Synthesis of the Metabolites of 4-(2-Methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide (KRP-197/ONO-8025)

Ichiro ARAYA,*[,a] Takeshi TSUBUKI,[a] Tatsuhiro SAITO,[a] Makoto NUMATA,[a] and Hiroyuki AKITA[b]

[a] *Research Center, Kyorin Pharmaceutical Co., Ltd.; 1848 Nogi, Nogi-machi, Shimotsuga-gun, Tochigi 329–0114, Japan: and* [b] *School of Parmaceutical Sciences, Toho University; 2–2–1 Miyama, Funabashi, Chiba 274–8510, Japan.*

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We synthesized the six presumed metabolites (2—7) of 4-(2-methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide [KRP-197/ONO-8025, 1], a urinary incontinence therapeutic agent, in order to confirm the structures of the metabolites. Metabolite (2) was synthesized *via* glucuronidaion of compound (1) and methyl 2,3,4-tri-*O*-benzoyl-1-methanesulfonyl-α-D-glucopyranuronate. Metabolite (3) was synthesized *via* 3-(*tert*-butoxycarbonyl)-2-methyl-1,3-imidazolidine-4,5-dione. Metabolites (4—7) were synthesized *via* 4-amino-2-diphenylbutanamide, respectively. The structures of the metabolites (2—7) in humans were identified by means of synthesis of the authentic compounds.

Key words KRP-197; ONO-8025; metabolite; glucronide; imidazolidine dion derivative; urinary incontinence

The synthesis and structure–activity relationships of novel 4-(imidazoyl-1-yl)butanamide derivatives as antimuscarinic activity agents were reported by the Kyorin Discovery Research group.[1—3] Among them, 4-(2-methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide [KRP-197/ONO-8025, **1**] is under clinical evaluation as a new type of treatment for urinary incontinence with highly subtype receptor selective antimuscarinic activity. During the course of the metabolite studies of **1**, using high performance liquid chromatography (HPLC)-mass spectrometry (LC-MS/MS) suggested degradation from the imidazole structure for four of the six metabolites of **1**, the imidazolidine dione structure and *N*-glucuronide (Chart 1). Especially, *N*-glucuronide was proposed to be the presence of quarter ammonium containing unique chemical structure **2** as a major metabolite in only humans. Thus, our efforts have been focused on the synthesis of the above metabolites, which were synthesized in order to confirm their pharmacological efficacy.

Synthesis of Ammonium *N*-Glucuronide (2) The synthetic route to quaternary *N*-glucuronide **2** from methyl 2,3,4-tri-*O*-benzoyl-1-methanesulfonyl-α-D-glucopyranuronate **9** as a glycosyl donor is shown in Chart 2. 1,2,3,4-tetra-*O*-benzoyl-β-D-glucopyranouronate **8**, as a starting material, was synthesized from D-(+)-glucurono-3,6-lacton by applying the reported method.[4] **8** was treated with methansulfonic acid in CH_2Cl_2 to afford α-methansulfonate **9** in 49% yield. The glycosidation reaction between **1** and **9** was carried out in $CHCl_3$ to provide **10** in 41% yield, and also stereoselectivity was only obtained for the single β-isomer. Deprotection and hydrolysis of the methyl ester afforded ammonium *N*-glucuronaide **2** as inner salt after HP-20SS resin treatment.

Synthesis of Imidazolidine Dion 3 The synthesis of the metabolite **3** is outlined in Chart 3. *N*-(1-Aminoethyl)benzamide hydrochloride **11**, prepared according to Carotti's method,[5] was transformed to **12** on treatment with chloroacethyl chloride followed by cyclization and protection by the Boc group in 30% yield (3 steps). The ring oxidation re-

