OPTIMIZED SYNTHESIS AND SOLID STATE INVESTIGATIONS ON THE DRUG CANDIDATE ENCENCILINE HYDROCHLORIDE

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This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – For the production of drug substances a robust, scalable process delivering the active pharmaceutical ingredient (API) in excellent chemical and polymorphic purity is required. For this purpose we developed a novel imidazole-mediated one-pot procedure for the preparation of encenicline hydrochloride monohydrate, which crystallizes directly from the reaction mixture as pure non-hygroscopic polymorph (Form I). Solid state studies revealed a series of additional new physical forms for which crystal structures have been determined by single crystal X-ray diffraction.

INTRODUCTION

EVP-5141, better known as encenicline (1), is a potent selective partial agonist at the human α7 receptor exhibiting co-agonistic activity by enhancing the response to the natural agonist acetylcholine (ACh) as well as its release in the cortex, hippocampus, and nucleus accumbens.1,2 Furthermore, the researchers demonstrated good brain penetration after oral administration and a memory enhancing effect in rats in...
These findings and evidence from literature resulted in clinical studies evaluating I as cognition enhancer in schizophrenia as well as Alzheimer's disease patients.

Patent literature discloses a two-step process for the preparation of I involving preparation of 7-chlorobenzo[b]thiophene-2-carboxylic acid 2 from 2,3-dichlorobenzaldehyde follow by amide bond formation with (R)-quinuclidin-3-amine dihydrochloride in the presence of Hünig's base (DIEA) and HATU as coupling agent. Purification by HPLC of the obtained residue and salt formation from dioxane/MeOH with hydrochloric acid provided I as hydrochloride in 65% yield. Other coupling agents used in the abovementioned patent disclosure are the systems HBTU/HOBt and EDC/HOBt. However, all these agents are rather expensive and require separation from the product in the course of an aqueous workup and/or chromatographic purification. Furthermore, it should be emphasized that bicyclooctanes bearing a nitrogen atom in the bridgehead-position, such as quinuclidine, and the related dibasic 1,4-diazabicyclo[2.2.2]octane (DABCO) are widely recognized for their preeminent basicity and nucleophilicity, which even allows access to chloromethyl-quinuclidinium salts just by using dichloromethane as simple reactant. The rigid and compact cage-like molecular architecture of such structures constitutes an unusually favorable characteristic, for it effectively relieves the steric hindrance substitution or coordination, which in tertiary aliphatic amines arises from the flexibility of the nitrogen-bonded alkyl groups. For example, the quinuclidine ring of potent 5-HT₃ receptor antagonists such as zacopride react with dichloromethane at room temperature to produce the corresponding chloromethyl-quaternary derivatives. Few others have also explored the formation of this type of originating from the abovementioned extraordinary reactivity features of the quinuclidinic nitrogen of cinchona alkaloids. Notably, these peculiarities came full circle, when the serendipitous discovery of N-fluoroquinuclidinium fluoride by Du-Boisson and Morton led to development of the bench stable, user-friendly ‘F⁺'-transfer agent Selectfluor™, based on cheap N-chloromethylated DABCONium chloride.
RESULTS AND DISCUSSION

Keeping in mind the pre-published knowledge mentioned above, we also were curious regarding the feasibility of simultaneous acylation and chloromethylation. Hence, we also explored a standard coupling protocol for the Schotten-Baumann reaction in the presence of dichloromethane as solvent. For this, by treatment of 2 with thionyl chloride in toluene, we prepared the acid chloride 3 which was then reacted with (R)-quinuclidin-3-amine dihydrochloride in dichloromethane, additionally using triethylamine (TEA) as an auxiliary base (A). Not unexpected, after work-up and purification we did not isolate our amine target product 1, but alkyl halide 4, derived from the anticipated additional quarternization reaction of 1 with dichloromethane. The structure of 4 could be unambiguously confirmed via standard analytical techniques, as well as by single crystal X-ray structure determination as shown in Figure 1.

