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Synthesis and conformational analysis of new naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives

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ABSTRACT

A new highly functionalized aminonaphthol derivative, 1-(amino(2-aminophenyl)methyl)-2-naphthol (**4**), was synthesized by the reaction of 2-naphthol, 2-nitrobenzaldehyde and *tert*-butyl carbamate or benzyl carbamate, followed by reduction and/or removal of the protecting group. The aminonaphthol derivative thus obtained was converted in ring-closure reactions with formaldehyde, benzaldehyde and/or phosgene to the corresponding naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives. The conformational analysis of some derivatives by NMR spectroscopy and accompanying molecular modelling are also reported.

1. Introduction

The Betti reaction is a convenient method for the preparation of α-aminobenzylnaphthol derivatives. This three-component modified Mannich reaction with 2-naphthol, benzaldehyde and ammonia earlier yielded 1,3-diphenylnaphthoxazine, subsequent hydrolysis of which led to the formation of the desired 1-α-aminobenzyl-2-naphthol.[1,2] The reaction can be extended by using substituted benzaldehydes[3–5] or formaldehyde[3] instead of benzaldehyde, and 1-naphthol[6] instead of 2-naphthol. In spite of the two potentially reactive functional groups of this type of compounds, relatively few publications have appeared in this field. In previous studies, the insertion of an additional hydroxy group was successfully achieved through the reactions of aminonaphthols with salicylaldehyde,[7] or by starting the synthesis from salicylaldehyde, leading to 1-(amino(2-hydroxyphenyl)methyl)-2-naphthol.[8] This versatile synthon was transformed to naphth[1,2-*e*][1,3]oxazino[3,4-*c*][1,3]benzoxazine derivatives by ring-closure reaction with oxo compounds.[8] Conformational analysis of the polycyclic derivatives revealed that the oxazine rings prefer a *twisted-chair* conformation. 8-Substituted 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinolines, as an analogous naphthoxazine ring system, were prepared by the cyclization of 1-(β-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinoline-line with formaldehyde, phosgene, 4-nitrobenzaldehyde and 4-chlorophenyl isothiocyanate.[9] The oxazine ring proved to prefer a *twisted-chair* conformation, and the isoquinoline ring a *twisted-chair* or *twisted-boat* conformation, depending on the substituent at position 8.

Since quinazoline derivatives exhibit a wide range of activities, such as anthelminthic, antimicrobial, neuroleptic and analgesic,[10] and quinazolinone has been found to have anticancer[11] and antihyperglycaemic[12] activity, our primary present aim was to synthesize naphthoxazinoquinazolines in order to extend the series of naphthoxazino-fused heterocyclic ring systems. A further aim was the conformational analysis of these polycyclic compounds by NMR spectroscopy and accompanying molecular modelling.

2. Results and discussion

2.1. Syntheses

For the synthesis of the proposed naphthoxazinoquinazoline derivatives, the preparation of 1-(amino(2-aminophenyl)methyl)-2-naphthol (**4**) as starting material was planned. In our initial experiment, we attempted the aminoalkylation of 2-naphthol with 2 equiv of 2-nitrobenzaldehyde in the presence of ammonia, followed by hydrolysis of the intermediate naphthoxazine. This

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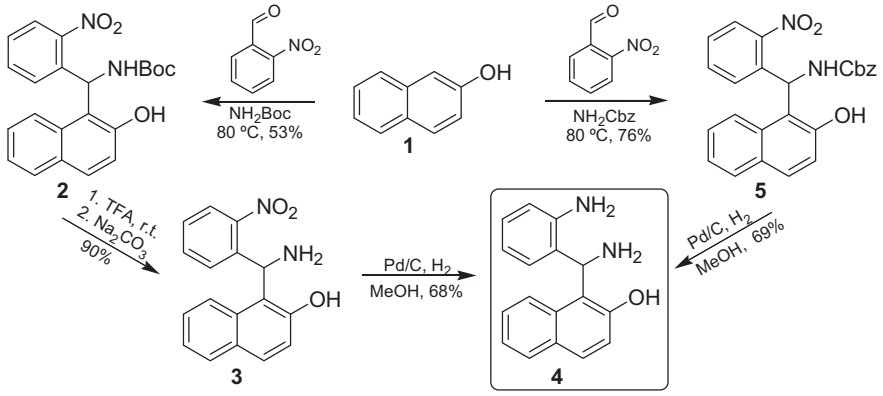
reaction resulted in the formation of a multi-spot reaction mixture based on the TLC. In the following experiment, ammonia was replaced by *tert*-butyl carbamate as a protected ammonia source, and a mixture of 2-naphthol, 2-nitrobenzaldehyde and *tert*-butyl carbamate was therefore heated under solvent-free conditions for 55 h at 60 °C. This furnished nitroderivative **2** in 46% yield. When the reaction was repeated at 80 °C, **2** was isolated in 53% yield after 47 h (Scheme 1). The Boc group was removed with trifluoroacetic acid, resulting in **3**. This step was followed by reduction of the nitro group by means of catalytic (Pd/C) hydrogenation, yielding **4** (Scheme 1).

we set out to examine the reactions of diamine **4** with substituted benzaldehydes. As in the previously reported processes,[3,6] **4** was dissolved in MeOH, 1.1 equiv of benzaldehyde was added and the mixture was left to stand at ambient temperature for 1 day. After a few hours, the product **7d** (X=H) started to separate out from the reaction mixture. In CD_2Cl_2 solution at 300 K, compound **7d** is potentially present as five-component tautomeric mixture of the chain tautomer (**A**), two epimers of quinazoline (**7B** and **7C**) and two epimers of naphthoxazine (**7D** and **7E**) derivatives (Scheme 3).

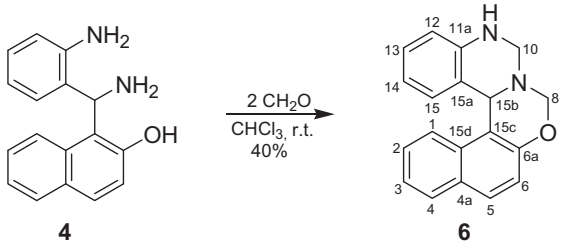
In the NMR spectra of **7d** in CD_2Cl_2 at 300 K, only three tautomeric forms were detected and identified. The *major* ring form was



Scheme 1. Synthesis of 1-(amino(2-aminophenyl)methyl)-2-naphthol (**4**).

Since **2** was formed in 53% yield only on starting from *tert*-butyl carbamate, our attention focused on another protected ammonia source, benzyl carbamate. From 2-naphthol, 2-nitrobenzaldehyde and benzyl carbamate under solvent-free conditions, **5** was synthesized in 71% yield at 60 °C after 46 h, whereas at 80 °C, in a shorter reaction time (32 h), the yield was 76%. Removal of the protecting group and reduction of the nitro group were accomplished in one step by catalytic (Pd/C) hydrogenation, yielding **4** (Scheme 1).