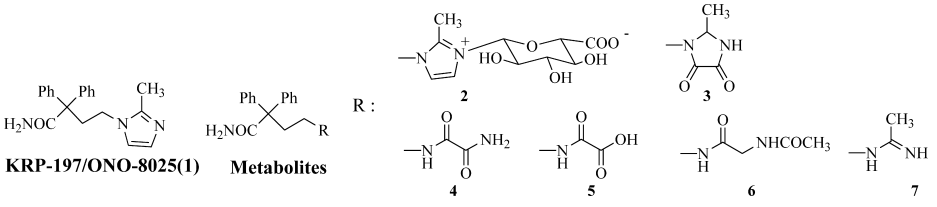

Chart 1

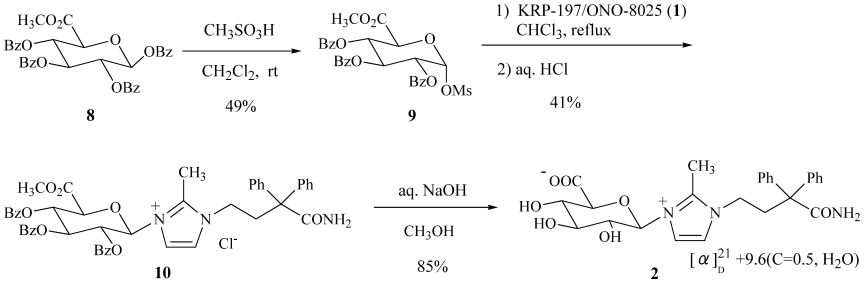

Chart 2

* To whom correspondence should be addressed. e-mail: ichirou.araya@mb.kyorin-pharm.co.jp

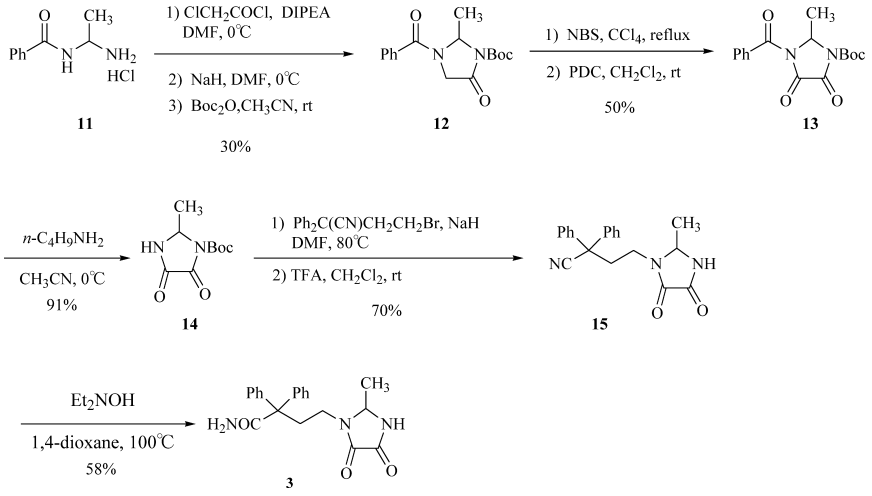

Chart 3

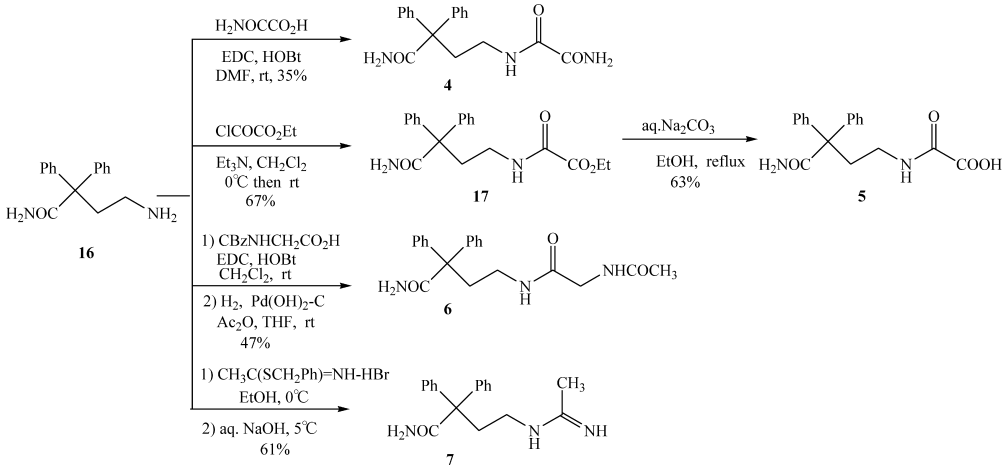

Chart 4

action of **12** was achieved by using bromination with *N*-bromosuccinimide (NBS) followed by pyridinium dichromate (PDC) treatment to give imidazolidinone **13** in 50% yield. Debenzoylation of **13** with *n*-butylamine as a benzoyl group accepter under high-dilution condition in CH_3CN at 0 °C gave imidazolidinone **14**. The obtained **14** was reacted with 4-bromo-2,2-diphenylbutyronitrile in the presence of NaH to afford the *N*-alkyl derivative **15**, which was subsequently treated with trifluoroacetic acid in CH_2Cl_2 and hydration of the CN group by using *N*,*N*-diethylhydroxylamine[6] to furnish the desired 4,5-dioxoimidazolidine compound **3** as a white powder in 41% yield (2 steps).

