# Rapid Access to N-Substituted Diketopiperazines by One-Pot Ugi-4CR/Deprotection+Activation/Cyclization (UDAC)

Cristiano R. B. Rhoden,[†] Daniel G. Rivera,[†] Oliver Kreye,[†] Anne K. Bauer,[†,‡] Bernhard Westermann,[†,‡] and Ludger A. Wessjohann*[,†,‡]

*Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120, Halle (Saale), Germany, and Institute of Chemistry, University of Halle, Kurt-Mothes-Str. 2, 06120 Halle (Saale), Germany*

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The most efficient diversity generating approaches to heterocycles are combinations of a multicomponent (MCR) with a cyclization reaction, for example, by Ugi-deprotection-cylization (UDC) protocols. If the desired post-Ugi reaction requires more than one deprotection, for example of two initially protected Ugi-reactive groups, or if it requires additional activation, for example, by an Ugi-activation-cyclization (UAC), either the isolation of intermediates or a sequential process or both become necessary. A recently introduced convertible isonitrile reagent allows a mild and chemoselective in situ post-Ugi activation of the isonitrile-born carboxylate with simultaneous deprotection of the nucleophilic amine, that is, liberation and activation of two Ugi-reactive groups, if desired also under subsequent lactam formation. This is exemplified by the synthesis of peptide-peptoid diketopiperazines.

The diketopiperazine (DKP) core is an important privileged scaffold in medicinal chemistry, as well as in naturally occurring heterocyclic pseudopeptides (Figure 1). DKPs can exhibit numerous medicinally relevant properties like antifungal,[1] antibacterial,[2] antitumor,[3] and antiviral activity. Examples for the latter two activities are the microtubulin active compound phenylahistin, and derivates mimicking nucleoside moieties,[4] respectively (Figure 1). Also the natural peptoid-peptide DKP tryprostatin A (Figure 1) is known for its microtubulin activity.[5] Other DKPs have proven to be potent and selective ligands for nonmedicinal biological targets.[6] For example, asparagines and their derivatives are the source of the bitter taste in some food such as coffee, beer, cacao, or chocolate.[7] As a consequence, intensive synthetic efforts to discover and develop new lead compounds based on this heterocyclic framework have been carried out.[8]

Multicomponent reactions (MCRs) are among the most powerful approaches for diversity-oriented synthesis.[9,10] Specifically for DKPs, the Ugi four-component reaction (Ugi-4CR) is almost ideally suited.[9] This isocyanide-based multicomponent reaction (IMCR) comprises the condensation of an amine, an oxo compound, a carboxylic acid, and an isocyanide to form a dipeptidic scaffold, which can be cyclized afterward through a variety of protocols to produce the DKP skeleton.[11−13] Accordingly, several strategies have been reported to vary the connectivity, substitution patterns, and functionalities on the DKP platform.[9,12,13] Among the different postmodification approaches known, the most versatile ones are the so-called UDC procedures (Ugi-4CR/deprotection/cyclization), and those that include convertible isocyanides as a manner to activate the terminal isocyanide derived amide carbonyl (UAC = Ugi-4CR/activation/cyclization).[8,11,13] Recently, we showed that microwave irradiation can significantly decrease reaction times in UDC-protocols toward DKPs even without forming an active ester,[12] and later Hulme could show the same for amides.[11d] Both types of post-Ugi-reactions UDC and UAC can be applied as one-pot procedures and are essentially simple, high yielding and amenable to solution and solid-phase combinatorial syntheses within drug discovery programs.[13] Recently a new and promising convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)-benzene (**1**) has been introduced, by the Wessjohann and Kobayashi groups.[14] It is stable, easily accessible, versatile,[14a] and reacts specifically, as proven elegantly in the total synthesis of (−)-Dysibetaine.[15] The mild acidic activation to the reactive ester allows addition of nucleophiles without affecting other peptidic or even ester moieties.[14a]

In this paper, we show that a combination of UDC and UAC, that is, the concomitant deprotection (at the nucleophile) and the activation (of the electrophile) allows a simple one-pot generation of mixed peptide-peptoid DKPs. Scheme