Figure 1. Molecular structure of 4 with non-H atoms represented as thermal ellipsoids drawn at the 50% probability level and H atoms drawn as spheres of arbitrary size

For the intentional preparation of 1 a switch to pyridine as solvent and base followed by subsequent stirring with a mixture of water/acetone at pH 8 gave the desired product, however, in only 35% yield (B). Further treatment of the free base with hydrochloric acid in diethyl ether gave the desired hydrochloride salt 1-HCl in 68% yield for the salt formation step and 24% yield over all steps. Finally, we succeeded by using four equivalents imidazole in acetonitrile, which transforms 3 into the corresponding acylimidazole intermediate and concomitantly binds the hydrochloric acid formed (C). All three pathways A - C are shown in Scheme 1. Addition of one equivalent of water after completion of the reaction mediates crystallization of encenicline hydrochloride monohydrate Form I Y (1-HCl) from the reaction mixture in excellent chemical and polymorphic purity. Yields ranging between 75 and 78% were constantly reached, being above that reported in the literature (65%).

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Stoner et al. have reported an imidazole-mediated peptide bond formation starting from an acyl chloride for the HIV protease inhibitor lopinavir. However, in their case the crude product obtained by evaporation of the solvent was just used for the next step.

In order to get a glimpse of the scope of this methodology, we used the same protocol for the reaction of benzoyl chloride (5) with (R)-quinoclidin-3-amine dihydrochloride and 1-methylpiperidin-4-amine dihydrochloride as shown in Scheme 2. Both transformations smoothly provided the desired products 6 and 7, however, isolated yields (27 and 28%) of the crystalline materials were clearly lower, probably due to better solubility in acetonitrile, and thus would require further optimization work.

The crystals of form A, Enc-HCl · i-PrOH, Enc-HCl · i-BuOH, Enc-HCl · ace, Enc-HCl · DCM have the space group symmetry $P2_12_12_1$. The asymmetric unit contains one formula unit consisting of an
encenicline cation (Figure 2), a chloride anion and, in the case of a solvate, additionally one solvent molecule. A comparison of molecular packing arrangements with the program XPac\textsuperscript{17} confirmed that Enc-HCl·i-PrOH is isostructural with Enc-HCl·i-BuOH and that Enc-HCl·ace is isostructural with Enc-HCl·DCM (see Figure S1 of the Supporting Information).

The conformation of the encenicline cation can be characterized in terms of three torsion angles (see Figure 2). The cations of the four Enc-HCl solvates display nearly coplanar benzothiophene and acetamide fragments, resulting in a torsion angle S–C–C–N (t\textsubscript{1} in Figure 1) close to 180°. By contrast, the planes defined by these two fragments form an angle of 24.1° in the cation of form A, and similar values are also found in the recently reported Enc-HCl monohydrates I – III (see Figure 3).\textsuperscript{18}

The encenicline cation contains two NH groups (with atoms N13 and N16) which can served as H-bond donor groups. In the isostructural Enc-HCl·ace and Enc-HCl·DCM solvates as well as in Form A, the chloride anion is used to form an N16–H16···Cl–···H13–N13 bridge between two cation moieties that are related by a 2\textsubscript{1} symmetry operation along the respective a axis (Figure 4a, b). In each case, the H16···Cl bond [A: 2.15(3) Å] is significantly shorter than the H13···Cl interaction [A: 2.46(3) Å]. The same type of N16–H16···Cl–···H13–N13 bridge is also present in the desolvates I\textsubscript{D} – III\textsubscript{D} of encenicline monohydrates reported by Bobrovs et al.,\textsuperscript{18} but the H16···Cl (IID: 2.09 Å) and H13···Cl (IID: 2.89 Å) distances differ even more substantially in these structures (see Table S1 of the Supporting Information).

