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Synthesis and stereochemistry of new naphth[1,3]oxazino[3,2-*a*]benzazepine and naphth[1,3]oxazino[3,2-*e*]thienopyridine derivatives

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ABSTRACT

Through the reactions of 1- or 2-naphthol and 4,5-dihydro-3*H*-benz[*c*]azepine or 6,7-dihydrothieno[3,2-*c*]pyridine, new aminonaphthol derivatives were prepared. The syntheses were extended by using N-containing naphthol analogues such as 5-hydroxyisoquinoline and 6-hydroxyquinoline. The ring closures of the novel bifunctional compounds were also achieved, resulting in new naphth[2,1-*e*][1,3]oxazines, naphth[1,2-*e*][1,3]oxazines, isoquinolino[5,6-*e*][1,3]oxazines and quinolino[5,6-*e*][1,3]oxazines. ^{1}H NMR spectra of the target heterocycles **16**, **20** and **21** were sufficiently resolved to indentify the present stereochemistry; therefore, beside computed structures, spatial experimental (dipolar coupling–NOE) and computed (ring current effect of the naphthyl moiety–TSNMRS) NMR studies were employed. The studied heterocycles exist exclusively as *S*(14b),*R*(N), *R*(14b),*S*(N), and *S*(16b)*S*(N) isomers, respectively. The flexible moieties of the studied compounds prefer.

1. Introduction

The Mannich reaction is one of the most frequently applied multicomponent reactions in organic chemistry.[1,2] In the original form of the reaction, the Mannich product is formed through the reaction of a C–H acid, formaldehyde and a secondary amine. A special alteration is the modified three-component Mannich reaction (*m*MR), in which formaldehyde is replaced by an aromatic aldehyde, the secondary amine by ammonia, and the C–H acid by an electron-rich aromatic compound such as 1- or 2-naphthol, quinolinol or isoquinolinol.[3] In consequence of the two or more functional groups in the structures of the Mannich bases prepared via such modified reactions, one of the most important areas of application of these aminonaphthol derivatives is the synthesis of new heterocycles.[3]

We earlier reported syntheses and conformational studies of a series of naphth[1,2-*e*][1,3]oxazino[3,4-*c*][1,3]benzoxazine,[4,5] naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline,[6] naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one[7] and naphth[1,3]oxazino[2,3-a]isoquinoline[8] derivatives. It was concluded that the annelation of the two partly saturated six-membered rings strongly determined the conformation of the heterocycles above. For these compounds, the 1,3-oxazine ring was condensed with another 1,3-oxazine, hexahydropyrimidine or piperidine, and the conformational search protocol revealed that the 1,3-oxazine moiety prefers twisted chair conformers.

In these previous studies, the 1,3-oxazine ring was condensed with another six-membered ring, and our present aim was therefore to prepare novel 1,3-oxazinoazepine-containing polyheterocycles to study the effects of the more flexible seven-membered ring on the conformation. While the previously studied heterocycles contained a benzene ring condensed to the flexible ring moieties, our next aim was to synthesize and study the conformational behaviour of heterocycles in which the benzene ring is replaced by an S-containing aromatic moiety such as thiophene. A further aim was to examine the possibility of extending the reaction by starting from N-containing naphthol analogues such as 5-hydroxyisoquinoline or 6-hydroxyquinoline instead of 1- or 2-naphthol.

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2. Results and discussion

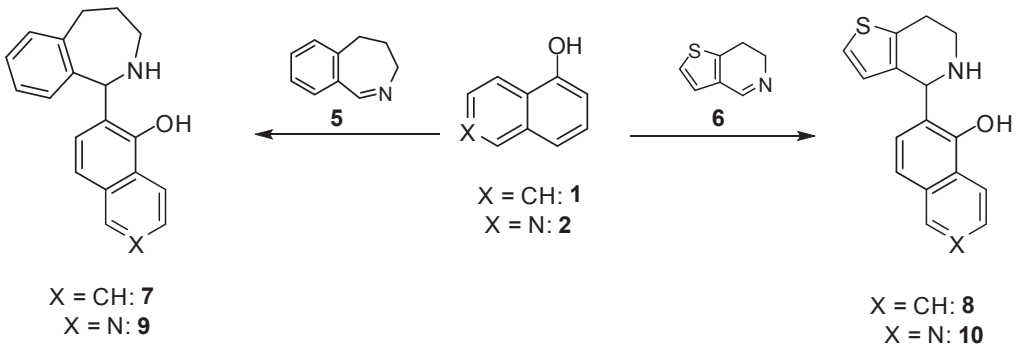
2.1. Syntheses

For the preparation of the novel polyheterocyclic naphthoxazine derivatives, the initial bifunctional aminonaphthols were first synthesized. The starting partially saturated amines **5** and **6** were synthesized on the basis of methods known in the literature. 4,5-Dihydro-3*H*-benz[*c*]azepine (**5**) was prepared from α-tetralone in 4 steps,[9,10] while 6,7-dihydrothieno[3,2-*c*]pyridine (**6**) was synthesized via Bischler-Napieralski cyclization from 2-thiophen-2-yl-ethylamine.[11]

In our first experiment, 1-naphthol (**1**) was reacted with 4,5-dihydro-3*H*-benz[*c*]azepine (**5**) or 6,7-dihydrothieno[3,2-*c*]pyridine (**6**), resulting in **7** and **8** in good yields (Scheme 1). The reactions were achieved by classical heating, but also by using microwave irradiation. After the optimization procedure, microwave irradiation was chosen because of the shorter reaction times and the higher yields, as shown in Table 1.

and hydroxyquinolylthienopyridine (**14**) formed were isolated and purified by crystallization or by column chromatography (see Experimental). In the syntheses of these types of compounds, microwave irradiation again proved better than classical heating: the desired products were isolated in shorter reaction times and in higher yields (Table 1). The thienopyridine derivatives reacted in shorter times and formed the desired polycycles in higher yields than in case of the benzazepine-condensed products. As concerns the electron-rich aromatic compounds, 2-naphthol displayed higher reactivity than 6-hydroxyquinoline.

After isolation of the initial bifunctional compounds, their ring closures led to new naphthoxazines, isoquinolinoxazines and quinolinoxazines. All the syntheses were performed at room temperature in CH_2Cl_2, using a 35% solution of HCHO as cyclizing agent. The reactions proved to be complete after relatively short reaction times (20–30 min) and the desired products **15**–**22** were isolated in excellent yields by simple crystallization from *n*-hexane, as shown in Table 2.