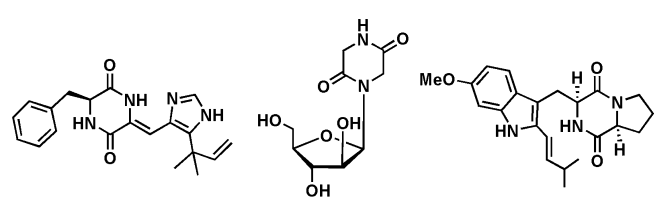


**Figure 1.** Selected diketopiperazines with biological and medicinal activities.

* To whom correspondence should be addressed. E-mail: wessjohann@ipb-halle.de. Fax: +49 (0)345 55821309.
[†] Leibniz Institute of Plant Biochemistry.
[‡] Martin-Luther-University of Halle-Wittenberg.

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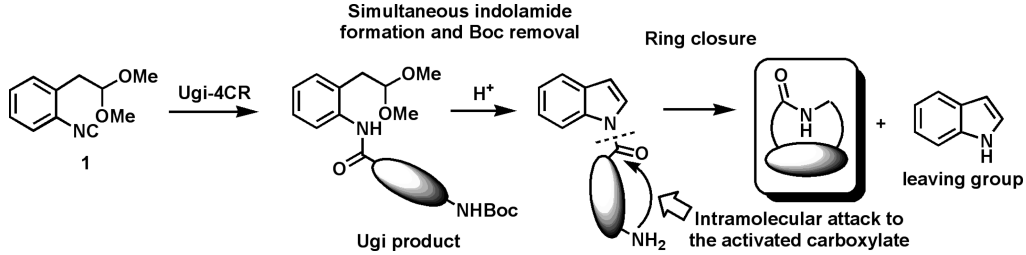
**Scheme 1.** New Convertible Isocyanide to Produce UDAC-Based Cyclic Scaffolds




1 illustrates the appropriate synthetic design based on a Ugi-4CR/deprotection+activation/cyclization (UDAC) one-pot procedure reported in this work. Following this principle, the acid convertible isocyanide **1** was used in combination with acid labile amino protected building blocks to produce a small library of DKPs from readily available reagents like amino acids and commercial aldehydes. The reaction takes place under mild conditions, with short reaction times and good yields. Heating usually is not required.

Table 1 shows the results for a combination of isonitrile **1** with various protected α-aminoacids, primary amines and aldehydes, taking advantage of the simultaneous removal of an N-terminal Boc-protecting group under acidic conditions. If acid cleavage and activation is performed carefully, the intermediate indolamide **6** can be isolated. However, usually the final cyclization is accomplished in one-pot by adding base. The addition of a biphasic mixture containing $CH_2Cl_2$/aqueous $NaHCO_3$ proved to be the best to complete the formation of the DKPs **7**, leaving formed salts directly in the aqueous phase and capturing the product in the organic phase. For example, at room temperature the reaction between the convertible isocyanide **1**, propylamine, formaldehyde, and *N*-Boc-L-phenylalanine afforded the corresponding diketopiperazine **7b** in 79% yield. Under the same conditions, diketopiperazine **7c** was obtained in only moderate 56% yield, which likely is due to the lower nucleophilicity of the secondary amine proline. This protocol is not restricted to simple aliphatic primary amines as starting material, benzylamines can be used too as evidenced by compound **7e**, obtained in 67% yield. In a changed workup system, the aqueous hydrogencarbonate was replaced by a basic ion-exchange resin (hydroxide form of Merck III) and the reaction monitored by mass spectrometry. Interestingly, under these conditions the intermediate **6**, proven to be deprotected by spectroscopy, was partially reprotected to form the Boc-protected **6** and only some diketopiperazine **7** was formed.

In summary, the Ugi-4CR/activation+deprotection/cyclization (UDAC) concept herein described, applying 1-isocyano-2-(2,2-dimethoxyethyl)-benzene **1** as a convertible isocyanide in a one-pot procedure for the synthesis of functionalized diketopiperazines, is fast, works under unusually mild conditions, and is suitable for an automation process.