An analogous N16–H16···Cl–···H13–N13 bridge in the isostructural i-PrOH and i-BuOH solvates displays H16···Cl and H13···Cl bonds of approximately equal length [Enc-HCl·i-PrOH: 2.56(4) vs. 2.46(3) Å] and connects encenicline cations related by a translation along [100]. The relative elongation of H16···Cl in comparison to the other Enc-HCl structures coincides with the involvement of the corresponding NH group in a second H-bond interaction with the carbonyl group of another cation, i.e. N16–H16···O11 [Enc-HCl·i-PrOH: H16···O11 = 2.23(4) Å]. As a result, the encenicline cations and Cl\textsuperscript{−} anions of Enc-HCl·i-PrOH and Enc-HCl·i-BuOH are linked into an H-bonded layer structure parallel to the ab plane. An additional O···H···Cl interaction [Enc-HCl·i-PrOH: H···Cl = 2.27(3) Å] connects the respective solvent molecule with the chloride anion (Figure 4c).

Figure 2. Molecular structure of the encenicline cation and definition of the torsion angles $\tau_1$, $\tau_2$ and $\tau_3$.\textsuperscript{18}
Figure 3. Molecular conformation of the encenicline cation in various forms of Enc-HCl: form A, two pairs of isostructural solvates and three monohydrates I−III. The 7-chloro-1-benzothiophene fragment in the cation of A was used a template onto which the corresponding inflexible molecule fragment (drawn in balls and sticks style) of each other structures was least-squares fitted.

Figure 4. H-Bonded structures based on N16–H16⋯Cl−⋯H13−N13 interactions in solid forms of Enc-HCl: H-bonded chains in a) form A, b) Enc-HCl · ace and c) an H-bonded chain in Enc-HCl · i-PrOH with O−H⋯Cl− bonded solvent molecule; additional N16–H16⋯O11 interactions between adjacent chains result in a H-bonded layer structure (not shown).
Table 1. Crystal data and structure refinement parameters for Enc-HCl form A, Enc-HCl solvates and 4

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EXPERIMENTAL

Reagents and solvents were purchased from Sigma-Aldrich. NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer. IR spectra were obtained with a Bruker ALPHA Platinum FT-ATR instrument. High resolution mass spectra were measured with a Finnigan MAT 95 mass spectrometer. Elemental analyses have been conducted at the Laboratory for Microanalysis Services, Technical University of Vienna, Währingerstr. 42, 1090 Vienna, Austria (https://chemie.univie.ac.at/en/services/service-facilities/lab-for-microanalysis-services).

Single crystal X-ray determination

Intensity data for A and the Enc-HCl solvates were collected at 173 K on an Oxford Diffraction Gemini-R Ultra diffractometer operated by the CrysAlisPro software, using Cu radiation (λ = 1.54184 Å) or, in the case of Enc-HCl · i-PrOH, Mo radiation (λ = 0.71073 Å). Intensity data for 4 were collected at 213 K on a Bruker APEX-II CCD diffractometer (Mo radiation). The data were corrected for absorption effects, and the structures were solved with direct methods procedures implemented in SIR2002 or SHELXT.
and full-matrix least-squares refinements on $F^2$ using SHELXL-2014 were carried out.\textsuperscript{22} Non-hydrogen atoms were located in difference maps and refined anisotropically. The hydrogen atoms bonded to C atoms were fixed in idealized positions and their thermal displacement parameters of were set to $1.2U_{eq}$ (or $1.5U_{eq}$ or in the case of Me groups) of the parent C atom. All H atoms bonded to N or O atoms were located in difference maps and refined using distance restraints, whilst their thermal displacement parameters were refined freely. The absolute structures were determined on the basis of anomalous-dispersion effects in diffraction measurements on the crystal.