Scheme 1. Reaction of 1-naphthol with 4,5-dihydro-3*H*-benz[*c*]azepine (**5**) or 6,7-dihydrothieno[3,2-*c*]pyridine (**6**) resulting in **7** and **8** in good yields.

The synthesis was then extended by reacting **5** and **6** with the N-containing 1-naphthol analogue 5-hydroxyisoquinoline **2**, which led to the formation of **9** and **10**. The aminonaphthols (**7** and **8**) were formed in a shorter time and in higher yield as compared with the aminoisoquinolinols (**9** and **10**, Table 1).

Table 1
Optimizing of the reaction conditions for the preparation of the bifunctional compounds **7**–**14**

Product	Conditions[a]	Yield[a](%)	Conditions[b]	Yield[b] (%)
7	150 min, 80 °C	54	60 min, 80 °C	73
8	150 min, 85 °C	59	60 min, 85 °C	63
9	10 h, 80 °C	58	100 min, 80 °C	68
10	10 h, 80 °C	60	80 min, 80 °C	84
11	150 min, 80 °C	64	90 min, 80 °C	74
12	150 min, 80 °C	65	90 min, 80 °C	58
13	8 h, 80 °C	43	120 min, 80 °C	64
14	10 h, 80 °C	42	120 min, 80 °C	80

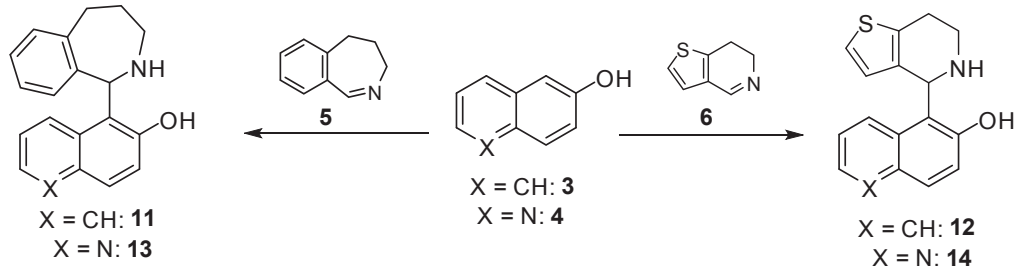
[a] Classical heating.
[b] Microwave irradiation.

To examine the possibility of the extension of the reaction, 2-naphthol (**3**) and its isostere 6-hydroxyquinoline (**4**) were applied as electron rich aromatic compounds. The partly saturated cyclic amines **5** and **6** were reacted with **3** and **4** (Scheme 2), and the new hydroxy-2-naphthylbenzazepine (**11**), hydroxy-2-naphthylthienopyridine (**12**), hydroxyquinolylbenzazepine (**13**)

2.2. Stereochemistry

The theoretical stereochemistry search protocol involved geometry optimization without restrictions. All calculations were performed by using the Gaussian 09 program package.[12] Density functional theory calculations were carried out at the B3LYP/6-311G** level of theory.[13,14] The molecular modelling software package SYBYL 7.3 was used to display results and geometries;[15] in calculation of the NMR parameters, the solvent was not considered. The target compounds **16**, **20** and **21** were studied with respect to the various isomers, preferred conformers or conformational equilibria. In **16**, **20**, and **21** one chiral centre C(14b) and C(16b), respectively is present; the frozen sp^3-nitrogen N(9) can be in the *R*/*S* configuration too. As result of the computations enantiomers were obtained; however, the studied compounds are diastereometrically pure only and exist (probably) as 1:1 mixtures of the depicted stereoisomers with their mirror images. A chiral NMR study employing optically active solvents or additives were not performed.

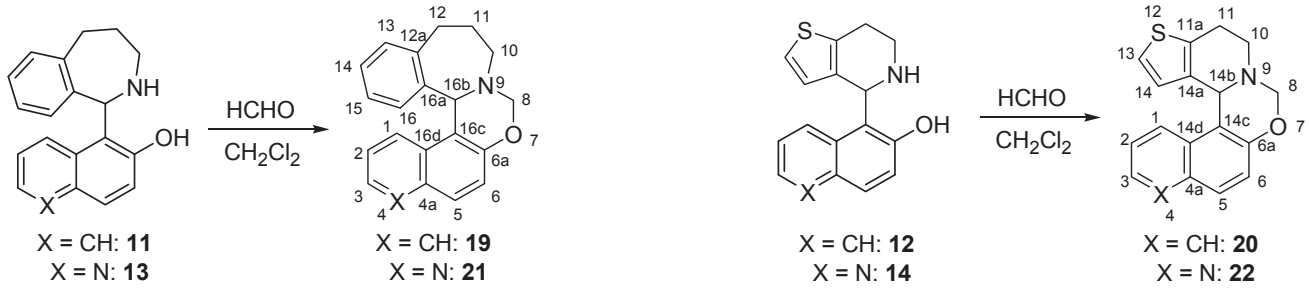
As the final result, the ***S*(14b),*R*(N)** configuration for **16**, the ***R*(14b),*S*(N)** configuration for **20** and the ***S*(16b)*S*(N)** configuration for **21** were obtained as the most stable ones; the energy differences to the energetically next coming isomer were >2.8 kcal mol^{-1}, discriminating for the significant population of another, energetically less stable conformer. The preferred stereoisomers in the most stable conformation are given in Fig. 1 and form the basis for employing the NMR spectroscopic structure elucidation.



Scheme 2. Reaction of the isostere electron rich aromatic compounds **3** and **4** with the partly saturated cyclic amines **5** and **6**.

Table 2
Ring closures of the bifunctional compounds **7**–**14**

Product	Reaction time	Yield (%)	Product	Reaction time	Yield (%)
15	20 min	92	**16**	25 min	85
17	30 min	82	**18**	30 min	83



Product	Reaction time	Yield (%)	Product	Reaction time	Yield (%)
19	30 min	87	**20**	30 min	89
21	30 min	88	**22**	30 min	78

The ^{1}H and ^{13}C NMR spectra of **16** and **20** are given in Table 3. The corresponding assignments of the protons and carbon atoms are congruent due to the parallel HSQC and HMBC 2D NMR experiments. Differences in chemical shifts of certain protons and carbon atoms can be consulted to extract useful information concerning the present stereochemistry (vide infra). In addition, and this was crucial, a number of configurationally/conformationally relevant NOEs could be found and proved to be stereochemically relevant.

