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Inter- and intramolecular hydrogen bonding in amide- and urea-substituted 8-hydroxyquinoline derivatives

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Abstract—Amide- and urea-substituted 8-hydroxyquinoline derivatives **3**, **5**, and **7** are prepared by standard methods. In the solid state **3a**, **5d**, and **7** form 8-hydroxyquinoline dimers with bifurcated inter- and intramolecular hydrogen bonds.

1. Introduction

Hydrogen bonding plays an important role in biology, allowing the reversible formation of aggregates which are non-covalently linked. Base pairing in DNA is only possible due to the complementary binding sites of the nucleobases guanine and cytosine or thymine and adenine. Due to the higher number of hydrogen bonds, the Watson–Crick pair of guanine and cytosine is more stable than the thymine–adenine complex.[1] More than ten years ago, Jorgensen found out that the stability of multiple hydrogen bonded 'dimers' depends not only on the number of hydrogen bonds but also on the hydrogen bonding pattern. Alternating hydrogen bond donor and acceptor functionalities (e.g. uracil/2,6-diaminopyridine) are less favored for complex formation than a non-alternating arrangement (e.g. guanine/cytosine) due to secondary repulsive or attractive interactions between local charges.[2]

We are investigating in the supramolecular chemistry of 8-hydroxyquinoline derivatives regarding the metal coordination[3] as well as the hydrogen bonding[4–6] ability of these molecules. In an ongoing project we study the dimerization behavior of 8-hydroxyquinoline[4] and of its derivatives to use this for the formation of hydrogen bonded polymers in the solid state.[5] Introduction of further hydrogen bonding donor/acceptor sites in the periphery of the 8-hydroxyquinoline skeleton also leads to hydrogen bonded networks.[6] Like the above mentioned thymine–adenine base pair, 8-hydroxyquinoline possesses an alternating H-bonding donor/acceptor motif which shows bifurcated hydrogen bond interactions.[4–6]

In this paper, we describe the synthesis of a series of 8-hydroxyquinoline derivatives which bear amide or urea substituents as additional hydrogen bond donor/acceptor moieties in 2- or 7-position. For two of the derivatives we obtained X-ray structural analyses showing dimeric 8-hydroxyquinoline units with bifurcated H-bonds in the solid state.

2. Results and discussion

2.1. Preparation and characterization of the 8-hydroxyquinoline derivatives

The preparation of the amide- and urea-substituted 8-hydroxyquinoline derivatives **3**, **5**, and **7** follows standard procedures. We already described the synthesis as well as the crystal structure of **3a**.[6] The amide-substituted derivatives **3b–d** are prepared similar to **3a**. Therefore the carboxylic acids **2b–d** are activated with carbonyldiimidazole (CDI)[7] and the activated esters by reaction with 7-amino-8-hydroxyquinoline (**1**) are transformed into the corresponding amides **3b–d** (yield: **b** 63%, **c** 63%, **d** 87%) (Scheme 1).

Reaction of the amine **1** with isocyanates **4a–d** in chloroform leads to precipitation of the urea derivatives **5a–d** (yield: **a** 87%, **b** 37%, **c** 55%, **d** 76%). The compound **7** which bears an amide unit in 2-position of the 8-hydroxyquinolin skeleton is obtained from the amine **6** and acetic acid by carbonyl diimidazole activation[7] in 89% yield.

The 8-hydroxyquinoline derivatives **3a–d**, **5a–d**, and **7** are

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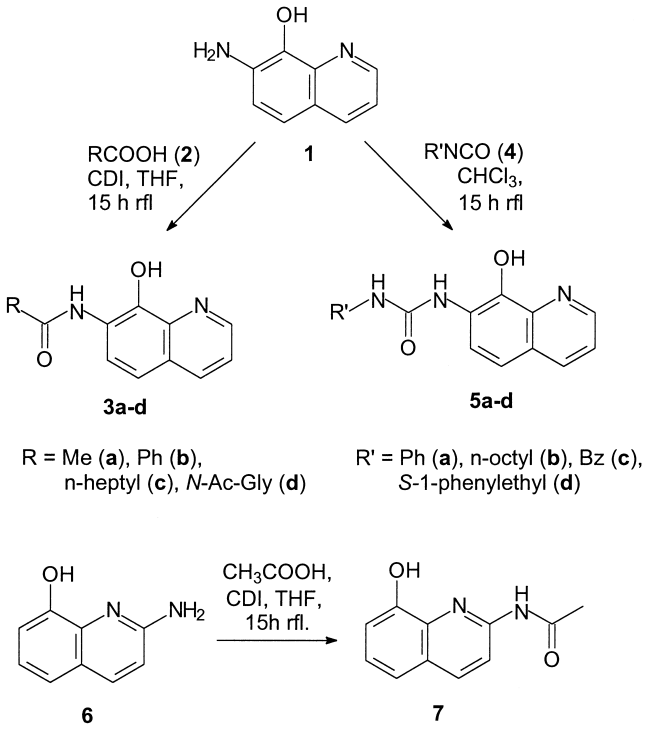


Scheme 1. Preparation of **3a**–**d**, **5a**–**d**, and **7** (CDI=carbonyldiimidazole).

characterized by NMR spectroscopic methods. The shifts of the protons which are attached to the 8-hydroxyquinoline moiety are listed in Table 1.

