)	1:0.33	89	-[g]

[a] syntheses were achieved at 80 °C using microwave irradiation
[b] diastereomeric ratio (*trans*:*cis*), calculated from the ^{1}HNMR spectra of the crude reaction mixtures
[c] the minor distereomer could not be detected
[d] conversion, calculated from the ^{1}HNMR spectra of the crude reaction mixtures
[e] isolated yields, obtained for the major (**A**) products
[f] the desired (**A** and **B**) and the by-product (**C**) could not be separated
[g] the diastereomers (**A** and **B**) could not be separated

It is important to mention that the formation of two diastereomers is possible in all cases. Therefore, the diastereomeric ratios were examined in the crude reaction mixture. The formation of the minor diastereomers **6bB**, **6dB**, **10bB** and **10dB** could only be detected when the reaction was performed with **5b** or **5d** as aminonaphthol starting materials (Tables 1 and 2). It can be concluded that the diastereoselectivity of the reaction depends on the steric effect of the aromatic ring at position 14 or 16 and on the position of annulation of the naphthyl ring.



Scheme 3. Synthesis of **9bA** starting from aminonaphthol derivatives **2b**, **11** and **12**

Since the separation of **3d, 9c** and **9d** from by-products **4c-d** failed, the development of an alternative synthetic pathway was necessary. The synthesis of **9bA** was chosen as a model reaction and **2b**[19] as primary, **11**[23] as secondary and **12**[15] as tertiary aminonaphthol derivatives, while **8** was selected as a cyclic imine (Scheme 3). The reason for selecting secondary and tertiary aminonaphthols as starting materials was that the formation of the naphthoxazine side products was not expected. In our systematic investigation, the highest conversion in the reaction of **8** with different aminonaphthols (**2b**, **11** and **12**) was found for *i*, albeit with the formation of byproduct **4b** in about 55%. The transformation of **12** (*iii*) proved to be better, because a conversion of 70% was measured in 60 min. In contrast, secondary aminonaphthol **11** gave a conversion of about 60% after an extended reaction time of 200 min (Figure 2).

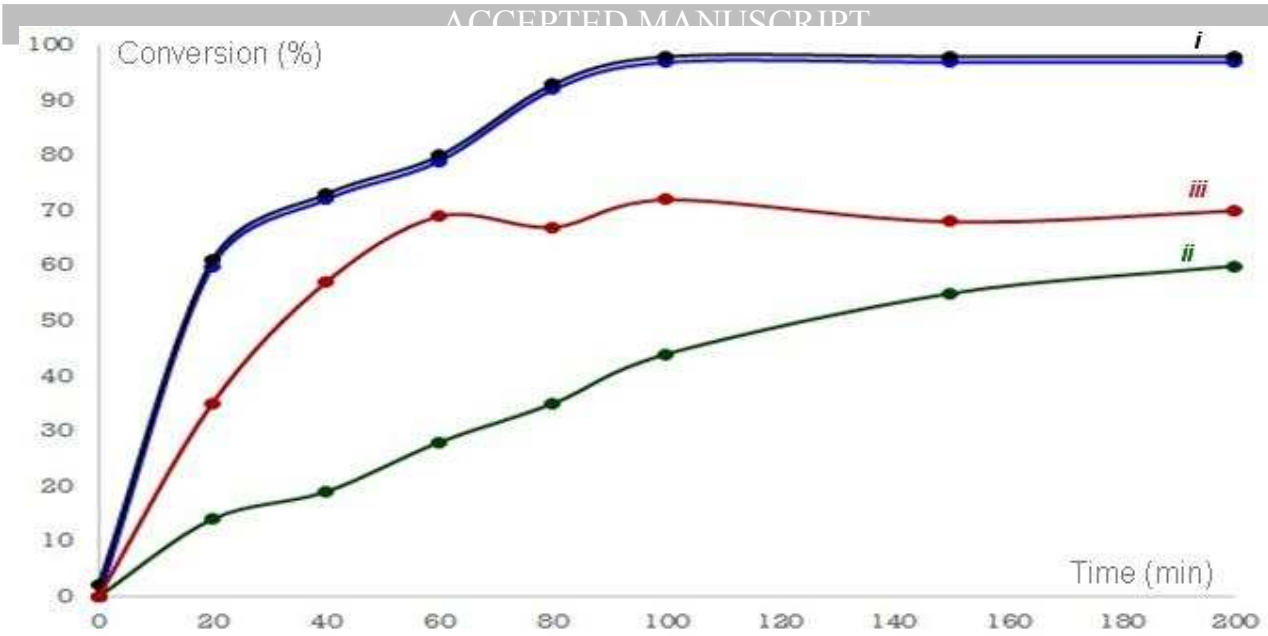
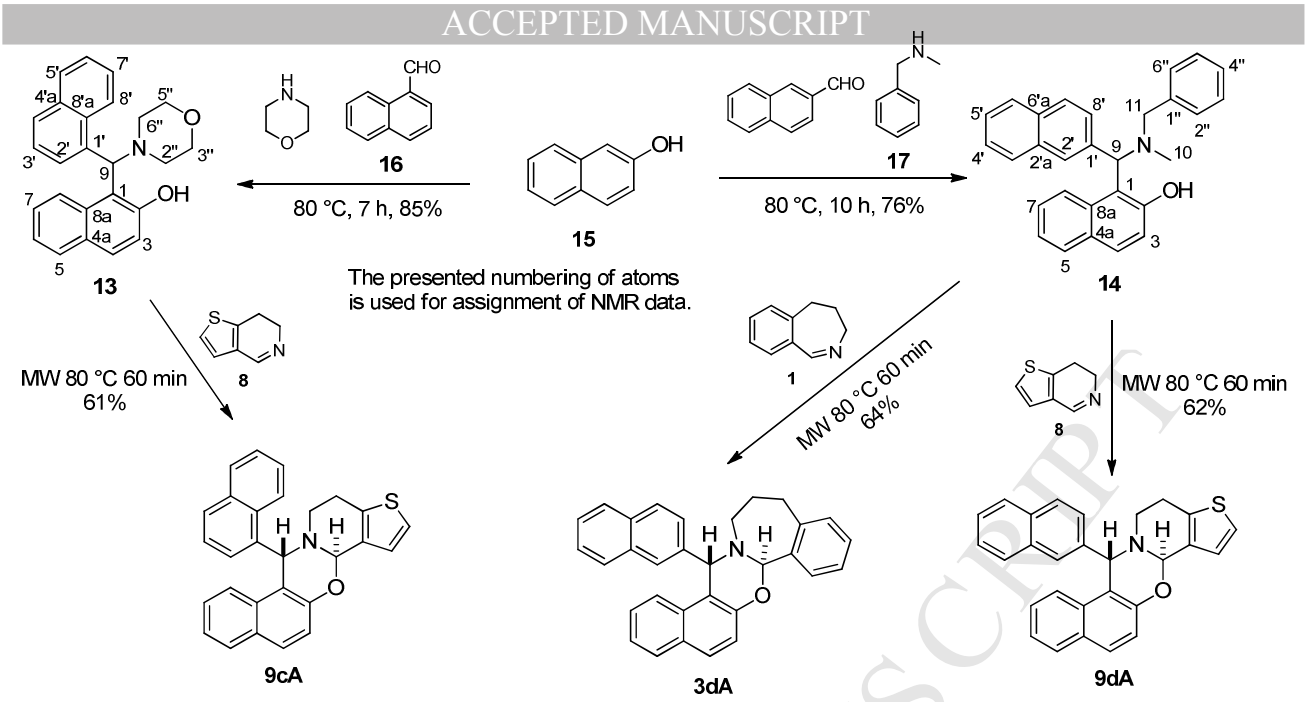
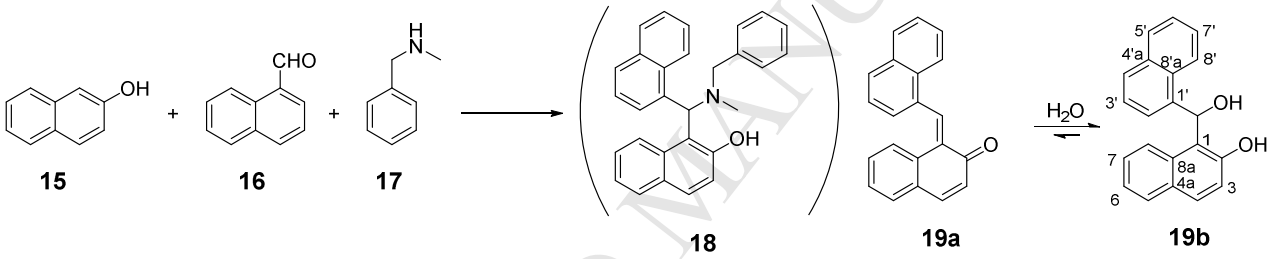


Figure 2

According to these observations (Figure 2), the selection of tertiary aminonaphthols as starting compounds and an optimal reaction time of 60 min appeared to be satisfactory. Accordingly, the synthesis of the missing derivatives **3d**, **9c** and **9d** was planned by reacting aminonaphthols **13**, **14** and cyclic imines **1** or **8**. The initial tertiary aminonaphthol **13** was synthesized from 2-naphthol (**15**), 1-naphthaldehyde (**16**) and morpholine, while the synthesis of **14** was achieved by mixing **15** with 2-naphthaldehyde and *N*-benzylmethylamine (**17**). When cyclic imines **1** or **8** and tertiary aminonaphthols **13** or **14** were reacted under microwave irradiation, the desired products **3d**, **6c** and **6d** were isolated by a simple crystallization in MeOH (Scheme 4). The NMR spectra of the crude reaction mixtures did not show the presence of the minor (*cis*) diastereomers (**3dB**, **9cB**, **9dB**), which supports the diastereoselectivity of the reaction.

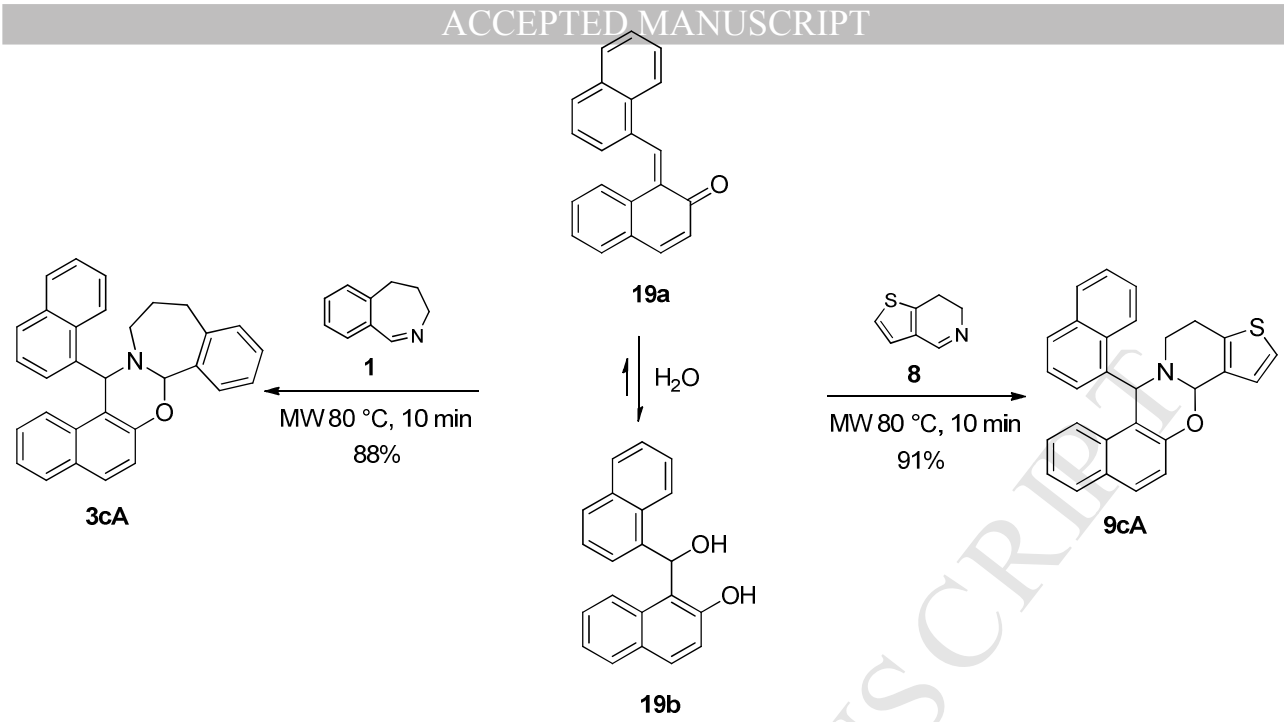


Scheme 4. Synthesis of **3dA**, **9cA** and **9dA** starting from tertiary aminonaphthols **13** and **14**