**(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate** (1) (from 7-chlorobenzo[b]thiophene-2-carboxylic acid chloride)

To a stirred solution of 7-chlorobenzo[b]thiophene-2-carboxylic acid chloride (5.40 g, 23.4 mmol) in MeCN (100 mL) imidazole (3.18 g, 46.7 mmol) was added. Formation of a sticky precipitate was observed. Then, (R)-quinuclidin-3-amine dihydrochloride (4.75 g, 23.8 mmol) and imidazole (3.25 g, 47.7 mmol) in MeCN (50.0 mL) were added. The reaction mixture was then stirred at room temperature for 24 h. Next, water (0.42 g, 23.3 mmol) was added dropwise. Stirring was continued for 1 h. A crystalline product formed, was separated by filtration and then washed with MeCN (10 mL). Drying of the residue obtained in vacuo provided 6.84 g (78%) of crystalline encenicline hydrochloride monohydrate Form I. The identity of the product with (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate was confirmed by $^1$H NMR in DMSO-$d_6$. The NMR data were in agreement with known literature or patent data.\textsuperscript{8} $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.75 (m, 1 H), 1.92 (m, 2 H), 2.02-2.28 (m, 2 H), 3.10-3.77 (m, 6 H), 4.33 (m, 1 H), 7.52 (dd, 1 H), 7.63 (m, 1 H), 7.98 (m, 1 H), 8.43 (s, 1 H), 9.17 (d, 1 H), 10.03 (s, 1 H, br) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 19.9, 25.7, 25.9, 46.4, 46.9, 47.6, 53.5, 124.4, 125.6, 126.6, 138.9, 140.7, 141.1, 161.6 ppm. HRMS (ESI$^+$): M+H$^+$ for C$_{16}$H$_{17}$ClN$_2$OS calcd. 321.0823; found 321.0817. Anal. Calcd for C$_{16}$H$_{20}$Cl$_2$N$_2$O$_2$S: C, 51.21; H, 5.37; N, 7.46; S, 8.55. Found: C, 50.57; H, 5.29; N, 7.38; S, 8.36.

**(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate** (1) (from 7-chlorobenzo[b]thiophene-2-carboxylic acid - one-pot procedure)

To 7-chlorobenzo[b]thiophene-2-carboxylic acid (5.00 g, 23.5 mmol) in toluene (3.00 mL) thionyl chloride (15.0 mL, 207 mmol) was added and the mixture stirred at 85 °C for 4 h. The clear solution was cooled down to room temperature and toluene together with volatile remains of the reagent was removed in vacuo. To the residue were added 5 mL of toluene and the solvent was again removed in vacuo. Then MeCN (100 mL) and imidazole (3.18 g, 46.7 mmol) were added to the crude
7-chlorobenzo[b]thiophene-2-carboxylic acid chloride (5.40 g, 23.4 mmol). Formation of a sticky precipitate was observed. Then, (R)-quinuclidin-3-amine dihydrochloride (4.75 g, 23.8 mmol), imidazole (3.25 g, 47.7 mmol) in MeCN (50 mL) were added. The reaction mixture was then stirred at room temperature for 24 h. Next, water (0.42 g, 23.3 mmol) was added dropwise. Stirring was continued for 1 h. The crystalline product was separated by filtration and washed with MeCN (10 mL). Drying of the obtained residue in vacuo provided crystalline encenicline hydrochloride monohydrate Form I.