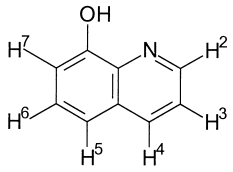
The resonances of **3c**, **6**, and **7** are assigned by two-dimensional NOESY NMR spectroscopy and the others by comparison of the shifts and by analysis of the coupling constants.

Most shifts of the compounds **3a**–**d** and **5a**–**d** with substituents in 7-position are found in typical regions (δ= 8.7–8.8 (H^2), 7.2–7.4 (H^3), 7.9–8.2 (H^4), 7.3–7.4 (H^5), 7.1 (H^6), 7.3 (H^7) ppm).[8] However, the signals of the protons in 6-position are shifted to low field (δ=8.1–8.6 ppm) compared to those of a derivative without an amide in this position (e.g. **1**, **6**, **7**). This is attributed to an anisotropic effect of the C=O—carbonyl unit located in 7-position (close to the 6-position) of the compounds. This indicates that the C=O unit is orientated *s-cis* to CH^6 as it is shown in rotamer **A** and not *s-trans* as in **B** (see bonds presented as bold lines).

Similar observations are made for the derivatives **6** and **7** with a substituent in 2-position. The resonance of H^3 of compound **7** is significantly low field shifted compared to **6** indicating a location of the C=O double bond close to this proton. The signal of H^6 is found in the region which is expected for a derivative without an amide substituent in 7-position (**6**: δ=6.98; **7**: δ=7.04).[8]

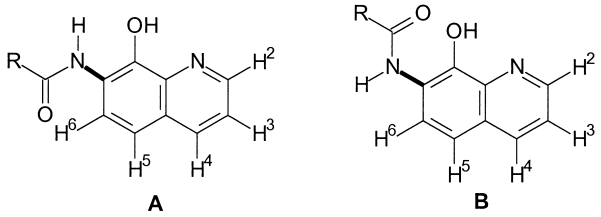
In order to try to follow the dimerization of the 8-hydroxyquinoline units of compounds **3**, **5**, and **7** in solution, we performed proton NMR studies with variable concentrations of the compounds. However, the derivatives **3** or **5** show only low solubility in non-polar solvents (e.g. $CDCl_3$). Upon addition of DMSO-d_6 (approx. 10%) the compounds dissolve but only marginal shift differences are observed depending on the concentration of the hydroxyquinoline derivatives. **7** shows a better solubility in chloroform and we observed a shifting of the amide proton depending on the concentration of the sample. This indicates a dimerization of **7** in solution. However, the compound started to precipitate before a final shift could be reached and therefore no thermodynamic data can be obtained.

Table 1. Comparison of the ^{1}H NMR spectroscopic shifts (in ppm) of the 8-hydroxyquinoline protons



	H^2	H^3	H^4	H^5	H^6	H^7	Solvent[a]
1	8.68	7.15	8.00	7.09/7.22		–	$CDCl_3$
3a	8.72	7.33	8.11	7.35	8.58	–	$CDCl_3$
3b	8.83	7.56	8.28	7.47	8.06	–	$CDCl_3$
3c	8.81	7.46	8.28	7.35	8.67	–	DMSO-d_6
3d	8.79	7.44	8.21	7.37	8.10	–	Methanol-d_4
5a	8.81	7.41	8.25	7.40	8.51	–	DMSO-d_6
5b	8.77	7.36	8.20	7.33	8.45	–	DMSO-d_6
5c	8.78	7.37	8.22	7.34	8.46	–	DMSO-d_6
5d	8.70	7.35	7.90	7.35	8.16	–	Methanol-d_4
6	–	6.78	7.85	7.08	6.98	6.86	DMSO-d_6
7	–	8.21	8.24	7.30	7.04	7.27	DMSO-d_6

[a] Different solvents lead to shift differences which, however, are not significant.



As was shown, a series of 8-hydroxyquinolines, which bear amide or urea substituents can be prepared. The example of the glycine derivative **3d** indicates that amino acids or peptides can be introduced, which opens up the way to chiral derivatives with additional hydrogen bonding functionalities. All derivatives **3a**–**d** and **5a**–**d** can be used in coordination studies to obtain trinuclear supramolecular complexes which possess a hexahelical structure.[3b] The coordination chemistry of the amide **7** with a substituent in 2-position still has to be studied.