Scheme 5. The formation of compound **19**

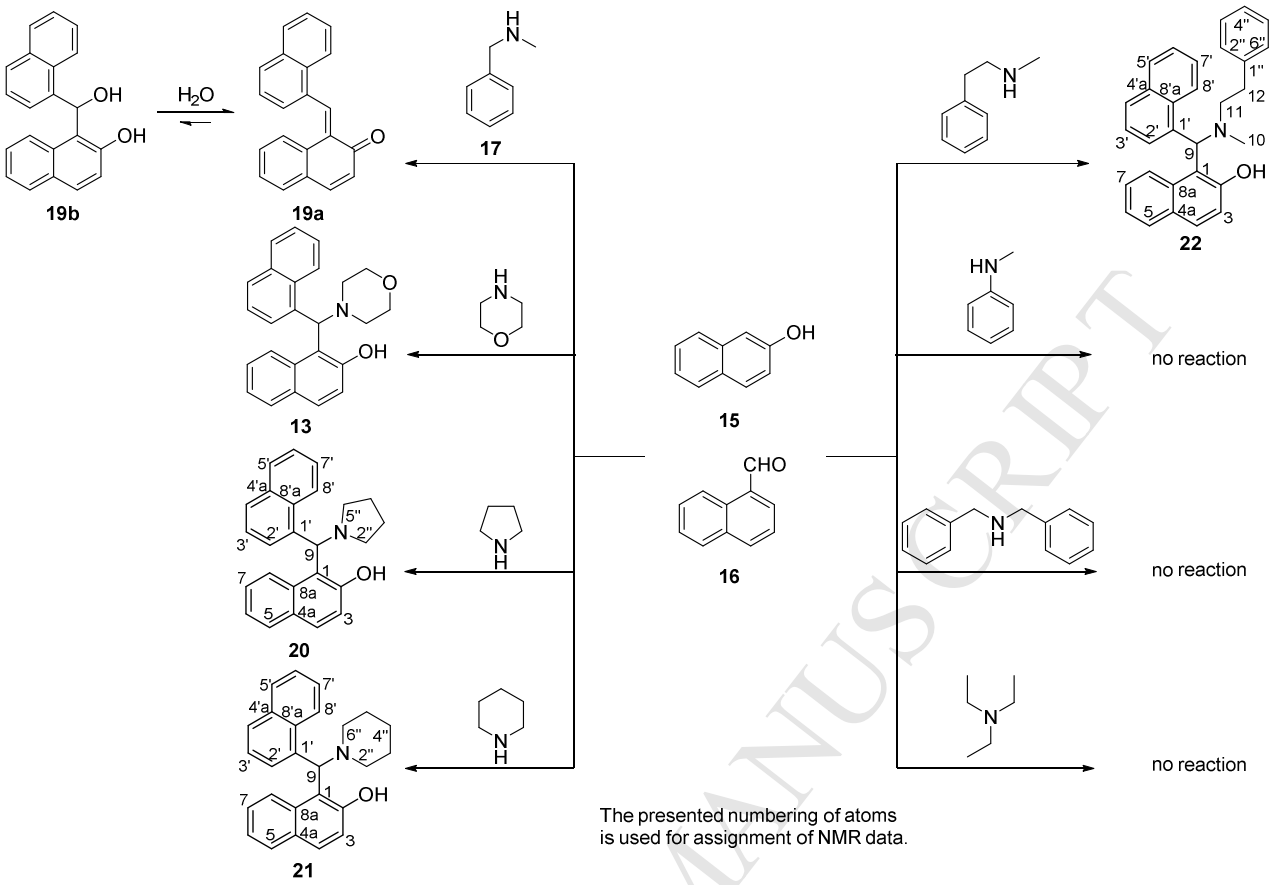
As mentioned, the preparation of **9cA** was achieved by using tertiary aminonaphthol **13** synthesized from 2-naphthol (**15**), 1-naphthaldehyde (**16**) and morpholine. Initially, the synthesis of **9cA** was attempted by the reaction of 6,7-dihydrothieno[3,2-*c*]pyridine (**8**) and **18**. For the synthesis of this latter compound, **15**, **16** and **17** were reacted (neat, 70 °C). The characteristic spot that formed according to TLC, was isolated. The NMR spectra of the product isolated by column chromatography adequately supported that this condition did not lead to the expected tertiary aminonaphthol derivative **18** (Scheme 5). The structure of the formed compound was proven to be **19b** that is the formal hydrate of *ortho*-quinonemethide (*o*QM) **19a**. The class of *o*QMs has previously been investigated as exciting short-lived intermediates. They were usually used to explain reaction pathways, and the difficulty of their isolation was also assessed.[24,25]



Scheme 6. Proof of the reactivity of **19**

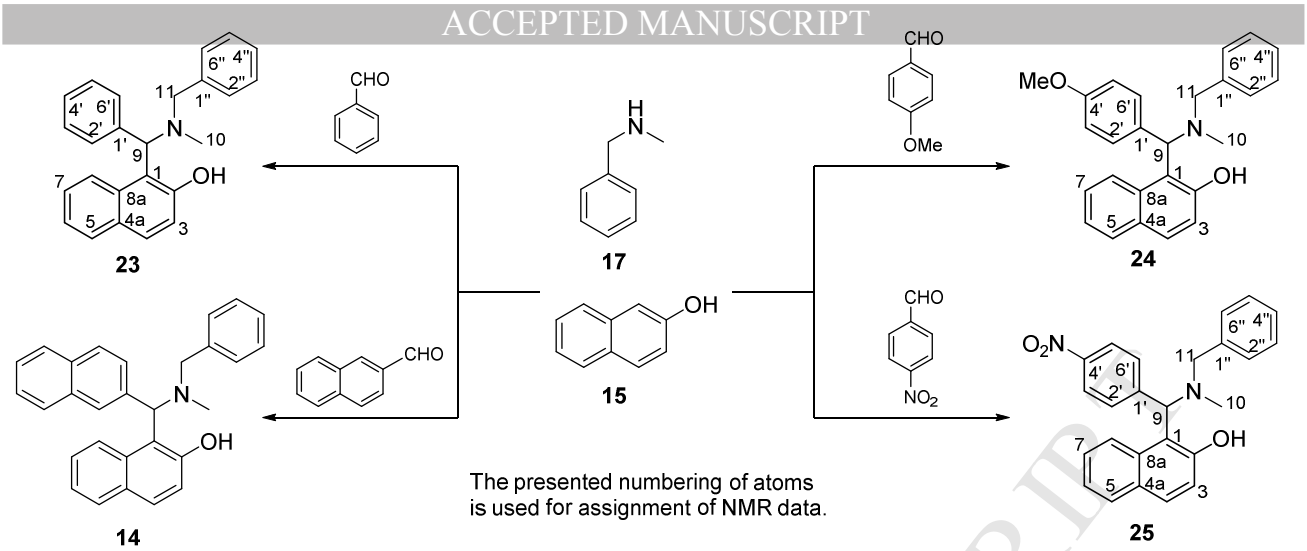
To test the reactivity of **19b**, it was reacted with representative cyclic imines **1** and **8**. Reactions were performed at 80 °C under MW irradiation and the desired compounds (**3cA** and **9cA**) formed in short reaction times were isolated in high yields (Scheme 6). Their formation can be mechanistically interpreted by the transformation of **19b** to **19a** followed by cycloaddition with cyclic imines **1** or **8**.[13] The NMR spectra of the crude products supported the diastereoselectivity of the reaction.

As it was shown the reaction of **15** as the electron-rich aromatic compound, **16** as the aldehyde and **17** as the amine component afforded **19b**. This urged us to start a systematic investigation to explore the scope and limitations of the synthesis of **19b** analogues. Scheme 7 summarizes the structures of products from the reactions of various amine components with **15** and **16**.



Scheme 7. Extension of the amine scope to form *o*QMs

First, the effect of *N*-benzylmethylamine on the formation of **19b** was examined. Mechanistically, if an *o*QM structure is formed, the amine component does become incorporated into the product; rather, it acts as a promoter. Amines with similar basicity such as piperidine, pyrrolidine, morpholine and dibenzylamine were evaluated. Under the conditions used (neat, 70 °C), secondary amines, with the exception of dibenzylamine gave the expected new aminonaphthol derivatives **13**, **20** and **21**. Of related amines, *N*-methylphenethylamine gave **22** as a single product, while *N*-methylaniline proved to be unreactive. A similar failed test included triethylamine, a tertiary amine (Scheme 7).



Scheme 8. Extension of the aldehyde scope to form oQMs

In the next step the aldehyde component **16** was changed. Benzaldehyde and 2-naphthaldehyde were both tested but they both gave the classical 3-component products **23**[15] and **14**. By the application of *p*-anisaldehyde and *p*-nitrobenzaldehyde, the effect of an electron donating and an electron withdrawing group were also examined. The formation of an *o*QM structure was again not observed and **24** and **25** were isolated as single products (Scheme 8).

The NMR data (listed in the Experimental section) are consistent with the structures of the novel compounds. However, the characteristics of the stereostructures of novel pentacycles **3**, **6**, **9** and **10** including their relative configuration and conformation must be commented on. The *trans* structure of compounds of type **A** was unambiguously evidenced by the NOESY cross peaks revealing interaction between the oxazine proton of the NC*H*O group (**3A**: H-7a; **6A**: H-15b; **9A** and **10A**: H-14a) and the proximal protons of the attached aryl substituent. Accordingly, the characteristic NOEs detected between the two oxazine protons of the isolated pentacycles (**6bB**, **6dB**, **10bB** and **10dB**) refer to their relative *cis* position on the fused heterocyclic skeleton.

In order to obtain information about the conformation and possible ring inversions of the pentacycles, we undertook a comparative DFT analysis of representative fused benzazepines (structures **3bA**, **3bB**, **6bB**, **9bA**, **9bB** and **10bB**) carried out by B3LYP functional[26] using 6-31G(d) as basis set[27] (Tables 3 and 4, Figures 3, 4 and 5). For benzazepine models, geometry optimization identified three minima on the potential energy surface (PES). These correspond to ring conformers connected by three saddle points representing transition states (TSs) of the inversions of the partially saturated azepine ring (Figure 4). The TS structures were localized by means of the QST2 method[28]. In case of **3bA**, conformer **3bA_I** was found to be the global minimum. It features a chair-shaped azepine ring carrying H-14$_B$, H-13$_A$, H-12$_B$ and O-7 atoms in *axial* position with C-14 in the tip and pyramidal N-15 atom as an additional stereogenic center.

The relative energy (Table 3) calculated for diastereomer **3bA_II** incorporating the azepine ring with boat conformation indicates its slightly decreased population relative to that of **3bA_I** in a ternary equilibrium. The local minimum represented by **3bA_III**, containing a boat-shaped azepine ring with opposite sign of bending, seems to have a minimum share in the conformer population, as suggested by its relative energy (Table 3). It is of pronounced importance that at room temperature the calculated low activation energies (Table 3) refer to rapid interconversion between the three components expected to produce time-average spectra under the applied conditions of the NMR measurements. This view gains support from the fact that the multiplets originated from the protons of the skeletal $(CH_2)_3$ chain appear as relatively broadened signals in the ^{1}H-NMR spectra of pentacycles **3A** and **6A**. Thus, theoretical NMR spectra were generated by the GIAO method[29] at the B3LYP/6-311+G(2d,p) level of theory[30] for each component of the assumed equilibrium (Table 3). The best match of the measured and calculated chemical shifts of H-7a, H-16, H-14_{AB}, H-13_{AB} and H-12_{AB} protons (see Table 3), in line with the relative energetics, indicates that **3bA_I** is unambiguously the dominant one in the mixture of the three conformers present in the DMSO-d_6 solution subjected to NMR experiments.