Synthesis of 4, 5, 6 and 7 The synthesis of the metabolite (**4**—**7**) from 4-amino-2-diphenylbutanamide **16**[7] as a key intermediate is shown in Chart 4. The reaction of **16** and oxamic acid in the presence of 1-ethyl-3-[3-(diethylamino)-propyl]carbodiimide hydrochloride (EDC-HCl)/1-hydroxybenzotriazole monohydrate (HOBt–H_2O) gave **4** in 35% yield. The reaction of **16** and ethyl chlorooxoacetate in the presence of Et_3N gave oxalamic acid ester congener **17** (67%), which was treated with aqueous Na_2CO_3 afforded **5** (63%). The coupling reaction of **16** and *N*-(benzyloxycarbonyl)glycine followed by consecutive catalytic hydrogenolysis and acetylation gave **6** in overall 47% yield. Amidine derivative **7** was synthesized from **16** with *S*-benzyl thioacetimidate hydrobromide[8] in 61% yield.

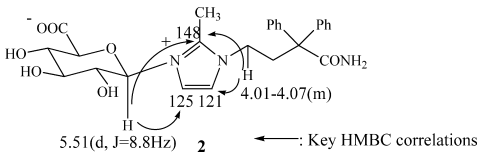

Chart 5

These synthetic compounds (**2**—**7**) were identical with the proposed metabolite structure on the basis of the MS, ^{1}H-NMR and HPLC comparisons. The configuration at the anomeric position of the glucuronic acid moiety of **2** was determined by using ^{1}H-NMR analysis as shown in Chart 5. A doublet at δ 5.52 in the ^{1}H-NMR spectrum was assigned to the anomeric proton (C_1-H) of the glucuronic acid moiety and the coupling constant of 8.3 Hz confirmed the β-anomeric assignment (*J* values for α and β-anomers of glucuronides are in the range 2 to 4 Hz and 7 to 10 Hz, respectively[9]). On the other hand, the conjugated position of the glucuronic acid moiety on the imidazole ring was confirmed

by a heteronuclear multiple bond connectivity (HMBC) spectrum, which demonstrated connectivity among C_5 of the imidazole ring and the anomeric proton (C_1-H), C_4 of the imidazole ring and 4′-methyene proton of the butanamide moiety individually was consistent with the above structure (Chart 5).

The antimuscarinic activity of the compounds was evaluated *in vitro*, although all of these compounds were not active. Therefore, it is suggested that the metabolites of **1** do not play a crucial role in the urinary incontinence therapy.

Experimental

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analyses are within ±0.3% of the theoretical values and were determined by a Yanaco CHN coder MT-5. Infrared spectra were recorded with a JASCO FT/IR-5300 spectrometer. Mass spectrometry (MS) and high-resolution MS (HR-MS) were performed with JEOL JMS SX-102A or JEOL JMS-T100LP mass spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL EX-400 (400 MHz) spectrometer. Spectra were run in either $CDCl_3$ or DMSO-d_6 using TMS as internal standard, or in D_2O using TSP as internal standard. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Thin-layer chromatography (TLC) plates (Merck: silica gel 60 F254, 0.25 mm, Art 5715) were used for TLC analysis. Column chromatography was performed with silica gel (Merck: silica gel 60 with particle size 0.040—0.063 mm).