2.2. The solid state structures of 5d and 7

The X-ray crystal structure of the acetamide **3a** was already described and it was shown that a double-stranded ladder-type polymeric structure is formed in the solid state with dimerization of the 8-hydroxyquinoline units. The backbone of the double-stranded system is formed by hydrogen bonding between amide NH and amide carbonyl units (Fig. 1).

The two hydroxyquinoline units of the **3a**-dimer are in one plane and intermolecular (a) as well as intramolecular (b)

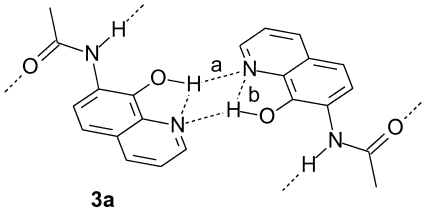


Figure 1. Schematic representation of the dimeric structure of **3a** in the solid state.

hydrogen bonding occurs between the hydroxy group and the quinoline nitrogen atom. The intermolecular hydrogen bond distance a=2.16 Å is shorter than the intramolecular distance b=2.32 Å. This observation was also made for other 8-hydroxyquinoline dimers and might be due to an unfavored small O–H–N angle of 113.7° (observed for **3a**) for the intramolecular interaction.[4,5] The corresponding intermolecular O–H–N angle of **3a** is 135.5°.[6]

X-Ray quality crystals of the chiral urea derivative **5d** were obtained. The compound crystallizes in the tetragonal space group $P4_12_12$ and was refined to R=0.062. The positions of the hydrogen atoms involved in hydrogen bonding were located.

In **5d**, the urea substituent is orientated with the carbonyl *cis* to H[6] and the urea NH are orientated parallel to the phenolic C–O group. This is in accordance with the structure **A** deduced from the results of the NMR spectra which were discussed earlier.

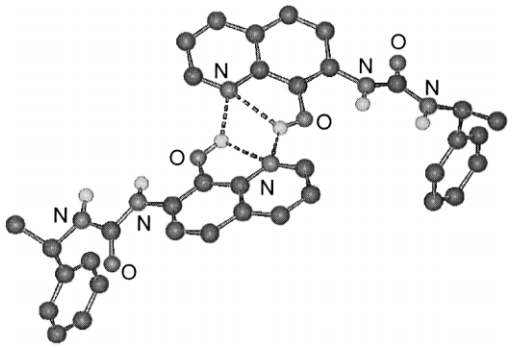


Figure 3. The 8-hydroxyquinoline-dimer found in the solid state structure of **5d**.

Similar as it was observed for **3a**, **5d** shows a separated hydrogen bonding behavior of the hydroxyquinoline unit and of the side chain in 7-position. The urea units form a helical hydrogen bonded polymeric strand, which has a fourfold screw-axis. Due to the *S*-configurated chiral substituent in the side chain only the right-handed helix is formed. Hereby the urea NH moieties act as 'tweezers' which form two hydrogen bonds to the urea oxygen atom of the next molecule (d(H–O)=2.23 and 1.97 Å). The hydroxyquinoline units are attached to this helix and by dimerization connect the linear strands to form a three-dimensional tetragonal network. For a schematic representation of one strand which is formed by hydrogen bonding of the ureas, see Fig. 2b.

