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Development of a Novel Process for the Kilogram Scale Synthesis of Spiro[1H-pyrido[2,3-d][1,3]oxazine-4,4'-piperidine]-2-one

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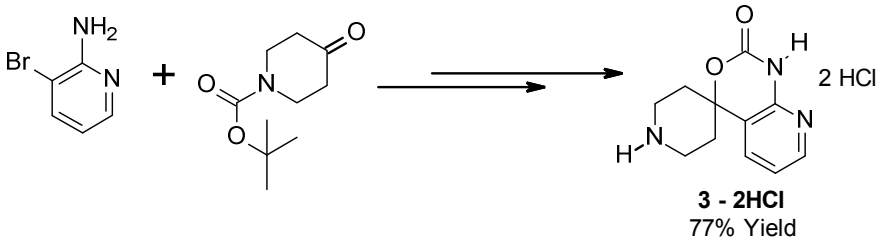
TOC figure



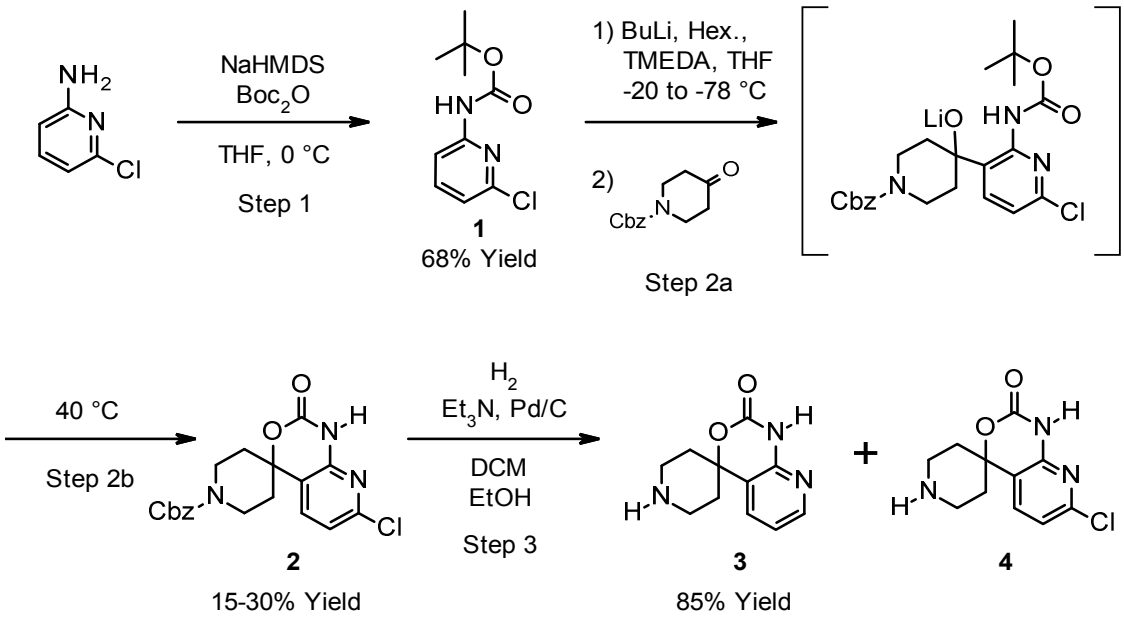
3 - 2HCl
77% Yield

ABSTRACT Spiro[1H-pyrido[2,3-d][1,3]oxazine-4,4'-piperidine]-2-one (**3**) is a key building block in many biologically active compounds. The synthesis of this compound, as reported in the literature, is low yielding. We have discovered and developed a robust, high-yielding process to generate **3** as a bis-HCl salt using alternative starting materials and reaction conditions. The developed process was successfully demonstrated on kilogram scale. A two-batch kilo lab campaign generated the bis-HCl salt of **3** in > 99 HPLC area percent purity and 77% overall yield.