Methyl 2,3,4-Tri-*O*-benzoyl-1-methanesulfonyl-α-D-glucopyranuronate (9) To a solution of methyl 1,2,3,4-tetra-*O*-benzoyl-β-D-glucopyranouronate **8**[4] (44.3 g, 72.4 mmol) in anhydrous CH_2Cl_2 (300 ml), was added methansulfonic acid (55.8 g, 581 mmol), and the whole mixture was stirred for 45 min at room temperature. The reaction was quenched with 5% aqueous sodium bicarbonate (1400 ml). The organic layer was separated, and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic solution was washed with water, dried over sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 : hexane : AcOEt = 10 : 5 : 1) and recrystallized from CH_2Cl_2–hexane to give a colorless solid **9** (20.6 g, 49%). **9**: mp 139—140 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.11 (3H, s), 3.70 (3H, s), 4.79 (1H, d, J=9.8 Hz), 5.54 (1H, dd, J=3.4, 9.8 Hz), 5.75 (1H, t, J=9.8 Hz), 6.17 (1H, t, J=9.8 Hz), 6.41 (1H, d, J=3.4 Hz), 7.31—7.57 (9H, m), 7.88—7.99 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 39.5, 53.1, 68.7, 69.1, 69.5, 70.8, 95.9, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 129.7, 129.8, 129.9, 133.5, 133.6, 133.8, 165.0, 165.2 165.3, 166.7. IR (KBr) cm^{-1}: 1763, 1731, 1272, 707. FAB-MS *m/z*: 597 $(M-H)^-$. *Anal*. Calcd for $C_{29}H_{26}O_{12}S$ (MW: 598.58): C, 58.19; H, 4.38. Found: C, 58.20; H, 4.30.

1-(3-Carbamoyl-3,3-diphenylpropy)-3-(2,3,4-tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-2-methylimidazolium Chloride (10) A solution of 4-(2-methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide **1** (45.4 g, 142 mmol) and **9** (10.0 g, 16.7 mmol) in anhydrous $CHCl_3$ (500 ml) was refluxed for 13 h under argon. After cooling, the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and 1 M HCl. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with 1 M HCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 3) and recrystallized from CH_2Cl_2–hexane to give the title compound **10** as a pale grayish powder (5.82 g, 41%): **10**: mp 164—167 °C (dec.). ESI-MS *m/z*: 822 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.38—2.45 (1H, m), 2.52 (3H, s), 2.69—2.76 (1H, m), 3.58 (3H, s), 3.68—3.85 (2H, m), 5.10 (1H, d, J=9.8 Hz), 5.87 (1H, t, J=9.8 Hz), 6.20 (1H, t, J=8.8 Hz), 6.25 (1H, t, J=9.3 Hz), 6.68 (1H, d, J=8.3 Hz), 6.76 (1H, br s), 7.15—7.85 (27H, m), 8.15 (1H, d, J=2.4 Hz). ^{13}C-NMR (DMSO-d_6) δ: 22.8, 38.9, 45.8, 52.7, 58.7, 69.0, 70.7, 72.2, 73.2, 81.5, 119.2, 122.8, 126.9, 127.0, 127.4, 128.1, 128.2, 128.2, 128.5, 128.9, 129.0, 129.0, 129.2, 134.0, 134.1, 134.3, 142.4, 145.1, 164.0, 164.7, 165.0, 166.3, 174.3. IR (KBr) cm^{-1}: 3420, 1734, 1261, 1070, 711. HR-MS (ESI) *m/z*: 822.30261 (Calcd for $C_{48}H_{44}N_3O_{10}$: 822.30267).

1-[3-(3-Carbamoyl-3,3-diphenyl)propyl-2-methyl-1-imidazolinio]-1-deoxy-β-D-glucopyranuronate Hydrate (2) To a solution of **10** (63.0 g, 73.4 mmol) in MeOH (2520 ml) was added 1 M NaOH (50 ml) over 30 min at −62 to −54 °C. After the addition, the cooling bath was removed. The resulting solution was stirred for 30 min at 0 °C and at room temperature for 30 min. The reaction mixture was neutralized with 6 M HCl and then the solvent was removed under reduced pressure. The residue was dissolved in water (600 ml), washed three times with CH_2Cl_2 (300 ml×3). The aqueous layer was concentrated under reduced pressure. The residue was purified by synthetic adsorbed beads DIAION HP-20SS column chromatography (H_2O : MeOH (gradient elution, 10 : 0—2 : 1)). The residual crystals were recrystallized two times from 2-propanol/water to give the title compound **2** as a colorless solid (32.4 g, 85%). **2**: mp 210—215 °C (dec). ^{1}H-NMR (D_2O) δ: 2.50 (3H, s), 2.95—2.98 (2H, m), 3.64—3.80 (3H, m), 4.00 (1H, d, J=9.3 Hz), 4.08—4.12 (2H, m), 5.52 (1H, d, J=8.3 Hz), 7.36—7.48 (11H, m), 7.67 (1H, d, J=2.4 Hz). ^{13}C-NMR (D_2O) δ: 11.9, 40.2, 48.1, 61.5, 73.8, 75.0, 77.9, 81.3, 87.2, 120.9, 124.4, 130.4, 130.9, 131.4., 143.7, 143.9, 147.5, 177.1, 181.2. IR (KBr) cm^{-1}: 3412, 1663, 1625. FAB-MS *m/z*: 496 $(M+H)^+$. $[\alpha]_D^{25}$ +9.2° (c=0.52, H_2O). *Anal*. Calcd for $C_{26}H_{29}N_3O_7$·1.1H_2O (MW: 515.34): C, 60.60; H, 6.10; N, 8.15. Found: C, 60.43; H, 5.88; N, 8.12.

