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2-Naphthol as a powerful chromophore for the configurational assignment of carboxylic acid groups via the CD exciton chirality method

Michaela Hartl and Hans-Ulrich Humpf*

Lehrstuhl für Lebensmittelchemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

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Abstract

A novel approach for the stereochemical assignment of carboxylic acid groups via the circular dichroism (CD) exciton chirality method using the 2-naphthyl chromophore is described. Direct esterification of carboxyl groups with 2-naphthol was effectively achieved with the employment of *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride as the activating reagent. The method was tested with several model compounds, including both cyclic and acyclic dicarboxylic acids, and also applied to the natural product abietic acid.

1. Introduction

The stereochemical assignment of chiral compounds has always been an important yet challenging task. With the CD exciton chirality method a non-empirical procedure is available that allows the quick, convenient and reliable determination of absolute configurations on a microscale. It utilizes the interaction of the electric transition moments of two or more chromophores, which may be identical (degenerate systems) or may not be identical (non-degenerate systems). The chromophores can either be introduced by derivatization of functional groups or already be present in the molecule, e.g., monoene and diene moieties. The interaction gives rise to characteristic bisignate split CD curves and the signs of the two Cotton effects reflect the spatial arrangement of the chromophores, leading to the assignment of the absolute configuration. If the orientation of the electric transition moments of the chromophores is clockwise (looking from the chromophore in front to the chromophore in back), defined as a positive twist, the CD shows a positive first Cotton effect (CE) at longer wavelength and a negative second CE at shorter wavelength and vice versa. Being extremely versatile, the exciton chirality method has an ever increasing scope of application and has become a valuable tool for structure elucidation, particularly with

* Corresponding author. Tel: +49-931-8885483; fax: +49-931-8885484; e-mail: humpf@pzlc.uni-wuerzburg.de

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newly isolated natural products.[1,2] To date it has been used most commonly with compounds bearing hydroxy or amino groups since they react readily with chromophores, disposing of a carboxyl function activated as imidazole, triazole, fluoride or chloride.[3–6] Regarding its application to carboxylic acid groups, a structural element often encountered in natural products, very few strategies have been developed to date. For the configurational assignment of α-hydroxy carboxylic acids the use of a 5-(*p*-carboxyphenyl)-10,15,20-triphenylporphyrin moiety as a chromophore with a very large extinction coefficient ($\varepsilon = 350\,000$) is described. The method comprises two steps since ethanolamine has to be introduced as a linker before derivatization with the porphyrin moiety.[7] Another possibility, well developed for hydroxy carboxylic acids, is the employment of the chromophoric combination 2-naphthoate/9-methylanthryl group, which is selectively introduced to the hydroxy and carboxy groups in a two-step procedure.[8,9] These are, to our knowledge, the only methods that report the use of the exciton chirality method with carboxylic acids.

Therefore, the aim of our studies was the search for a suitable strategy for the chromophoric derivatization of the carboxyl function. Though the 9-methylanthryl group can be introduced easily by using the highly reactive diazomethane,[9] its methyl moiety provides additional flexibility and increases the number of possible conformations. Especially with acyclic compounds, whose CD spectra are influenced by the equilibrium mixture of preferred minimum energy conformations, this is an unwelcome effect, thus making the association of the observed CD spectrum with the absolute stereochemistry more complex and difficult. Besides, due to their reactivity the diazomethanes are not very stable and begin to decompose when stored over longer time periods, which is a problem encountered particularly with 2-naphthyldiazomethane. For this reason, the direct esterification with 2-naphthol seemed to be a more promising pathway and we present here an effective and convenient method, which enables the exciton chirality circular dichroism to be utilized for the stereochemical assignment of carboxylic acid groups.

