Bioisoster of Capsaicin: Synthesis of 1-Hydroxy-2-pyridone Analogue

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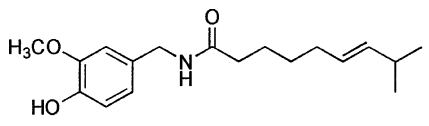
After capsaicin (**1**), a pungent principle of *capsicums*,[1] was known to act on a subset of peripheral sensory neuron,[2] molecular approach toward more potent capsaicin agonists which are anticipated to be useful as novel analgesic agents has been extensively studied.[3] Three parts of capsaicin structure - the aromatic ring region, the amide bond region, and the side chain region - were modified and it was found that the catechol moiety in capsaicin is important for the analgesic activity.[3a]

By application of bioisosterism, we previously found that the analogue which replaced the catechol moiety in dopamine with 1-hydroxy-2-pyridone system also revealed the similar dopaminergic activity.[4] Based on our result, we now replaced the functional catechol moiety in capsaicin with 1-hydroxy-2-pyridone system whose isosteric/isoelectric character is considered to be equivalent. And, therefore, they are interchangeable as far as its contribution to biological activity.[5] Here, we report the synthesis and the biological activity of 1-hydroxy-2-pyridone analogue (**2**) of capsaicin.

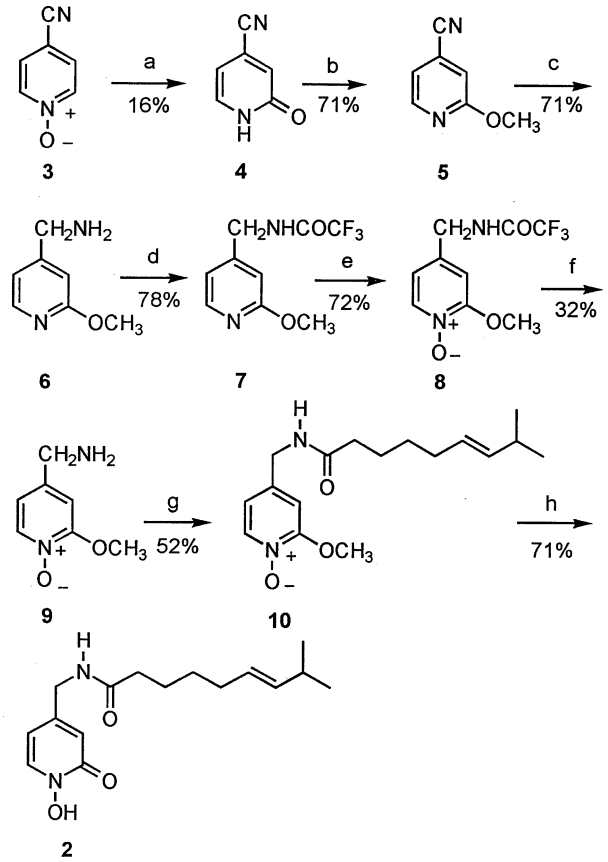
The synthesis of target compound **2** was started with the conversion of pyridine-N-oxide into pyridone compound (Scheme 1). Thus, 4-cyanopyridine-N-oxide **3** was refluxed with acetic anhydride followed by acid hydrolysis with acetic acid to give the pyridone **4**. After *O*-methylation of pyridone,[6] the free amine **6** was obtained from the reduction of the cyano group in **5** with $LiAlH_4$. Protection of the free amine with trifluoroacetyl group followed by N-oxidation of the resulting compound **7** with m-chloroperbenzoic acid gave the N-oxide **8**, where the trifluoroacetyl group was then deprotected under basic condition to give 4-aminomethyl-2-methoxypyridine-1-oxide (**9**). Coupling reaction of **9** with (E)-8-methyl-6-nonenoic acid (**11**), which was prepared by the reported method,[7] under DCC/DMAP condition gave **10** in 52% yield. Finally, the methyl group was removed by refluxing with acetyl chloride followed by hydrolysis with acetone-water mixture[8] to give **2**. However, it is interesting to note that the coupling reaction of 4-aminomethyl-1-hydroxy-2-pyridone (**12**), which was prepared from **8**, with the corresponding acid **11** under various conditions was unsuccessful to obtain **2** (Scheme 2).

The analgesic activity of **2** was determined by the reported

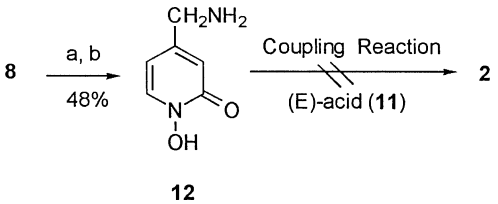


Capsaicin (1)

Figure 1



Scheme 1. (a) i) Ac_2O, reflux, ii) AcOH, reflux, (b) Ag_2CO_3, CH_3I, benzene, (c) $LiAlH_4$, ether, (d) TFAA, CH_2Cl_2, (e) mCPBA, CH_2Cl_2, (f) K_2CO_3, MeOH, (g) (E)-8-Methyl-6-nonenoic acid (**11**), DCC, DMAP, CH_2Cl_2, (h) i) AcCl, ii) H_2O, acetone.