1-Benzoyl-3-(*tert*-butoxycarbonyl)-2-methyl-1,3-imidazolidin-4-one (12) An ice-cooled suspension of *N*-(1-aminoethyl)benzamide hydrochloride **11**[5] (47.2 g, 235 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF, 35 ml) was treated with diisopropylethylamine (98.2 ml, 564 mmol) for 1 h, and then chloroacetylchoride (22.4 ml, 282 mmol) was added dropwise to the above reaction mixture over a period of 30 min. After the addition, the reaction mixture was stirred under ice cooling for 2 h and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1500 ml), washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with Et_2O to give *N*-{1-[(chloroacetyl)-amino]ethyl}benzamide (29.8 g) as a crude product. The crude product (28.9 g, 120 mmol) was dissolved in anhydrous DMF (35 ml). To this solution was added NaH (60% dispersion in mineral oil, 14.4 g, 360 mmol) at 0 °C, and the reaction mixture was stirred for 4 h at ambient temperature. The reaction was quenched with AcOH (30 ml). After being stirred for 30 min at room temperature, the mixture was allowed to stand overnight. The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (300 ml) and water (100 ml). The organic layer was removed and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue (19.8 g) was dissolved in anhydrous CH_3CN (485 ml). Di(*tert*-butyl)dicarbonate (Boc_2O, 23.3 g, 107 mmol) and 4,4-dimethylaminopyridine (DMAP, 593 mg, 4.85 mmol) were added to above solution, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) and triturated with petroleum ether (50 ml). The precipitate was collected by filtration, dried under vacuum to give the title compound **12** as a white powder (20.0 g, 30%). **12**: mp 139—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.66 (12H, m), 4.05—4.28 (2H, m), 6.24 (1H, br), 7.44—7.52 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.1, 28.0, 50.8, 69.0, 84.5, 127.3, 128.7, 131.2, 134.1, 147.7, 166.4, 168.5. IR (KBr) cm^{-1}: 2976, 1802, 1646, 1365, 1153. FAB-MS *m/z*: 305 $(M+H)^+$. *Anal*. Calcd for $C_{16}H_{20}N_2O_4$ (MW: 304.34): C, 63.14; H, 6.62; N, 9.20. Found: C, 62.97; H, 6.72; N, 9.24.

1-Benzoyl-3-(*tert*-butoxycarbonyl)-2-methyl-1,3-imidazolidine-4,5-dione (13) A mixture of **12** (19.2 g, 63.0 mmol), *N*-bromosuccinimide (NBS, 12.3 g, 69.3 mmol), benzoyl peroxide (10.0 mg) and tetrachloromethane (315 ml) was refluxed for 30 min. After cooling, the reaction mixture was washed with saturated aqueous sodium bicarbonate (200 ml), saturated aqueous sodium aqueous hydrogen sulfite (520 ml) and water (50 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (315 ml), and pyridinium dichromate (PDC, 47.4 g, 126 mmol) was added. The reaction mixture was stirred for 20 min at room temperature. The insoluble part was removed by filtration with the aid of a celite bed and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) and triturated with pentane. The resulting precipitate was collected by filtration, and dried under vacuum to give the title compound **13** as a white powder (10.1 g, 50%). **13**: mp 139—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (9H, s), 1.78 (3H, d, J=5.9 Hz), 6.07 (1H, q, J=5.9 Hz), 7.46—7.50 (2H, m), 7.62—7.66 (1H, m), 7.69—7.71 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.7, 28.0, 65.2, 86.2, 128.3, 129.6, 133.7, 147.5, 154.0, 154.2, 167.9. IR (KBr) cm^{-1}: 1813, 1695, 1388, 1282, 1149. CI-MS *m/z*: 219, 319 $(M+H)^+$. HR-MS (CI) *m/z*: 319.1321 (Calcd for $C_{16}H_{19}N_2O_5$: 319.1294).