In the first stage of the transformations of **4** to heterocyclic derivatives, an sp^3 carbon was inserted between the hydroxy and amino groups (in position C-8 or C-10). Compound **4** was stirred with 2 equiv of aqueous formaldehyde in $CHCl_3$ at rt. After 1.5 h, when TLC showed no presence of the starting material, the reaction was stopped and 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline (**6**) was isolated by column chromatographic purification (Scheme 2). Since **6** was formed from aqueous formaldehyde in $CHCl_3$ in 40% yield only, another solvent (MeOH) and the use of paraformaldehyde were also tried, but these reactions resulted in the formation of a multi-spot reaction mixture based on the TLC.



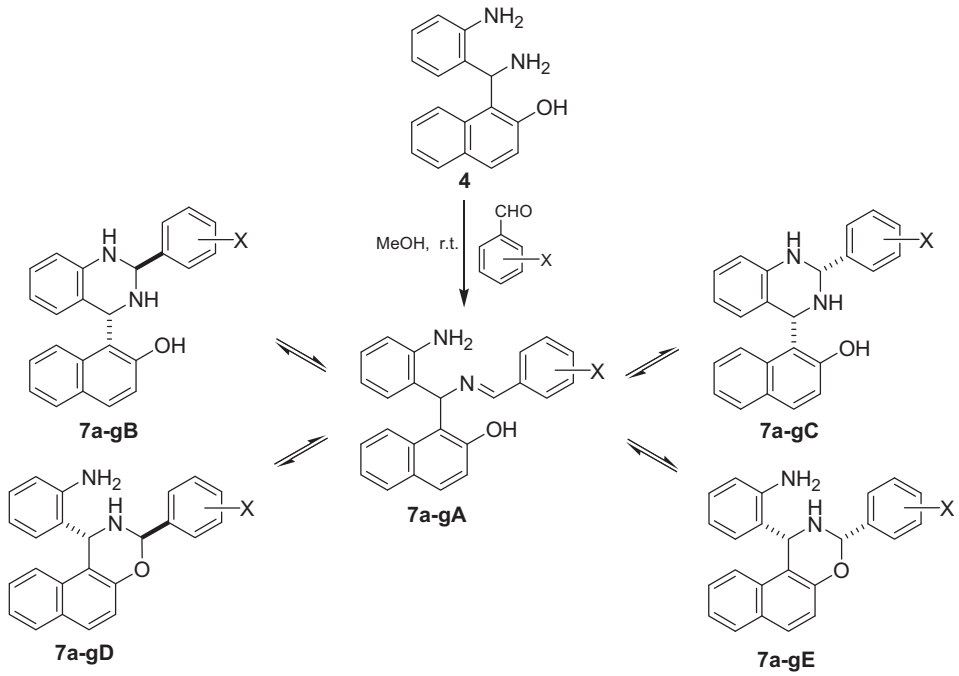
Scheme 2. Ring-closure reaction of **4** with formaldehyde.

Since the reactions of amino diols with aromatic aldehydes earlier led to the formation of five-component tautomeric mixtures,[13,14] found to be 2-phenyl-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazoline (**7dB** or **7dC**); the NOESY spectrum proved that the *major* ring-closed tautomer in equilibria contains H-2 and H-4 in the trans position (**7dB**). Formation of the quinazoline derivative as the *major* product can be explained by the stabilization caused by the strong intramolecular hydrogen-bonds between the lone pair of the N atom and the OH group and the higher nucleophilic character of NH_2 than that of OH. The *minor* ring forms were found to be 8-phenyl-10-(2-aminophenyl)-8,9-dihydro-7*H*-naphth[1,2-*e*][1,3]-oxazine (**7dD** and **7dE**). The NOE interaction observed between H-8 and H-10 showed that the relative configuration of the *major* naphthoxazine epimer attains the cis arrangement (**7dE**), while for the *minor* epimer the lack of the cross-peak for H-8 and H-10 proves their trans arrangement (**7dD**). The chain tautomer (**A**) and the *cis* quinazoline (**C**) were not detected in the NMR spectra.

To characterize the effects of the aryl substituents on the tautomeric equilibria of this ring system, 2-(aryl-substituted)-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolines (**7a**–**c** and **7e**–**g**) were also prepared (Scheme 3). The proportions of the ring-closed tautomers (**B**, **D** and **E**) of the tautomeric equilibria of **7a**–**g** (Table 1) were determined by integration of the quinazoline and naphthoxazine proton singlets or doublets in the ^1H NMR spectra (see the Experimental section).

The tautomeric composition (e.g., the proportions of the ring-closed forms) demonstrated a small, but systematic dependence on the Hammett–Brown parameter[15,16] (σ^+) of the aryl substituent, which characterizes the electronic character of the substituent in question (Table 1).

The plots of the proportions of the tautomeric forms (**B**, **D** and **E**) for **7a**–**g** versus σ^+ (Fig. 1) gave good correlations for all three forms (0.951 for **B**, 0.938 for **D** and 0.978 for **E**). It can be concluded that electron-donating substituents prefer the quinazoline form (**B**), while electron-withdrawing substituents increase the proportions of the naphthoxazine forms (**D** and **E**). As concerns the slopes, the dependence for **B** seems to be the most characteristic; for **E**, only small changes were observed for the various substitutions (Fig. 1).



Scheme 3. Synthesis and ring-chain tautomerism of 2-(aryl-substituted)-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolines (**7a**–**g**).

Table 1
Proportions (%) of the tautomeric forms (**A**, **B**, **C**, **D** and **E**) in tautomeric equilibrium for compounds **7a**–**g** (CD_2Cl_2, 300 K)

X	σ^+	**A** (%)	**B** (%)	**C** (%)	**D** (%)	**E** (%)
p-NO_2	0.79	—	79.1	—	5.8	15.1
m-Cl	0.40	—	80.6	—	5.5	13.9
p-Cl	0.11	—	82.0	—	5.3	12.7
H	0.00	—	84.5	—	4.8	10.7
p-Me	−0.31	—	85.2	—	4.5	10.3
p-OMe	−0.78	—	87.0	—	4.1	8.9
p-NMe_2	−1.70	—	88.6	—	3.5	7.9