2. Results and discussion

For chromophoric derivatization of carboxylic acids a suitable one-pot/one-step reaction was desired, leaving an extra activation of the carboxy group prior to esterification with the naphthol unnecessary. Also, the possibility of the direct employment of 2-naphthol seemed favorable as it is a powerful chromophore with a large extinction coefficient (λ_{max} 222 nm, $\varepsilon = 54\,000$, MeCN) and easily available. Our search led us to a method that utilizes *N*,*N*-bis[2-oxo-3-oxazolidinyl]-phosphorodiamidic chloride **1** for activation of the carboxyl group.[10] This reagent is accessible in a simple synthesis with 2-oxazolidinone and phosphorus pentachloride. The mechanism of activation is believed to consist of a nucleophilic substitution at the phosphorus atom by the carboxylate anion followed by a nucleophilic attack of the hydroxy group at the carbonyl moiety.[10] We applied this method to several model compounds starting with *trans*-cyclohexane dicarboxylic acid [Fig. 1(C)]. The reaction was quantitative and completed within several hours. While the (1*R*,2*R*)-enantiomer was available in enantiomerically pure form, we had to employ a racemic mixture of *trans*-cyclohexane dicarboxylic acid in order to obtain the data for the (1*S*,2*S*)-enantiomer. The enantiomers were separated as their dinaphthyl derivatives since the fluorescence of the chromophoric products greatly facilitates purification and allows a sensitive detection. Fig. 1(A) shows the UV and CD spectra of both enantiomers. For the (1*R*,2*R*)-dinaphthylester **5** (dashed line) the interaction between the ^1B_b bands[11] of the two chromophores

gives rise to a negative split CD curve with extrema at 225 nm ($\Delta\varepsilon = -73.9$) and 216 nm ($\Delta\varepsilon = +55.5$) and an amplitude A of –129.4, thus establishing a negative chirality and reflecting a counterclockwise orientation of the electric transition dipoles. The enantiomer (*S*,*S*)-**5** [Fig. 1(A), solid line] reveals a curve of similar shape but opposite Cotton effects (CE) at 225 nm ($\Delta\varepsilon = +75.8$) and 215 nm ($\Delta\varepsilon = -43.8$), amplitude $A = +119.6$. These results are in agreement with predictions based on a MontoCarlo conformational search using MacroModel 5.0.[13] When compared to the CD curve of the corresponding (1*R*,2*R*)-methylnaphthylester, obtained by derivatization with naphthyldiazomethane (data not shown), the amplitude observed here is about 10-fold more intense. These data demonstrate that the two enantiomers can be clearly distinguished via the CD effects of their dinaphthylesters and the absolute configuration of the *trans*-cyclohexane dicarboxylic acid can be deduced from a single CD measurement.