Table 3. Diagnostic ^{1}H NMR shifts (experimental and calculated) and calculated relative energetics[a] along with activation barriers[a] of the appropriate interconversions between the possible conformers of selected model benzazepines **3bA**, **3bB** and **6bB**

		3bA_I *E_{rel} = 0*	**3bA_II** E_{rel} = 0.6	**3bA_III** E_{rel} = 2.8		**3bB_I** E_{rel} = 2.2	**3bB_II** E_{rel} = 0.9	**3bB_III** *E_{rel} = 0*			**6bB_I** E_{rel} = 2.2	**6bB_II** E_{rel} = 1.9	**6bB_III** *E_{rel} = 0*
		$E^{‡}$(I→II) = 7.2					$E^{‡}$(III→II) = 5.1					$E^{‡}$(III→II) = 7.8	
			$E^{‡}$(II→III) = 4.8			$E^{‡}$(II→I) = 7.2					$E^{‡}$(I→II) = 7.0		
		$E^{‡}$(I→III) = 9.9				$E^{‡}$(III→I) = 9.2					$E^{‡}$(III→I) = 9.3		
No. of atoms	Exp. ^{1}H	***Calcd. ^{1}H***	Calcd. ^{1}H	Calcd. ^{1}H	Exp. ^{1}H	Calcd. ^{1}H	Calcd. ^{1}H	Calcd. ^{1}H	No. of atoms	Exp. ^{1}H	Calcd. ^{1}H	Calcd. ^{1}H	Calcd. ^{1}H
H-7a	5.69	*5.75*	6.30	5.92	-	6.11	6.58	5.80	H-15b	5.99	6.42	6.92	6.00
H-16	5.55	*5.50*	5.51	5.69	-	6.57	6.64	5.76	H-7	5.44	6.43	6.44	5.42
H-14_B	3.30-3.18	*3.55*	3.56	3.21	-	3.36	3.10	2.94	H-9_B	2.51	3.34	3.20	2.70
H-14_A		*3.23*	2.72	3.64	-	2.29	2.56	2.69	H-9_A	2.45	2.54	2.81	2.65
H-13_B	1.94	*1.93*	1.74	2.09	-	1.76	1.36	1.50	H-10_B	1.68	1.81	1.40	1.71
H-13_A	1.87	*2.03*	2.44	1.64	-	1.65	1.48	1.23	H-10_A	1.33	1.72	1.42	1.27
H-12_B	3.03	*3.27*	2.37	4.01	-	3.70	2.30	3.89	H-11_B	3.22	3.75	2.31	3.68
H-12_A	2.89	*2.65*	3.96	2.61	-	2.65	3.94	2.42	H-11_A	2.78	2.71	3.85	2.54

[a] in kcal/mol

Table 4. Diagnostic ^{1}H NMR shifts (experimental and calculated) and calculated relative energetics[a] along with activation barriers[a] of the appropriate interconversions between the possible conformers of selected model thienopyridines **9bA**, **9bB** and **10bB**

No. of atoms		**9bA_I** E_{rel} = *0*	**9bA_II** E_{rel} = 0.6		**9bB_I** E_{rel} = 1.5	**9bB_II** E_{rel} = 0			**10bB_I** E_{rel} = 1.7	**10bB_II** E_{rel} = 0
		$E^{\ddagger}$(I→II) = 7.2			$E^{\ddagger}$(II→I) = 6.4				$E^{\ddagger}$(II→I) = 6.9	
No. of atoms	Exp. ^{1}H	***Calcd.*** ***^{1}H***	Calcd. ^{1}H	Exp. ^{1}H	Calcd. ^{1}H	***Calcd.*** ***^{1}H***	No. of atoms	Exp. ^{1}H	Calcd. ^{1}H	***Calcd.*** ***^{1}H***
H-14a	**5.61**	5.72	5.84	-	6.06	5.70	H-14a	**5.63**	6.49	5.82
H-7	**5.25**	5.47	5.70	-	6.64	5.02	H-7	**4.98**	6.41	5.06
H-5_B	**3.15**	3.05	3.28	-	3.16	3.10	H-5_B	**2.95-**	3.20	3.00
H-5_A	**3.27**	3.44	3.94	-	2.20	2.82	H-5_A	**2.85**	2.46	2.93
H-4_B	**2.91**	2.87	3.55	-	2.64	2.87	H-4_B	**2.80-**	2.70	2.85
H-4_A	**3.05**	3.12	3.00	-	2.84	2.65	H-4_A	**2.71**	2.86	2.68

[a] in kcal/mol

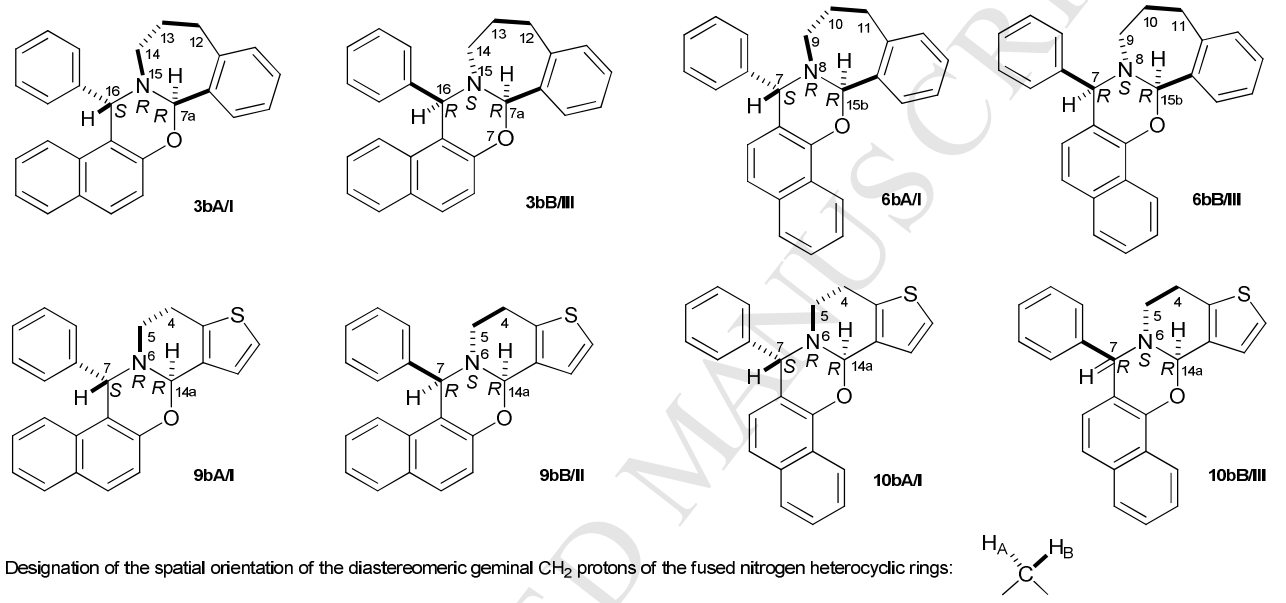
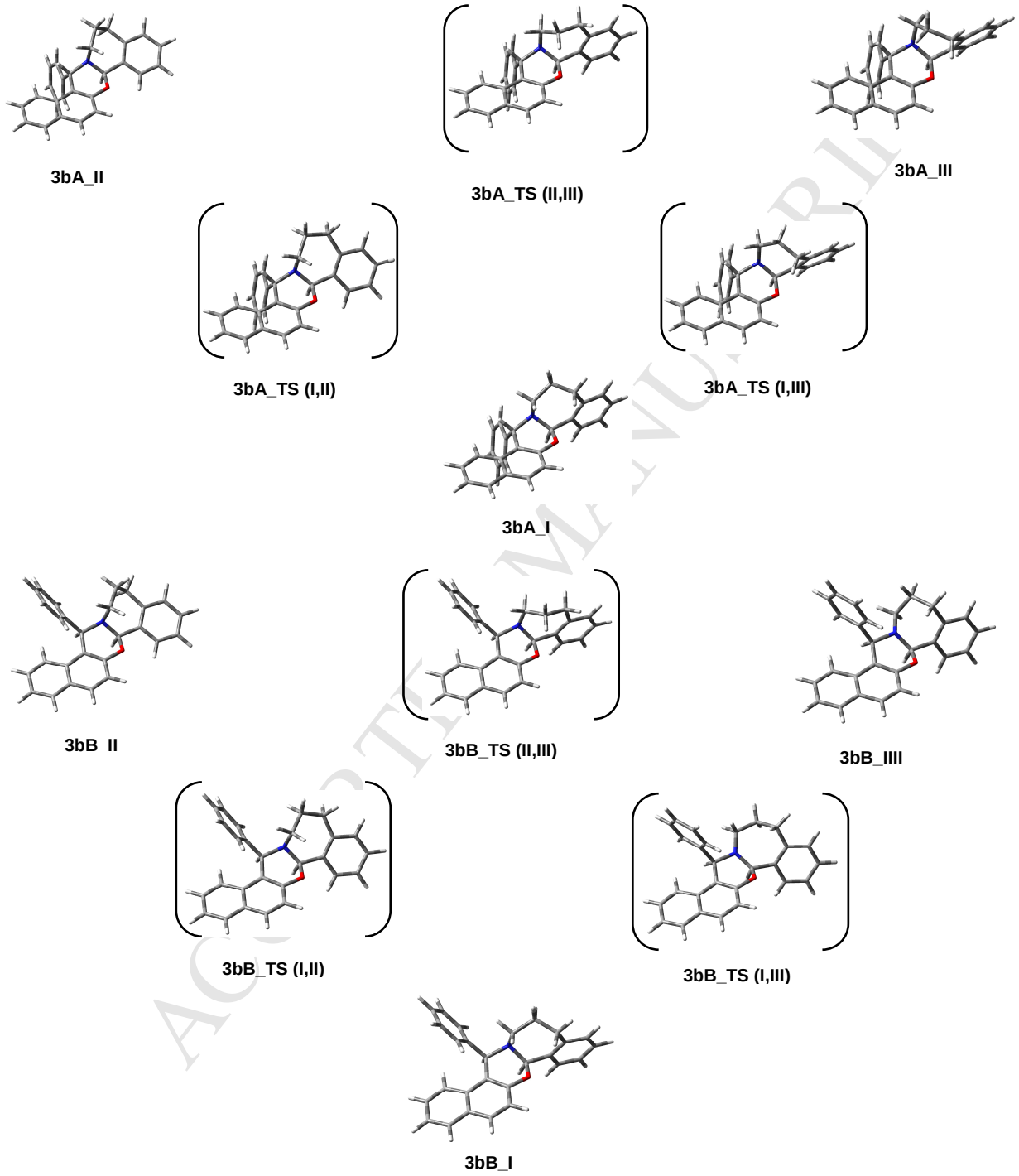


Figure 3: Relative (and, consequently, absolute) configurations of the most favored conformers of pentacycles **3bA**/**B**, **6bA**/**B**, **9bA**/**B** and **10bA**/**B** (arbitrarily selected enantiomers) established by combined NMR methods and complementary DFT modelling studies (cf. Relative energetics of the particular confomers listed in Tables 3 and 4.)

As indicated earlier, *cis*-isomer **3bB** could not be isolated and characterized. Therefore, in addition to its calculated data, the measured and theoretical chemical shifts obtained for detectable pentacycle **6bB**, comprising the same structural fragments, are also listed in Table 3. In accord with the relative energetics, the comparison of the aforementioned experimental and calculated chemical shift values suggests that **3bB_III** and **6bB_III**, with boat-shaped azepine ring and inverted N-15 (in **3bB_III**)/N-8 (in **6bB_III**) stereogenic centers, can be stated as the most populated components in the assumed ternary equilibria. These equilibria involve the three conformers (**3bB_I,II,III** and **6bB_I,II,III**, for **3bB** and **6bB**, respectively) identified on the appropriate PES (cf. Figure 4). It is noteworthy that conformers **3bB_I** and **6bB_I**, featuring bridgehead nitrogen with retained configuration and chair-shaped azepine ring with stereochemical characteristics identical to those found in stable **3bA_I**, represent the least populated local minima. Additionally, according to the calculated relative energy data, conformers **3bB_II** and **6bB_II**, containing bridgehead nitrogen

with retained configuration and boat-shaped azepine ring, have a small, but somewhat larger share in the conformational equilibria than do **3bB_I** and **6bB_I**, respectively. It must also be pointed out that at room temperature the calculated low barriers allow fast interconversions between these conformers taking place by ring flips and inversion of the bridgehead nitrogen atom (Figure 4).