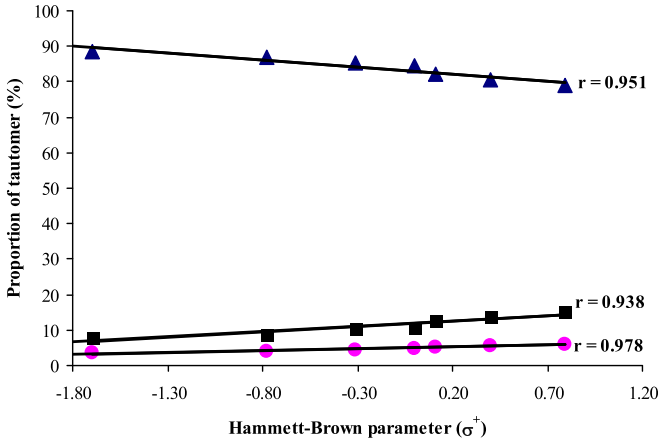
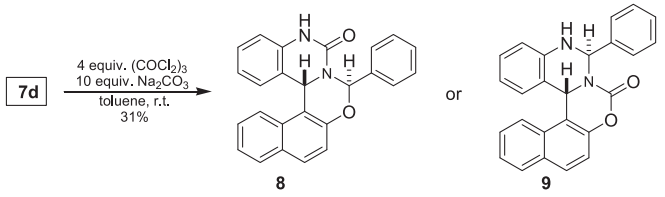


Fig. 1. Plots of proportions of the tautomers (in CD_2Cl_2), B (▲), D (■), E (●) for **7a**–**g** versus Hammett–Brown parameter (σ^+).

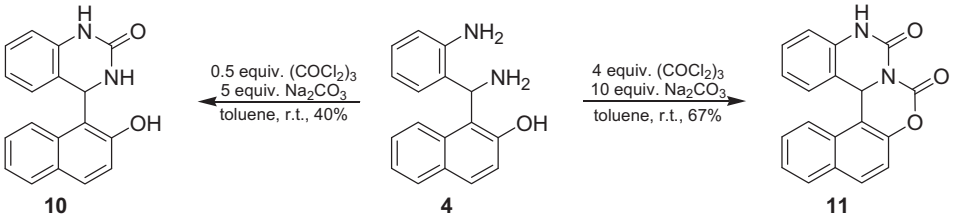
The ability of **7d** to undergo transformation was further tested by its reaction with phosgene. When **7d** was reacted with 4 equiv of triphosgene in the presence of Na_2CO_3 in toluene for 6.5 h at rt, the product (**8** or **9**) was isolated after column chromatographic purification in a yield of 31%. Full assignment of the NMR signals in DMSO supported the formation of the quinazolinone derivative (**8**). The two possible ring systems have very similar chemical environments; the cross-peak between C-6a (150.5 ppm) and H-8 (7.04 ppm) in the HMBC spectrum should be the only difference supporting the presence of 8-phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-10-one (**8**) instead of 10-phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-8-one (**9**). To support the structure found by NMR measurement, we decided to record the mass spectrum of crystalline product **8**. The condition was electron impact ionization and MeOH was chosen as solvent. The electron ionization (EI) mass spectrum of the crystalline product **8** is characterized by the fragment ion $[M-CONH]^+$ at *m*/*z* 335. This ion is probably formed by direct loss of this fragment from the molecular ion at *m*/*z* 378, as described already for naphthoxazin-3-one and barbituric acid.[17,18] This proves that the newly inserted oxo group is at position 10. This unexpected structure can be explained through the tautomeric equilibrium present for **7d** in solution and, probably because of the stronger nucleophilic character of NH_2 (**7dD**, Scheme 3) than that of OH (**7dB**, Scheme 3), this minor tautomeric form reacts with triphosgene to give **8**. During the reaction, the formation of two diastereomers is possible; the diastereomeric ratio was therefore checked by NMR spectroscopy on the crude product. It was found that only one diastereomer is present. The NOE measurements on purified **8** adequately proved the trans arrangement of H-8 and H-15b (Scheme 4).



Scheme 4. Reaction of **7d** with phosgene.

To study the direct ring-closure reaction of diamine **4** with phosgene, **4** was stirred with 0.5 equiv of triphosgene in toluene in

the presence of Na_2CO_3 (Scheme 5). The appearance of two new TLC spots was observed. The products formed were separated by column chromatography and the mass spectra confirmed that one was the oxo compound and the other was the corresponding 8,10-dione. The 2D NMR measurements of the single ring-closed compound supported the structure of the quinazolin-2-one derivative (**10**). For its preparation, a reaction time of 45 h was found to be optimal, but it should be mentioned that **10** was separated in only 40% yield, which can be explained in terms of the parallel formation of 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-8,10-dione (**11**). To isolate **11** in higher yield, and to avoid the formation of **10**, the reaction of **4** was repeated but with 4 equiv of triphosgene. After a reaction time of 8.5 h, **11** was isolated in 67% yield (Scheme 5).



Scheme 5. Selective ring-closure reaction of **4** with phosgene.

To examine the ring-closure ability of **10**, it was reacted with benzaldehyde. In consequence of the decreased nucleophilic character of the carbamide NH (PhCH*N*H), despite a long reaction time (refluxing in toluene for 51 h), the presumed oxo derivative **8** was not formed.

2.2. Conformational analysis

The conformational search protocol involved PM3 geometry minimization, followed by geometry optimization without restrictions. All calculations were carried out by using the Gaussian 09 program package.[19] Different conformations of the studied compounds were preoptimized by using the PM3 Hamiltonian. Density functional theory calculations were carried out at the B3LYP/6-31G** level of theory.[20,21] The self-consistent reaction field method (SCRF) and the Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEF-PCM) were applied to take solvent effects (CH_2Cl_2) into account.[22] The molecular modelling software package SYBYL 7.1 was used to display results and geometries.[23]

While **6** can be accepted as the basic ring system (unsubstituted 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline), full geometry optimization was performed by using *DFT* calculations. The unsaturated ring system **6** contains invertible N atoms. Both the *R* and the *S* configurations of the N atoms and of carbon atom C-15b must be considered. All isomers/enantiomers were studied by DFT calculations with respect to the present conformational equilibria. The preferred conformers thus obtained, together with other proximate conformers with similar energy, were collected and studied with respect to ring puckering as the second variable beside the N-interconversion. The energy difference values (ΔE) obtained for the lowest-energy conformers for each configuration are listed in Table 2.

It can be concluded that the relative configurations of C-15b and N-9 exert characteristic effects on the ΔE values (Table 2, geometries I, II versus III, IV). As the NMR measurements were recorded in CD_2Cl_2, the energies of the participating conformers were calculated with consideration of the effect of the solvent too (CH_2Cl_2). Table 2 shows the same tendency for the ΔE values. Unfortunately, the conformations obtained are not characteristic in a stereochemical frame, especially because of the nearly planar –NH– structures. Thus, general conclusions concerning the conformers of compound **6** could not be drawn.