Dimerization of the hydroxyquinoline units of **5d** proceeds

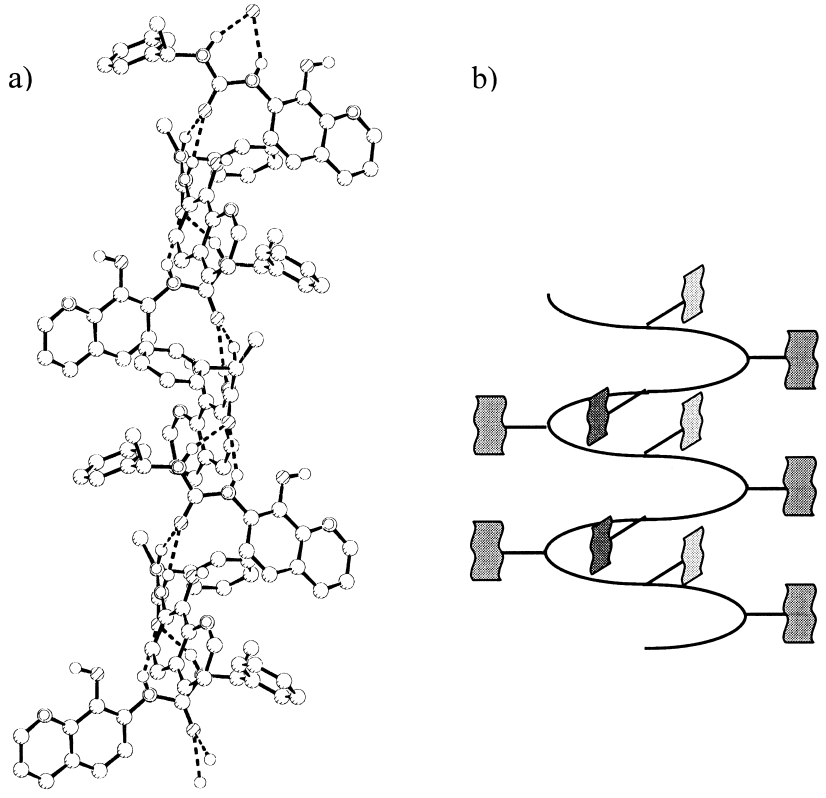


Figure 2. (a) The urea-bridged helical polymer observed for **5d** in the solid state. (b) A schematic representation of the structure of **5d**.

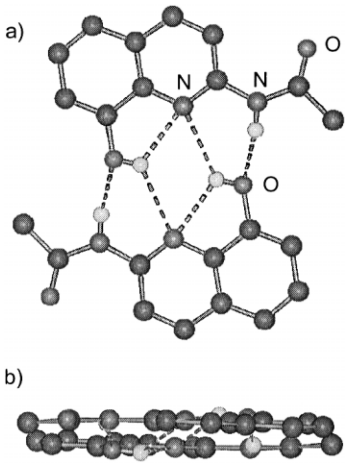


Figure 4. The dimer of **7** as found in the solid state: (a) top view and (b) side view.

similar as observed for compound **3a**. However in case of **5d** not a planar dimer is formed but the two aromatic planes are twisted by approximately 27.4° against each other. Again a relatively long intramolecular (d(H–N)=2.31 Å) and a short intermolecular hydrogen bond interaction (d(H–N)= 1.97 Å) is observed (Fig. 3).

Thus the amide **3a** and the urea derivative **5d** in some respect behave similar in the solid state. The amide and urea moieties form a linear polymeric strand while the hydroxyquinoline units interconnect the strands. However, in **5d** a helical twist is induced by the chiral substituents leading to a three-dimensional network, while for **3a** a linear double-stranded structure is observed.

Shifting the amide unit from 7- to the 2-position results in a different structure in the solid state. Compound **7** crystallizes in the monoclinic space group $P2_1/c$ and was refined to R=0.046. Again the positions of the hydrogen atoms that are involved in hydrogen bonding could be located. As indicated by NMR spectroscopy in solution the amide C═O is orientated towards H[3].

7 does not form a polymeric structure in the solid state but dimeric units are observed. Hereby the hydroxy group, the quinoline nitrogen atom, and the amide NH form hydrogen bonds (Fig. 4).

In addition to the two bifurcated inter/intramolecular OH–N hydrogen bonds, two more intermolecular hydrogen bonding interactions are observed between the amide NH and the phenolic oxygen atoms. The distance of this interaction is 2.05 Å. This additional H-bonding does not influence the intramolecular H–N distance, which shows a typical separation of 2.20 Å. However, the intermolecular H–N interaction is weakened and a relatively long distance of 2.78 Å results. Reason for this might be the additional H-bond which influences the hydrogen bonding ability of the hydroxy group by electronic and/or steric factors. The overall structure of the dimer is close to planar with a slight shift of the two quinoline units from the plane.

3. Conclusions

In this publication we presented the syntheses of some new 8-hydroxyquinoline derivatives which bear amide (**3a**–**d**) or urea moieties (**5a**–**d**) in 7-position or an acetamide in 2-position of the quinoline. [1]H NMR spectroscopy indicates that the amides and ureas are orientated with the N–H bonds directed to the 'face' of the molecule and the C═O double bond to the 'back'.

The crystal structure of **3a** was described earlier[6] and in addition we now were able to obtain crystals of **5d** and **7** for structure determination. All structures show dimeric 8-hydroxyquinoline units with bifurcated inter- and intramolecular hydrogen bonds. The compounds **3a** and **5d** with substituents in 7-position show related H-bond length with a long internal and a short intermolecular separation. This is also found for other 8-hydroxyquinoline derivatives.[4–6] The amide or urea substituents of **3a** and **5d** form hydrogen bonds leading to polymeric superstructures in the solid state.

The compound **7** with an amide in 2-position shows a different behavior. Additional intermolecular hydrogen bonds are formed upon dimer formation, which weaken the intermolecular OH–$N_{quinoline}$ bond strength. However, the distance of the intramolecular interaction is not influenced.