Designation of the geminal CH_2 protons on the opposite faces of the fused azepine ring as referred in the text and Tables 3 and 4:

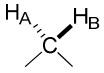


Figure 4. Optimized structures of the conformers and the corresponding transition states involved in ternary equilibria assumed for *trans* and *cis* isomer models **3bA** and **3bB**, respectively.

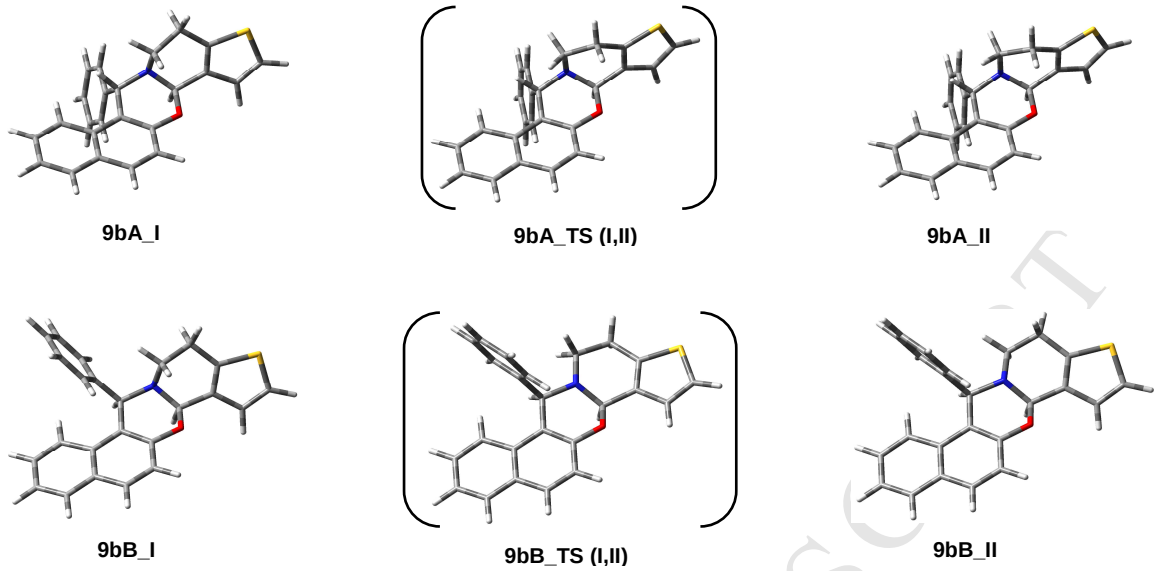


Figure 5. Optimized structures of the conformers and the corresponding transition states involved in binary equilibria assumed for *trans* and *cis* isomer models **9bA** and **9bB**, respectively.

Optimization processes searching for stationary points on the PES representing local minima and transition states were also conducted at the B3LYP/6-31G(d) level of theory for selected thienopyridines (**9bA**, undetectable **9bB** and isolated **10bB**, Figure 5). For these models, the calculations identified two conformers containing a tetrahydropyridine ring adopting a half-chair conformation of opposite helicity connected by a TS. This represents a relatively low energy barrier allowing their interconversion to take place rapidly at room temperature by ring-flip coupled with simultaneous nitrogen inversion (Table 4). In the case of *trans* isomer **9bA**, conformer **9bA_I** was found to be somewhat more stable than **9bA_II**. This is a sterically more congested isomer in which the 5-CH_2 group is situated in the proximity of the bulky phenyl substituent. Accordingly, referring to the relative shares in the conformational equilibrium, the diagnostic ^{1}H chemical shift values calculated for **9bA_I** match better the experimental data than do the analogous values obtained for **9bA_II** (Table 4). On the other hand, for *cis* isomers **9bB** and **10bB**, the modelling studies revealed that conformers **9bB_II** and **10bB_II**, both containing the phenyl and 5-CH_2 groups in the oppsite faces of the heterocyclic skeleton, must be considered as the major components in the conformational equilibria **9bB_I⇆9bB_II** and **10bB_I⇆10bB_II**, repectively. This view is convincingly supported by comparison of the diagnostic ^{1}H chemical shifts measured and calculated for the appropriate conformer pairs (Table 4).

In summary, it can be concluded that in the most stable conformers of the investigated model pentacycles the phenyl and, in general, the aryl group and the N-CH_2 group are situated on

the oppsite faces of the heterocyclic skeletons characterized by the relative configurations of the carbon and nitrogen stereogenic centers as presented on Figure 3.

Conclusion

By the reaction of 4,5-dihydro-3*H*-benz[*c*]azepine or 6,7-dihydrothieno[3,2-*c*]pyridine and different substituted aminonaphthols, a new modified Mannich-type synthetic pathway was applied to form naphth[1,3]oxazino-benzazepines and –thienopyridines. By carrying out the reactions under microwave irradiation at 80 °C, the products were formed in short reaction times. The conversion and the diastereomeric ratio was monitored by crude product NMR spectra in all cases. Because of the formation of the undesired naphthoxazine by-products, separation and purification failed in some cases therefore a new strategy was needed for the synthesis of **3dA**, **9cA** and **9dA** wherein the reactions were performed starting from the corresponding tertiary aminonaphthol derivatives.

During the preparation of the initial tertiary aminonaphthols, the unexpected formation of **19** occurred. A systematic study was started to probe the reactivity of **19** and investigate the scope and limitations of the generation of an *ortho*-quinonemethide structure. NMR conformational studies and theoretical calculations were also performed that corroborated the experimental results.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO solutions in 5 mm tubes, at room temperature, with a Bruker spectrometer at 500 (^{1}H) and 125 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. In the characterization of the compounds, the ^{1}H- and ^{13}C NMR signals originated from the Ph, 1-Nph and 2-Nph groups attached to the heterocyclic skeletons or the amine moiety are assigned to the atoms referred to as H-1', H-2', C-1', C-2' and H-1", H-2", C-1", C-2", etc.

Melting points were determined on a Hinotek X-4 melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel $60F_{254}$ plates were used for TLC. The microwave reactions were performed with a CEM Discover SP microwave reactor.

The starting compounds **1**,[17,18] **2a-d**,[21] **5b-d**,[21] **8**,[22] **11**,[23] **12**[15] and **23**[15] were synthesized using literature methods.

General procedure for the synthesis of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepines (3a-c, 6b-d) and naphth[1,2-*e*][1,3]oxazino[2,3-*a*]thienopyridines (9a, 9b, 10b-d) starting from primary aminonaphthols (2a-c and 5b-d)

A mixture of the appropriate aminonaphthol hydrochloride (0.44 mmol), 4,5-dihydro-3*H*-benz[*c*]azepine (**1**, 0.4 mmol) or 6,7-dihydrothieno[3,2-*c*]pyridine (**8**, 0.4 mmol) and Et_3N (83 uL, 0.6 mmol) in 1,4-dioxane (5 mL) was placed in a 10 mL reaction vial and heated in a CEM microwave reactor under the conditions given in Table 1. The solvent was then evaporated under reduced pressure and the residue purified by column chromatography (*n*-hexane–ethyl-acetate).

Naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (3a)

Column chromatography; eluent: *n*-hexane:EtOAc (2:1; R_f = 0.75), crystallized from *n*-hexane (5 mL). Mp: 155-157 °C. Light yellow powder. Yield: 93 mg (77 %). ^{1}H NMR (DMSO-d_6, 500 MHz): 7.86 (d, *J* = 7.8 Hz, 1H, H-4), 7.77 (d, *J* = 8.9 Hz, 1H, H-5), 7.66 (d, *J* = 7.8 Hz, 1H, H-1), 7.49 (t, *J* = 7.8 Hz, 1H, H-2), 7.37 (t, *J* = 7.8 Hz, 1H, H-3), 7.24 (t, *J* = 7.3 Hz, 1H, H-10), 7.15 (d, *J* = 8.9 Hz, 1H, H-6), 7.13 (t, *J* = 7.3 Hz, 1H, H-9), 7.11 (d, *J* = 7.3 Hz, 1H, H-11), 7.02 (d, *J* = 7.3 Hz, 1H, H-8), 6.14 (s, 1H, H-7a), 4.51 (d, *J* = 16.1 Hz, 1H, H_A-16), 4.01 (d, *J* = 16.1 Hz, 1H, H_B-16), 3.34 (overlapped by the HDO signal of the solvent, thus assigned by HQSC measurement, H_A-14), 3.17-3.14 (m, 1H, H_B-14), 3.05-3.03 (m, 1H, H_A-12), 2.92-2.89 (m, 1H, H_B-12), 1.95-1.91 (m, 1H, H_A-13 1.77-1.73 (m, 1H, H_B-13); ^{13}C NMR (DMSO-d_6, 125 MHz): 153.6 (C-6a); 142.8 (C-7b), 136.0 (C-11a), 133.1 (C-16b), 131.2 (C-8), 130.1 (C-11), 129.5 (C-4a), 129.2 (C-4), 129.4 (C-9), 128.5 (C-5), 127.1 (C-2), 126.4 (C-10), 123.9 (C-3), 122.1 (C-1), 118.6 (C-6), 112.0 (C-16a), 92.9 (C-7a), 53.3 (C-14), 50.3 (C-16), 34.9 (C-12), 26.3 (C-13). Anal. calcd. for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.73; H, 6.32; N, 4.66.

(7a*S,16*R**)-16-Phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (3bA)**

Column chromatography; eluent: *n*-hexane:EtOAc (2:1; R_f = 0.80), crystallized from *n*-hexane (5 mL). Mp: 140-143 °C. White powder. Yield: 56 mg (37%). ^{1}H NMR (DMSO-d_6, 500 MHz): 7.88 (d, *J* = 7.8 Hz, 1H, H-4), 7.85 (d, *J* = 8.9 Hz, 1H, H-5), 7.34-7.31 (m, 5H, H-(1-3) and H-3',5'), 7.29 (t, *J* = 7.5 Hz, 1H, H-4'), 7.27 (d, *J* = 7.5 Hz, 2H, H-2'6'), 7.24 (t, *J* = 7.3 Hz, 1H, H-10), 7.19 and 7.18 (two partly overlapping ds, *J* = 8.9 Hz and 7.3 Hz, resp., 2H, H-6 and H-11), ~~7.16 (d, *J*=8.9 Hz, 1H, H-13),~~ 7.11 (t, *J*=7.3 Hz, 1H, H-9), 6.92 (d, *J*=7.3 Hz, 1H, H-8), 5.69 (s, 1H, H-7a), 5.55 (s, 1H, H-16), 3.30-3.18 (m, 2H, H_A-14 and H_B-14), 3.05-3.02 (m, 1H, H_B-12), 2.91-2.88 (m, 1H, H_A-12), 1.96-1.93 (m, 1H, H_A-13), 1.89-1.85 (m, 1H, H_B-13); ^{13}C NMR (DMSO-d_6, 125 MHz):

153.2 (C-6a); 143.6 (C-1'), 142.3 (C-7b), 135.8 (C-11a), 132.8 (C-16b), 130.9 (C-8), 130.1 (C-11), 129.7 (C-2',6'), 129.5 (C-5), 129.4 (C-9), 129.3 (C-4a), 129.0 (C-4), 128.6 (C-3',5'), 127.8 (C-4'), 127.0 (C-2), 126.5 (C-10), 123.9 (C-3), 123.4 (C-1), 118.9 (C-6), 112.9 (C-16a), 90.5 (C-7a), 64.9 (C-16), 52.7 (C-14), 34.4 (C-12), 28.9 (C-13). Anal. calcd. for $C_{27}H_{23}NO$ (377,48): C, 85.91; H, 6.14; N, 3.71. Found: C, 85.87; H, 6.17; N, 3.73.