Table 2
Calculated energy differences for **6**

Optimized geometry	C-15b	N-**9**	N-**11**	ΔE^a (kcal/mol)	ΔE^b (kcal/mol)
I	S	R	R	0	0
II	S	R	S	0.41	0.26
III	S	S	R	13.12	12.66
IV	S	S	S	13.27	13.80

[a] Gas phase.
[b] Solvent CH_2Cl_2.

To distinguish between structures I and II (Fig. 2), low-temperature NMR measurements were recorded. The dynamic process in which conformers I and II are equilibrated, N-inversion, is still fast on the NMR time-scale, even at the lowest temperatures. Thus, it was not possible experimentally to differentiate between the two conformers.

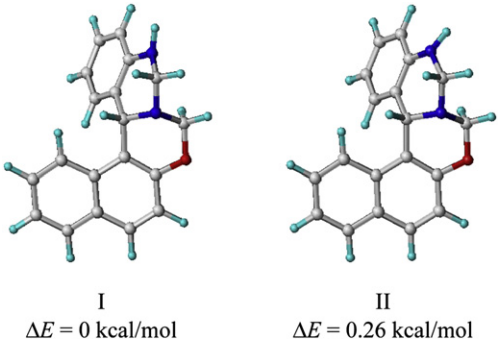


Fig. 2. Calculated global minimum-energy conformations of **6**.

While the formation of **8** versus **9** was experimentally proved, our further aim was to support this finding by using DFT calculations. For the studied compounds (**8** and **9**), theoretical calculations were performed for all of the stereoisomers as regards the inversion possibilities for **8** (C-15b and C-8) and for **9** (C-15b, N-11 and C-10). It was found that the geometry of the nitrogen atoms (N-9 and N-11 for **8** and N-9 for **9**) are parts of planar amide bonds. Calculations were performed for all cis and trans isomers of **8** and **9**. The results of the optimization are given in Table 3 for **8** and in Table 4 for **9**.

Table 3
Calculated energy differences for **8**

Optimized geometry	C-15b	C-8	ΔE (kcal/mol)
*trans*_I	S	R	0
*cis*_I	S	S	1.33

It can be concluded (Table 3) that the trans arrangement of H-15b and H-8 is favourable for **8**. Fig. 3 shows the global minimum-energy structures of the *trans* and *cis* diastereomers of **8**.

Table 4
Calculated energy differences for **9**

Optimized geometry	C-15b	N-11	C-10	ΔE (kcal/mol)
*trans*_I	S	S	R	0
*trans*_II	S	R	R	0.48
*cis*_I	S	S	S	3.81
*cis*_II	S	R	S	5.45

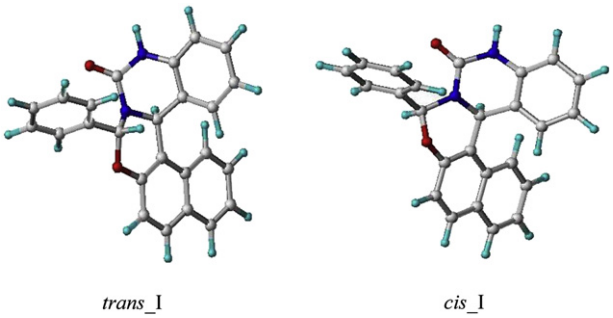


Fig. 3. Global minimum-energy structures of the *trans* and *cis* diastereomers of **8**.

For **9**, the trans orientation of H-15b and H-10 is favourable. Fig. 4 depicts the global minimum-energy structures of the two *trans* diastereomers (*trans*_I and *trans*_II) of **9**.

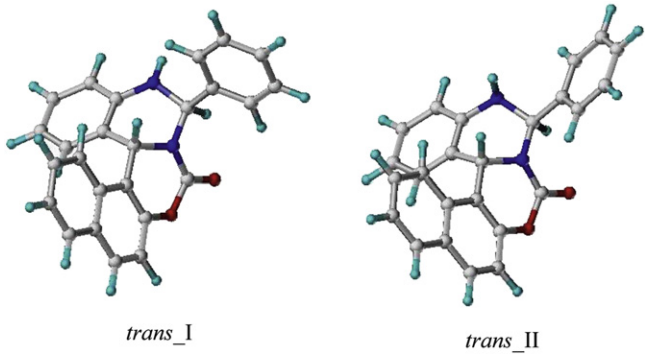


Fig. 4. Global minimum-energy structures of the *trans* diastereomers of **9**.

Since our original aim was to explain the formation of **8** instead of **9**, we calculated the energy difference between the global minimum-energy structures *trans*_I of **8** and *trans*_I of **9**. It was found to be 0.74 kcal/mol, which clearly supports our experimental results, i.e., **8** is the preferred product, corresponding to the MS results.

3. Conclusions

1-(Amino(2-aminophenyl)methyl)-2-naphthol (**4**) was synthesized from 2-naphthol, *tert*-butyl carbamate and 2-nitrobenzaldehyde, followed by removal of the protecting group and reduction. The reaction pathway was simplified when *tert*-butyl carbamate was replaced by benzyl carbamate. The aminonaphthol derivative thus obtained was converted in ring-closure reactions with formaldehyde to 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline. The ring-closure reaction of the starting diamine with phosgene and/or benzaldehyde led to the formation of new naphthoxazinoquinozolinone derivatives. The products obtained via the reactions of **4** with substituted benzaldehydes can potentially furnish five-component tautomeric mixtures in CD_2Cl_2 at 300 K. We managed to detect three of the five components: one epimeric quinazoline (**B**) and two epimeric naphthoxazines (**D** and **E**). The influence of aryl substituents on the tautomeric composition could be described in terms of the Hammett–Brown parameter. Compounds **6**, **8** and **9** were studied in all the configurations at the DFT level of theory with respect to the preferred conformers and conformational equilibria. Due to the N-interconversion, which was still fast on the NMR time-scale at the lowest temperatures, the corresponding conformational equilibria could not be frozen out for adjustment with the theoretical results. However, the experimental NMR parameters obtained were in general agreement with the theoretical findings.

4. Experimental

4.1. General

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser. Merck Kieselgel $60F_{254}$ plates were used for TLC. The ^1H and ^{13}C NMR spectra were recorded in DMSO or in CD_2Cl_2 solutions in 5 mm tubes, at rt, on a Bruker Avance III spectrometer at 600.13 (^1H) and 150.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. All spectra (^1H, ^{13}C, gs-H, H-COSY, gs-HMQC, gs-1D-HMQC, gs-HMBC and NOESY) were acquired and processed with the standard BRUKER software. For the equilibria to be established in tautomeric mixtures, the samples were dissolved in CD_2Cl_2 and the solutions were allowed to stand at ambient temperature for 1 day before the ^1H NMR spectra were run. The number of scans was usually 24.