INTRODUCTION Spiro[1H-pyrido[2,3-d][1,3]oxazine-4,4'-piperidine]-2-one (**3**) is an important fragment in various CGRP receptor antagonists,[1] TRPA1 modulators,[2] muscarinic acetylcholine receptor agonists,[3] β3-adrenergic receptor agonists,[4] C-C chemokine receptor-8 antagonists,[5] and MCP-1 antagonists.[6]

Several patents describe the synthesis of **3**.[1n-p, r-u, 3b] In all cases, the synthetic route is identical to that shown in Scheme 1. 2-Amino-6-chloropyridine is protected as its Boc derivative through the use of sodium hexamethyl disilazide (NaHMDS) and di-tert-butyl dicarbonate (Boc_2O). After directed ortho-metalation with butyl lithium under cryogenic conditions, benzyl 4-oxopiperidine-1-carboxylate is added to the resulting anion. Intramolecular cyclization of the intermediate followed by hydrogenation to deprotect the CBZ group and remove the chlorine affords **3** in a 17% overall yield over 3 steps.

Scheme 1: Literature Synthesis of **3**



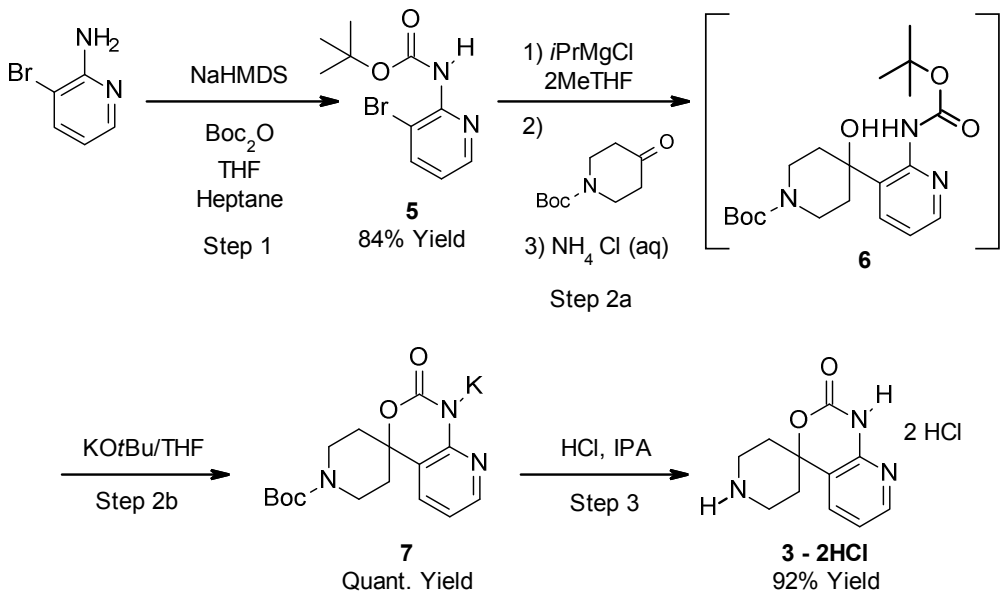
ROUTE DEVELOPMENT For a recent project, kilogram quantities of **3** were required. The published route has several issues that were necessary to address before scaling this process. According to the literature,[1k] ortho metalation and cyclization attempts without the chlorine group present were unsuccessful. The use of the chloro group, however, necessitated its removal via hydrogenation, which can be hazardous on large scale. Additionally, the chloro was not completely removed during the hydrogenation step, and chromatography was required to separate the chlorinated product **4** from **3**. Step 2a and 2b were also problematic from a scale-up perspective. This overall transformation was very low yielding, had poor reproducibility, and required cryogenic conditions.

In order to circumvent these issues, an alternative route was developed. Utilization of 3-bromo-2-aminopyridine as the starting point for the synthesis provided two advantages. This readily available commercial starting material, which is comparable in price to 2-amino-6-chloropyridine, allowed directed anion formation while avoiding the need to later remove the chlorine. In addition, use of 1-Boc-4-piperidone in place of 1-Cbz-4-piperidone allowed the final hydrogenation conditions to be avoided completely.

Preparation of the Boc protected 3-bromo-2-aminopyridine was straight forward, but installation of the spirocycle remained challenging. Though a CO_2 quench of the lithium anion showed that no 3-bromo-2-aminopyridine remained, LCMS showed that the major product after addition of 1-Boc-4-piperidone was 2-aminopyridine. It was hypothesized based on this data that the lithium species was not stable even at -40 °C.