(7a*S,16*R**)-16-Naphth-1-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (3cA)**

Column chromatography; eluent: *n*-hexane:EtOAc (4:1; R_f = 0.80), crystallized from *n*-hexane (4 mL). Mp: 225-227 °C. White powder. Yield: 58 mg (34%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.50 (d, *J* = 8.3 Hz, 1H, H-8'), 7.99 (d, *J* = 8.0 Hz, 1H, H-5'), 7.90, 7.89 and 7.88 (three partly overlapping ds, *J* = 8.9 Hz, 7.8 Hz and 8.0 Hz, 3H, H-5, H-4 and H-4'), 7.68 (t, *J* = 8.0 Hz, 1H, H-7'), 7.59 (t, *J* = 8 Hz, 1H, H-6'), 7.34 (t, *J* = 8.0 Hz, 1H, H-3'), 7.30 (t, *J* = 8 Hz, 1H, H-3), 7.25 and 7.23 (partly overlapping d and t, *J* = 8.9 Hz and 7.9 Hz, resp., 2H, H-6 and H-2), 7.19 (t, *J* = 7.3 Hz, 1H, H-9), ~~7.17 (d, *J* = 8.9 Hz, 1H, H-13),~~ 7.15 and 7.13 (partly overlappin d and t, *J* = 7.9 Hz and 7.3 Hz, resp., 2H, H-1 and H-11), 7.05 (t, *J* = 7.3 Hz, 1H, H-10), 6.94 (d, *J* = 8.0 Hz, 1H, H-2'), 6.91 (d, *J* = 7.3 Hz, 1H, H-8), 6.21 (s, 1H, H-16), 5.92 (s, 1H, H-7a), 3.60-3.56 (m, 1H, H_A-14), 3.40.3.36 (m, 1H, H_B-14), 3.02-2.98 (m, 1H, H_A-12), 2.86-2.82 (m, 1H, H_B-12), 2.02-1.98 (m, 1H, H_A-13), 1.94-1.90 (m, 1H, H_B-13); ^{13}C NMR (DMSO-d_6, 125 MHz): 153.7 (C-6a), 142.2 (C-7b), 138.8 (C-1'), 135.5 (C-11a), 134.3 (C-4'a), 132.4 (C-16b), 131.6 (C-8'a), 131.0 (C-8), 130.1 (C-11), 129.6 (C-5), 129.5 (C-4a), 129.3 (C-9), 129.1 (two coalesced lines, C-4 and C-5'), 128.9 (C-2'), 128.8 (C-4'), 127.0 (C-2), 126.9 (C-7'), 126.5 (C-10), 126.4 (C-6'), 125.7 (C-3'), 123.8 (C-3), 123.3 (C-1), 118.9 (C-6), 112.2 (C-16a), 90.7 (C-7a), 62.3 (C-16), 52.1 (C-14), 34.2 (C-12), 29.0 (C-13). Anal. calcd. for $C_{31}H_{25}NO$ (427.54): C, 87.09; H, 5.89; N, 3.28. Found: C, 87.02; H, 5.93; N, 3.31.

(7a*S,16*R**)-16-Phenylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (6bA)**

^{1}H NMR (DMSO-d_6, 500 MHz): 8.18-8.15 (m, 1H,. H-1), 7.87-7.84 (m, 1H, H-4), 7.55-7.52 (m, 2H, H-2 and H-3), 7.38 (d, *J* = 8.8 Hz, 1H, H-5), 7.34 (t, *J* = 7.8 Hz, 2H, H-3',5'), 7.23 (d, *J* = 7.7 Hz, 1H, H-12), 7.30-7.28 (m, 3H, H-2',6' and H-4'), 7.20 (t, *J* = 7.7 Hz, 1H, H-13), 7.03-7.00 (m, 1H, H-14), 6.92 (d, *J* = 8.0 Hz, 1H, H-15), 6.85 (d, *J* = 8.8 Hz, 1H, H-6), 6.16 (s, 1H, H-15b), 4.92 (s, 1H, H-7), 3.23-3.19 (m, 1H, H-9_A), 3.13-3.09 (m, 1H, H-9_B), 2.99 (t, *J* =5.9 Hz, 2H, H-11_A and H-11_B), 1.88-1.84 (m, 1H, H-10_A) 1.70-1.66 (m, 1H, H-10_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 148.9 (C-16a), 143.2 (C-1'), 141.6 (C-15a), 137.2 (C-11a), 133.5 (C-4a), 130.3 (C-12), 129.6 (C-2',6'), 129.1 (C-15), 128.9 (two coalesced lines, C-3',5' and C-13), 128.2 (C-4), 128.1 (C-4'), 127.3

(C-6), 126.8 (C-2), 126.3 (C-14), 126.2 (C-3), 124.6 (C-16b), 121.5 (C-1), 120.0 (C-5), 117.5 (C-6a), 89.9 (C-15b), 62.0 (C-7), 51.8 (C-9), 35.1 (C-11), 26.2 (C-10).

(7a*S,16*S**)-16-Phenylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (6bB)**

Characteristic signals assigned for the minor component in the complex spectra registered of a mixture of **6bA** and **6bB**: ^{1}H NMR (DMSO-d_6, 500 MHz): 8.07-8.04 (m, 1H, H-1), 7.32 (d, J = 8.8 Hz, 1H, H-5), 6.74 (d, J = 8.8 Hz, 1H, H-6), 5.99 (s, 1H, H-15b), 5.44 (s, 1H, H-7), 3.24-3.20 (m, 1H, H-11$_A$) 2.80-2.76 (m, 1H, H-11$_B$), 2.53-2.49 (m, 1H, H-9$_A$) and 2.46-2.42 (m, 1H, H-9$_B$), 1.70-1.66 (m, 1H, H-10$_A$), 1.35-1.31 (m, 1H, H-10$_B$); ^{13}C NMR (DMSO-d_6, 125 MHz): 149.7 (C-16a), 121.6 (C-1), 121.0 (C-6), 120.1 (C-5), 93.2 (C-15b), 66.8 (C-7), 43.9 (C-9), 30.1 (C-11), 21.6 (C-10).

(7a*S,16*R**)-16-Naphth-1-yl-naphth[2,1-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (6cA)**

Column chromatography; eluent: *n*-hexane:EtOAc (6:1; R_f = 0.75), crystallized from cold *n*-hexane (3 mL). Yellow powder. Mp: 149-152 °C. Yield: 55 mg (32%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.34 (d, J = 7.9 Hz, 1H, H-8'), 8.19-8.16 (m, 1H, H-1), 7.93 (d, J = 7.9 Hz, 1H, H-5'), 7.87 and 7.86 (partly overlapping ds, J = 7.7 Hz, 2H, H-4 and H-4', resp.), 7.54-7.49 (m, 4H, H-2, H-3, H-6' and H-7'), 7.41 (t, J = 7.7 Hz, 1H, H-3'), 7.38 (d, J = 8.9 Hz, 1H, H-5), 7.19-7.17 (m, 2H, H-12 and H-13), 7.11 (d, J = 7.7 Hz, 1H, H-2'), 7.04-7.02 (m, 2H, H-14 and H-15), 6.92 (d, J = 8.9 Hz, 1H, H-6), 6.14 (s, 1H, H-15b), 5.65 (s, 1H, H-7), 3.43-3.39 (m, 1H, H-9$_A$), 3.24-3.20 (m, 1H, H-9$_B$), 2.95 (t, J = 5.9 Hz, 2H, H-11$_A$ and H-11$_B$), 1.93-1.89 (m, 1H, H-10$_A$), 1.85-1.81 (m, 1H, H-10$_B$); ^{13}C NMR (DMSO-d_6, 125 MHz): 149.4 (C-16a), 141.6 (C-15a), 138.8 (C-1'), 137.5 (C-11a), 133.6 (C-4a), 131.8 (C-8'a), 130.3 (C-12), 129.8 (C-15), 129.4 (C-2'), 129.0 (C-5'), 128.6 (two coalesced lines, C-4 and C-13), 128.3 (C-4'), 127.1 (C-6), 126.9 (C-4'a), 126.6 (C-7'), 126.4 (C-6'), 126.3 (C-14), 126.2 (C-2), 126.1 (C-1), 125.4 (C-3'), 125.3 (C-8'), 124.5 (C-16b), 120.2 (C-5), 114.4 (C-6a), 90.3 (C-15b), 63.1 (C-7), 51.8 (C-9), 34.4 (C-11), 27.2 (C-10). Anal. calcd. for $C_{31}H_{25}NO$ (427.54): C, 87.09; H, 5.89; N, 3.28. Found: C, 87.02; H, 5.93; N, 3.31.

(7a*S,16*R**)-16-Naphth-2-yl-naphth[2,1-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (6dA)**

^{1}H NMR (DMSO-d_6, 500 MHz): 8.21-8.19 (m, 1H, H-1), 7.89, 7.87 and 7.86 (partly overlapping ds, J = 7.8 Hz for each, 3H, H-4, H-4' and H-5'), 7.83 (d, J = 7.7 Hz, 1H, H-8'), 7.72 (br s, 1H, H-1'), 7.56-7.54 (m, 2H, H-2 and H-3), 7.50 (td, J = 7.7 Hz and 1.8 Hz, 1H, H-6'), 7.47 (td, J = 7.7 Hz and 1.8 Hz, 1H, H-7'), 7.45 (d, J = 7.8 Hz, 1H, H-3'), 7.37 (d, J = 8.9 Hz, 1H, H-5), 7.24 (d, J = 7.6 Hz, 1H, H-12), 7.19 (t, J = 7.6 Hz, 1H, H-13), 6.97 (t, J = 7.6 Hz, 1H, H-14), 6.90 (d, J = 7.6 Hz,

1H, H-15), 6.88 (d, *J* = 8.9 Hz, 1H, H-6), 6.25 (s, 1H, H-15b), 5.05 (s, 1H, H-7), 3.29-3.25 (m, 1H, H-9_A), 3.15-3.11 (m, 1H, H-9_B), 3.00 (t, *J* = 5.9 Hz, 2H, H-11_A and H-11_B), 1.92-1.89 (m, 1H, H-10_A), 1.70-1.66 (m, 1H, H-10_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 149.0 (C-16a), 141.5 (C-15a), 140.6 (C-2'), 137.3 (C-11a), 133.5 (C-4a), 133.1 (C-4'a), 133.0 (C-8'a), 130.4 (C-12), 128.9 (C-15), 128.8 (C-13), 128.7 (C-1'), 128.6 (C-4), 128.4 (C-8'), 128.1 (C-4'), 128.0 (C-5'), 127.4 (C-3'), 127.3 (C-6), 126.9 (C-3), 126.6 (two coalesced lines, C-6' and C-7'), 126.2 (two coalesced lines, C-2 and C-14), 124.5 (C-16b), 120.0 (C-5), 118.3 (C-6a), 89.9 (C-15b), 62.9 (C-7), 52.0 (C-9), 35.2 (C-11), 26.0 (C-10).

(7a*S,16*S**)-16-Naphth-2-yl-naphth[2,1-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (6dB)**

Characteristic signals assigned for the minor component in the complex spectra registered of a mixture of **6dA** and **6dB**: ^{1}H NMR (DMSO-d_6, 500 MHz): 6.77 (d, *J* = 8.9 Hz, 1H, H-6), 6.05 (s, 1H, H-15b), 5.60 (s, 1H, H-7), 261-2.57 (m, 1H, H-9_A), 2.49-2.46 (m, 1H, H-9_B), 3.30-3.26 (m, 1H, H-11_A), 2.84-2.80 (m, 1H, H-11_B); 1.74-1.70 (m, 1H, H-10_A) 1.44-1.38 (m, 1H, H-10_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 148.6 (C-16a), 126.7 (C-6), 93.1 (C-15b), 66.8 (C-7), 44.0 (C-9), 30.2 (C-11), 25.1 (C-10).

Naphth[1,2-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (9a)

Column chromatography; eluent: *n*-hexane:EtOAc (2:1; R_f = 0.75), crystallized from *n*-hexane (5 mL). Light yellow powder. Mp: 161-164 °C. Yield: 87 mg (74%). ^{1}H NMR (DMSO-d_6, 500 MHz): 7.82 (d, *J* = 8.0 Hz, 1H, H-11), 7.69 (two overlapping ds, *J* = 7.8 Hz and 8.9 Hz, 2H, H-8 and H-12, resp.), 7.53 (t, *J* = 7.7 Hz, 1H, H-9), 7.40 (t, *J* = 7.7 Hz, 1H, H-10), 7.24 (d, *J* = 5.1 Hz, 1H, H-1), 7.16 (d, *J* = 5.1 Hz, 1H, H-2), 5.76 (s, 1H, H-14a), 4.76 (d, *J* =16.3 Hz, 1H, H-7_A), 4.35 (d, *J* =16.3 Hz, 1H, H-7_B), 3.51-3.48 (m, 1H, H-5_A), 3.16-3.12 (m, 1H, H-4_A), 3.08-3.04 (m, 1H, H-4_B), 3.03-2.99 (m, 1H, H-5_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 151.4 (C-13a), 138.1 (C-3a), 133.3 (C-14b), 131.4 (C-7b), 129.0 (C-11a), 128.7 (C-11), 128.2 (C-12), 126.6 (C-9), 125.6 (C-1), 123.8 (C-2), 123.6 (C-10), 121.1 (C-8), 118.9 (C-13), 111.3 (C-7a), 84.1 (C-14a), 51.0 (C-7), 46.4 (C-5), 25.9 (C-4). Anal. calcd. for $C_{18}H_{15}NOS$ (293.38): C, 73.69; H, 5.15; N, 4.77. Found: C, 73.74; H, 5.11; N, 4.81.