The low-resolution EI mass spectra (for compounds **6** and **8** or **9**) were obtained by using a GC–MS TRACE DSQ II mass spectrometer (Thermo Fisher Scientific Dreieich, Germany), with an electron energy of 70 eV and a source temperature of 180 °C, using a direct insertion probe with a DEP (Direct Desorption Probe) filament in positive ion mode. The ESI mass spectra (for compounds **10** and **11**) were recorded (from 200 to 2200 amu) by using the AGILENT 1100 LC/MSD TRAP instrument in positive ion mode.

tert-Butyl carbamate[24] and benzyl carbamate[25] were prepared according to the literature processes.

*4.1.1. tert-Butyl (2-hydroxynaphthalen-1-yl)(2-nitrophenyl)methylcarbamate (**2**).* A mixture of 2-naphthol (**1**, 7.20 g, 0.050 mol), 2-nitrobenzaldehyde (7.56 g, 0.050 mol) and *tert*-butyl carbamate (6.44 g, 0.055 mol) was heated at 80 °C under solvent-free conditions for 47 h. The residue was crystallized from EtOAc (50 mL), filtered off and washed with EtOAc (2×10 mL).

Yield: 10.45 g (53%), mp: 226–228 °C. ^1H NMR (600 MHz, DMSO): δ=1.38 (s, 9H, C(C*H*$_3$)$_3$), 7.05 (d, 1H, 3-H, *J*=8.8 Hz), 7.21 (d, 1H, PhC*H*NH, *J*=8.6 Hz), 7.28 (t, 1H, 5′-H, *J*=7.4 Hz), 7.40–7.48 (m, 2H, 7-H, 4′-H), 7.51 (br d, 1H, CHN*H*, *J*=8.6 Hz), 7.56 (d, 1H, 6′-H, *J*=7.8 Hz), 7.63 (t, 1H, 6-H, *J*=7.6 Hz), 7.73 (d, 2H, 4-H, 8-H, *J*=8.4 Hz), 7.79 (d, 1H, 5-H, *J*=8.0 Hz), 7.92 (d, 1H, 3′-H, *J*=8.5 Hz), 9.80 (br s, 1H, O*H*). ^{13}C NMR (150 MHz, DMSO): δ=28.2 (C(*C*H$_3$)$_3$), 47.3 (PhCHNH), 78.4 (*C*(CH$_3$)$_3$), 116.3 (C-1), 118.5 (C-3), 122.5 (C-5′), 122.6 (C-3′), 123.9 (C-8), 126.6 (C-7), 127.7 (C-4′), 128.1 (C-4a), 128.4 (C-5), 129.0 (C-6′), 129.8 (C-4), 132.0 (C-6), 132.9 (C-8a), 136.7 (C-1′), 148.8 (C-2′), 153.6 (C-2), 155.2 (NH*C*OO). Anal. Calcd for $C_{22}H_{22}N_2O_5$ (394.42): C, 66.99; H, 5.62; N, 7.10. Found: C, 66.91; H, 5.60; N, 7.07.

*4.1.2. 1-(Amino(2-nitrophenyl)methyl)-2-naphthol (**3**).* Compound **2** (5.92 g, 0.015 mol) was suspended in TFA (15 mL, 99%). The mixture was stirred at rt for 10 min, after which the TFA was evaporated off and the residue was crystallized by treatment with EtOAc (30 mL). The crystals were filtered off and the solid residue was made alkaline with 10% Na_2CO_3 solution and extracted with $CHCl_3$ (3×30 mL). The organic extracts were combined, dried

(Na_2SO_4) and concentrated under reduced pressure. The residue was crystallized from *n*-hexane/EtOAc (20 mL:1 mL).

Yield: 3.97 g (90%), mp: 120–122 °C. ^{1}H NMR (600 MHz, DMSO): δ=6.54 (s, 1H, PhC*H*NH$_2$), 7.09 (d, 1H, 3-H, *J*=8.8 Hz), 7.20 (t, 1H, 6-H, *J*=7.4 Hz), 7.30 (t, 1H, 7-H, *J*=7.6 Hz), 7.37 (d, 1H, 6′-H, *J*=7.9 Hz), 7.42 (d, 1H, 8-H, *J*=8.6 Hz), 7.52 (t, 1H, 4′-H, *J*=7.8 Hz), 7.58 (t, 1H, 5′-H, *J*=7.5 Hz), 7.76 (d, 2H, 4-H, 5-H, *J*=8.5 Hz), 8.07 (d, 1H, 3′-H, *J*=8.1 Hz). ^{13}C NMR (150 MHz, DMSO): δ=50.1 (PhCHNH$_2$), 115.0 (C-1), 120.4 (C-3, C-8), 122.2 (C-6), 124.8 (C-3′), 126.7 (C-7), 127.8(C-4a), 128.7 (C-5), 129.1 (C-4′), 129.7 (C-4), 130.1 (C-6′), 131.7 (C-8a), 133.8 (C-5′), 136.7 (C-1′), 148.5 (C-2′), 158.3 (C-2). Anal. Calcd for $C_{17}H_{14}N_2O_3$ (294.30): C, 69.38; H, 4.79; N, 9.52. Found: C, 69.29; H, 4.74; N, 9.49.

*4.1.3. 1-(Amino(2-aminophenyl)methyl)-2-naphthol (**4**); starting from **3**.* Compound **3** (3.53 g, 0.012 mol) was dissolved in MeOH (15 mL). In parallel, Pd/C (1.32 g) was suspended in MeOH (10 mL). The mixture was hydrogenated at atmospheric pressure for 1.5 h. The catalyst was then filtered off and washed with MeOH (2×10 mL). The filtrate was concentrated to dryness under reduced pressure and the residue was crystallized from *n*-hexane (20 mL). The product was purified by recrystallization from *i*-Pr$_2$O (20 mL).

Yield: 2.15 g (68%), mp: 128–130 °C. ^{1}H NMR (600 MHz, DMSO): δ=5.37 (br s, 2H, PhN*H*$_2$), 6.14 (s, 1H, PhC*H*NH$_2$), 6.34 (t, 1H, 4′-H, *J*=7.5 Hz), 6.63 (d, 1H, 3′-H, *J*=7.8 Hz), 6.75 (d, 1H, 6′-H, *J*=8.0 Hz), 6.92 (t, 1H, 5′-H, *J*=7.7 Hz), 7.03 (d, 1H, 3-H, *J*=8.8 Hz), 7.17 (t, 1H, 6-H, *J*=7.5 Hz), 7.27 (t, 1H, 7-H, *J*=7.7 Hz), 7.47 (d, 1H, 8-H, *J*=8.7 Hz), 7.70 (d, 1H, 4-H, *J*=8.9 Hz), 7.73 (d, 1H, 5-H, *J*=8.0 Hz). ^{13}C NMR (150 MHz, DMSO): δ=50.1 (PhCHNH$_2$), 115.7 (C-1), 115.8 (C-6′), 116.4 (C-4′), 120.3 (C-3), 121.7 (C-8), 121.9 (C-6), 126.1 (C-7), 127.7 (C-4a), 127.9 (C-3′), 128.1 (C-5′), 128.4 (C-4, C-5), 128.7 (C-1′), 132.0 (C-8a), 145.6 (C-2′), 158.2 (C-2). Anal. Calcd for $C_{17}H_{16}N_2O$ (264.32): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.32; H, 6.08; N, 10.56.