Generation of the anion with iso-propyl magnesium chloride (iPrMgCl) provided a stable magnesium species at 0-15 °C and led to an effective addition of this species to 1-Boc-4-piperidone. However, the final ring closure to form the spirocycle was not viable using these conditions. It was hypothesized that the magnesium in the intermediate was impeding the ring closure, and in fact, when the intermediate was quenched to remove the magnesium and subjected to potassium *t*-butoxide (KOtBu), the ring closure progressed smoothly. The product was isolated as a potassium salt by direct filtration of the reaction mixture. After acidic Boc deprotection using HCl, **3 - 2HCl** was isolated via direct filtration in ~ 77% yield over three steps from 3-bromo-2-aminopyridine. This yield is nearly 4 times the yield of the original literature route. The optimized synthesis is shown in Scheme 2.

Scheme 2. Modified Synthesis of **3 - 2HCl**



PROCESS DEVELOPMENT With proof of concept that the new spirocycle formation conditions were superior, the focus was shifted to optimizing the process for scale. The Boc protection of 3-bromo-2-amino pyridine suffered from several process issues. It had emulsion issues in the workup, suffered from stability issues in the final solvent switch procedure, and was generally volume inefficient.

The initial aqueous quench of the reaction resulted in a cloudy emulsion, making separation of the layers difficult. This was found to be directly related to the pH of the mixture after the HCl quench. The emulsion was successfully eliminated by adjusting the mixture, after the water quench, to pH 7-7.4 using 6N HCl and then adding a dilute 20 wt% solution of ammonium chloride (final pH 6.5-6.9). This use of ammonium chloride not only broke up the residual rag layer, but also helped to ensure that a slight overcharge at the end of the pH adjustment didn't drive the pH low enough to cause deprotection of the Boc group.

The lab scale isolation was done by drying the organic layer over sodium sulfate followed by concentration to a residue. Trituration of the residue in EtOH at 70 °C gave filterable solids. To scale up this procedure it was adjusted to a solvent switch in which the water was azeotroped off

and then anhydrous ethanol was used portion wise in a azeotropic distillation to reduce the amount of residual 2-MeTHF to minimize losses. Unfortunately, the elevated temperatures required to make the distillation times viable on scale (80 °C, 100 mbar) caused the formation of significant impurities. An ethyl carbamate impurity began forming at 45-50 °C. The long heat times during the concentration led to the production of up to 15% of the ethyl carbamate impurity over 1 hour in ethanol. Also, at elevated temperatures the Boc group was unstable. These impurities tracked throughout the subsequent steps and were not rejected in the final isolation of **3 - 2HCl**.

To eliminate these impurities the solvent system was optimized to reduce the temperature in the solvent switch. The reaction solvent was changed from 2-MeTHF to the lower boiling THF. In addition, alternative anti-solvents which couldn't react with the product were evaluated. EtOAc and heptane looked promising, but EtOAc generated tacky final solids which retained HMDS that tracked through to **3 - 2HCl**. Heptane proved to be ideal, and the use of THF and heptane prevented the formation of the ethyl carbamate impurity and allowed the distillation to proceed at 40 °C, thereby eliminating the deprotection issues. Solids were isolated from this precipitation in > 99 LCAP (HPLC Area%) with 10% losses.

Finally, early lab experiments were run at a volume of 25-30 times of the starting material, too inefficient for an effective scale-up campaign. 1N NaHMDS was the source of a significant portion of this volume. Making a more concentrated NaHMDS solution in house allowed for use of a 2N NaHMDS solution. Just after the scale-up detailed in this paper, a commercial supplier of bulk 2N NaHMDS was identified and this reagent was shown to be equivalent to the material made in house. Use of this material in future scale-up would eliminate the need to manipulate solid NaHMDS.

The volumes were further reduced by adding solid 3-bromo-2-aminopyridine directly to the 2M NaHMDS/THF solution and then adding Boc_2O in 0.5 volumes of THF rather than the original 15 volumes. Evaluation of the exotherms for these two additions informed the decision to handle them differently. The addition of 3-bromo-2-aminopyridine generated 32.5 kJ/mol which, given the reaction mass, was equivalent to a modest ~ 8 °C adiabatic temperature rise. It was therefore deemed acceptable to add the 3-bromo-2-aminopyridine in one portion. However, addition of Boc_2O generated 289 kJ/mol or ~ 61 °C adiabatic temperature rise. This was a significant thermal event and prompted the use of a solution of Boc_2O in THF to allow the addition rate to assist in controlling the batch temperature. Overall, the changes to the NaHMDS concentration, and to the additions of the other two reagents led to a more acceptable 10-12 total volumes. This procedure was successfully scaled up in two batches in the kilo lab to generate 2.3 kg of **5** in > 99 LCAP.