(7a*S,14*R**)-14-Phenylnaphth[1,2-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (9bA)**

Column chromatography; eluent: *n*-hexane:EtOAc (20:1; R_f = 0.70), crystallized from cold *n*-hexane (3 mL). White powder. Mp: 152-154 °C. Yield: 56 mg (38%). ^{1}H NMR (DMSO-d_6, 500 MHz): 7.81 (d, *J* = 8.0 Hz, 1H, H-11), 7.77 (d, *J* = 8.9 Hz, H, H-12), 7.69 (d, *J* = 7.8 Hz, 1H, H-8),

7.38-7.25 (m, 7H, H-9,10 and H-2'-6'), 7.17 (d, *J* = 5.1 Hz, 1H, H-2), 7.03 (d, *J* = 5.1 Hz, 1H, H-1), 5.71 (s, 1H, H-14a), 5.52 (s, 1H, H-7), 3.47-3.44 (m, 1H, H-5_A), 3.28-3.24 (m, 1H, H-4_A), 3.23-3.19 (m, 1H, H-5_B), 3.00-2.96 (m, 1H, H-4_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 151.8 (C-13a), 142.3 (C-1'), 138.0 (C-3a), 133.3 (C-14b), 132.4 (C-7b), 129.4 (C-3',5'), 129.0 (C-11a), 128.6 (C-11), 128.4 (C-2',6'), 127.5 (C-4'), 126.7 (C-9), 125.8 (C-1), 123.6 (C-2), 123.2 (C-10), 122.6 (C-8), 118.9 (C-13a), 111.0 (C-7a), 79.0 (C-14a), 62.4 (C-7), 46.9 (C-5), 26.2 (C-4). Anal. calcd. for $C_{24}H_{19}NOS$ (369,48): C, 78.02; H, 5.18; N, 3.79. Found: C, 78.12; H, 5.10; N, 3.68.

(7a*S,14*R**)-14-Phenylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (10bA)**

^{1}H NMR (DMSO-d_6, 500 MHz): 8.00 (d, *J* = 8.0 Hz, 1H, H-13), 7.84 (d, *J* = 8.0 Hz, 1H, H-10), 7.49 (t, *J* = 7.9 Hz, 1H, H-12), 7.46 (t, *J* = 7.9 Hz, 1H, H-11), 7.43 (d, *J* = 8.2 Hz, 1H, H-9), 7.38 (d, *J* = 5.0 Hz, 1H, H-2), 7.31 (t, *J* = 7.7 Hz, 2H, H-3',5'), 7.26-7.22 (m, 3H, H-2',6' and H-4'), 7.15 (d, *J* = 5.0 Hz, 1H, H-1), 7.13 (d, *J* = 8.2 Hz, 1H, H-8), 5.61 (s, 1H, H-14a), 5.25 (s, H-7), 3.27 (dd, *J* = 11.4 Hz and 5.0 Hz, 1H, H-5_A), 3.15 (td, *J* = 11.4 Hz and 5.0 Hz, 1H, H-5_B), 3.05 (td, *J* = 15.9 Hz and 4.2 Hz, 1H, H-4_A), 2.91 (dd, *J* = 15.9 Hz and 5.0 Hz, 1H, H-4_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 148.9 (C-13b), 143.8 (C-1'), 138.4 (C-3a), 133.7 (C-9a), 133.6 (C-14b), 129.4 (C-2',6'), 128.6 (C-3',5'), 128.1 (C-10), 127.7 (C-4'), 127.5 (C-8), 126.8 (C-11), 126.7 (C-1), 125.8 (C-12), 124.5 (C-13a), 124.4 (C-2), 121.6 (C-13), 119.6 (C-9), 113.9 (C-7a), 79.7 (C-14a), 63.5 (C-7), 45.6 (C-5), 26.0 (C-4).

(7a*S,14*S**)-14-Phenylnaphth[2,1-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (10bB)**

Characteristic signals assigned for the minor component in the complex spectra registered of a mixture of **10bA** and **10bB**: ^{1}H NMR (DMSO-d_6, 500 MHz): 8.19 (d, *J* = 8.1 Hz, 1H, H-13), 7.78 (d, *J* = .0 Hz, 1H, H-10), 7.32 (d, *J* = 8.2 Hz, 1H, H-9), 6.70 (d, *J* = 8.2 Hz, 1H, H-8), 5.63 (s, 1H, H-14a), 4.98 (s, H-7), 2.95-2.85 (m, 2H, H-5_A and H-5_B), 2.80-2.71 (m, 2H, H-4_A and H-4_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 148.2 (C-13b), 138.1 (C-1'), 137.6 (C-3a), 133.9 (C-14b), 128.2 (C-10), 126.3 (C-8), 121.5 (C-13), 120.8 (C-9), 87.6 (C-14a), 67.0 (C-7), 46.9 (C-5), 25.1 (C-4).

(7a*S,14*R**)-14-Naphth-1-yl-naphth[2,1-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (10cA)**

Column chromatography; eluent: *n*-hexane:EtOAc (4:1; R_f = 0.75), crystallized from *n*-hexane (3 mL). Light yellow powder. Mp: 154-157 °C. Yield: 57 mg (34%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.43 (d, *J* = 8.0 Hz, 1H, H-13), 8.06 (d, *J* = 8.1 Hz, 1H, H-5'), 7.97 (d, *J* = 8.0 Hz, 1H, H-10), 7.90

(d, *J* = 7.9 Hz, 1H, H-8'), 7.86 (d, *J* = 8.0 Hz, 1H, H-4'), 7.67 (t, *J* = 7.9 Hz, 1H, H-12), 7.59-7.55 (m, 2H, H-11 and H-7'), 7.51 (t, *J* = 8.1 Hz, 1H, H-6'), 7.48 (d, *J* = 8.3 Hz, 1H, H-9), 7.38-7.35 (m, 2H, H-3' and H-1), 7.16 (d, *J* = 8.3 Hz, 1H, H-8), 7.12 (d, *J* = 5.1 Hz, 1H, H-2), 6.80 (d, *J* = 8.0 Hz, 1H, H-2'), 6.02 (s, 1H, H-7), 5.68 (s, H-14a), 3.65 (dd, *J*=11.4 Hz and 5.0 Hz, 1H, H-5_A), 3.26 (td, *J*=11.4 Hz and 5.0 Hz, 1H, H-5_B), 3.07-2.94 (m, 2H, H-4_A and H-4_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 149.3 (C-13b), 139.2 (C-1'), 138.4 (C-3a), 134.3 (C-4'a), 133.7 (C-9a), 132.7 (C-14b), 132.0 (C-8'a), 129.0 (C-10), 128.6 (C-4'), 128.3 (C-2'), 128.2 (C-8'), 127.5 (C-8), 126.7 (three coalesced lines, C-6', C-7' and C-12), 126.5 (C-2), 126.3 (C-11), 125.0 (C-13), 124.9 (C-3'), 124.5 (C-1), 124.3 (C-13a), 121.7 (C-5'), 119.8 (C-9), 113.5 (C-7a), 79.5 (C-14a), 60.7 (C-7), 45.3 (C-5), 26.0 (C-4). Anal. calcd. for $C_{28}H_{21}NOS$ (419,54): C, 80.16; H, 5.05; N, 3.34. Found: C, 80,24; H, 5,01; N, 3.31.

(7a*S,14*R**)-14-Naphth-2-yl-naphth[2,1-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (10dA)**

^{1}H NMR (DMSO-d_6, 500 MHz): 8.06 (d, *J* = 7.6 Hz, 1H, H-13), 7.92 (d, *J* = 7.9 Hz, 1H, H-4'), 7.90 (d, *J* = 7.6 Hz, 1H, H-10), 7.89 (d, *J* = 7.7 Hz, 1H, H-5'), 7.77 (d, *J* = 7.7 Hz, 1H, H-8'), 7.54 (t, *J* = 7.6 Hz, 1H, H-12), 7.67 (dd, *J* = 7.9 Hz and 1.8 Hz, 1H, H-3'), 7.50-7.46 (m, 4H, H-9, H-11, H-7' and H-6'), 7.44 (br s, 1H, H-1'), 7.39 (d, *J* = 5.4 Hz, 1H, H-2), 7.23 (d, *J* = 8.8 Hz, 1H, H-8), 7.14 (d, *J* = 5.4 Hz, 1H, H-1), 5.68 (s, 1H, H-14a), 5.45 (s, 1H, H-7), 3.38 (dd, *J*=11.5 Hz and 4.2 Hz, 1H, H-5_A), 3.22 (td, *J* = 11.5 Hz and 3.5 Hz, 1H, H-5_B), 3.13 (ddd, *J* = 16.4 Hz, 11.5 Hz and 3.5 Hz, 1H, H-4_A), 2.97 (d, *J* = 16.4 Hz, 1H, H-4_B), ^{13}C NMR (DMSO-d_6, 125 MHz): 153.8 (C-6a); 149.0 (C-13b), 141.5 (C-2'), 138.4 (C-3a), 133.8 (C-9a), 133.6 (C-14b), 132.7 (two coalesced lines, C-4'a and C-8'a), 128.4 (two coalesced lines, C-4' and C-8'), 128.3 (C-3'), 128.1 (C-10), 127.9 (C-5'), 127.6 (C-8), 126.8 (C-11), 126.7 (C-7'), 126.6 (two coalesced lines, C-1 and C-1'), 126.5 (C-6'), 124.5 (C-13a), 124.4 (C-2), 121.7 (C-13), 119.7 (C-9), 113.7 (C-7a), 79.7 (C-14a), 63.5 (C-7), 45.7 (C-5), 26.1 (C-4).

(7a*S,14*S**)-14-Naphth-2-yl-naphth[2,1-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (10dB)**

Characteristic signals assigned for the minor component in the complex spectra registered of a mixture of **10dA** and **10dB**: ^{1}H NMR (DMSO-d_6, 500 MHz): 8.24 (d, *J* = 7.6 Hz, 1H, H-13), 7.32 (d, *J* = 8.8 Hz, 1H, H-9), 6.76 (d, *J* = 8.8 Hz, 1H, H-8), 5.73 (s, 1H, H-14a), 5.17 (s, 1H, H-7), 3.00 (m, 1H, H-5_B), 2.83 (m, 2H, H-5_A and H-4_B) 2.76 (m, 1H, H-4_A), ^{13}C NMR (DMSO-d_6, 125 MHz): 148.4 (C-13b), 140.1 (C-2'), 137.5 (C-3a), 134.1 (C-14b), 133.0 (C-9a), 126.3 (C-8), 121.5 (C-13), 120.8 (C-9), 120.0 (C-7a), 87.7 (C-14a), 67.2 (C-7), 46.9 (C-5), 25.2 (C-4).

General procedure for the synthesis of tertiary aminonaphthols (13 and 14)

Morpholine or *N*-benzylmethylamine (4 mmol) and 1-naphthaldehyde (4 mmol) were mixed and placed in a 10 mL reaction vial and heated in oil bath at 70 °C for 1 h. Then 4 mmol 2-naphthol was added and stirred under neat conditions at 70 °C. After 4 h reaction time, the desired tertiary aminonaphthols were crystallized from methanol (18 mL) and then recrystallized from methanol (20 mL).