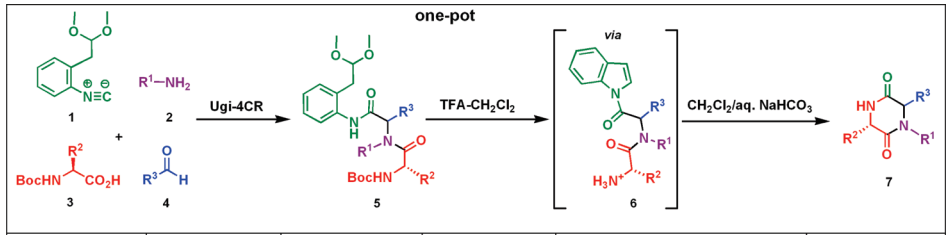
## Experimental Section

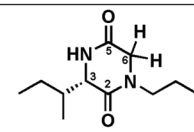
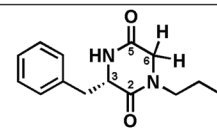
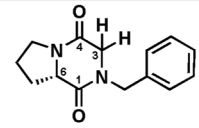
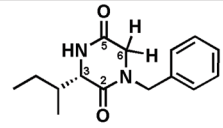
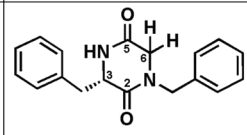
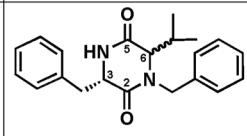
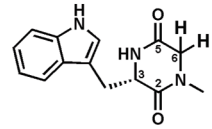
Synthesis of the convertible isonitrile **1** was previously described.[14] All other chemicals and solvents used were commercial. Purification of the crude products was achieved by column chromatography on silica gel 60 (230−400 mesh, 0.040−0.063 mm). TLC identifications of reactants and products were performed on silica gel coated aluminum foil (silica gel 60 F254 with fluorescence indicator). Melting points were determined on a Leica DM LS2 and are uncorrected. NMR spectra were obtained in $CDCl_3$ or $CD_3OD$. All $^1H$ NMR spectra are reported in ppm relative to TMS. All $^{13}C$ NMR spectra are reported in ppm relative to the solvent signals. Electronspray ionization mass spectra (ESI-MS) were recorded on an API 150, Applied Biosystems. High-resolution mass spectra (HRMS) were recorded on a 70 eV FT-ICR spectrometer. Analytic RP-HPLC was performed on ODS-A 120, 5 $\mu$m 4.6 × 159 mm + VS (SNr. 176), conditions: MeOH/$H_2O$ linear gradient MeOH 2% ($t$ = 0 min) > MeOH 100% ($t$ = 20 min) > MeOH 100% ($t$ > 20 min), detection: UV 210 nm.

**General Procedure for the Synthesis of Diketopiperazines by the UDAC Method (7a−g).** A mixture of amine **2** (1 mmol) and aldehyde **4** (1 mmol) in methanol (10 mL) was stirred at room temperature for 30 min. The N-protected amino acid **3** (1 mmol) and isocyanide **1** (1 mmol) were added, and the resulting reaction mixture was stirred for an additional 6 h. The volatiles were evaporated under reduced pressure, and trifluoracetic acid (3 mL) in dichloromethane (7 mL) was added. The reaction mixture was stirred for 1 h and then concentrated under reduced pressure. The remaining TFA was removed by addition of further dichloromethane and evaporation. To the resulting crude product was added a mixture of dichloromethane (50 mL) and aqueous 10% $NaHCO_3$ (10 mL), and the mixture was stirred at room temperature for 3 h. After cyclization was complete (followed, e.g., by ESI-MS analysis), the solution was diluted with chloroform (100 mL), and the organic phase was separated and washed with brine (50 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/methanol 9:1) to afford the desired diketopiperazine **7**. The intermittent removal of solvent and trifluoroacetic acid in vacuo can be skipped if higher amounts of acid and neutralizing base are used, but volumes, reaction times, and work up effort are increased and yields are decreased.