It is known, that hydroxyquinoline in solution shows a monomer dimer equilibrium.[9] Our results suggest, that in the monomeric form a strong intramolecular hydrogen bond is present.[10] Two such monomers lead to the dimer by formation of additional hydrogen bonding yielding the bifurcated hydrogen bonds and H–N–H nitrogen bridges (Fig. 5).

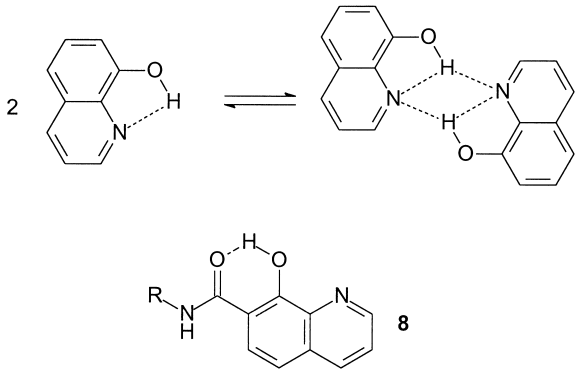


Figure 5.

The dimer is able to dissociate, while the intramolecular interaction only can be broken if appropriate hydrogen bond acceptors are attached which act as competitors to the quinoline nitrogen atoms as was observed, e.g. for **8**.[5]

4. Experimental

4.1. General remarks

[1]H and [13]C NMR spectra were recorded on a Bruker DRX 500, AM 400, or WM 250 NMR spectrometer using DEPT

techniques for the assignment of the multiplicity of carbon atoms. FT-IR spectra were recorded by diffuse reflection (KBr) on a Bruker IFS spectrometer. Mass spectra (EI, 70 eV) were measured on a Finnigan MAT 90 mass spectrometer. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Solvents were purified by standard methods. Melting points: Büchi 535 (uncorrected). 7-Amino-8-hydroxyquinoline **1** was prepared as described in the literature.[11]

Data sets were collected with Enraf–Nonius CAD4 and Nonius KappaCCD diffractometer, the later one equipped with a rotating anode generator Nonius FR591. Programs used: data collection EXPRESS (Nonius B.V., 1994) and COLLECT (Nonius B.V., 1998), data reduction MolEN (K. Fair, Enraf–Nonius B.V., 1990) and Denzo-SMN, absorption correction for CCD data SORTAV, structure solution SHELXS-97, structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997).[13]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 168436 and 168437. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK (fax: +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. 7-Benzoylamido-8-hydroxyquinoline 3b. Benzoic acid (153 mg, 1.249 mmol) and CDI (222 mg, 1.369 mmol) are refluxed in dry THF (10 ml) for 1 h. After the addition of 7-amino-8-hydroxyquinoline (200 mg, 1.249 mmol) the mixture is refluxed over night. Solvent is removed and the residue is dissolved in dichloromethane, which is washed with water. The organic phase is dried ($MgSO_4$), solvent is evaporated in vacuum and the crude product is recrystallized from dichloromethane. Yield: 195 mg (63%) white solid. Mp: 180°C. ^{1}H NMR (methanol-d_4): δ=8.83 (dd, J=4.3, 1.6 Hz, 1H), 8.27 (dd, J=8.3, 1.6 Hz, 1H), 8.06 (d, J=8.9 Hz, 1H), 8.04–8.02 (m, 2H), 7.64–7.61 (m, 1H), 7.58–7.54 (m, 2H), 7.48 (dd, J=8.3, 4.3 Hz, 1H), 7.45 (d, J=8.9 Hz, 1H). ^{13}C NMR (methanol-d_4): δ=168.8 (C), 149.9 (CH), 145.4 (CH), 140.3 (C), 137.4 (C), 135.7 (C), 133.2 (CH), 129.8 (CH), 128.7 (CH), 125.0 (CH), 123.7 (CH), 122.3 (CH), 118.8 (CH). IR (KBr): ν= 3312, 1952, 1899, 1875, 1763, 1650, 1627, 1582, 1504, 1466, 1431, 1408, 1377, 1332, 1304, 1279, 1252, 1187, 1135, 1125, 1092, 1076, 1040, 1027, 1000, 972, 958, 940, 922, 903, 826, 791, 722, 690, 673, 658 cm^{-1}. MS (EI, 70 eV): m/z=264 (59%) [M^+], 105 (100%). HRMS calcd for $C_{16}H_{12}N_2O_2$: 264.0899, found: 264.0893. Elemental analysis calcd for $C_{16}H_{12}N_2O_2 \cdot 0.25H_2O$: C, 71.50; H, 4.68; N, 10.42; found: C, 71.61; H, 4.59; N, 10.40.