*4.1.4. Benzyl (2-hydroxynaphthalen-1-yl)(2-nitrophenyl)methylcarbamate (**5**).* A mixture of 2-naphthol (**1**, 3.60 g, 0.025 mol), 2-nitrobenzaldehyde (3.78 g, 0.025 mol) and benzyl carbamate (3.77 g, 0.025 mol) was heated at 80 °C for 32 h under neat conditions. When TLC showed that no starting material remained, the residue was crystallized from MeOH (30 mL) and the beige crystals that separated out were filtered off and washed with MeOH (2×10 mL).

Yield: 8.14 g (76%), mp: 204–206 °C. ^{1}H NMR (600 MHz, DMSO): δ=5.08 (m, 2H, PhC*H*$_2$), 7.05 (d, 1H, 3-H, *J*=8.9 Hz), 7.26–7.31 (m, 3H, 4″-H, 6-H, PhC*H*NH), 7.33–7.37 (m, 4H, 3″-H, 5″-H, 2″-H, 6″-H), 7.41 (t, 1H, 7-H, *J*=7.3 Hz), 7.47 (t, 1H, 4′-H, *J*=7.4 Hz), 7.58–7.66 (m, 2H, 5′-H, 6′-H), 7.73 (d, 1H, 4-H, *J*=8.8 Hz), 7.76 (d, 1H, 3′-H, *J*=8.0 Hz), 7.79 (d, 1H, 5-H, *J*=8.0 Hz), 7.91 (d, 1H, 8-H, *J*=8.7 Hz), 8.14 (br d, 1H, CHN*H*, *J*=8.4 Hz), 9.81 (br s, 1H, O*H*). ^{13}C NMR (150 MHz, DMSO): δ=47.9 (PhC*H*NH), 65.5 (PhC*H*$_2$), 116.0 (C-1), 118.4 (C-3), 122.5 (C-4″), 122.6 (C-8), 124.1 (C-3′), 126.6 (C-7), 127.4 (C-2″, C-6″), 127.7 (C-6), 127.8 (C-4′), 128.1 (C-4a), 128.3 (C-3″, C-5″), 128.5 (C-5), 129.0 (C-6′), 130.0 (C-4), 132.2 (C-5′), 132.9 (C-8a), 136.4 (C-1′), 137.1 (PhCH$_2$), 148.6 (C-2′), 153.7 (C-2), 155.9 (NHCOO). Anal. Calcd for $C_{25}H_{20}N_2O_5$ (428.44): C, 70.08; H, 4.71; N, 6.54. Found: C, 70.15; H, 4.69; N, 6.49.

*4.1.5. 1-(Amino(2-aminophenyl)methyl)-2-naphthol (**4**); starting from **5**.* The nitroderivative **5** (5.14 g, 0.012 mol) was dissolved in MeOH (15 mL). In parallel, Pd/C (3.43 g) was suspended in MeOH (10 mL). The mixture was hydrogenated at atmospheric pressure for 2 h. The catalyst was then removed by filtration and washed with MeOH (2×10 mL). The filtrate was concentrated under vacuum and the residue was crystallized from *n*-hexane (20 mL). The product was purified by recrystallization from *i*-Pr$_2$O (20 mL).

Yield: 2.19 g (69%), mp: 127–129 °C. The NMR and analytical data were identical with those of the material synthesized starting from **3**.

*4.1.6. 10,11-Dihydro-8H,15bH-naphth[1,2-e][1,3]oxazino[3,4-c]quinazoline (**6**).* Aqueous formaldehyde (0.53 mL, 30%) was added to a solution of **4** (0.53 g, 0.002 mol) in $CHCl_3$ (15 mL). The mixture was stirred at rt for 1.5 h. The solution was then dried (Na_2SO_4) and the solvent was evaporated off. The product was isolated by column chromatography (*n*-hexane/EtOAc 2:1 v/v), crystallized from Et$_2$O (10 mL) and recrystallized from *i*-Pr$_2$O (12 mL).

Yield: 0.23 g (40%), mp: 145–147 °C. ^{1}H NMR (600 MHz, CD_2Cl_2): δ=4.40 (d, 1H, 10-H$_{ax}$, *J*=12.2 Hz), 4.84 (d, 1H, 8-H$_{eq}$, *J*=7.3 Hz), 4.91 (d, 1H, 8-H$_{ax}$, *J*=7.3 Hz), 4.96 (d, 1H, 10-H$_{eq}$, *J*=12.2 Hz), 5.83 (s, 1H, 15b-H), 6.42 (t, 1H, 14-H, *J*=7.5 Hz), 6.50 (d, 1H, 12-H, *J*=8.0 Hz), 6.75 (d, 1H, 15-H, *J*=7.7 Hz), 6.98 (t, 1H, 13-H, *J*=7.6 Hz), 7.09 (d, 1H, 6-H, *J*=8.9 Hz), 7.38 (t, 1H, 3-H, *J*=7.5 Hz), 7.51 (t, 1H, 2-H, *J*=7.5 Hz), 7.74 (d, 1H, 5-H, *J*=8.9 Hz), 7.82 (d, 1H, 4-H, *J*=8.3 Hz), 7.87 (d, 1H, 1-H, *J*=7.4 Hz). ^{13}C NMR (150 MHz, CD_2Cl_2): δ=54.4 (C-15b), 61.5 (C-10), 78.4 (C-8), 114.5(C-12), 115.8 (C-15c), 117.8 (C-14), 119.0 (C-6), 120.6 (C-15a), 123.4 (C-1), 123.7 (C-3), 127.1 (C-2), 128.4 (C-13), 128.8 (C-4), 129.1 (C-4a), 129.5 (C-5), 129.8 (C-15), 133.2 (C-15d), 141.2 (C-11a), 150.5 (C-6a). MS: (EI) *m*/*z* (%)=288 (50) [M]$^+$, 259 (100), 230 (42), 115 (35). Anal. Calcd for $C_{19}H_{16}N_2O$ (288.34): C, 79.14; H, 5.59; N, 9.72. Found: 79.21; H, 5.56; N, 9.68.