2.2.1. Spatial NMR information (dipolar coupling–NOE). The strong NOEs of H-14b to the protons H-11ax of the flexible ethylene bridge $-CH_2(10)-CH_2(11)-$ in **20** (on the same side of the isomer) are discriminating; in **16**, adequate information could not be obtained from the corresponding NOEs (in this isomer on the reversed side of the molecule), with the exception of a weak NOE between H-14b and H-10ax which corroborates the calculated distance of 3.74 Å. Further, the proximity of H-14b to the naphthyl proton H-1 in **20** is proved by the corresponding NOEs; the same dipolar interaction in **16** is not indicated.

Since the spatial NOE information relating to the stereochemistry of the thienopyridines in the case of **16** was limited in comparison with **20**, the spectra of the pyridino analogues **18** and **22** were recorded, computed (same conditions) and studied within the same stereochemistry context (cf. Table 3). The $\delta(^{1}H)$/ppm and $\delta(^{13}C)$/ppm values in the NMR spectra and the results of the computations are comparable and lead to identical conclusions with respect to the present stereochemistry (vide supra). In contrast with **16** the strong intra-aromatic NOE in **18** and the medium NOE between H-1 and H-14 proves the stereochemistry of both **18** and **22**.

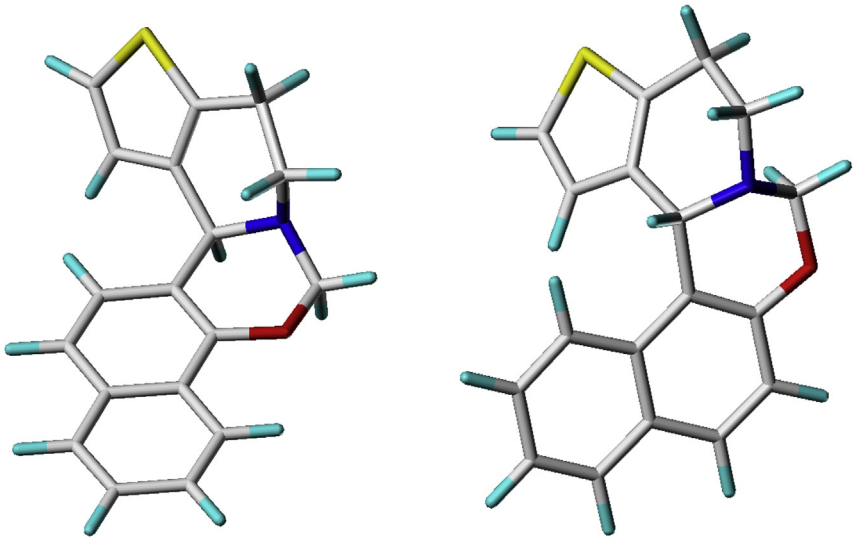


Fig. 1. Stereochemistry of **16** [*S*(14b),*R*(N)] and **20** [*R*(14b),*S*(N)] as obtained by DFT calculations and supported by the corresponding spatial NOE information.

Table 3
Experimental NMR data of **16**, **18**, **20**, **and 22** (δ in ppm, J in Hz)

Position	**16**		**18**		**20**		**22**	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	125.5	7.31 (1H, m)	127.0	7.36 (d, 8.6)	123.2	7.91 (1H, d, 8.4)	131.2	8.17 (d, 8.3)
2	119.6	7.31 (1H, m)	118.8	7.33 (d, 8.5)	126.7	7.53 (1H, ddd, 8.4, 6.9, 1.4)	121.4	7.36 (dd, 8.2, 3.8)
2a	133.6		128.6 (br)					
3	127.6	7.72 (1H, m)	152.0	9.02 (s, br)	123.6	7.39 (1H, ddd, 8.0, 6.9, 1.1)	147.8	8.70 (br)
4	126.3	7.44 (1H, m)			128.8	7.82 (1H, d, 8.2)		
4a					129.4		144.7	
5	125.5	7.44 (1H, m)	142.8	8.39 (br)	129.3	7.71 (1H, d, 8.9)	130.6	7.85 (d, 9.1)
6	121.8	8.14 (1H, m)	114.9 (br)	7.82 (d, 5.4)	118.9	7.05 (1H, d, 8.9)	122.4	7.19 (d, 9.1)
6a	124.8		127.4		150.8		150.9	
6b	147.8		147.2					
8	84.9	a: 5.40 (1H, d, 10.0) b: 5.21 (1H, d, 10.0)	85.1	a) 5.14 (d, 10.1) b) 5.32 (d, 10.0)	77.6	a: 4.79 (1H, d, 7.0) b: 4.74 (1H, dd, 7.0, 0.9)	77.8	a) 4.69 (d, 6.9) b) 4.72 (d, 6.9)
10	44.0	3.24 (2H, m)	44.2	a) 3.11 (td, 11.4, 4.0) b) 3.16 (ddd, 11.8, 6.6, 1.0)	47.6	ax: 3.68 (1H, ddd, 14.3, 12.2, 6.0) eq: 3.59 (1H, ddd, 14.4, 6.8, 0.6)	47.5	a) 3.51 (dd, 14.2, 6.7) b) 3.59 (td, 13.1, 5.8)
11	25.8	ax: 3.11 (1H, m) eq: 2.81 (1H, ddd, 15.9, 2.7, 2.7)	25.8	a) 2.72 (dd, 15.9, 3.0) b) 3.02 (m)	21.7	ax: 2.97 (1H, ddddd, 17.1, 12.2, 7.0, 2.3, 0.6) eq: 2.83 (1H, ddd, 17.2, 5.9, 1.0)	21.6	a) 2.75 (dd, 17.0, 4.9) b) 2.89 (m)
11a	135.3		135.5		132.7		132.8	
13	123.1	7.28 (1H, d, 5.2)	123.4	7.21 (d, 5.1)	122.1	6.95 (1H, d, 5.3)	122.5	6.90 (d, 4.9)
14	127.6	7.24 (1H, d, 5.2)	127.4	7.14 (d, 5.2)	128.0	6.62 (1H, d, 5.2)	127.5	6.45 (d,5.0)
14a	134.5		133.8		135.7		135.2	
14b	55.5	5.58 (1H, s)	55.4	5.49 (s)	54.2	5.62 (1H, s)	53.7	5.51 (s)
14c	116.4		120.7		116.0		115.7	
14d					132.3		127.3	