4.1.2. 7-Caproylamido-8-hydroxyquinoline 3c. 7-Caproylamido-8-hydroxyquinoline is prepared similar to 7-benzoylamido-8-hydroxyquinoline. The crude product is purified by column chromatography (silica gel, hexane/ethyl acetate 1:1). Yield: 223 mg (63%) white solid. Mp: 134–137°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=8.72 (br, 1H), 8.64 (d, J=8.1 Hz, 1H), 8.13 (d, J=8.1 Hz, 1H), 7.92 (br, 1H), 7.36 (d, J=9.1 Hz, 1H), 7.34 (d, J=9.1 Hz, 1H), 2.47 (br, 2H), 1.40–1.29 (m, 8H), 0.88 (t, J=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ=171.8 (C), 148.2 (CH), 139.3 (C), 137.4 (C), 136.5 (CH), 125.0 (CH), 123.8 (C), 121.4 (CH), 120.3 (CH), 118.0 (CH), 38.0 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). IR (KBr): ν=3306, 3050, 2950, 2035, 2917, 2869, 2850, 1941, 1918, 1897, 1661, 1630, 1583, 1535, 1506, 1468, 1430, 1409, 1376, 1357, 1332, 1290, 1280, 1253, 1224, 1191, 1134, 1111, 1094, 1066, 1044, 1032, 1002, 980, 948, 933, 891, 825, 799, 784, 766, 735, 722, 709, 684, 669 cm^{-1}. MS (EI, 70 eV): m/z=286 (26%) [M^+], 160 (100%). HRMS calcd for $C_{17}H_{22}N_2O_2$: 286.1681, found: 286.1685. Elemental analysis calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78; found: C, 71.13; H, 7.66; N, 9.75.

4.1.3. 8-Hydroxyqinoline-7-yl-*N*-acetylglycylamide 3d. **3d** was prepared as described for **3b**. Yield: 282 mg (87%) gray solid. Mp: 191°C. ^{1}H NMR (methanol-d_4): δ=8.79 (dd, J=4.2, 1.5 Hz, 1H), 8.21 (dd, J=8.3, 1.5 Hz, 1H), 8.10 (d, J=8.9 Hz, 1H), 7.44 (dd, J=8.3, 4.2 Hz, 1H), 7.37 (d, J=8.9 Hz, 1H), 4.12 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (methanol-d_4): δ=174.1 (C), 170.3 (C), 149.8 (CH), 144.0 (C), 137.2 (CH), 127.6 (C), 123.9 (C), 122.1 (CH), 118.7 (CH), 44.3 (CH_2), 22.4 (CH_3). IR (KBr): ν=3390, 3049, 2239, 1975, 1918, 1882, 1665, 1634, 1578, 1540, 1510, 1473, 1434, 1408, 1369, 1343, 1306, 1277, 1247, 1187, 1134, 1092, 1048, 1026, 1013, 916, 888, 834, 724, 674, 651, 609 cm^{-1}. MS (EI, 70 eV): m/z=259 (29%) [M^+], 187 (100%). HRMS calcd for $C_{13}H_{13}N_3O_3$: 259.0957, found: 259.0948. Elemental analysis calcd for $C_{13}H_{13}N_3O_3$: C, 56.31; H, 5.45; N, 15.15; found: C, 56.36; H, 5.59; N, 14.95.

4.2. General procedure for the preparation of urea derivatives

7-Amino-8-hydroxyquinoline (200 mg, 1.249 mmol) is dissolved in 10 ml of dry chloroform and isocyanate (1.249 mmol) is added. Refluxing over night results in precipitation of a white solid material, which is isolated by filtration.

4.2.1. *N*-(8-Hydroxyqinolin-7-yl)-*N'*-phenyl urea 5a. Yield: 305 mg (87%) white solid. Mp: 370°C (decomp.). ^{1}H NMR (DMSO-d_6): δ=10.2 (br, 1H), 9.44 (s, 1H), 8.81 (dd, J=4.2, 1.6 Hz, 1H), 8.56 (s, 1H), 8.51 (d, J=9.0 Hz, 1H), 8.25 (dd, J=8.3, 1.6 Hz, 1H), 7.47 (d, J=7.4 Hz, 2H), 7.41 (dd, J=8.3, 4.2 Hz, 1H), 7.40 (d, J=9.0 Hz, 1H), 7.28 (t, J=7.4 Hz, 2H), 6.96 (t, J=7.4 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ=152.5 (C), 148.4 (CH), 139.8 (C), 139.6 (C), 137.9 (C), 136.0 (CH), 128.8 (CH), 125.4 (C), 123.8 (C), 121.8 (CH), 120.2 (CH), 119.7 (CH), 118.0 (CH), 117.3 (CH). IR (KBr): ν=3313, 3033, 1937, 1880, 1646, 1632, 1597, 1557, 1507, 1499, 1473, 1447, 1434, 1409, 1378, 1333, 1297, 1280, 1254, 1225, 1190, 1159, 1135, 1095, 1050, 960, 902, 889, 786, 753, 742, 712, 694, 665 cm^{-1}. MS (EI, 70 eV): m/z=279 (28%) [M^+], 160 (100%). HRMS calcd for $C_{18}H_{25}N_3O_2$: 279.1008, found: 279.0996. Elemental analysis calcd for $C_{16}H_{13}N_3O_2 \cdot 0.25H_2O$: C, 67.71; H, 4.79; N, 14.81; found: C, 68.00; H, 4.72; N, 14.79.