**(*R*)-3-(1′-Methyl propyl)-1-propylpiperazine-2,5-dione (7a).** Convertible isocyanide **1** (57 mg, 0.3 mmol), propylamine **2a** (25 $\mu$L, 0.3 mmol), *N*-Boc-isoleucine **3a** (69 mg, 0.3 mmol), and paraformaldehyde **4a** (10 mg, 0.3 mmol) were reacted according to the general procedure to give after purification 47 mg (74%) of **7a**. White solid. mp: 108−109 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.91 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = −2.1 ($c$ 0.05, MeOH). $^1H$ NMR ($CD_3OD$, 300 MHz): $\delta$ = 0.82 (d, $J$ = 7.68 Hz, 3 H), 0.92

**Table 1.** Synthesis of N-Monosubstituted DKPs by Sequential Ugi-4CR/Deprotection+Activation/Cyclization (UDAC) Using Convertible Isocyanide **1**[a]




| Entry | $R^1$ | $R^2$ | $R^3$ | DKP 7 | Yield (%) |
|---|---|---|---|---|---|
| a | Pr | *i*-Bu | H |  | 74 |
| b | Pr | Bn | H |  | 79 |
| c | Bn | $C_3H_6$ | H |  | 56 |
| d | Bn | *i*-Bu | H |  | 73 |
| e | Bn | Bn | H |  | 67 |
| f | Bn | Bn | *i*-Pr |  | 60 |
| g | Me | indolyl | H |  | 58 |

[a] All compounds were purified by silica gel column chromatography and characterized by NMR and HRMS.

(ddd, $J$ = 3.29/3.28/2.93 3 H), 0.93 (d, $J$ = 7.32 Hz, 3 H), 1.25 (m, 2 H), 1.60 (m, 1H), 1.94 (m, 2 H), 3.22 (dd, $J$ = 13.4/8.1/6.6 Hz, 1 H), 3.49 (dd, $J$ = 13.4/8.4/6.6 Hz, 1 H), 3.82 (d, $J$ = 4.1 Hz, 1 H), 3.87 (d, $J$ = 17.93 Hz, 1 H), 4.13 (d, $J$ = 17.93 Hz, 1 H) ppm. $^{13}$C NMR ($CD_3OD$, 75 MHz): $\delta$ = 11.49, 11.98, 15.53, 20.79, 25.48, 41.54, 50.40, 49.23, 61.31, 167.82, 168.25 ppm. HRMS $C_{11}H_{20}N_2O_2$: $[M + Na]^+$ calcd 235.14225, found 235.14169.

**(*R*)-3-Benzyl-1-propylpiperazine-2,5-dione (7b).** Convertible isocyanide **1** (57 mg, 0.3 mmol), propylamine **2b** (25 $\mu$L, 0.3 mmol), *N*-Boc-Phenylalanine **3b** (80 mg, 0.3 mmol) and paraformaldehyde **4b** (10 mg, 0.3 mmol), were reacted according to the general procedure, to give after purification 58 mg (79%) of **7b**. White solid. mp: 123−125 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.53 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = 20.3 ($c$ 0.05, MeOH). $^1$H NMR ($CD_3OD$, 300 MHz): $\delta$ = 0.82 (t, $J$ = 7.4 Hz, 3 H), 1.39 (m, 2 H), 2.69 (d, $J$ = 17.7 Hz, 1 H), 2.96 (dd, $J$ = 13.6/4.5 Hz, 1H), 3.05 (ddd, $J$ = 13.4 /9.2/6.3 Hz, 1 H), 3.24 (ddd, $J$ = 13.4/9.2/6.3 Hz, 1 H), 3.47 (d, $J$ = 17.7 Hz, 1 H), 4.26 (dd, $J$ = 4.5/4.1 Hz, 2 H), 7.12−7.19 (m, 3 H), 7.25−7.32 (m, 2 H) ppm. $^{13}$C NMR ($CD_3OD$, 75 MHz): $\delta$ = 11.50, 20.57, 41.18, 49.27, 49.82, 57.83, 128.46, 129.58 (2C), 131.75 (2C), 136.26, 167.56, 168.14 ppm. HRMS $C_{14}H_{18}N_2O_2$: $[M + Na]^+$ calcd 269.1266, found 269.12604.