1-(Morpholino(naphthalen-1-yl)methyl)naphthalen-2-ol (13)

Light brown powder. R_f = 0.85 (4:1, *n*-hexane:EtOAc). Mp.: 152-154 °C. Yield: 1370 mg (85%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.85 (d, *J* = 8.2 Hz, 1H, H-8'), 7.94 (d, *J* = 8.2 Hz, 1H, H-5'), 7.82 (d, *J* = 8.0 Hz, 1H, H-4'), 7.75-7.70 (m, 4H, H-4, H-5, H-2' and H-7'), 7.69 (d, *J* = 7.9 Hz, 1H, H-8), 7.57 (dd, *J* = 8.2 Hz and 7.6 Hz, 1H, H-6'), 7.40 (t, *J* = 8.0 Hz, 1H, H-3'), 7.18-7.11 (m, 3H, H-3, H-6 and H-7), 6.33 (s, 1H, H-9), 3.61 and 3.17 (2xbr s's 2x2H, H-3",5"), 2.69 (br s 4H, H-2",6") ^{13}C NMR (DMSO-d_6, 125 MHz): 156.2 (C-2), 135.5 (C-1'), 133.9 (C-4'a), 133.0 (C-8a), 132.6 (C-8'a), 129.8 (C-5), 129.6 (C-5'), 129.1 (C-4'), 129.0 (C-4), 128.9 (C-4a), 127.3 (C-7'), 127.1 (C-2'), 126.8 (C-7), 126.3 (C-3'), 126.2 (C-6'), 123.8 (C-8'), 122.8 (C-6), 122.0 (C-8), 120.2 (C-3), 116.6 (C-1), 64.4 (C-9), 66.9 (C-3",5"), 51.9 (C-2",6"). Anal. calcd. for $C_{25}H_{23}NO_2$ (369,46): C, 81.27; H, 6.27; N, 3.79. Found: C, 81.33; H, 6.21; N, 3.79.

1-((Benzyl(methyl)amino)(naphthalen-2-yl)methyl)naphthalen-2-ol (14)

Grey powder. R_f = 0.85 (2:1, *n*-hexane:EtOAc). Mp.: 173-176 °C; Yield: 1122 mg (76%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.25 and 8.24 (partly overlapping br s and d, *J* = 8.0 Hz, 2H, H-8' and H-8, resp.), 7.91 (d, *J* = 7.7 Hz, 1H, H-3'), 7.81 (d, *J* = 7.7 Hz, 1H, H-6'), 7.86 (br s 2H, H-7' and H-8'), 7.76 and 7.75 (partly overlapping d's, *J* = 7.4 Hz and 8.8 Hz, 2H, H-5 and H-4, resp.), 7.50 (t, *J* = 7.7 Hz, 1H, H-5'), 7.46 (t, *J* = 7.7 Hz, 1H, H-4'), 7.44 (t, *J* = 7.4 Hz, 1H, H-7), 7.39 (t, *J* = 7.8 Hz, 2H, H-3",5"), 7.33 (d, *J* = 7.8 Hz, 2H, H-2",6"), 7.31 (tt, *J* = 7.8 Hz and 1.5 Hz, 1H, H-4"), 7.24 (td, *J* = 7.4 Hz and 1.8 Hz, 1H, H-6), 7.19 (d, *J* = 8.8 Hz, 1H, H-3), 5.68 (s, 1H, H-9), 3.71 (d, *J* = 12.9 Hz, 1H, H-11$_A$), 3.59 (d, *J* = 12.9 Hz, 1H, H-11$_B$), 2.15 (s, 3H, H-10); ^{13}C NMR (DMSO-d_6, 125 MHz): 155.2 (C-2), 138.5 (C-1'), 137.6 (C-1"), 133.2 (C-2'a), 132.9 (C-6'a), 132.3 (C-8a), 130.0 (C-4), 129.5 (C-2",6"), 129.3 (C-7'), 129.2 (C-5), 129.1 (C-3",5"), 128.7 (C-4a), 128.3 (C-3'), 128.2 (C-2'), 128.0 (C-4"), 127.9 (C-6'), 127.1 (C-7), 126.9 (C-4'), 126.7 (C-5'), 126.2 (C-8'), 123.0 (C-6), 122.0 (C-8), 120.1 (C-3), 116.8 (C-1), 70.7 (C-9), 59.7 (C-11), 40.3 (C-10). Anal. calcd. for $C_{29}H_{25}NO$ (403,51): C, 86.32; H, 6.24; N, 3.47. Found: C, 86.39; H, 6.19; N, 3.51.

General procedure for the synthesis of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine 3dA and naphth[1,2-*e*][1,3]oxazino[2,3-*a*]thienopyridines (9cA and 9dA) starting from tertiary aminonaphthols (13 and 14)

The mixture of the appropriate tertiary aminonaphthol (0.44 mmol) and 4,5-dihydro-3*H*-benz[*c*]azepine (**1**, 58 mg, 0.4 mmol) or 6,7-dihydrothieno[3,2-*c*]pyridine (**8**, 48 mg, 0.4 mmol) in 1,4-dioxane (5 mL) was placed in a 10 mL reaction vial and heated in a CEM microwave reactor for 60 min at 80 °C. The solvent was then evaporated under reduced pressure and the desired products were crystallized from methanol (6-8 mL) and then recrystallized from methanol (4-6 mL).

(7a*S,16*R**)-16-Naphth-2-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (3dA)**

White powder. R_f = 0.85 (4:1, *n*-hexane:EtOAc). Mp: 194-198 °C. Yield: 109 mg (64%). ^{1}H NMR (DMSO-d_6, 500 MHz):7.87 (d, *J* = 7.8 Hz, 1H, H-5'), 7.86 (d, *J* = 7.8 Hz, 1H, H-4'), 7.84 (d, *J* = 8.8 Hz, 1H, H-5), 7.82 (d, *J* = 2.5 Hz, 1H, H-1'), 7.67 (d, *J* = 8.0 Hz, 1H, H-8'), 7.62 (d, *J* = 7.8 Hz, 1H, H-3'), 7.45-7.42 (m, 2H, H-7' and H-4), 7.38 (t, *J* = 7.8 Hz, 1H, H-6'), 7.30 (d, *J* =7.8 Hz, 1H, H-1), 7.27 (t, *J* = 7.8 Hz, 1H, H-3), 7.24 (t, *J* = 7.8 Hz, 1H, H-2), 7.18 (d, *J* = 8.8 Hz, 1H, H-6), 7.16 (t, *J* = 7.8 Hz, 1H, H-9), 7.12 (d, *J* = 7.8 Hz, 1H, H-11), 6.98 (t, *J* = 7.8 Hz, 1H, H-10), 6.81 (d, *J* = 7.8 Hz, 1H, H-8), 5.73 (s, 1H, H-7a), 5.63 (s, 1H, H-16), 3.32-3.28 (m, 1H, H-14$_A$), 3.24-3.21 (m, H-14$_B$), 3.02-2.98 (m, 1H, H-12$_A$), 2.85-2.81 (m, 1H, H-12$_B$), 1.94-1.92 (m, 1H, H-13$_A$), 1.85-1.81 (m, 1H, H-13$_B$); ^{13}C NMR (DMSO-d_6, 125 MHz): 153.8 (C-6a); 142.7 (C-7b), 141.7 (C-2'), 135.8 (C-11a), 133.0 (C-16b), 132.9 (two coalesced lines, C-4'a and C-8'a), 130.9 (C-8), 130.0 (C-11), 129.6 (C-5), 129.4 (C-4a), 129.3 (C-9), 129.1 (C-1'), 128.5 (C-4), 128.4 (two coalesced lines, C-5' and C-8'), 128.2 (C-3'), 128.0 (C-4'), 127.1 (C-2), 126.7 (two coalesced lines, C-6' and C-7'), 126.5 (C-10), 124.0 (C-3), 123.4 (C-1), 118.9 (C-6), 113.0 (C-16a), 91.0 (C-7a), 63.2 (C-16), 53.1 (C-14), 34.8 (C-12), 28.8 (C-13). Anal. calcd. for $C_{31}H_{25}NO$ (427,54): C, 87.09; H, 5.89; N, 3.28. Found: C, 87.02; H, 5.93; N, 3.31.

(7a*S,14*R**)-14-Naphth-1-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (9cA)**

White powder. R_f = 0.75 (4:1, *n*-hexane:EtOAc). Mp: 144-147 °C. Yield: 104 mg (61%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.58 (d, *J* = 8.1 Hz, 1H, H-8'), 7.99 (d, *J* = 8.1 Hz, 1H, H-5'), 7.89 (d, *J* =

8.9 Hz, 1H, H-11), 7.87 (d, *J* = 8.9 Hz, 1H, H-12), 7.84 (d, *J* = 8.0 Hz, 1H, H-4'), 7.82 (d, *J* = 8.0 Hz, 1H, H-2'), 7.72 (dd, *J* = 8.2 Hz and 8.2 Hz, 1H, H-7'), 7.60 (dd, *J* = 8.2 Hz and 8.2 Hz, 1H, H-6'), 7.32 (d, *J* = 5.2 Hz, 1H, H-2), 7.31-7.27 (m, 2H, H-10 and H-3'), 7.20 (d, *J* = 7.5 Hz, 1H, H-8), 7.16 (d, *J* = 8.9 Hz, 1H, H-13), 6.40 (s, 1H, H-7), 5.67 (s, H-14a), 3.69 (dd, *J* = 11.4 Hz and 5.0 Hz, 1H, H-5_A), 3.24 (td, *J* = 11.4 Hz and 5.0 Hz, 1H, H-5_B), 3.05-2.93 (m, 2H, H-4_A and H-4_B); ^{13}C NMR (DMSO-d_6, 125 MHz): 152.1 (C-13a), 138.3 (C-3a), 138.2 (C-1'), 133.4 (C-4'a), 133.4 (C-14b), 132.2 (C-7b), 131.6 (C-8'a), 129.7 (C-12), 129.6 (C-11), 129.2 (C-11a), 129.0 (C-5'), 128.7 (C-4'), 127.9 (C-2'), 127.1 (C-9), 127.0 (C-7'), 126.6 (C-1), 126.4 (C-6'), 125.2 (two coalesced lines, C-10 and C-3'), 125.1 (C-8'), 124.3 (C-2), 123.0 (C-8), 118.8 (C-13), 111.3 (C-7a), 78.9 (C-14a), 58.3 (C-7), 45.3 (C-5), 26.0 (C-4). Anal. calcd. for $C_{28}H_{21}NOS$ (419,54): C, 80.16; H, 5.05; N, 3.34. Found: C, 80,24; H, 5,01; N, 3.31.

(7a*S,14*R**)-14-Naphth-2-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (9dA)**

White powder. R_f = 0.85 (4:1, *n*-hexane:EtOAc). Mp: 240-242 °C. Yield: 106 mg (62%). ^{1}H NMR (DMSO-d_6, 500 MHz, 55 ^{o}C): 7.87 (d, *J* = 8.6 Hz, 1H, H-4'), 7.86-7.82 (m, 3H, H-5', H-11 and H-12), 7.67 (d, *J* = 7.9 Hz, 1H, H-8'), 7.64 (dd, *J* = 8.6 Hz and 1.6 Hz, 1H, H-3'), 7.45 (br s, 1H, H-1'), 7.45-7.42 (m, 3H, H-5', H-7' and H-8), 7.39 (t, *J* = 7.9 Hz, 1H, H-6'), 7.31-7.26 (m, 3H, H-3, H-9 and H-10), 7.12 (d, *J* = 8.9 Hz, 1H, H-13), 7.00 (d, *J* = 5.1 Hz, 1H, H-1), 5.80 (s, 1H, H-7), 5.64 (s, 1H, H-14a), 3.37 (dd, *J* = 10.9 Hz and 5.5 Hz, 1H, H-5_A), 3.22 (td, *J* = 10.9 Hz and 3.4 Hz, 1H, H-5_B), 3.15-3.11 (m, 1H, H-4_A), 2.93 (dd, *J* = 16.1 Hz and 3.0 Hz, 1H, H-4_B); ^{13}C NMR (DMSO-d_6, 125 MHz, 55 ^{o}C): 151.9 (C-13a), 140.7 (C-2'), 138.2 (C-3a), 133.6 (C-14b), 132.9 (C-4'a), 132.5 (C-7b), 129.6 (C-12), 129.2 (C-11a), 129.0 (C-11), 128.4 (C-4'), 128.3 (C-8'), 128.0 (two coalesced lines, C-1' and C-3'), 127.8 (C-5'), 127.0 (C-9), 126.6 (C-1), 126.5 (two coalesced lines, C-6' and C-7'), 125.7 (C-8'a), 124.1 (two coalesced lines, C-2 and C-10), 123.0 (C-8), 118.9 (C-13), 111.4 (C-7a), 79.1 (C-14a), 61.7 (C-7), 46.0 (C-5), 26.0 (C-4). Anal. calcd. for $C_{28}H_{21}NOS$ (419,54): C, 80.16; H, 5.05; N, 3.34. Found: C, 80,24; H, 5,01; N, 3.31.