4.2.2. *N*-(8-Hydroxyqinolin-7-yl)-*N'*-*n*-octyl urea 5b. Yield: 147 mg (37%) gray solid. Mp: 183–190°C. ^{1}H NMR (DMSO-d_6): δ=10.05 (br, 1H), 8.77 (dd, J=4.1, 1.6 Hz, 1H), 8.45 (d, J=9.0 Hz, 1H), 8.21 (s, 1H), 8.20

(dd, J=8.1, 1.6 Hz, 1H), 7.36 (dd, J=8.1, 4.1 Hz, 1H), 7.33 (d, J=9.0 Hz, 1H), 6.96 (t, J=5.6 Hz, 1H), 3.09 (dt, J=6.7, 5.6 Hz, 2H), 1.41 (q, J=6.7 Hz, 2H), 1.25–1.27 (m, 10H), 0.84 (t, J=6.6 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ=155.3 (C), 148.2 (CH), 138.8 (C), 137.9 (C), 135.8 (CH), 126.3 (C), 123.3 (C), 120.3 (CH), 119.3 (CH), 117.1 (CH), 39.0 (CH_2), 31.3 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 26.4 (CH_2), 22.1 (CH_2), 14.0 (CH_3). IR (KBr): ν=3339, 2959, 2854, 1941, 1689, 1639, 1587, 1555, 1504, 1479, 1464, 1435, 1408, 1373, 1331, 1273, 1233, 1203, 1184, 1140, 1120, 1089, 1052, 943, 888, 825, 790, 771, 751, 723, 707, 675 cm^{-1}. MS (EI, 70 eV): m/z=315 (6%) [M$^+$], 160 (100%). HRMS calcd for $C_{18}H_{25}N_3O_2$: 315.1947, found: 315.1953. Elemental analysis calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32; found: C, 68.22; H, 7.80; N, 12.83.

4.2.3. *N*-(8-Hydroxyqinolin-7-yl)-*N′*-benzyl urea 5c. Yield: 200 mg (55%) white solid. Mp: 212–214°C (decomp.). ^{1}H NMR (DMSO-d_6): δ=10.06 (br, 1H), 8.78 (d, J=3.9 Hz, 1H), 8.46 (d, J=8.9 Hz, 1H), 8.38 (s, 1H), 8.22 (d, J=8.1 Hz, 1H), 7.45 (t, J=5.5 Hz, 1H), 7.38–7.30 (m, 6H), 7.25 (m, 1H), 4.33 (d, J=5.5 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ=155.4 (C), 148.2 (CH), 140.2 (C), 139.0 (C), 137.9 (C), 136.0 (CH), 128.4 (CH), 127.1 (CH), 126.8 (CH), 126.1 (C), 123.5 (C), 120.4 (CH), 119.4 (CH), 117.2 (CH), 42.8 (CH_2). IR (KBr): ν=3318, 1731, 1639, 1588, 1556, 1506, 1469, 1433, 1408, 1378, 1335, 1277, 1232, 1191, 1134, 1091, 969, 822, 786, 749, 703, 664 cm^{-1}. MS (EI, 70 eV): m/z=293 (14%) [M$^+$], 160 (100%). HRMS calcd for $C_{17}H_{15}N_3O_2$: 293.1164, found: 293.1170. Elemental analysis calcd for $C_{17}H_{15}N_3O_2 \cdot 0.25H_2O$: C, 68.56; H, 5.25; N, 14.11; found: C, 68.28; H, 5.09; N, 13.77.