The spirocycle formation also required some optimization for scale-up. It was observed that when the equivalents of iPrMgCl was minimized, the reaction was particularly sensitive to water in the solvents. In addition, the aqueous quench of the intermediate contained solids, and the final product slurry was very thick.

During the development of this step, the charge of iPrMgCl was optimized to 2.2 equivalents. With this charge set, it was found that THF with 200-500 ppm of water caused quenching of the organometallic. This promoted the formation of high levels of des-bromo impurity which tracked through to **3 - 2HCl**. For the kilo lab scale which is detailed in this paper, the purchase of anhydrous THF was still viable, but for further scale up it is difficult and expensive to procure THF this dry. To alleviate this issue, experiments were done to show that increasing the iPrMgCl charge would overcome this sensitivity. It was determined that after charging 2.2

equivalents, an additional charge based on the HPLC area percent of remaining 3-bromo-2-aminopyridine could be used to complete the metal halogen exchange. It was observed that excess iPrMgCl led to poor conversion to the desired intermediate. This is presumably due to deprotonation of 1-Boc-4-piperdone which alters its primary electrophilic functional group.

The quench of the magnesium salt of the intermediate was initially done with 1N HCl and saturated NH_4Cl. This combination was used in an attempt to mitigate the likelihood of dropping the pH too low and removing the Boc group used in the spirocycle formation. Unfortunately, this quench led to solids throughout both layers which only dissolved after overnight age. The pH continued to change throughout the dissolution of these solids making the pH ~ 7 target difficult to hit. Optimization led to a 50% saturated NH_4Cl quench which dissolved all solids rapidly and allowed effective pH adjustment.

The spirocycle formation was completed by charging KOtBu in THF to the organic layer after the NH_4Cl quench. This ring closure was not sensitive to residual water in the organic layer, and the product could be isolated by direct filtration with < 1% losses after it precipitated as the potassium salt. However, the slurry that developed during ring closure was particularly thick and there were concerns with how the slurry would scale. The simple addition of 5 volumes of 2-MeTHF allowed this slurry to mix, transfer, and filter well upon scale-up. With this procedure in place, two batches were executed successfully in the kilo labs to give 2.6 kg in > 99 LCAP.

Early development work on the Boc deprotection focused on using anhydrous HCl in various organic solvents. This was initially attractive due to the direct isolation of the bis-HCl salt from the reaction mixture. However, after screening various mixtures of MeOH, EtOH, and IPA with anhydrous HCl it was evident that the slurries that were generated were too thick to scale effectively. To overcome this, 12N HCl (aq) was added to a slurry of **7** in IPA to effect the

deprotection and allow for the slurry's properties to be amenable to scale-up. The IPA still afforded a direct isolation by filtration with ≤ 5% losses, but the small amount of water allowed the slurry to stir, transfer, and filter easily. This conversion to aqueous HCl had the added benefit of being more cost effective.

The HCl charge was initially 15 equivalents. Attempts to optimize this charge showed 7 equivalents of 12N HCl caused the reaction to stall at about 45-50 % completion. Based on this result and the 12-18 hour age times required when 15 equivalents of HCl were used, it was determined that the initial charge was appropriate.

We used this deprotection to successfully execute two batches in the kilo labs to provide **3 - 2HCl** (1.6 kg of free base 3 present) in > 99 LCAP. The weight percent of free base **3** in the solids was typically 50-60% by HPLC. When the mass was corrected for this weight percent the yield over the last two steps was 85-90%. It was hypothesized that the weight percent was due not only to the bis-HCl salt, but also to 1 equivalent of KCl which would have originated from **7**. To evaluate this hypothesis, elemental analysis was done on **3 - 2HCl**. (Table 1) The results support the presence of two equivalents of HCl and one equivalent of KCl. These inorganics were acceptable for the subsequent chemistry, and so were left as part of the final isolated solids. However, if necessary, it is likely that an aqueous workup with pH adjustment could be used to provide inorganic-free neutral **3**.