*4.1.7. 2-(Aryl-substituted)-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolines (**7a**–**g**).* The appropriate aromatic aldehyde (0.0022 mol; freshly distilled if liquid) was added to a solution of **4** (0.53 g, 0.002 mol) in MeOH (30 mL). The mixture was left to stand for 1 day at ambient temperature, during, which crystalline material separated out. The crystalline product (**7a**–**g**) was filtered off, washed with cold MeOH (2×5 mL) and recrystallized from a mixture of *i*-Pr$_2$O/EtOAc. All of the recrystallized new compounds (**7a**–**g**) gave satisfactory data on elemental analysis (C, H, N). The physical and analytical data for **7a**–**g** are listed in Table 5.

Table 5
Physical and analytical data on 2-(aryl-substituted)-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolines (**7a**–**g**)

Compd	Mp (°C)	Yield (%)	Formula	MW	C% found (calculated)	H% found (calculated)	N% found (calculated)
7a[a]	191–194	77	$C_{24}H_{19}N_3O_3$	397.43	72.49 (72.53)	4.78 (4.82)	10.52 (10.57)
7b[a]	174–176	52	$C_{24}H_{19}ClN_2O$	386.87	74.58 (74.51)	4.91 (4.95)	7.21 (7.24)
7c[b]	179–182	63	$C_{24}H_{19}ClN_2O$	386.87	74.62 (74.51)	4.92 (4.95)	7.28 (7.24)
7d[c]	172–174	88	$C_{24}H_{20}N_2O$	352.43	81.68 (81.79)	5.79 (5.72)	7.92 (7.95)
7e[b]	168–171	66	$C_{25}H_{22}N_2O$	366.45	81.97 (81.94)	6.01 (6.05)	7.61 (7.64)
7f[b]	174–176	90	$C_{25}H_{22}N_2O_2$	382.45	78.62 (78.51)	5.75 (5.80)	7.35 (7.32)
7g[a]	148–151	57	$C_{26}H_{25}N_3O$	395.5	78.85 (78.96)	6.32 (6.37)	10.59 (10.62)

[a] Recrystallized from *i*-Pr$_2$O/EtOAc (15 mL:5 mL).
[b] Recrystallized from *i*-Pr$_2$O/EtOAc (15 mL:2 mL).
[c] Recrystallized from *i*-Pr$_2$O/EtOAc (15 mL:1 mL).

4.1.8. (2S,4S*)-2-Phenyl-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazoline (**7d**).* Yield: 0.62 g (88%), mp: 172–174 °C. ^{1}H NMR (600 MHz, CD_2Cl_2): δ=4.33 (br s, 1H, 3-H), 5.50 (s, 1H, 2-H),

6.49 (s, 1H, 4-H), 6.50–6.54 (m, 2H, 5-H, 6-H), 6.66 (d, 1H, 8-H, *J*=7.9 Hz), 7.03 (t, 1H, 7-H, *J*=6.8 Hz), 7.07 (d, 1H, 3′-H, *J*=8.9 Hz), 7.35 (t, 1H, 6′-H, *J*=7.5 Hz), 7.44–7.48 (m, 3H, 4″-H, 3″-H, 5″-H), 7.54 (t, 1H, 7′-H, *J*=7.2 Hz), 7.66 (d, 2H, 2″-H, 6″-H, *J*=7.8 Hz), 7.74 (d, 1H, 4′-H, *J*=8.8 Hz), 7.82 (d, 1H, 5′-H, *J*=7.8 Hz), 8.10 (d, 1H, 8′-H, *J*=8.6 Hz), 11.49 (br s, 1H, O*H*). ^{13}C NMR (150 MHz, DMSO): δ=55.9 (C-4), 71.5 (C-2), 115.6 (C-8), 118.3 (C-1′), 119.4 (C-6), 120.5 (C-3′), 121.9 (C-8′), 122.8 (C-4a), 123.2 (C-6′), 127.5 (C-7′), 127.8 (C-5), 128.0 (C-2″, C-6″), 128.4 (C-7), 128.8 (C-4a′), 129.4 (C-5′), 129.5 (C-3″, C-5″), 130.1 (C-4″), 130.3 (C-4′), 134.0 (C-8a′), 140.6 (C-1″), 144.0 (C-8a), 156.3 (C-2′).

Representative ^{1}H NMR data for **7a**–**g** are presented in Table 6.

Table 6
NMR spectroscopic data on 2-(aryl-substituted)-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolines (**7a**–**g**)

X	**A**	**B**		**C**		**D**		**E**	
	N=C*H* (N=*C*H)	C_2-*H* (C_2)	C_4-*H* (C_4)	C_2-*H* (C_2)	C_4-*H* (C_4)	C_8-*H* (C_8)	C_{10}-*H* (C_{10})	C_8-*H* (C_8)	C_{10}-*H* (C_{10})
p-NO_2	—	5.65 (s) (70.1)	6.53 (s) (55.2)	—	—	5.76 (d) *J*=4.7 Hz (66.1)	5.68 (s) (48.2)	5.88 (s) (81.3)	5.81 (s) (51.5)
m-Cl	—	5.51 (s) (70.4)	6.50 (s) (55.3)	—	—	5.64 (d) *J*=4.1 Hz (66.4)	5.73 (s) (48.4)	5.76 (s) (81.6)	5.78 (s) (51.6)
p-Cl	—	5.51 (s) (70.3)	6.50 (s) (55.4)	—	—	5.64 (d) *J*=4.3 Hz (66.5)	5.73 (s) (48.4)	5.76 (s) (81.7)	5.77 (s) (51.6)
H	—	5.50 (s) (71.5)	6.49 (s) (55.9)	—	—	5.62 (d) *J*=3.9 Hz (67.6)	5.75 (s) (48.9)	5.79 (s) (82.8)	5.77 (s) (52.0)
p-Me	—	5.48 (s) (70.8)	6.50 (s) (55.4)	—	—	5.60 (d) *J*=2.8 Hz (67.0)	5.77 (s) (48.5)	5.74 (s) (82.4)	5.76 (s) (51.6)
p-OMe	—	5.47 (s) (70.4)	6.49 (s) (55.4)	—	—	5.59 (d) *J*=3.2 Hz (66.7)	5.77 (s) (48.5)	5.73 (s) (82.1)	5.75 (s) (51.4)
p-NMe_2	—	5.41 (s) (70.5)	6.48 (s) (55.5)	—	—	5.52 (s) (67.1)	5.82 (s) (48.6)	5.69 (s) (82.6)	5.74 (s) (51.5)

4.1.9. (8R,15bS*)-Phenyl-10,11-dihydro-8H,15bH-naphth[1,2-e][1,3]oxazino[3,4-c]quinazolin-10-one (**8**).* To a stirred solution of **7d** (0.36 g, 0.001 mol) in toluene (15 mL), triphosgene (1.19 g, 0.004 mol) and Na_2CO_3 (1.06 g, 0.010 mol) were added. The mixture was stirred for 6.5 h at rt in a bomb tube, after which the inorganic salts formed were filtered off and the solvent was evaporated off under reduced pressure. The product was then isolated by column chromatography, eluent: *n*-hexane/EtOAc 2:1 v/v, crystallized with Et_2O (15 mL) and recrystallized from *i*-Pr_2O/EtOAc (10 mL:2 mL).