**(*R*)-2-Benzyl-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (7c).** Convertible isocyanide **1** (191 mg, 1 mmol), benzylamine **2c** (109 μL, 1 mmol), *N*-Boc-proline **3c** (215 mg, 1 mmol), and paraformaldehyde **4c** (30 mg, 1 mmol), were reacted according to the general procedure to give after purification 136 mg (56%) of **7c**. White solid. mp: 137−138 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.44 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = −95.2 (*c* 0.05, MeOH). $^1$H NMR ($CD_3OD$, 300 MHz): δ = 1.82 − 2.10 (m, 3H), 2.31 − 2.43 (m, 1H), 3.50 (d, *J* = 16.83 Hz, 2H), 3.72 (d, *J* = 16.6 Hz, 1H), 4.13 (d, *J* = 16.6 Hz, 1H), 4.17 (d, *J* = 14.4 Hz, 1H), 4.28 (m, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 7.22 − 7.38 (m, 5H) ppm. $^{13}$C NMR ($CD_3OD$, 75 MHz): δ = 23.49, 29.79, 46.22, 50.05, 51.88, 60.21, 128.95, 129.12, 129.88, 137.18, 165.44, 169.53 ppm. HRMS $C_{14}H_{16}N_2O_2$: $[M + Na]^+$ calcd 267.11095, found 267.11039.

**(*R*)-3-(1′-Methyl propyl)-1-benzylpiperazine-2,5-dione (7d).** Convertible isocyanide **1** (96 mg, 0.5 mmol), benzylamine **2d** (55 μL, 0.5 mmol), *N*-Boc-isoleucine **3d** (116 g, 0.5 mmol), and paraformaldehyde **4d** (15 mg, 0.5 mmol), were reacted according to the general procedure, to give after purification 94 mg (73%) of **7d**. White solid. mp: 96−97 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.86 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = 9.1 (*c* 0.05, MeOH). $^1$H NMR ($CD_3OD$, 300 MHz): δ = 0.89 (t, *J* = 7.3 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.25 (m, 1H), 1.96 (m, 2H), 3.76 (d, *J* = 18.0 Hz, 1H), 3.91 (d, *J* = 18.0 Hz, 1H), 3.98 (d, *J* = 4.0 Hz, 1H), 4.44 (dd, *J* = 14.6, 1H), 4.71 (d, *J* = 14.6 Hz, 1 H), 7.29 (m, 5H) ppm. $^{13}$C NMR ($CD_3OD$, 75 MHz): δ = 11.99, 15.53, 25.37, 42.63, 49.70, 50.36, 61.16, 129.07, 129.43, 129.85, 136.90, 167.79, 167.90 ppm. HRMS $C_{15}H_{20}N_2O_2$: $[M + Na]^+$ calcd 283.14225, found 283.14169.

**(*R*)-1,3-Dibenzylpiperazine-2,5-dione (7e).** Convertible isocyanide **1** (191 mg, 1 mmol), benzylamine **2e** (109 μL, 1 mmol), *N*-Boc-phenylalanine **3e** (265 mg, 1 mmol), and paraformaldehyde **4e** (30 mg, 1 mmol), were reacted according to the general procedure to give after purification 196 mg (67%) of **7e**. White solid. mp: 180−181 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.57 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = 18 (*c* 0.05, MeOH). $^1$H NMR ($CDCl_3$, 300 MHz): δ = 2.90 (d, *J* = 17.6 Hz, 1 H), 3.13 (dd, *J* = 13.8/5.8 Hz, 1H), 3.21 (dd, *J* = 13.8/5.8 Hz, 1H), 3.49 (d, *J* = 17.6 Hz, 1 H), 4.36 (s, 1 H), 4.45 (d, *J* = 14.5 Hz, 1 H), 4.47 (d, *J* = 14.5 Hz, 1H), 7.03 (s, 1 H), 7.25 (m, 19 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ = 40.54, 48.29, 49.60, 56.42, 127.45, 128.07, 128.62, 128.66, 128.78, 129.94, 134.37, 134.73, 165.20, 166.16 ppm. HRMS $C_{18}H_{28}N_2O_2$: $[M + Na]^+$ calcd 317.33749, found 317.12636.