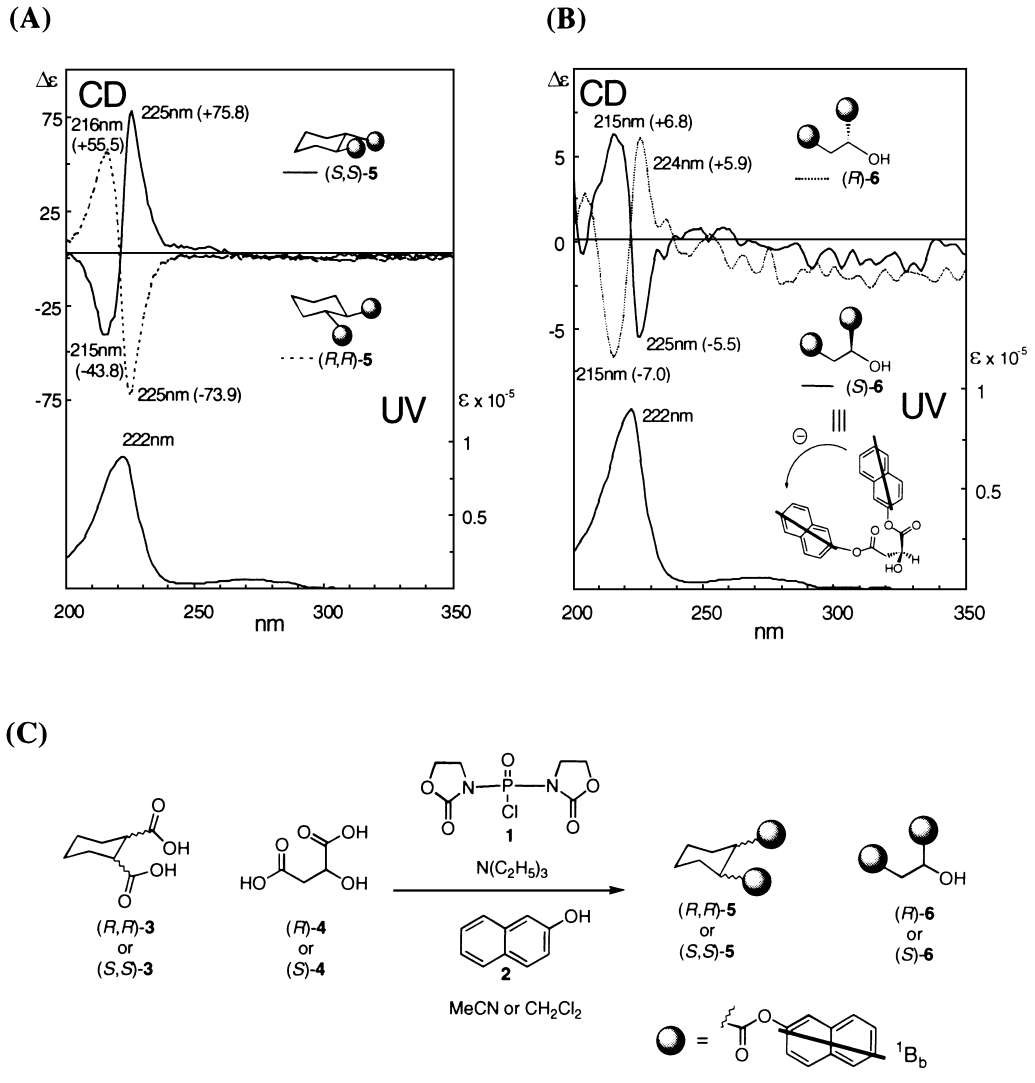

Figure 1. UV and CD spectra of **(A)** (*R*,*R*)- and (*S*,*S*)-cyclohexane dicarboxylic acid dinaphthylester **5** and **(B)** (*R*)- and (*S*)-malic acid dinaphthylester **6** in acetonitrile. **(C)** Chromophoric derivatization of *trans*-cyclohexane dicarboxylic acid **3** and malic acid **4** to the corresponding naphthylesters (bar indicates the location of the electric transition dipole).

We also applied this method to malic acid **4**, serving as a representative example for acyclic compounds [Fig. 1(C)]. Enantiomerically pure (*S*)-**4** and (*R*)-**4** were converted to their naphthylesters, the CD spectra of which are depicted in Fig. 1(B). (*S*)-Malic acid dinaphthylester **6** (solid line) shows a negative couplet with a negative first CE (225 nm, $\Delta\varepsilon = -5.5$) and a positive second CE (215 nm, $\Delta\varepsilon = +6.8$) and an overall amplitude A of –12.3. Its enantiomer (*R*)-**6** reveals a mirror image CD curve with extrema at 224 nm ($\Delta\varepsilon = +5.9$) and 215 nm ($\Delta\varepsilon = -7.0$), amplitude $A = +12.9$ [Fig. 1(B), dashed line]. With non-cyclic compounds lacking a fixed conformation, the CD spectrum is influenced by the equilibrium mixture of the possible staggered conformational isomers and represents the sum of all contributions, which in the case of opposite effects may lead to diminished amplitudes.[12] This factor can probably be held responsible for the relatively small A values observed for (*R*)-**6** and (*S*)-**6**. However, the crucial point is the agreement of the CD effects with the predictions based on theoretical calculations using MacroModel 5.0[13] and the modified Allinger MM2 force field. The preferred minimum energy conformations for both enantiomers were obtained after energy minimization and a MonteCarlo conformational search and showed a clockwise orientation of the chromophoric transition moments for the (*R*)-enantiomer, predicting a positive chirality, and a counterclockwise arrangement for the *S*-enantiomer [see (*S*)-**6**, Fig. 1(B)], suggesting a negative chirality, exactly as was experimentally observed.