Yield: 0.11 g (31%), mp: 298–300 °C. ^{1}H NMR (600 MHz, DMSO): δ=6.12 (d, 1H, 15-H, *J*=7.8 Hz), 6.42 (s, 1H, 15b-H), 6.71 (t, 1H, 14-H, *J*=7.8 Hz), 7.04 (s, 1H, 8-H), 7.11 (d, 1H, 12-H, *J*=7.8 Hz), 7.17 (t, 1H, 4′-H, *J*=7.4 Hz), 7.21 (t, 1H, 13-H, *J*=7.7 Hz), 7.26 (t, 2H, 3′-H, 5′-H, *J*=8.0 Hz), 7.34 (d, 1H, 6-H, *J*=8.9 Hz), 7.39–7.44 (m, 4H, 2-H, 3-H, 2′-H, 6′-H), 7.54 (d, 1H, 1-H, *J*=8.3 Hz), 7.87–7.90 (m, 2H, 4-H, 5-H), 10.06 (br s, 1H, N*H*). ^{13}C NMR (150 MHz, DMSO): δ=49.1 (C-15b), 79.9 (C-8), 113.4 (C-15c), 114.4 (C-12), 120.1 (C-6), 121.3 (C-14), 121.6 (C-15a), 123.1 (C-1), 124.4 (C-3), 125.1 (C-15), 126.3 (C-2′, C-6′), 126.9 (C-2), 128.2 (C-4′), 128.3 (C-13), 128.5 (C-3′, C-5′), 128.6 (C-4), 129.1 (C-4a), 129.8 (C-5), 131.1 (C-15d), 137.2 (C-1′), 139.1 (C-11a), 150.5 (C-6a), 154.7 (C-10). MS: (EI) *m*/*z* (%)=378 (57) $[M]^+$, 335 (37), 231 (100), 132 (38), 77 (27). Anal. Calcd for $C_{25}H_{18}N_2O_2$ (378.42): C, 79.35; H, 4.79; N, 7.40. Found: C, 79.39; H, 4.75; N, 7.37.

*4.1.10. 4-(2-Hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolin-2-one (**10**).* To a solution of **4** (0.53 g, 0.002 mol) in toluene (20 mL), triphosgene (0.30 g, 0.001 mol) and Na_2CO_3 (1.06 g, 0.010 mol) were added. The mixture was stirred for 45 h at rt in a bomb tube, after which the inorganic salts formed were filtered off and the solvent was evaporated off under vacuum. The product was then isolated by column chromatography, eluent: *n*-hexane/EtOAc 1:4 v/v, and crystallized with *i*-Pr_2O (15 mL).

Yield: 0.23 g (40%), mp: 322–325 °C. ^{1}H NMR (600 MHz, DMSO): δ=6.48 (d, 1H, 5-H, *J*=7.5 Hz), 6.62 (t, 1H, 6-H, *J*=7.5 Hz), 6.75 (s, 1H, PhC*H*NH), 6.83 (d, 1H, *J*=7.8 Hz), 6.93 (br s, 1H, PhCHN*H*), 7.02 (t, 1H, 7-H, *J*=7.7 Hz), 7.12–7.25 (m, 2H, 6′-H, 7′-H), 7.32 (d, 1H, 3′-H, *J*=8.5 Hz), 7.69 (d, 1H, 4′-H, *J*=9.0 Hz), 7.73 (d, 1H, 5′-H, *J*=8.0 Hz), 7.83 (d, 1H, 8′-H, *J*=8.0 Hz), 9.22 (br s, 1H, O*H*), 9.26 (br s, 1H, PhN*H*). ^{13}C NMR (150 MHz, DMSO): δ=49.3 (C-4), 113.8 (C-8), 116.6 (C-1′), 119.3 (C-3′), 121.4 (C-6), 121.8 (C-4a), 121.9 (C-7′), 122.0 (C-6′), 126.0 (C-5), 127.7 (C-7), 128.8 (C-8′), 129.0 (C-5′), 129.6 (C-4′), 132.6 (C-8a′), 135.2 (C-4a′), 137.8 (C-8a), 155.3 (C-2′), 157.2 (NH*C*ONH). MS: (ESI) *m*/*z*=313 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{14}N_2O_2$ (290.32): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.39; H, 4.83; N, 9.60.

*4.1.11. 10,11-Dihydro-8H,15bH-naphth[1,2-e][1,3]oxazino[3,4-c]quinazolin-8,10-dione (**11**).* To a stirred solution of **4** (0.40 g, 0.0015 mol) in toluene (15 mL), triphosgene (1.78 g, 0.006 mol) and Na_2CO_3 (1.59 g, 0.015 mol) were added. The mixture was stirred for 8.5 h at rt in a bomb tube, after which the inorganic salts formed were filtered off and the solvent was evaporated off under reduced pressure. The residue was then crystallized from Et_2O/EtOAc (10 mL:1 mL) and recrystallized from *i*-Pr_2O/EtOAc (10 mL:2 mL).

Yield: 0.32 g (67%), mp: 252–255 °C. ^{1}H NMR (600 MHz, DMSO): δ=6.33 (d, 1H, 15-H, *J*=7.6 Hz), 6.76 (s, 1H, PhC*H*N), 6.90 (t, 1H, 14-H, *J*=7.5 Hz), 7.16 (d, 1H, 12-H, *J*=7.8 Hz), 7.33 (t, 1H, 13-H, *J*=7.3 Hz), 7.43 (d, 1H, 6-H, *J*=8.9 Hz), 7.56–7.71 (m, 3H, 3-H, 2-H, 1-H), 8.09 (d, 1H, 4-H, *J*=7.4 Hz), 8.15 (d, 1H, 5-H, *J*=9.0 Hz), 11.1 (br s, 1H, N*H*). ^{13}C NMR (150 MHz, DMSO): δ=53.2 (C-15b), 108.4 (C-15c), 115.8 (C-12), 116.5 (C-6), 123.1 (C-14), 123.3 (C-1), 123.7 (C-15), 124.3 (C-15a), 125.7 (C-3), 127.9 (C-2), 128.7 (C-4), 129.1 (C-13), 129.7 (C-15d), 130.3 (C-4a), 131.4 (C-5), 136.7 (C-11a), 145.0 (C-8), 146.5 (C-6a), 149.9 (C-10). MS: (ESI) *m*/*z*=339 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{12}N_2O_3$ (316.31): C, 72.15; H, 3.82; N, 8.86. Found: C, 72.17; H, 3.79; N, 8.81.

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