2.2.2. Spatial magnetic properties—TSNMRS. Additional validation of correct preferred stereoisomers comes from ^{1}H NMR spectra: First the ring current effect of the naphthyl moiety on the protons in **16** and **20** was computed. For this purpose, our spatial NICS approach[16] was employed. These through-space NMR shieldings (TSNMRSs) can be visualized[16] as iso-chemical-shielding surfaces (ICSSs) and employed to quantify the anisotropic effects of functional groups on proton chemical shifts (for determination of the stereochemistry of nuclei proximal to the functional group),[17–27] to separate the anisotropic effect of functional groups from the influence of steric hindrance on the same proton chemical shifts.[28] The preferred structures of **16** and **20** including the ring current effect of the naphthyl moieties are given in Fig. 2. While the two thiophenyl protons in **16** are positioned within the ICSS of −0.1 ppm deshielding [which proves to be of only minor influence: δ(H-14)=7.24 ppm and δ(H-13)=7.28 ppm] the same protons are found in the ICSS=0.5 ppm shielding in **20** and are highfield-shifted adequately [δ(H-14)=6.62 ppm and δ(H-13)=6.95 ppm]. The assignments of isomers **16** and **20**, existing in the preferred conformations given in Fig. 2, were therefore confirmed.

The main difference in δ(^{1}H)/ppm values between **16** (**18**) and **20** (**22**), respectively, is observed between the aliphatic protons in the two isomeric groups of compounds: while δ(^{1}H)/ppm of the methylene protons H-11 and the bridge-head proton 14b are similar (close to identical), the −N−CH_2(−CH_2−) protons in **20** and **22** are low-field-shifted (by ca. 0.4 ppm) with respect to the corresponding δ(^{1}H)/ppm values in **16** and **18**. In contrast with the latter results, the corresponding −N−CH_2−O− protons are high-field-shifted (by ca. 0.5 ppm) indicating structural differences in the aliphatic part of the studied molecules between **20** and **22**, and between **16** and **18**. The explanation is again revealed by the TSNMRS study of these structures: while the configuration and conformation of **20** (and **22**) and **16** (and **18**) remain constant (cf. Figs. 3 and 4), the stereochemistry changes slightly and the combined

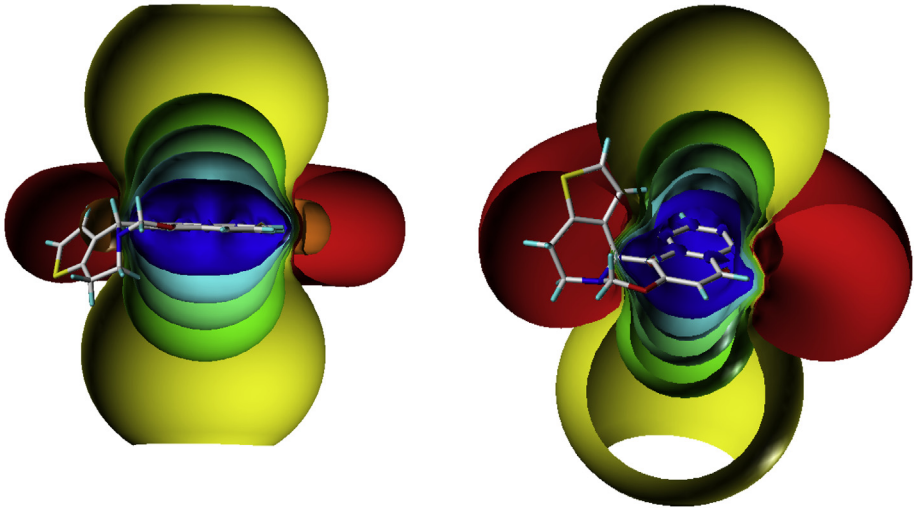


Fig. 2. Ring current effect of the naphthyl moiety in the stereochemistry of **16** (left) and **20** as obtained by DFT calculations and supported by the corresponding spatial NOE information; visualization of the TSNMRSs (ICSSs: blue represents 5 ppm shielding, cyan 2 ppm shielding, green-blue 1 ppm shielding, green 0.5 ppm shielding, yellow 0.1 ppm shielding, red −0.1 ppm deshielding and orange −0.5 ppm deshielding).

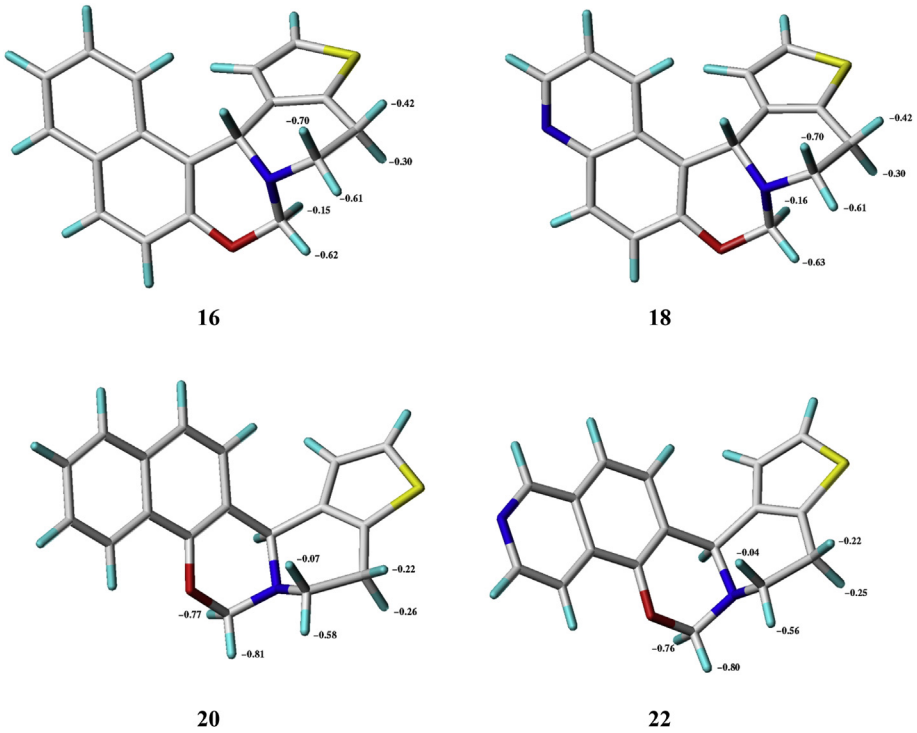
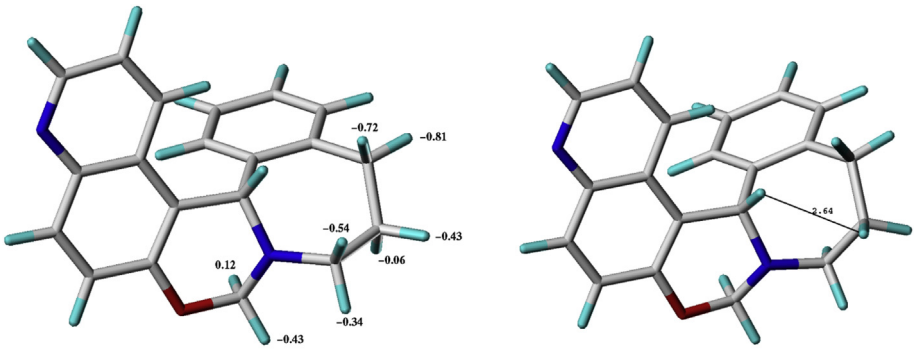