**(*R*)-1,3-Dibenzyl-6-isopropylpiperazine-2,5-dione (7f).** Convertible isocyanide **1** (96 mg, 0.5 mmol), benzylamine **2f** (55 μL, 0.5 mmol), *N*-Boc-Phenylalanine **3f** (133 g, 0.5 mmol), and isobutyraldehyde **4f** (46 μL, 0.5 mmol), were reacted according to the general procedure to give after purification 100 mg (60%) of **7f**. White solid. mp: 158−159 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.79 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = −28.8 (*c* 0.05, MeOH). $^1$H NMR ($CD_3OD$, 300 MHz): δ = 0.95 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 2.27 − 1.88 (m, 1H), 3.07 (dd, *J* = 14.1/4.5 Hz, 1H), 3.12 (dd, *J* = 13.6/7.9 Hz, 1H), 3.23 (dd, *J* = 13.6/4.4 Hz, 1H), 3.60 (d, *J* = 4.3 Hz, 1H), 3.79 (dd, *J* = 14.1/7.3 Hz, 1H), 3.89 (d, *J* = 15,0 Hz, 1H), 4.22 (d, *J* = 15.0 Hz, 1H), 4.31 (dd, *J* = 7.8/4.3 Hz, 1H), 4.34 (d, *J* = 4.3 Hz, 1H), 4.50 (d, *J* = 4.3 Hz, 1H), 5.14 (d, *J* = 15.0 Hz, 1H), 5.27 (d, *J* = 15.0 Hz, 1H), 7.23 (m, 20 H) ppm. $^{13}$C NMR ($CD_3OD$, 75 MHz): δ = 17.31, 18.13, 20.10, 20.89, 32.52, 32.94, 38.81, 41.55, 48.20, 50.35, 56.25, 58.35, 65.18, 66.28, 128.05, 128.22, 128.64, 128.78, 129.72, 129.80, 129.74, 129.76, 129.77, 129.79, 131.05, 131.67, 136.57, 136.80, 137.45, 137.60, 168.03, 168.41, 168.43, 168.55 ppm. HRMS $C_{21}H_{24}N_2O_2$: $[M + Na]^+$ calcd 359.17355, found 359.17299.

**(*R*)-3-((1*H*-indol-3-yl)methyl)-1-methylpiperazine-2,5-dione (7g).** Convertible isocyanide **1** (38 mg, 0.2 mmol), methylamine **2g** (67 μL, 0.3 mmol, 33% solution in ethanol), *N*-Boc-tryptophan **3g** (61 mg, 0.2 mmol), and paraformaldehyde **4g** (6 mg, 0.2 mmol) were reacted according to the general procedure to give after purification 30 mg (58%) **7g**. White solid. mp: 180−181 °C. Purity (HPLC) > 96%. TLC $R_f$ = 0.39 (ethyl acetate/MeOH 9:1). $[\alpha]_D^{20}$ = 85.8 (*c* 0.05, MeOH). $^1$H NMR ($CD_3OD$, 400 MHz): δ = 2.22 (d *J* = 17.4 Hz, 1H), 2.47 (s, 3H), 3.07 (dd, *J* = 14.6/4.5 Hz, 1H), 3.28 (d, *J* = 17.4 Hz, 1H), 3.47 (dd, *J* = 14.6/3.2 Hz, 1H), 4,22 (dd, *J* = 4.5/3.2 Hz, 1H), 7.00 (s, 3H), 7.01 (dt, *J* = 8.0/7.0/1.1 Hz, 1H), 7.09 (dt, *J* = 8.2/7.0/1.2 Hz, 1H), 7.35 (dt, *J* = 8.1/1.1/0.8 Hz, 1H), 7.45 (d, *J* = 8.0/1.2/0.9 Hz, 1H) ppm. $^{13}$C NMR ($CD_3OD$, 100 MHz): δ = 31.78, 33.77, 51.51, 57.43, 108.67, 112.33, 119.76, 120.09, 122.71, 126.43, 128.45, 137.86, 168.38, 168.85. HRMS $C_{14}H_{15}N_3O_2$ $[M + Na]^+$ calcd 280.27757, found 280.10564.

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