3-(*tert*-Butoxycarbonyl)-2-methyl-1,3-imidazolidine-4,5-dione (14) A solution of *n*-buthylamine (2.27 g, 31.0 mmol) in CH_3CN (155 ml) was added dropwise to an ice-cooled solution of **13** (9.87 g, 31.0 mmol) in CH_3CN (1550 ml) over a period of 2 h. After the addition, the reaction mixture was concentrated under reduced pressure. The residue was triturated

with petroleum ether (30 ml). The precipitate was collected by filtration, dried over vacuum to give the title compound **14** as a white powder (6.07 g, 91%). **14**: mp 160—162 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.59 (9H, s), 1.66 (3H, d, J=5.9 Hz), 5.38 (1H, q, J=5.9 Hz,), 9.37 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 21.7, 27.9, 63.5, 85.3, 147.7, 157.0, 178.0. IR (KBr) cm^{-1}: 3219, 1794, 1394, 1176. FAB-MS m/z: 213 $(M-H)^-$. *Anal*. Calcd for $C_9H_{14}N_2O_4$ (MW: 214.22): C, 50.46; H, 6.69; N, 13.08. Found: C, 50.26; H, 6.56; N, 13.12.

4-(2-Methyl-4,5-dioxoimidazolidin-1-yl)-2,2-diphenylbutyronitrile (15) An ice-cooled solution of **14** (6.00 g, 28.0 mmol) in anhydrous DMF (35 ml) was treated with NaH (60% dispersion in mineral oil, 1.34 g, 33.6 mmol). After stirring for 30 min at the same temperature followed by stirring for 1 h at room temperature, 4-bromo-2,2-diphenylbutyronitrile (84.1 g, 280 mmol) was added to the solution, and heated at 80 °C for 2 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in AcOEt (500 ml), washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 ml). Trifluoroacetic acid (100 ml) was added to the above ice-cooled solution, and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (280 ml), washed with saturated aqueous sodium bicarbonate (200 ml×2) and water (50 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with ether (300 ml). The precipitate was collected by filtration, dried under vacuum to give the title compound **15** as a white powder (6.53 g, 70%). **15**: mp 204—205 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, d, J=5.9 Hz), 2.66—2.74 (1H, m), 2.82—2.90 (1H, m), 3.38—3.45 (1H, m), 3.70—3.77 (1H, m), 4.90 (1H, q, J=5.9 Hz), 7.30—7.45 (10H, m), 9.00 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 20.3, 36.5, 38.3, 50.0, 63.7, 121.5, 126.6, 128.4, 129.2, 129.2, 138.6, 138.7, 158.5, 160.2. IR (KBr) cm^{-1}: 1777, 1728, 1710, 698. EI-MS m/z: 333 (M^+), 192, 165. *Anal*. Calcd for $C_{20}H_{19}N_3O_2$ (MW: 333.38): C, 72.05; H, 5.74; N, 12.60. Found: C, 71.89; H, 5.91; N, 12.58.

4-(2-Methyl-4,5-dioxoimidazolidin-1-yl)-2,2-diphenylbutanamide (3) A mixture of **15** (6.33 g, 19.0 mmol), *N*,*N*-diethylhydroxylamine (100 ml, 950 mmol) and 1,4-dioxane (317 ml) was heated for 96 h at 100 °C. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 15 : 1) and crystallized from $CHCl_3$, and further purified by recrystallization ($CHCl_3$/acetone) to give the title compound **3** as a white powder (3.90 g, 58%). **3**: mp 203—204 °C. IR (KBr) cm^{-1}: 3236, 1747, 1666. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, d, J=5.9 Hz), 2.38 (1H, ddd, J=5.4, 12.7, 17.6 Hz), 2.68 (1H, ddd, J=3.9, 12.7, 16.9 Hz), 2.78—2.85 (1H, m), 3.26 (1H, ddd, J=5.4, 13.2, 17.6 Hz), 4.95 (1H, q, J=5.9 Hz), 6.87 (1H, br s), 7.24—7.36 (11H, m), 9.80 (1H, br s). ^{13}C-NMR (DMSO-d_6) δ: 19.7, 35.3, 37.5, 58.7, 61.9, 126.7, 126.7, 128.0, 128.6, 128.7, 142.9, 143.0, 158.1, 159.1, 174.7. EI-MS m/z: 193, 211, 351 $(M)^+$. *Anal*. Calcd for $C_{20}H_{21}N_3O_3$·0.3H_2O (MW: 356.80): C, 67.32; H, 6.10; N, 11.78. Found: C, 67.13; H, 5.99; N, 11.96.