Since the derivatization procedure emerged to work quickly and effectively, we were interested to apply it to natural products with more demanding steric structures. The diterpene abietic acid **7** is a well known major constituent of gum or wood rosin and is used in the manufacturing of lacquers, soaps, and plastics. The molecule consists of the typical hydrophenanthrene system and contains an (*R*)-configured carboxylic group in position 1 (Fig. 2B). This group was successfully

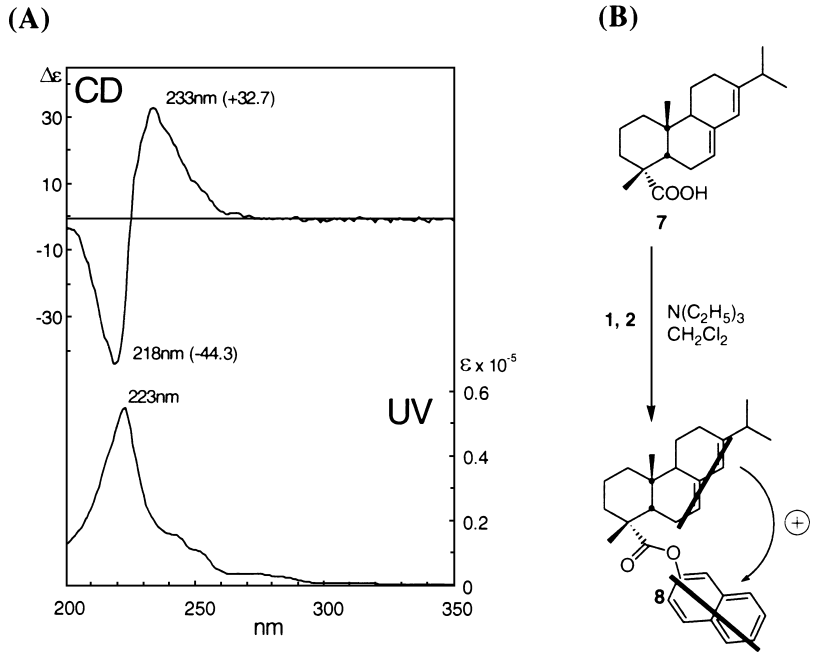

Figure 2. **(A)** UV and CD spectra of abietic acid mononaphthylester **8** in acetonitrile. **(B)** Conversion of abietic acid **7** to the chromophoric derivative **8** (bars indicate the locations of the electric transition dipoles).

derivatized with 2-naphthol to yield the mononaphthylester **8**. For exciton coupling at least two chromophores are required and in the case of abietic acid the ^1B_b band of the napthyl group interacts with the diene moiety at ca. 235 nm ($\varepsilon = 21\,500$, MeCN) already pre-existing in the molecule. The resulting CD spectrum is shown in Fig. 2(A). It is characterized by extrema at 233 nm ($\Delta\varepsilon = +32.7$) and 218 nm ($\Delta\varepsilon = -44.3$), constituting a positive chirality, just as expected from the orientation of the two transition moments as the structure in Fig. 2(B) demonstrates. The amplitude A of +77.0 is about 2.5-fold higher than the one revealed by the previously synthesized methylnaphthylester obtained by derivatization with 2-naphthyldiazomethane (A value of +29.7).[14] This finding is similar to the results for the cyclohexane dicarboxylic acid and supports the assumption that with compounds having a fixed conformation the naphthyl derivatives generally yield stronger CD effects than the corresponding methylnaphthylesters, which have greater conformational flexibility due to the additional methyl moiety.

3. Conclusions

The presented one-step method has been shown to be a potent and effective way for the esterification of carboxylic acids with 2-naphthol, achieving conversion to the naphthylester under mild conditions and in high yields. It enables the circular dichroism exciton chirality method to be utilized for the stereochemical assignment of carboxyl groups, a moiety that is often encountered in natural products, but for which only very few CD approaches had been developed so far. The chromophoric derivatization with 2-naphthol yields highly fluorescent products, thus facilitating purification and allowing one to work on a microscale. This can be especially valuable with the configurational assignment of natural products as the amounts of enantiomerically pure or enriched material may be rather limited. The examples with the model compounds and abietic acid demonstrate the versatility of this approach, working both for cyclic and acyclic compounds. Although the amplitudes for the latter are smaller than for cyclic substances, nonetheless unambiguous stereochemical assignment is possible.