(R)-7-Chloro-N-1-chloromethyl-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide chloride (4)
A solution of 7-chlorobenzo[b]thiophene-2-carboxylic acid chloride (1.00 g, 4.3 mmol) in CH₂Cl₂ (10.0 mL) was added in a dropwise manner to a solution of (R)-quinuclidin-3-amine dihydrochloride (0.86 g, 4.30 mmol) in triethylamine (1.80 mL, 13.0 mmol). The mixture was stirred at 22 °C for 48 h and a brown precipitate formed. The crude product was removed by filtration, washed with CH₂Cl₂ (2 x 2 mL) and dried in high vacuum (2.10 g). This material was stirred with saturated aqueous sodium bicarbonate solution (10.0 mL) and then 1N aqueous sodium hydroxide (12 mL). A clear solution resulted upon the addition of water (20.0 mL). CH₂Cl₂ (30.0 mL) was added and the pH was adjusted to 7 with diluted hydrochloric acid and sodium hydrogen carbonate and then the mixture was stirred for 30 min. An insoluble precipitate formed and was removed by filtration. It was washed sparingly with water and dried to obtain 0.21 g of compound (4) in 12% yield. ¹H-NMR (300 MHz, DMSO-d₆): δ 1.92 (m, 1 H), 2.06 (m, 2 H), 2.27 – 3.32 (m, 2 H), 3.50 – 3.72 (m, 5 H), 3.96 (t, 1 H), 4.42 (bd, 1 H), 5.31 (s, 2 H, N-CH₂-Cl), 7.52 (t, J = 7.8 Hz, 1 H), 7.63 (d, J = 7.6 Hz, 1 H), 7.97 (d, J = 7.9 Hz, 1 H), 8.44 – 8.46 (m, 1 H), 9.31 (m, 1 H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 18.18, 21.86, 24.47, 45.60, 52.79, 52.88, 57.45, 67.79, 124.37, 125.96, 126.54, 126.80, 126.97, 139.00, 139.97, 140.51, 161.64 ppm. IR (neat): ν 3236 (w), 2997 (w), 2977 (w), 1641 (s), 1534 (s), 1455 (m), 1320 (m), 1216 (m), 1091 (m), 898 (m), 789 (s), 711 (s), 602 (m) cm⁻¹. HRMS (ESI⁺): M+H⁺ for C₁₇H₁₉Cl₂N₂O₅S calcd. 369.0595; found 369.0590.

Single crystals of (R)-7-chloro-N-1-chloromethyl-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide chloride (4)
(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (500 mg) was dissolved in a mixture of CH₂Cl₂ (10 mL) and 1M aqueous sodium hydroxide (10.0 mL). The organic layer was removed and the aqueous layer extracted with CH₂Cl₂ twice (5.00 mL each). The combined organic extracts were dried over anhydrous sodium sulfate. Aliquots of the resulting CH₂Cl₂ solution of the free base were stored in glass vials at room temperature for three days while crystals grew. The crystalline material was analyzed via NMR spectroscopy and found to give identical spectra as compound
Single crystals of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride form A

(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate form I was annealed on a Kofler hot bench at 250 °C for 3 h in a sublimation ring whereat single crystals of anhydrous (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride form A were formed.

Single crystals of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride isopropanol solvate

(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate form I (100 mg) was suspended in iPrOH (0.50 mL) and heated to reflux temperature. After separation of the solution from the remaining solid by filtration the hot solution was allowed to cool to room temperature whereat single crystals appear within 24 h.

Single crystals of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride isobutanol solvate

(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate form I (50.0 mg) was dissolved in iBuOH (5.00 mL) and heated to a jacket temperature of 120 °C. The water in the crystal lattice was removed by azeotrope distillation. After 3 h the solution was allowed to cool and single crystals could be isolated at room temperature.

Single crystals of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride acetone solvate

(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate form I (50.0 mg) was suspended in acetone (2.00 mL) and heated to reflux temperature. The resulting hot clear solution was filtrated and the solvent was allowed to evaporate through a cannula.

Single crystals of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride dichloromethane solvate
(R)-7-Chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate form I (50.0 mg) was suspended in CH$_2$Cl$_2$ (2.00 mL) and heated to reflux temperature. The resulting hot clear solution was filtrated and the solvent was allowed to evaporate through a cannula.