***N*-(3-Carbamoyl-3,3-diphenylpropyl)oxamide (4)** To a solution of **16**[7] (1.58 g, 6.21 mmol), oxamic acid (0.57 g, 6.40 mmol), 1-hydroxybenzotriazole monohydrate (HOBt–H_2O, 1.70 g, 6.40 mmol) and triethylamine (0.65 g, 6.42 mmol) in DMF (30 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC–HCl, 1.21 g, 6.31 mmol). After being stirred for 2.5 h at room temperature, the mixture was allowed to stand overnight at the same temperature. The reaction mixture was poured into water (150 ml), extracted two times with AcOEt and the combined organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) and recrystallized from MeOH–H_2O to give the title compound **4** as a white solid (0.71 g, 35%). **4**: mp 178—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.47—2.51 (2H, m), 2.78—2.83 (2H, m), 6.99 (1H, s), 7.22—7.32 (6H, m), 7.73 (1H, s), 8.02 (1H, s), 8.70 (1H, t, J=5.9 Hz). ^{13}C-NMR (DMSO-d_6) δ: 36.3, 36.4, 58.7, 126.4, 127.8, 128.7, 143.2, 160.2, 162.1, 175.1. IR (KBr) cm^{-1}: 3424, 3360, 3328, 3279, 3191, 1728, 1655, 1620. *Anal*. Calcd for $C_{18}H_{19}N_3O_3$ (MW: 325.36): C, 66.45; H, 5.89; N, 12.91. Found: C, 66.34; H, 5.87; N, 12.86. FAB-MS m/z: 326 $(M+H)^+$.

Ethyl *N*-(3-Carbamoyl-3,3-diphenylpropyl)oxamic Acid (17) To a solution of **16** (6.77 g, 26.6 mmol) in CH_2Cl_2 (200 ml) containing triethylamine (3.00 g, 29.6 mmol) was added dropwise ethyl chlorooxoacetate (4.00 g, 29.3 mmol) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with CH_2Cl_2 (200 ml), washed with water (200 ml) and saturated aqueous sodium bicarbonate (200 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with EtOH (10 ml), and the precipitate was collected by filtration, and dried under vacuum to give the title compound **17** as a white powder (7.29 g, 67%). **17**: mp 203—206 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.3 Hz), 2.69 (2H, t, J=6.8 Hz), 3.21 (2H, q, J=6.4 Hz), 4.31 (2H, q, J=7.3 Hz), 5.70 (2H, d, J=7.8 Hz), 7.26—7.38 (10H, m), 7.96 (1H, br s). ^{3}C-NMR ($CDCl_3$) δ: 13.9, 37.3, 37.8, 59.8, 62.8, 127.4, 128.5, 128.7, 142.7, 156.7 160.6, 176.8. IR (KBr) cm^{-1}: 3443, 1725, 1700, 1660, 1236. FAB-MS m/z: 355 $(M+H)^+$.

***N*-(3-Carbamoyl-3,3-diphenylpropyl)oxamic Acid (5)** A suspension of **17** (10.6 g, 30.0 mmol) and 10% aqueous sodium carbonate (106 ml) in EtOH (500 ml) was refluxed for 4 h. After cooling, the reaction mixture was concentrated under reduced pressure. Water (800 ml) was added to the residue and the insoluble part was removed by filtration. The filtrate was washed with CH_2Cl_2 (400 ml) and AcOEt (400 ml), and neutralized with 2 M HCl. The precipitate was collected by filtration, and purified by recrystallization from EtOH, dried under vacuum at 100 °C to give the title compound **5** as a white solid (6.16 g, 63%). **5**: mp 193—195 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.47—2.51 (2H, m), 2.78—2.83 (2H, m), 6.95 (1H, s), 7.23—7.37 (11H, m), 8.81 (1H, t, J=5.4 Hz), 13.77 (1H, br s). ^{13}C-NMR (DMSO-d_6) δ: 36.3, 36.6, 42.0, 58.8, 126.6, 127.9, 128.8, 143.1, 158.1 161.9, 175.2. IR (KBr) cm^{-1}: 3428, 3319, 3251, 1759, 1654, 1159, 701. *Anal*. Calcd for $C_{18}H_{18}N_2O_4$ (MW: 326.35): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.07; H, 5.58; N, 8.64. FAB-MS m/z: 327 $(M+H)^+$.