4. Experimental

4.1. General experimental procedures

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker WM 400 or a DMX 600 spectrometer (Bruker, Ettlingen, Germany) operating at 400 and 600 MHz, respectively. Chemical shifts are relative to $CHCl_3$ ($\delta = 7.26$ppm); coupling constants (J) are given in Hertz (Hz). Electrospray ionization mass spectra (ESI-MS) were measured via loop injection on a Finnigan TSQ 7000 Triple Stage Quadrupol mass spectrometer equipped with an ESI interface (Finnigan MAT, Bremen, Germany). Electron impact-high resolution mass spectra (EI-HRMS) were measured on a Finnigan MAT 90 mass spectrometer (Finnigan MAT, Bremen, Germany). UV–vis and CD spectra were recorded as acetonitrile solutions in a 1 cm cell on a Shimadzu UV-2101 PC spectrometer and a Jasco J-600 spectropolarimeter, respectively (Jasco, Gross-Umstadt, Germany). The UV–vis and CD spectra were obtained in spectral grade solvents (Merck, Darmstadt, Germany). All derivatization reactions were carried out in gradient grade solvents dried over molecular sieves. For HPLC analyses a Knauer Maxi Star pump and a Knauer

variable wavelength monitor UV detector were used (Knauer, Berlin, Germany). Chromatographic separations were performed on a Eurospher 100 C18 column (250×4 mm, Knauer, Berlin, Germany) and enantiomeric separation was achieved on a Ceramospher Chiral RU-1 column (250×4.6 mm, Shiseido, Tokyo, Japan). 1*R*,2*R*-Cyclohexane dicarboxylic acid was from Merck (Darmstadt, Germany); all other chemicals were purchased from Fluka (Neu-Ulm, Germany).

4.2. *Preparation of* N,N-*bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride* **1**

To a solution of oxazolidinone (6.96 g, 80 mmol) in nitromethane (76 mL), phosphorus pentachloride (8.32 g, 40 mmol) was added in one portion. The solution was stirred for 4 h at room temperature, for 1 h at 40–45°C and then cooled to 0°C. A mixture of water (3 mL) and 1,2-dimethoxyethane (10 mL) was added within 5 min and the solvent was removed under reduced pressure. The resulting white crystals were filtered, washed with 1,2-dimethoxyethane and dried at 50°C, yield 60%. IR (KBr): $\nu = 1765$ cm^{-1} (C=O), 760 cm^{-1} (P–Cl). ^{1}H NMR ($CDCl_3$): δ 4.20 (4H, t, $J = 8.1$ Hz), 4.55 (4H, t, $J = 8.1$ Hz) ppm.

4.3. *General procedure for the preparation of the naphylesters*

In a dry glass vial 10 mg of the carboxylic acid was dissolved in dry dichloromethane or acetonitrile (0.5 mL), then triethylamine (2 equiv. per COOH group) and 2-naphthol **2** (1.04 equiv. per COOH group) were added. For activation *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride **1** (1 equiv. per COOH group) was added and the resulting suspension was stirred at room temperature. After about 10 min the reagent had completely dissolved. The mixture was monitored via thin layer chromatography and allowed to react until no starting material could be detected (< 24 h).

After treatment with slightly basic water (0.5 mL) the organic layer was separated and dried over Na_2SO_4. The esters were further purified by preparative thin layer chromatography (TLC) and/or high performance liquid chromatography (HPLC).

4.3.1. trans-*(1*R*,2*R*)-Cyclohexane dicarboxylic acid dinaphthylester (*R,R*)-**5**

Prepared from enantiomerically pure 1*R*,2*R*-cyclohexane dicarboxylic acid (*R*,*R*)-**3** in dichloromethane as solvent. Purified by HPLC on a Eurospher 100 C18 column using an acetonitrile/water gradient and UV detection at 222 nm. ESI-MS *m*/*z*: 442 $[M+NH_4]^+$. EI-HRMS *m*/*z* for $C_{28}H_{24}O_4$ calcd 424.1675, found 424.1675. ^{1}H NMR ($CDCl_3$): δ 1.70 (4H, m), 2.0 (2H, brd, $J = 8.8$ Hz), 2.44 (2H, brd, $J = 12.9$ Hz), 3.08 (2H, m), 7.22 (2H, d, $J = 8.8$ Hz), 7.47 (4H, t, $J = 3.5$ Hz), 7.55 (2H, s), 7.77 (2H, d, $J = 8.8$ Hz), 7.85 (4H, d, $J = 8.8$ Hz) ppm.