Table 1. Elemental Analysis of **3 - 2HCl**

Element	Expected wt%	Measured wt%
C	36	33
H	4	4
N	12	10

Cl	29	26
K	11	12

CONCLUSION

A novel synthesis of spiro[1H-pyrido[2,3-d][1,3]oxazine-4,4'-piperidine]-2-one (**3**) as a bis-HCl salt has been discovered and optimized for scale-up. The robust and simple synthesis has allowed generation of 1.6 kg of **3** as a bis-HCl salt in 77% overall yield.

EXPERIMENTAL SECTION

All commercially available chemicals and solvents were used as received without any further purification. The NMR spectra were acquired on a Bruker Avance spectrometer at frequencies of 400 and 500 MHz, respectively, in the solvents indicated. HPLC spectra were collected on an Agilent 1100 or 1200 series instrument. LCAP is defined as the area percent purity as determined by HPLC

Synthesis of tert-butyl N-(3-bromo-2-pyridyl)carbamate (**5**)

Reagent grade THF (8.6 L, 10 vol) was charged to a 50 L glass reactor under a nitrogen atmosphere. Using an charging bag which docked to the reactor head, solid NaHMDS (2.01 kg, 10.94 mol, 2.2 equiv) was charged to the reactor and the batch was cooled to 0-5 °C. Solid 2-bromo-3-aminopyridine (0.86 kg, 4.97 mol, 1.0 equiv) was introduced in portions under inert conditions while maintaining a batch temperature below 15 °C. The charging port was rinsed with fresh THF (0.43 L, 0.5 vol) and the batch was agitated for 10 minutes at 5-10 °C. A prepared solution of Boc_2O (1.41 kg, 6.46 mol, 1.3 equiv) in THF (0.43 L, 0.5 vol) was added using dose control to maintain a batch temperature below 15 °C. The batch was agitated for at least 1 hour at 15 ± 5 °C and was monitored by HPLC. The batch was cooled to -5 to 0 °C and

using dose control, water (3.4 L, 4 vol) was added to the reaction while the batch temperature was maintained below 20 °C. The batch was then pH adjusted to pH 7-7.5 with 6N hydrochloric acid (2.9 L, 3.4 vol, as needed) using an in-line calibrated pH meter to monitor the adjustment. After the batch was agitated for 10 minutes at 15 °C, an aqueous solution of saturated ammonium chloride solution (3.4 L, 4 vol) was added below 25 °C and stirred for 5-10 minutes. The final pH range was between 6.5-7.1. The layers were separated over 15-30 minutes and the lower aqueous layer was drained to a waste drum. To remove minor particulates, a 5 micron cartridge filter was used to filter the organic solution into a drum. The solution was distilled on a rotary evaporator at 40-45 °C bath temperature (80-140 mBar) to the minimum stir volume, and then *n*-heptane (4.0 L, 4.6 vol) was introduced. The mixture was transferred to a reactor and *n*-heptane (13.2 L, 15.3 vol) was added. The mixture was stirred for 15 hours at ambient temperature, and then cooled to 0-5 °C. The product was collected on an Aurora filter and the cake was washed with *n*-heptane (1.7 L, 2 vol), and dried under vacuum. The dried cake was 1.2 kg of tan solids at > 99 LCAP, and 95.3 wt%. After applying the weight percent 1.14 kg of **5** was present which was an 84% yield. ^{1}H NMR (DMSO)-d_6 δ 9.32 (s,1H), 8.03 (dd, J =1.77, 4.54 Hz, 1H), 8.10 (dd, J = 1.77 Hz, 8.03 Hz, 1 H), 7.19 (dd, J = 4.54 Hz, 8.03 Hz, 1 H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.37, 81.79, 109.51, 119.88, 141.14, 147.54, 148.85, 150.76. HRMS-ESI (m/z): $[M+Na]^+$ Calcd for $C_{10}H_{13}BrN_2NaO_2$: 295.0053; found: 295.0081.

Synthesis of (1-tert-butoxycarbonyl-2'-oxo-spiro[piperidine-4,4'-pyrido[2,3-d][1,3]oxazine]-1'-yl)potassium (**7**)

Tert-butyl N-(3-bromo-2-pyridyl)carbamate, **5**, (1.09 kg, 3.99 mol, 1.0 equiv) was charged to a 50 L reactor and diluted with anhydrous 2-MeTHF (8.3L, 7.5 vol). The mixture was cooled to 0-

5 °C and 2M iPrMgCl in THF (4.56 kg, 9.35 mol, 1.2 equiv) was dosed while maintaining a batch temperature below 15 °C. The resultant solution was agitated for 10-15 minutes at 15 °C and an aliquot was quenched into water to monitor anion formation by HPLC.