1-(Hydroxy(naphthalen-1-yl)methyl)naphthalen-2-ol (19b)

Yellow powder. R_f = 0.90 (2:1, *n*-hexane:EtOAc). Mp.: 134-136 °C. Due to extremely overlapped aromatic signals with poor resolution, only the unambiguous assignments of H-9 C-3 and C-9 of diagnostic importance are given along with ^{1}H chemical shift ranges and the signals of naphthalene CH carbons detected by 2D-HMQC measurements: ^{1}H NMR (DMSO-d_6, 500 MHz): 7.98 (d, *J* = 8.0 Hz, 1H), 7.9-7.7 (m, 6H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J*=7.8 Hz 1H), 7.4-7.1 (m, 5H), 6.50

(s, 1H, H-9); ^{13}C NMR (DMSO-d_6, 125 MHz): 129.9, 129.7, 129.3 (two signals as detected by two HMQC cross peaks), 129.2, 128.1, 127.6, 127.3, 126.9, 126.4, 126.3, 122.9, 121.9, 120.2 (C-3), 63.8 (C-9).

General procedure for the synthesis of various substituted tertiary aminonaphthols (20-22, 24-25)

The appropriate amine (0.4 mmol) and aldehyde (0.4 mmol) component were placed in a 10 mL reaction vial and heated in an oil bath at 70 °C for 1 h. Then 2-naphthol was added and stirred under neat conditions at 70 °C. After 7 hours reaction time, the desired products were crystallized from methanol (4-6 mL) and then recrystallized from methanol (6-8 mL).

1-(Naphthalen-1-yl(pyrrolidin-1-yl)methyl)naphthalen-2-ol (20)

Yellow powder. R_f = 0.80 (2:1, *n*-hexane:EtOAc). Yield: 114 mg (81%). Mp.: 109-112 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): 8.91 (d, *J* = 8.2 Hz, 1H, H-8'), 7.95 (d, *J* = 8.2 Hz, 1H, H-5'), 7.82 (d, *J* = 8.0 Hz, 1H, H-4'), 7.73-69 (m, 4H, H-4, H-5, H-2' and H-7'), 7.64 (d, *J* = 7.8 Hz, 1H, H-8), 7.57 (dd, *J* = 8.2 Hz and 7.6 Hz, 1H, H-6'), 7.40 (t, *J* = 8.0 Hz, 1H, H-3'), 7.18-7.11 (m, 3H, H-3, H-6 and H-7), 6.37 (s, 1H, H-9), 2.6 (very br s, 4H, H-2",5"), 1.74 (br s, 4H, H-3",4") ^{13}C NMR (DMSO-d_6, 125 MHz): 156.7 (C-2), 137.7 (C-1'), 133.9 (C-4'a), 132.4 (C-8a), 131.9 (C-8'a), 129.6 (two coalesced lines, C-5 and C-5'), 129.0 (C-4), 128.9 (C-4'), 128.5 (C-4a), 127.3 (C-7'), 126.9 (C-2'), 126.8 (C-7), 126.3 (C-3'), 126.2 (C-6'), 123.9 (C-8'), 122.7 (C-6), 121.8 (C-8), 120.3 (C-3), 117.8 (C-1), 62.6 (C-9), 53.7 (C-2",5"), 23.4 (C-3",4"). Anal. calcd. for $C_{25}H_{23}NO$ (353.46): C, 84.95; H, 6.56; N, 3.96. Found: C, 84.88; H, 6.64; N, 3.90.

1-(Naphthalen-1-yl(piperidin-1-yl)methyl)naphthalen-2-ol (21)

Orange powder. R_f = 0.85 (2:1, *n*-hexane:EtOAc). Mp.: 187-189 °C. Yield: 113 mg (77%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.86 (d, *J* = 8.2 Hz, 1H, H-8'), 7.98 (d, *J* = 8.2 Hz, 1H, H-5'), 7.85 (d, *J* = 8.0 Hz, 1H, H-4'), 7.77 (dd, *J* = 8.2 Hz and 7.6 Hz, 1H, H-7'), 7.74 (d, *J* = 8.9 Hz, 1H, H-8), 7.71 (dd, *J* = 7.5 Hz and 2.1 Hz, 1H, H-5), 7.63 (d, *J* = 8.0 Hz, 1H, H-2'), 7.61 (dd, *J* = 8.2 Hz and 7.6 Hz, 1H, H-6'), 7.56 (d, *J* = 7.9 Hz, 1H, H-8), 7.41 (t, *J* = 8.0 Hz, 1H, H-3'), 7.18-7.11 (m, 3H, H-3, H-6 and H-7), 6.29 (s, 1H, H-9), 2.28 and 2.18 (2xbr s, 2x2H, H-2",6"), 1.55 (br s, 4H, H-3",5"), 1.28 (br s, 2H, H-4) ^{13}C NMR (DMSO-d_6, 125 MHz): 152.9 (C-2), 135.8 (C-1'), 133.8 (C-4'a), 132.9 (C-8a), 132.6 (C-8'a), 129.6 (C-5'), 129.5 (C-4), 129.1 (C-5), 129.0 (C-4'), 128.6 (C-4a), 127.5 (C-7'), 127.3 (C-2'), 126.9 (C-7), 126.4 (C-3'), 126.3 (C-6'), 123.8 (C-8'), 122.7 (C-6),

121.6 (C-8), 120.4 (C-3), 117.1 (C-1), 64.2 (C-9), 50.1 (C-2",6"), 26.5 (C-3",5"), 25.0 (C-4"). Anal. calcd. for $C_{26}H_{25}NO$ (367,48): C, 84.98; H, 6.86; N, 3.81. Found: C, 85.07; H, 6.93; N, 3.69.

1-((methyl(phenethyl)amino)(naphthalen-1-yl)methyl)naphthalen-2-ol (22)

Yellow powder. R_f = 0.90 (4:1, *n*-hexane:EtOAc). Mp.: 71-73 °C. Yield: 133 mg (80%). ^{1}H NMR (DMSO-d_6, 500 MHz, 55 ^{o}C): 8.34 (d, *J* = 8.2 Hz, 1H, H-8'), 7.97 (d, *J* = 8.2 Hz, 1H, H-5'), 7.84 (d, *J* = 8.0 Hz, 1H, H-4'), 7.76 (dd, *J* = 8.2 Hz and 7.6 Hz, 1H, H-7'), 7.73 (d, *J* = 7.9 Hz, 1H, H-5), 7.71 (d, *J* = 8.6 Hz, 1H, H-4), 7.68 (d, *J* = 7.8 Hz, 1H, H-8), 7.66 (d, *J* = 8.0 Hz, 1H, H-2'), 7.57 (dd, *J* = 8.2 Hz and 7.6 Hz, 1H, H-6'), 7.39 (t, *J* = 8.0 Hz, 1H, H-3'), 7.20 (tt, *J* = 7.8 Hz and 2.0 Hz, 1H, H-4"), 7.16-7.11 (m, 5H, H-3, H-6, H-7 and H-3",5"), 6.96 (d, *J* = 7.9 Hz, 2H, H-2",6"), 6.38 (s, 1H, H-9), 2.8 (very br s, 7H, H-10, H-11and H-12);^{13}C NMR (DMSO-d_6, 125 MHz, 55 ^{o}C): 156.7 (C-2), 136.7 (C-1'), 133.9 (C-4'a), 132.9 (C-8a), 132.6 (C-8'a), 129.6 (two coalesced lines,C-5 and C-5'), 129.0 (two coalesced lines, C-4' and C-7'), 128.8 (two coalesced lines, C-2",6" and C-3",5"), 128.6 (C4a), 127.4 (two coalesced lines, C-4 and C-2'), 126.7 (C.4"), 126.5 (C-7), 126.2 (two coalesced lines, C-3' and C-6'), 123.8 (C-8'), 122.6 (C-6), 121.9 (C-8), 120.3 (C-3), 117.5 (C-1), 64.6 (C-9), 56.8 (C-11), 33.8 (C-10), 27.6 (C-12). Anal. calcd. for $C_{30}H_{27}NO$ (417,54): C, 86.30; H, 6.52; N, 3.35. Found: C, 86.39; H, 6.48; N, 3.41.

1-((Benzyl(methyl)amino)(4-methoxyphenyl)methyl)naphthalen-2-ol (24)

Pale pink powder. R_f = 0.80 (2:1, *n*-hexane:EtOAc). Mp.: 110-112 °C. Yield: 123 mg (80%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.09 (d, *J* = 7.9 Hz, 1H, H-8), 7.77 (d, *J* = 7.9 Hz, 1H, H-5), 7.74 (d, *J* = 8.9 Hz, 1H, H-4), 7.62 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.43 (t, *J* = 7.8 Hz, 1H, H-7), 7.38 (t, *J* = 7.8 Hz, 2H, H-3",5"), 7.32-7.28 (m, 3H, H-2",6" and H-4"), 7.26 (t, *J* = 7.9 Hz, 1H, H-6), 7.14 (d, *J* = 8.9 Hz, 1H, H-3), 6.87 (d, *J* = 8.6 Hz, 2H, H-3',5'), 5.44 (s, 1 ^{13}C NMR (DMSO-d_6, 125 MHz): 159.2 (C-4'), 155.1 (C-2), 137.7 (C-1"), 132.8 (C-1'), 132.3 (C-8a), 130.2 (C-2',6'), 129.6 (C-4), 129.5 (C-2",6"), 129.2 (C-3",5"), 129.1 (C-5), 128.7 (C-4a), 128.0 (C-4"), 127.0 (C-7), 122.9 (C-6), 122.0 (C-8), 120.0 (C-3), 117.4 (C-1), 114.6 (C-3',5'), 69.9 (C-9), 59.5 (C-11), 55.5 (OCH_3), 39.8 (C-10). Anal. calcd. for $C_{27}H_{28}N_2O$ (396,52): C, 81.78; H, 7.12; N, 7.06. Found: C, 81.88; H, 7.11; N, 6.99.

1-((Benzyl(methyl)amino)(4-nitrophenyl)methyl)naphthalen-2-ol (25)

Light orange powder. R_f = 0.85 (2:1, *n*-hexane:EtOAc). Mp.: 81-83 °C. Yield: 132 mg (83%). ^{1}H NMR (DMSO-d_6, 500 MHz): 8.26 (d, *J* = 7.8 Hz, 1H, H-8), 8.15 (d, *J* = 8.9 Hz, 2H, H-3',5'), 7.98 (d, *J* = 8.9 Hz, 2H, H-2',6'), 7.76 (d, *J* = 7.9 Hz, 1H, H-5), 7.73 (d, *J* = 8.9 Hz, 1H, H-4), 7.44 (dd, *J* = 8.4 Hz and 7.0 Hz, 1H, H-7), 7.36 (t, *J* = 7.8 Hz, 2H, H-3",5"), 7.31 (d, *J* = 7.3 Hz, 2H, H-2",6"),

7.28 (t, *J* = 7.3 Hz, 1H, H-4"), 7.25 (t, *J* = 7.7 Hz, 1H, H-6), 7.15 (d, *J* = 8.9 Hz, 1H, H-3), 5.72 (s, 1 ^{13}C NMR (DMSO-d_6, 125 MHz): 155.0 (C-2), 149.0 (C-1'), 147.3 (C-4'), 137.6 (C-1"), 132.3 (C-8a), 130.4 (C-4), 129.9 (C-2',6'), 129.4 (C-2",6"), 129.2 (C-5), 129.1 (C-3",5"), 128.8 (C-4a), 128.0 (C-4"), 119.9 (C-3), 116.6 (C-1), 68.9 (C-9), 59.7 (C-11), 40.5 (C-10). Anal. calcd. for $C_{25}H_{22}N_2O_3$ (398,45): C, 75.36; H, 5.57; N, 7.03. Found: C, 75.42; H, 5.59; N, 6.98.

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Graphical Abstract

Synthesis and detailed conformational analysis of new naphthoxazino[2,3-*a*]benz[*c*]azepine and naphthoxazino [2,3-*a*]thieno[3,2-*c*]pyridine derivatives

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