2-Acetylamino-*N*-(3-carbamoyl-3,3-diphenylpropyl)acetamide (6) To a solution of **16** (509 mg, 2.0 mmol), *N*-(benzyloxycarbonyl)glycine (418 mg, 2.00 mmol) and HOBt–H_2O (270 mg, 2.00 mmol) in CH_2Cl_2 (10 ml) were added EDC-HCl (383 mg, 2.0 mmol) and triethylamine (558 μl, 4.00 mmol). After being stirred for 8 h at room temperature, the mixture was allowed to stand overnight at the same temperature. The reaction mixture was diluted with AcOEt, washed with 1 M NaOH, 1 M HCl and water, dried over Na_2SO_4, and concentrated under reduced pressure to give crude benzyl [*N*-(3-carbamoyl-3,3-diphenylpropyl)carbamoylmethyl]carbamic acid as a colorless solid. The obtained carbamic acid derivative was dissolved in THF (16 ml), 7.5% Pd–C (162 mg) and acetic anhydride (189 μl, 2.00 mmol) were added. The reaction mixture was stirred for 6 h at room temperature under hydrogen atmosphere, and then DMF was added until the resulting precipitate was dissolved. The catalyst was removed by filtration through celite, and the filtrate was concentrated. The residue was recrystallized from EtOH to give the title compound **6** as a white solid (320 mg, 47%). **6**: mp 214—215 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.84 (3H, s), 2.40—2.44 (2H, m), 2.67—2.73 (2H, m), 3.58 (2H, d, J=5.9 Hz), 7.23—7.35 (10H, m). ^{13}C-NMR (DMSO-d_6) δ: 22.5, 36.2, 36.8, 42.0, 58.7, 126.4, 127.8, 128.7, 143.2, 169.0 169.5, 175.0. IR (KBr) cm^{-1}: 3432, 1682, 1655, 1632. *Anal*. Calcd for $C_{20}H_{23}N_3O_3$ (MW: 353.41): C, 67.97; H, 6.56; N, 11.89. Found: C, 67.95; H, 6.65; N, 11.88. FAB-MS m/z: 354 $(M+H)^+$.

4-[(Acetimidoyl)amino]-2,2-diphenylbutanamide (7) *S*-Benzyl thioacetimidate hydrobromide[8] (4.92 g, 20.0 mmol) was added in small portions to an ice-cooled mixture of **16** (5.09 g, 20.0 mmol) and EtOH (100 ml), and the solution was stirred for 2 h at the same temperature. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with EtOH (50 ml). The resulting precipitates were collected by filtration, and purified by recrystallization (EtOH) to give the hydrobromide of **7** (3.87 g). The obtained hydrobromide **7** (2.63 g, 7.00 mmol) was suspended in water (53 ml) and cooled at 5 °C. 1 M NaOH (7.7 ml, 7.70 mmol) was added to the above mixture, and the mixture was stirred for 2 h at ambient temperature. The resulting precipitate was collected by filtration, and purified by recrystallization (CH_3CN/IPE) to give the title compound **7** as a white powder (1.26 g, 61%). **7**: mp 166—167 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.78 (3H, s), 2.52—2.61 (4H, m), 6.21 (2H, br), 7.10 (1H, s), 7.11—7.30 (10H, m), 8.94 (1H, br). ^{13}C-NMR (DMSO-d_6) δ: 22.8, 36.2, 38.9, 58.4, 126.1, 127.6, 128.6, 144.7, 161.6, 175.1. IR (KBr) cm^{-1}: 3418, 1619, 1384, 695. *Anal*. Calcd for $C_{18}H_{21}N_3O$ (MW: 295.38): C, 73.19; H, 7.17; N, 14.23. Found: C, 73.04; H, 7.18; N, 14.20. FAB-MS m/z: 296 $(M+H)^+$.

References and Notes

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