A prepared solution of 1-Boc-4-piperidone (0.97 kg, 4.88 mol, 1.2 equiv) in 2-MeTHF (3.3 L, 3 vol) was dosed below 15 °C. The mixture was stirred for 30 minutes and monitored by HPLC for reaction completion.

Upon reaction completion, 20 wt% NH_4Cl solution (13 L, 11.8 vol,) was slowly added while maintaining a batch temperature below 20 °C. The solution was agitated for about 30 minutes, and then the layers were settled over 15 minutes. The bottom aqueous layer was removed to waste. The top organic solution was filtered through a 5 micron cartridge filter and the clarified solution was charged to a reactor and cooled to 0-5 °C. A 1M KOtBu solution in THF (5.5 kg, 6.1 mol, 1.5 equiv) was dosed while maintaining a batch temperature below 20 °C. Additional 2-MeTHF (4.8 kg, 5 vol) was added to aid in mobility of the resultant precipitate. The slurry was agitated over 15 hours at 20 °C and **7** was collected on an Aurora filter, and dried under vacuum. After drying to < 10% volatiles by LOD, 1.78 kg of solids were isolated at > 99 LCAP. These solids contained 1.43 kg (quantitative yield by HPLC assay) of (1-tert-butoxycarbonyl-2'-oxo-spiro[piperidine-4,4'-pyrido[2,3-d][1,3]oxazine]-1'-yl)potassium.

^{1}H NMR (DMSO)-d_6 δ 7.85 (dd, 1.80, 1H), 7.13 (dd, J = 1.80, 7.30 Hz, 1H), 6.41 (dd, J = 4.78, 7.30 Hz, 1H), 3.9 (m, 2 H), 3.12 (s, 2H), 1.75 (d, J = 12.01, 2 H), 1.64 (dt, J = 4.77, 12.01, 2H, 1.41 (s, 9 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.59, 35.57, 38.94 (bm), 80.17, 80.66, 119.46, 120.35, 132.32, 148.25, 148.30, 150.60, 154.79. HRMS-ESI (m/z): $[M+H]^+$ Calcd for $C_{16}H_{22}N_3O_4$: 319.1532; found: 319.1528.

Synthesis of spiro[1H-pyrido[2,3-d][1,3]oxazine-4,4'-piperidine]-2-one bis-HCl (**3 - 2HCl**)

(1-tert-butoxycarbonyl-2'-oxo-spiro[piperidine-4,4'-pyrido[2,3-d][1,3]oxazine]-1'-yl)potassium, **7**, (1.65 kg; adjusted wt: 1.27 kg, 3.98 mol) was charged to a reactor. Isopropyl alcohol (10 kg, 12.7 L, 10 vol) was charged and the mixture was cooled to -5 to 0 °C. Hydrochloric acid (12N, 6 L, 18 mol eq) was dosed while maintaining a batch temperature below 15 °C.

The reaction was agitated over 12-18 hours at 15-20 °C. The process was monitored by HPLC analysis for conversion. Upon complete conversion, the mixture was cooled to 0-5 °C, filtered and dried under vacuum at ambient temperature to yield 1.38 kg of solids containing **3** as a bis-HCl salt with 1 equivalent of KCl (> 99 A%, 59.2 wt%, contains 0.816 kg **3** free base, 91.5% yield).

1H NMR (DMSO)-d_6 δ 10.9 (s, 1H), 9.56 (bs, 1 H), 9.34 (bs, 1 H), 8.25 (dd, J = 1.59, J = 4.97 Hz, 1 H), 7.62 (dd, J = 1.59, J = 7.56 Hz, 1 H), 7.15 (dd, J = 4.97, J = 7.56 Hz, 1 H), 3.3 (d, J = 12.00, 2 H), 3.1 (q, J = 12.01, 2 H), 2.44 (dt, J = 4.72, J = 14.7 Hz, 2 H), 2.2 (d, J = 14.17 Hz, 2 H) ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.37, 38.72, 77.35, 118.88, 119.17, 132.20, 147.86, 148.48, 149.27. HRMS-ESI (m/z): $[M+H]^+$ Calcd for $C_{11}H_{14}N_3O_2$: 219.1008; found: 219.1001.

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