Fig. 3. TSNMRS values of the protons of the aliphatic part of (**16**, **20**, **18** and **22**) due to the combined ring current effects of the thiophenyl and the naphthyl aromatic moieties within the structures.

ring current effects of the thiophenyl and naphthyl moieties in these structures change: the $-N-CH_2(-CH_2-)$ protons in **20** (and **22**) are deshielded by more than 0.35 ppm as compared with the $\delta(^1H)$/ppm values in **16** (and **18**), and the $-N-CH_2-O-$ protons in **20** (and **22**) are more shielded by 0.4 ppm as compared with those in **16** and **18**, both in good to excellent agreement with the experimental results. The spatial magnetic properties (TSNMRS) were obviously of about the same value as the spatial NOE information for the study of the stereochemistry of comparable structures.

*2.2.3. Stereochemistry of the 7-membered azepine ring in compound **21**.* Of the corresponding heterocycles containing the 7-membered ring moiety **15**, **17**, **19** and **21**, only the proton NMR spectra of **21** could be interpreted; the corresponding spectra of **15**, **17** and **19** could not be examined since they were mixtures of several conformers of similar populations and due to the pseudo-rotational dynamic process (fast on the NMR time scale). Especially the ^1H NMR study but also the computational results on **21**, were highly informative (cf. Table 4 and Fig. 4); the existence of only one preferred isomer/conformer [**S(16b)S(N)**] proves sufficient for the examination of clean NMR spectra. The energetically next coming conformer proves to be 1.75 kcal mol^{-1} less stable. The pseudo rotational dynamic process is still fast on the NMR time scale, but only the preferred conformer participates.

In Fig. 4 the ring current effects (as TSNMRS values) of the phenyl and naphthyl moieties on the various protons are given. To



21 preferred conformer **21** next coming conformer (calc. 5%)

Fig. 4. Computed preferred conformers of **21**.

Table 4
Experimental NMR data of **21** (δ in ppm, J in Hz)

Position	^{13}C	^{1}H
1	131.1	7.53 (d, 8.6)
2	121.2	7.09 (m)
3	147.7	8.59 (dd, 4.1, 5.0)
4a	144.7	
5	130.6	7.87 (d, 9.2)
6	122.5	7.26 (d, 9.2)
6a	152.6	
8	79.3	a) 4.43 (dd, 7.7, 0.9)
		b) 4.48 (d, 7.7)
10	52.4 (br)	a) 2.76 (m)
		b) 3.20 (t, 11.5)
11	26.3	a) 1.71 (m)
		b) 1.95 (m)
12	33.7	a) 2.89 (td, 14.8, 5.6)
		b) 3.38 (ddd, 14.9, 9.3, 5.7)
12a	141.5	
13	129.7	7.17 (d, 7.4)
14	127.9	7.09 (m)
15	126.1	7.85 (t, 7.5)
16	130.0	6.38 (d, 7.6)
16a	138.2	
16b	57.3	5.69 (s)
16c	114.9	
16d	126.9	

start with the NOE spatial information, the H…H distances obtained are in complete agreement with the computed preferred conformer, with the exception H-16b…H-11b. The distance computed to be 3.9 Å and 4.0 Å, respectively, was represented by a medium NOE which implicates a much shorter distance. The only explanation, therefore, remains the participation of a relatively small population of the energetically next coming conformer: in the latter stereostructure, the *pseudo-chair conformation of the seven-membered ring* inverts to the corresponding boat conformer with the considered near proximity of one H-11 proton to the bridgehead proton H-16b. Even if the population of the boat conformer of the seven-membered ring moiety is probably very small (<10%), the powerful NOE (due to a distance of only ca. 2.6 Å in the boat conformer) increases the spatial NOE information to the value obtained.

Next, the quantification of the ring current effects in **21** as computed as TSNMRS values must be considered. While the aliphatic protons in **21** are comparable [$\Delta\delta(^1$H)/ppm < 0.2 ppm] to the corresponding ones in **20** and **22**, the $\delta(^1$H)/ppm values of the aromatic protons H-16 and H-1 are very sensitive to the latter shift influences due to the obvious proximity of these two protons in the preferred conformer. This effect proves to be dramatic for H-16, which is positioned heavily within the shielding range of the naphthyl ring current effect; $\Delta\delta(^1$H)/ppm=1.33 ppm shielding was computed. The experimental $\delta(^1$H)/ppm value of the proton was found to be heavily shielded [δ(H-16)=6.38 ppm] for an aromatic proton near the olefin $\delta(^1$H)/ppm shift range. The ring current effect on H-1 was computed to be less extensive [$\Delta\delta$(H-1)=0.42 ppm], experimentally found at δ(H-1)=7.53 ppm [still positioned at 8.17 ppm (in **22**) and 7.91 ppm (in **20**)], again in excellent agreement with the computed value.

3. Conclusions

Starting from 4,5-dihydro-3*H*-benz[*c*]azepine and different electron-rich aromatic compounds such as 1- or 2-naphthol, 5-hydroxyisoquinoline or 6-hydroxyquinoline, new aminonaphthols, aminoisoquinolinols and aminoquinolinols were synthesized. Through extension of the reaction by using 6,7-dihydrothieno[3,2-*c*]pyridine as initial partially saturated cyclic amine, 4-hydroxynaphthyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines, 4-(5-hydroxyisoquinolin-6-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and 4-(6-hydroxyquinolin-5-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine were prepared. The cyclization of these novel bifunctional compounds was also achieved and new naphth[2,1-*e*][1,3]oxazines, naphth[1,2-*e*][1,3]oxazines, isoquinoline[5,6-*e*][1,3]oxazines and quinoline[5,6-*e*][1,3]oxazines were isolated in good to excellent yields.