(R)-N-(Quinuclidin-3-yl)benzamide hydrochloride (6) (from benzenecarboxylic acid chloride - one-pot)
To a solution of imidazole (0.68 g, 10.0 mmol) in MeCN (10.0 mL) benzoyl chloride (0.67 g, 4.80 mmol) in MeCN (1 mL) was slowly added at room temperature. Formation of a sticky precipitate was observed. Then, solid (R)-quinuclidin-3-amine dihydrochloride (1.00 g, 5.00 mmol) and solid imidazole (0.68 g, 10.0 mmol) were added. The reaction mixture was then stirred at room temperature until completion. Then, water (0.09 g, 5.00 mmol) was added dropwise. Stirring was continued for 3 h. The crystalline product was separated by filtration and washed with Et$_2$O (5.00 mL). Drying of the residue obtained in vacuo provided 370 mg (27%) pure (R)-N-(quinuclidin-3-yl)benzamide hydrochloride as a crystalline solid. Mp 248 °C (upon a phase transition at 217-220 °C), Mp 245 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.69 (m, 1 H), 1.89 (m, 2 H), 2.10 (m, 1 H), 2.17 (m, 1 H), 3.17 (m, 3 H), 3.38 (m, 2 H), 3.58 (m, 1 H), 4.33 (m, 1 H), 7.46 (t, $J$ = 7.3 Hz, 2 H), 7.54 (t, $J$ = 7.2 Hz, 1 H), 7.96 (d, $J$ = 7.0 Hz, 2 H), 8.84 (d, $J$ = 6.1 Hz, 1 H), 10.8 (br, 1 H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 17.2, 21.5, 24.5, 44.7, 44.9, 45.3, 50.2, 127.6 (2C), 128.2 (2C), 131.4, 133.9, 166.7 ppm. IR (neat): $\nu$ 3230 (w), 2916 (w), 2632 (w), 2538 (m), 2479 (m), 1651 (s), 1521 (s), 1486 (m), 1311 (m), 707 (s), 619 (s) cm$^{-1}$. HRMS (ESI$^+$): M+H$^+$ for C$_{14}$H$_{18}$N$_2$O calcd. 231.1492; found 231.1488. Anal. Calcd for C$_{14}$H$_{21}$ClN$_2$O: C, 59.05; H, 7.43; N, 9.84. Found: C, 59.13; H, 7.04; N, 10.12.

N-(1-Methyl-4-piperidinyl)benzamide hydrochloride (7) (from benzenecarboxylic acid chloride - one-pot)
To a solution of imidazole (0.36 g, 5.30 mmol) in MeCN (5.00 mL) benzoyl chloride (0.36 g, 2.50 mmol) in MeCN (1.00 mL) was slowly added at room temperature. Formation of a sticky precipitate was observed. Then, solid 4-amino-1-methylpiperidine dihydrochloride (0.50 g, 2.70 mmol) and solid imidazole (0.36 g, 5.30 mmol) were added. The reaction mixture was then stirred at room temperature until completion. Then, water (0.05 g, 5.00 mmol) was added dropwise. Stirring was continued for 3 h. The crystalline product was separated by filtration and washed with Et$_2$O (5.00 mL). Drying of the residue obtained in vacuo provided 190 mg (28%) N-(1-methyl-4-piperidinyl)benzamide hydrochloride as a crystalline solid. Mp 213-214 °C (upon a phase transition at 205 °C), Mp 207-209 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.97 (m, 4 H), 2.69 (s, 3 H), 3.37 (m, 4 H), 4.02 (m, 1 H), 7.44 (t, $J$ = 7.2 Hz, 2 H), 7.52 (t, $J$ = 7.2 Hz, 1 H), 7.89 (d, $J$ = 7.2 Hz, 1 H), 8.60 (d, $J$ = 6.4 Hz, 1 H), 11.0 (br, 1 H) ppm. $^{13}$C
NMR (75 MHz, DMSO-\textit{d}_6): \delta 28.6, 42.4, 44.4, 52.4, 127.4, 128.1, 131.2, 134.2, 165.8 ppm. IR (neat): \nu 3243 (w), 3055 (w), 2945 (w), 2455 (m), 1628 (s), 1537 (s), 1467 (m), 1311 (m), 960 (m), 696 (s) cm\textsuperscript{-1}.

HRMS (ESI\textsuperscript{+}): M+H\textsuperscript{+} for C\textsubscript{13}H\textsubscript{18}N\textsubscript{2}O calcd. 219.1492; found 219.1488.

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REFERENCES