4.2.4. *N*-(8-Hydroxyquinolin-7-yl)-*N′*-(*S*)-1-phenylethyl urea 5d. Yield: 290 mg (76%) slightly yellow solid. Mp: 350°C (decomp.). ^{1}H NMR (methanol-d_4): δ=8.74 (d, J=3.6 Hz, 1H), 8.16 (d, J=8.7 Hz, 2H), 7.90 (s, 1H), 7.39–7.31 (m, 7H), 7.23 (t, J=7.1 Hz, 1H), 4.97–4.93 (m, 1H), 1.49 (d, J=6.9 Hz, 3H). ^{13}C NMR (methanol-d_4): δ=157.5 (C), 149.7 (CH), 146.1 (C), 141.3 (C), 139.8 (C), 137.2 (CH), 129.6 (CH), 128.0 (CH), 126.9 (CH), 126.1 (C), 126.0 (C), 122.4 (CH), 120.9 (CH), 118.7 (CH), 50.8 (CH), 23.5 (CH_3). IR (KBr): ν=3337, 3291, 3030, 2974, 1947, 1645, 1622, 1587, 1553, 1505, 1465, 1431, 1408, 1374, 1348, 1268, 1233, 1210, 1186, 1137, 1090, 952, 825, 789, 753, 701, 672 cm^{-1}. MS (EI, 70 eV): m/z=307 (6%) [M$^+$], 160 (100%). HRMS calcd for $C_{18}H_{17}N_3O_2$: 307.1321, found: 307.1331. Elemental analysis calcd for $C_{18}H_{17}N_3O_2 \cdot 0.25H_2O$: C, 69.33; H, 5.66; N, 13.47; found: C, 69.45; H, 5.59; N, 13.20.

X-Ray structural analysis of **5d**:[12] formula $C_{18}H_{17}N_3O_2$, M=307.35, colorless crystal 0.20×0.15×0.10 mm^3, a=13.895(3), c=16.776(1) Å, V=3239.0(10) Å^3, ρ_{calcd}=1.261 g cm^{-3}, μ=6.81 cm^{-1}, empirical absorption correction via ψ scan data (0.876≤T≤0.935), Z=8, tetragonal, space group $P4_12_12$ (No. 92), λ=1.54178 Å, T=223 K, $\omega/2\theta$ scans, 3674 reflections collected ($+h$, $+k$, $+l$), [(sin θ)/λ]=0.62 Å^{-1}, 3294 independent (R_{int}=0.114) and 2625 observed reflections [I≥2σ(I)], 218 refined parameters, R=0.062, wR^2=0.157, max. residual electron density 0.24 (−0.26) e Å^{-3}, hydrogens at O1, N11, and N13 from difference Fourier map, others calculated and all refined as riding atoms.

4.2.5. 2-Acetamido-8-hydroxyquinoline 7. 2-Amino-8-hydroxyquinoline (200 mg, 1.249 mmol) and 1-acetyl imidazole (137 mg, 1.249 mmol) in dry THF (10 ml) are refluxed over night. Solvent is removed, the residue is dissolved in dichloromethane, washed with water, dried (Na_2SO_4) and dichloromethane is evaporated again. Yield: 226 mg (89%) white solid. Mp: 189°C. ^{1}H NMR (methanol-d_4): δ=8.19 (d, J=9.0 Hz, 1H), 8.15 (d, J=9.0 Hz, 1H), 7.31–7.26 (m, 2H), 7.05 (dd, J=6.9, 1.9 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (methanol-d_4): δ=172.2 (C), 153.0 (C), 151.1 (C), 139.4 (CH), 138.0 (C), 128.0 (C), 126.9 (CH), 118.0 (CH), 115.8 (CH), 112.4 (CH), 24.2 (CH_3). IR (KBr): ν=3422, 333, 3238, 3124, 3080, 3059, 1985, 1920, 1841, 1764, 1704, 1598, 1544, 1508, 1437, 1398, 1374, 1357, 1329, 1296, 1266, 1245, 1228, 1202, 1168, 1135, 962, 863, 851, 764, 733, 724, 696 cm^{-1}. MS (EI, 70 eV): m/z=202 (56%) [M$^+$], 160 (100%). HRMS calcd for $C_{11}H_{10}N_2O_2$: 202.0742, found: 202.0729. Elemental analysis calcd for $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.99; N, 13.68; found: C, 65.13; H, 4.98; N, 13.72.

X-Ray structural analysis of **7**:[12] formula $C_{11}H_{10}N_2O_2$, M=202.21, colorless crystal 0.25×0.15×0.10 mm^3, a=11.211(1), b=6.542(31), c=13.965(1) Å, β=110.16(1)°, V=961.5(2) Å^3, ρ_{calcd}=1.397 g cm^{-3}, μ=0.99 cm^{-1}, no absorption correction (0.976≤T≤0.990), Z=4, monoclinic, space group $P2_1/c$ (No. 14), λ=0.71073 Å, T=198 K, ω and φ scans, 3381 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ)/λ]=0.62 Å^{-1}, 1922 independent (R_{int}=0.039) and 1227 observed reflections [I≥2σ(I)], 143 refined parameters, R=0.046, wR^2=0.107, max. residual electron density 0.16 (−0.21) e Å^{-3}, hydrogens at O4 and N12 from difference Fourier map, others calculated and all refined as riding atoms.

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