The configurations and conformations of **16** (and **18**), **20** (and **22**) and **21** were elucidated by theoretical calculations at the DFT level; isomers ***S*(14b),*R*(N)** for **16**, ***R*(14b),*S*(N)** for **20** and ***S*(16b)*S*(N)** for **21** were preferred as the most stable ones on theoretical level. The experimental spatial dipolar NOE information and the computed ring current effect of the naphthyl moiety on present protons in the preferred isomers/conformers confirm the computationally obtained structures.

4. Experimental section

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 various different conformations and configurations of the studied compounds **16** and **20** were optimized.[29] The B3LYP density functional method was selected for all calculations. The method was based on Becke's three-parameter hybrid functionals[29] and the correlation functional of Lee et al.[30] All optimizations were carried out without any restriction at this B3LYP/6-31G** level of

theory.[13,14] Visualization was carried out with the modelling software SYBYL 7.3.[15]

The ^{1}H and ^{13}C NMR spectra were recorded in CD_2Cl_2 or $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker Avance III spectrometer at 600.13 (^{1}H) and 150.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS (for ^{1}H) or the solvent (for ^{13}C) as internal standard. All spectra (^{1}H, ^{13}C, gs-H, H–COSY, edited HSQC, gs-HMBC and NOESY) were acquired and processed with the standard BRUKER software.

4.1. General procedure for the synthesis of hydroxynaphthyl-, hydroxyquinolyl- and hydroxy-isoquinolylbenzazepines and -thienopyridines (7–14)

Method A: The cyclic imine (4,5-dihydro-3*H*-benz[*c*]azepine (**5**) or 6,7-dihydrothieno[3,2-*c*]pyridine (**6**), 3.5 mmol) and the electron-rich aromatic compound (1-naphthol (**1**), 2-naphthol (**2**), 5-hydroxyisoquinoline (**3**) or 6-hydroxyquinoline (**4**), 3.5 mmol) were mixed in a 50 mL flask. The mixture was dissolved in 2–3 mL CH_2Cl_2 and heated in an oil bath at 80 or 85 °C. Reaction times are shown in Table 1.

Method B: The mixture of the cyclic imine (4,5-dihydro-3*H*-benz[*c*]azepine (**5**) or 6,7-dihydrothieno[3,2-*c*]pyridine (**6**), 3.5 mmol) and the electron-rich aromatic compound (11-naphthol (**1**), 2-naphthol (**2**), 5-hydroxyisoquinoline (**3**) or 6-hydroxyquinoline (**4**), 3.5 mmol) was placed in a 10 mL pressurized reaction vial and heated in a CEM LabMate microwave reactor under the microwave conditions given in Table 1.

4.2. 1-(1-Hydroxynaphth-2-yl)-2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (7)

Column chromatography; eluent: *n*-hexane:EtOAc (4:1), crystallized from *n*-hexane (3 mL). Light brown crystals; Mp: 139–143 °C. ^{1}H NMR ($CDCl_3$): 1.80–1.92 (m, 1H), 2.03–2.16 (m, 1H), 2.99–3.18 (m, 3H), 3.43–3.55 (m, 1H), 6.31 (s, 1H), 6.69 (d, 1H, *J*=7.7 Hz), 7.01 (t, 1H, *J*=7.3 Hz), 7.18–7.37 (m, 7H), 7.78 (d, 2H, *J*=8.9 Hz); ^{13}C NMR (150 MHz, CD_2Cl_2): 154.2, 143.2, 140.7, 134.3, 130.4, 130.1, 128.3, 127.4, 126.7, 126.6, 126.3, 125.2, 124.9, 122.5, 118.1, 115.7, 65.4, 45.4, 35.6, 30,0. Anal. Calcd for $C_{20}H_{19}NO$ (289.37): C, 83.01; H, 6.62; N, 4.84. Found: C, 83.06; H, 6.59; N, 4.87.

4.3. 4-(1-Hydroxynaphth-2-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8)

Crystallized from Et_2O (3 mL), recrystallized from *i*Pr_2O (4 mL). Light brown crystals. Mp: 174–177 °C. ^{1}H NMR ($CDCl_3$): 2.91–3.00 (m, 1H), 3.13–3.27 (m, 2H), 3.43–3.52 (m, 1H), 5.38 (s, 1H), 6.56 (d, 1H, *J*=5.3 Hz), 7.03 (d, 1H, *J*=5.1 Hz), 7.25 (d, 1H, *J*=8.5 Hz), 7.37 (d, 1H, *J*=8.2 Hz), 7.42–7.50 (m, 2H), 7.78 (d, 1H, *J*=8.2 Hz), 8.25 (d, 1H, *J*=7.7 Hz); ^{13}C NMR (150 MHz, CD_2Cl_2): 153.5, 135.7, 134.3, 133.8, 127.4, 127.0, 126.3, 126.3, 125.8, 125.0, 122.7, 122.4, 119.2, 118.3, 60.0, 43.1, 25.6. Anal. Calcd for $C_{17}H_{15}NOS$ (281.37): C, 72.57; H, 5.37; N, 4.98. Found: C, 72.51; H, 5.42; N, 4.93.

4.4. 1-(5-Hydroxyisoquinolin-6-yl)-2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (9)

Column chromatography; eluent: EtOAc:MeOH (9:1), crystallized from *n*-hexane (4 mL). Light brown crystals. Mp: 144–146 °C. ^{1}H NMR (DMSO): 1.63–1.78 (m, 1H), 1.94–2.06 (m, 1H), 2.63–2.75 (m, 1H), 2.87–3.06 (m, 3H), 6.23 (s, 1H), 6.37 (d, 1H, *J*=7.7 Hz), 6.96 (t, 1H, *J*=7.4 Hz), 7.18 (t, 1H, *J*=7.4 Hz), 7.23–7.36 (m, 3H), 7.81–7.94 (m, 2H), 8.57–8.62 (m, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): 153.6, 151.9, 143.0, 142.1, 140.0, 130.5, 130.1, 129.3, 128.5, 128.0, 127.7, 126.8, 120.1, 117.4, 115.5, 65.5, 45.6, 35.5, 29.8. Anal. Calcd for $C_{19}H_{18}N_2O$ (290.36): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.55; H, 6.21; N, 9.69.