4.3.2. trans-*(1*S*,2*S*)-Cyclohexane dicarboxylic acid dinaphthylester (*S,S*)-**5**

Prepared from racemic *trans*-cyclohexane-1,2-dicarboxylic acid. Purification by HPLC on a Eurospher 100 C18 column using an acetonitrile/water gradient and UV detection at 222 nm. The enantiomeric separation of the chromophoric derivatives was achieved on a Ceramospher Chiral RU-1 column at 50°C with 100% methanol. Assignment of the enantiomers was done according to their elution order by comparison with (*R*,*R*)-**5**. ESI-MS *m*/*z*: 442 $[M+NH_4]^+$. EI-HRMS *m*/*z* for $C_{28}H_{24}O_4$ calcd 424.1675, found 424.1671. ^{1}H NMR ($CDCl_3$): δ 1.70 (4H, m), 2.0 (2H, brd, $J = 8.8$ Hz), 2.42 (2H, brd, $J = 12.9$ Hz), 3.08 (2H, m), 7.22 (2H, d, $J = 8.8$ Hz), 7.47 (4H, t, $J = 3.5$ Hz), 7.55 (2H, s), 7.79 (2H, d, $J = 8.8$ Hz), 7.87 (4H, d, $J = 8.8$ Hz) ppm.

4.3.3. (S)-(−)-Malic acid dinaphthylester (S)-6

Reaction was performed in acetonitrile as solvent. Excess of 2-naphthol was removed by preparative TLC [silica gel, chloroform:methanol (14:2)] and the product was further purified by HPLC (Eurospher 100 C18, acetonitrile/water, UV 222 nm). ESI-MS m/z: 404 $[M+NH_4]^+$. ^1H NMR ($CDCl_3$): δ 3.38 (2H, dd, $J=5.2/4.8$ Hz), 4.94 (1H, dd, $J=4.8$ Hz), 7.30 (2H, d, $J=8.8$ Hz), 7.50 (4H, t, $J=5.2$ Hz), 7.63 (2H, s), 7.81 (2H, d, $J=7.4$ Hz), 7.88 (4H, d, $J=8.8$ Hz) ppm.

4.3.4. (R)-(+)-Malic acid dinaphthylester (R)-6

Residual 2-naphthol was separated from the product by preparative TLC [silica gel, chloroform: methanol (14:2)] and further purification was achieved by HPLC (Eurospher 100 C18, acetonitrile/water, UV 222 nm). ESI-MS m/z: 404 $[M+NH_4]^+$. ^1H NMR ($CDCl_3$): δ 3.38 (2H, dd, $J=5.5/5.0$ Hz), 4.94 (1H, dd, $J=4.8$ Hz), 7.30 (2H, d, $J=8.8$ Hz), 7.50 (4H, t, $J=5.2$ Hz), 7.63 (2H, s), 7.81 (2H, d, $J=8.1$ Hz), 7.88 (4H, d, $J=8.8$ Hz) ppm.

4.3.5. Abietic acid naphthylester 8

The product was separated from residual 2-naphthol by preparative TLC on silica gel plates [diethyl ether:pentane (1:1)]. Further purification was by HPLC on a Eurospher 100 C18 column using an acetonitrile/water gradient and UV detection at 222 nm. EI-HRMS m/z for $C_{30}H_{36}O_2$ calcd 428.2715, found 428.2717. ^1H NMR ($CDCl_3$): δ 0.90 (3H, s), 1.02 (3H, d, $J=7.0$ Hz), 1.04 (3H, d, $J=6.6$ Hz), 1.42 (3H, s), 5.48 (1H, m), 5.82 (1H, s), 7.16 (1H, d, $J=8.8$ Hz), 7.45 (1H, t, $J=7.0$ Hz), 7.47 (1H, s), 7.49 (1H, t, $J=6.8$ Hz), 7.80 (1H, d, $J=8.6$ Hz), 7.84 (2H, d, $J=8.8$ Hz) ppm.

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