4.5. 4-(5-Hydroxyisoquinolin-6-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (10)

Column chromatography; eluent: EtOAc:MeOH (20:1), crystallized from *n*-hexane (5 mL). Orange brown crystals. Mp: 168–170 °C. ^{1}H NMR ($CDCl_3$): 2.91–3.04 (m, 1H), 3.12–3.32 (m, 2H), 3.44–3.55 (m, 1H), 5.41 (s, 1H), 6.55 (d, 1H, *J*=5.2 Hz), 7.06 (d, 1H, *J*=5.1 Hz), 7.40 (d, 1H, *J*=8.6 Hz), 7.49 (d, 1H, *J*=8.4 Hz), 7.99 (d, 1H, *J*=5.7 Hz), 8.48 (d, 1H, *J*=5.7 Hz), 9.19 (s, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): 152.8, 152.0, 142.3, 134.8, 134.2, 129.2, 128.3, 128.2, 126.1, 123.3, 122.9, 117.7, 115.3, 59.9, 42.9, 25.5. Anal. Calcd for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92. Found: C, 68.11; H, 5.03; N, 9.86.

4.6. 1-(2-Hydroxynaphth-1-yl)-2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (11)

Column chromatography; eluent: *n*-hexane:EtOAc (4:1), crystallized from *n*-hexane (4 mL). Yellowish brown crystals. Mp: 156–158 °C. ^{1}H NMR (DMSO): 1.56–1.76 (m, 2H), 2.70–2.82 (m, 2H), 2.83–2.92 (m, 1H), 2.98–3.07 (m, 1H), 5.66 (s, 1H), 6.57 (d, 1H, *J*=8.5 Hz), 7.12–7.30 (m, 5H), 7.42–7.48 (m, 2H), 7.73–7.78 (m, 1H), 8.15–8.20 (m, 1H). Anal. Calcd for $C_{20}H_{19}NO$ (289.37): C, 83.01; H, 6.62; N, 4.84. Found: C, 82.95; H, 6.74; N, 4.81.

4.7. 4-(2-Hydroxynaphth-1-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (12)

Crystallized from Et_2O (5 mL), recrystallized from *i*Pr_2O (5 mL). Light brown crystals. Mp: 148–151 °C. ^{1}H NMR ($CDCl_3$): 2.94–3.03 (m, 1H), 3.23–3.35 (m, 2H), 3.60–3.73 (m, 1H), 6.06 (s, 1H), 6.26 (d, 1H, *J*=5.3 Hz), 6.91 (d, 1H, *J*=5.3 Hz), 7.10 (d, 1H, *J*=8.9 Hz), 7.36 (t, 1H, *J*=7.4 Hz), 7.53 (t, 1H, *J*=7.8 Hz), 7.70 (d, 1H, *J*=8.9 Hz), 7.82 (d, 1H, *J*=8.3 Hz), 8.03 (t, 1H, *J*=8.7 Hz); ^{13}C NMR (150 MHz, CD_2Cl_2): 156.6, 135.5, 133.8, 132.9, 129.8, 129.1, 128.7, 127.1, 126.0, 122.8, 122.7, 121.5, 120.2, 117.0, 54.9, 44.2, 25.6. Anal. Calcd for $C_{17}H_{15}NOS$ (281.37): C, 72.57; H, 5.37; N, 4.98. Found: C, 72.59; H, 5.34; N, 5.02.

4.8. 1-(6-Hydroxyisoquinolin-5-yl)-2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (13)

Column chromatography; eluent: EtOAc:MeOH (9:1), crystallized from *n*-hexane (5 mL). Yellowish brown crystals. Mp: 173–175 °C. ^{1}H NMR (DMSO): 1.60–1.77 (m, 2H), 2.70–2.80 (m, 2H), 2.87–2.96 (m, 1H), 2.99–3.08 (m, 1H), 5.72 (s, 1H), 6.76 (d, 1H, *J*=8.3 Hz), 7.12 (d, 1H, *J*=7.12 Hz), 7.18–7.25 (m, 1H), 7.25–7.31 (m, 2H), 7.37 (d, 1H, *J*=8.4 Hz), 7.95 (d, 1H, *J*=6.6 Hz), 8.43 (d, 1H, *J*=6.8 Hz), 9.15 (s, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): 158.5, 146.7, 144.1, 140.7, 138.0, 131.1, 130.2, 129.4, 128.5, 127.5, 127.3, 127.1, 124.2, 121.1, 113.6, 59.3, 45.9, 32.5, 28.1. Anal. Calcd for $C_{19}H_{18}N_2O$ (290.36): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.55; H, 6.21; N, 9.69.

4.9. 4-(6-Hydroxyquinolin-5-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (14)

Column chromatography; eluent: EtOAc:MeOH (20:1), crystallized from *n*-hexane (4 mL). Beige crystals. Mp: 178–181 °C. ^{1}H NMR ($CDCl_3$): 2.95–3.05 (m, 1H), 3.22–3.35 (m, 2H), 3.62–3.71 (m, 1H), 5.98 (s, 1H), 6.18 (d, 1H, *J*=5.2 Hz), 6.94 (d, 1H, *J*=5.2 Hz), 7.32 (d, 1H, *J*=8.9 Hz), 7.41–7.47 (m, 1H), 8.00 (d, 1H, *J*=9.1 Hz), 8.39 (d, 1H, *J*=8.7 Hz), 8.80 (s, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): 156.7, 147.0, 144.0, 135.0, 134.1, 131.0, 129.6, 127.7, 125.7, 123.6, 123.0, 121.7, 116.5, 54.5, 44.1, 25.5. Anal. Calcd for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92. Found: C, 68.02; H, 4.96; N, 9.95.

4.10. General procedure for the synthesis of naphthoxazino-, isoquinolinoxazino- and quinolinoxazino-benzazepines and thienopyridines (15–22)

0.135 mmol of aminonaphthol (**7**–**8**, **11**–**12**), aminoisoquinolinol (**9**–**10**) or aminoquinolinol (**13**–**14**) was dissolved in 10 mL CH_2Cl_2. 50 uL (0.6 mmol) 35% formalin solution was then added and the mixture was stirred at room temperature for the reaction time depicted in Table 2. The mixture was next extracted with 10 mL distillated water. The organic phase was collected, and then dried on Na_2SO_4. The solvent was evaporated off and the desired compound was isolated by crystallization and purified by recrystallization.

4.11. Naphth[2,1-*e*][1,3]oxazino[3,4-*a*]benz[*c*]azepine (15)

Crystallized from *n*-hexane (5 mL), recrystallized from *n*-hexane:*i*Pr_2O (2:1, 4 mL). Yellow crystals. Mp: 102–104 °C. ^{1}H NMR ($CDCl_3$): 1.88–2.06 (m, 2H), 2.74–2.85 (m, 1H), 2.94–3.14 (m, 2H), 3.15–3.25 (m, 1H), 4.86 (d, 1H, *J*=8.7 Hz), 4.98 (d, 1H, *J*=8.4 Hz), 5.64 (s, 1H), 6.88 (d, 1H, *J*=8.7 Hz), 6.97 (d, 1H, *J*=7.4 Hz), 7.14–7.28 (m, 3H), 7.36 (d, 1H, *J*=8.6 Hz), 7.48–7.55 (m, 2H), 7.77–7.83 (m, 1H), 8.21–8.27 (m, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): 150.2, 142.1, 139.0, 133.7, 130.5, 129.7, 128.0, 127.7, 126.3, 126.2, 126.1, 125.6, 125.1, 121.6, 119.8, 117.2, 83.0, 62.4, 52.1, 33.4, 27.2. Anal. Calcd for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.64; H, 6.37; N, 4.62.

4.12. Naphth[2,1-*e*][1,3]oxazino[3,4-*e*]thieno[3,2-*c*]pyridine (16)

Crystallized from *n*-hexane (4 mL), recrystallized from *n*-hexane:*i*Pr_2O (2:1, 5 mL). Light brown crystals. Mp: 195–198 °C. ^{1}H NMR (CD_2Cl_2) ans see Table 3; ^{13}C NMR (150 MHz): see Table 3. Anal. Calcd for $C_{18}H_{15}NOS$ (293.38): C, 73.69; H, 5.15; N, 4.77. Found: C, 73.65; H, 5.17; N, 4.71.

4.13. Isoquinoline[5,6-*e*][1,3]oxazino[3,4-*a*]benz[*c*]azepine (17)

Crystallized from *n*-hexane (4 mL), recrystallized from *n*-hexane:*i*Pr_2O (2:1, 4 mL). Light brown crystals. Mp: 112–114 °C. ^{1}H NMR (DMSO): 1.65–1.92 (m, 2H), 2.55–3.39 (m, 4H), 4.69–5.15 (m, 2H), 5.66 (s, 1H), 6.77–7.63 (m, 6H), 8.00 (d, 1H, *J*=7.3 Hz), 8.57 (d, 1H, *J*=8.5 Hz), 9.21 (s, 1H). Anal. Calcd for $C_{20}H_{18}N_2O$ (302.37): C, 79.44; H, 6.00; N, 9.26. Found: C, 79.40; H, 6.03; N, 9.29.

4.14. Isoquinoline[5,6-*e*][1,3]oxazino[3,4-*e*]thieno[3,2-*c*]pyridine (18)

Crystallized from *n*-hexane (3 mL), recrystallized from *n*-hexane:*i*Pr_2O (2:1; 4 mL). Yellowish brown crystals. Mp: 95–97 °C; ^{1}H NMR (CD_2Cl_2) and ^{13}C NMR (150 MHz) see Table 3. Anal. Calcd for $C_{17}H_{14}N_2OS$ (294.37): C, 69.36; H, 4.79; N, 9.52. Found: C, 69.31; H, 4.76; N, 9.58.

4.15. Naphth[1,2-*e*][1,3]oxazino[3,4-*a*]benz[*c*]azepine (19)

Crystallized from *n*-hexane (4 mL), recrystallized from *n*-hexane:*i*Pr_2O (4:1, 4 mL). Brown crystals. Mp: 193–195 °C. ^{1}H NMR ($CDCl_3$): 1.26–1.34 (m, 1H), 1.82–1.95 (m, 1H), 2.07–2.19 (m, 1H), 2.79–2.89 (m, 1H), 2.96–3.05 (m, 1H), 3.24–3.34 (m, 1H), 3.48–3.59 (m, 1H), 4.52 (d, 1H, *J*=7.8 Hz), 4.61 (d, 1H, *J*=7. Frau Špíšková,6 Hz), 5.84 (s, 1H), 6.60 (d, 1H, *J*=7.5 Hz), 6.99 (t, 1H, *J*=7.3 Hz), 7.15–7.23 (m, 3H), 7.24–7.34 (m, 5H); ^{13}C NMR (150 MHz, CD_2Cl_2): 152.5, 141.5, 138.4, 131.9, 129.9, 129.6, 129.2, 129.2, 128.7, 127.7, 126.6, 126.0, 123.4, 123.0, 119.0, 115.0, 79.1, 57.6, 52.3, 33.6, 26.2. Anal. Calcd for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.71; H, 6.32; N, 4.60.

4.16. Naphth[1,2-*e*][1,3]oxazino[3,4-*e*]thieno[3,2-*c*]pyridine (20)

Crystallized from *n*-hexane (4 mL), recrystallized from *n*-hexane:*i*Pr_2O (4:1; 5 mL). Brown crystals. Mp: 169–172 °C. ^{1}H NMR (CD_2Cl_2) and ^{13}C NMR (150 MHz) see Table 3. Anal. Calcd for $C_{18}H_{15}NOS$ (293.38): C, 73.69; H, 5.15; N, 4.77. Found: C, 73.68; H, 5.11; N, 4.73.

4.17. Quinoline[5,6-*e*][1,3]oxazino[3,4-*a*]benz[*c*]azepine (21)

Crystallized from *n*-hexane (5 mL), recrystallized from *n*-hexane:*i*Pr_2O (4:1, 5 mL). Light brown crystals. Mp: 144–146 °C. ^{1}H NMR (CD_2Cl_2) and ^{13}C NMR (150 MHz), see Table 4. Anal. Calcd for $C_{20}H_{18}N_2O$ (302.37): C, 79.44; H, 6.00; N, 9.26. Found: C, 79.47; H, 5.98; N, 9.23.

4.18. Quinoline[5,6-*e*][1,3]oxazino[3,4-*e*]thieno[3,2-*c*]pyridine (22)

Crystallized from *n*-hexane (4 mL), recrystallized from *n*-hexane:*i*Pr_2O (4:1; 5 mL). Brown crystals. Mp: 171–173 °C. ^{1}H NMR (CD_2Cl_2) and ^{13}C NMR (150 MHz), see Table 3. Anal. Calcd for $C_{17}H_{14}N_2OS$ (294.37): C, 69.36; H, 4.79; N, 9.52. Found: C, 69.42; H, 4.73; N, 9.64.

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