Scheme 2. (a) i) AcCl, ii) H_2O, (b) MeOH : H_2O : c-HCl (1 : 2 : 2).

method[3a] and observed to be inactive (ED_{50} = > 50 μmol/kg).[9] It can therefore be concluded that the catechol moiety in capsaicin makes a major contribution to the analgesic activity.

Experimental

Instrument. Melting points were determined on a

Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz. Chemical shifts were given in relative tetramethylsilane. Infrared spectra were recorded on a Nicolet FT-IR 550 spectrometer. Elemental analyses were performed by Fisons Eager 200 instrument, Italy. Column chromatography was done by using Merck silica gel 60 (230-400 mesh). All reactions were performed under a nitrogen atmosphere.

4-Cyano-2-pyridone (4). A solution of 4-cyanopyridine-N-oxide (50.0 g, 0.140 mol) in acetic anhydride (500 mL) was refluxed for 18 h and then concentrated. The residue was dissolved in ethyl acetate to give black precipitate which was identified with reactant. After filtering the precipitate, the filtrate was concentrated to give a brown residue, which was chromatographed on a silica gel column (ethyl acetate : hexane = 1 : 1) to give 4-cyano-2-acetoxypyridine (11.5 g, 23%) as a yellow solid. mp 60 °C, IR (KBr) 2243, 1775, 1196 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, -CH_3), 7.33 (s, 1H, 3-py-H), 7.44 (d, 1H, 5-py-H, *J* = 4.8), 8.53 (d, 1H, 6-py-H, *J* = 4.8), ^{13}C NMR ($CDCl_3$) δ 20.8, 115.4, 118.7, 123.2, 123.4, 149.7, 158.0, 168.0. A solution of 4-cyano-2-acetoxypyridine (8.5 g, 50 mmol) in acetic acid (300 mL) was heated at 100-110 °C for 3 h and then concentrated. The resulting residue was recrystallized from methanol to give **4** (4.4 g, 70%) as a violet solid. mp 235 °C, IR (KBr) 2237, 1676 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 6.46 (dd, 1H, 5-py-H, *J* = 1.0, 6.6 Hz), 6.97 (s, 1H, 3-py-H), 7.65 (dd, 1H, 6-py-H, *J* = 1.0, 6.6 Hz), 12.25 (br., 1H, -NH), ^{13}C NMR (DMSO-d_6) δ 104.8, 116.5, 123.9, 126.0,138.4, 160.8, Anal. Calcd for $C_6H_4N_2O$: C, 59.99; H, 3.36; N, 23.32. Found: C, 59.78; H, 3.37; N, 23.23.

4-Cyano-2-methoxypyridine (5). To a solution of **4** (6.2 g, 50 mmol) in benzene (50 mL) was added silver carbonate (15 g, 54 mmol) and iodomethane (18 mL, 290 mmol). The reaction mixture was stirred for 48 h at room temperature and then concentrated. The brown residue was chromatographed on a silica gel column (ethyl acetate : hexane = 1 : 1) to give **5** (5.0 g, 71%) as a pale yellow solid. mp 64 °C, IR (KBr) 2237, 1041 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H, -OCH_3), 7.00 (s, 1H, 3-py-H), 7.08 (dd, 1H, 5-py-H, *J* = 1.1, 5.2 Hz), 8.32 (d, 1H, 6-py-H, *J* = 5.2 Hz), ^{13}C NMR ($CDCl_3$) δ 53.9, 114.1, 116.4, 117.5, 122.3, 148.4, 164.3, Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.55; H, 4.50; N, 20.64.

4-Aminomethyl-2-methoxypyridine (6). To a suspension of $LiAlH_4$ (1.6 g, 2.0 eq.) in anhydrous ether (200 mL) was slowly added **5** (2.4 g, 18 mmol) in ether (15 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature and then quenched with 10% aqueous NaOH solution (10 mL). After the resulting gray precipitate was filtered, the organic solvent was removed. The residue was chromatographed on a silica gel column (ethyl acetate : methanol = 1 : 5) to give **6** (1.7 g, 71%) as a yellow oil. IR (neat) 3367, 3317 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 2H, -CH_2), 3.93 (s, 3H, -OCH_3), 6.70 (s, 1H, 3-py-H), 6.83 (d, 1H, 5-py-H, *J* = 5.2 Hz), 8.08 (d, 1H, 6-py-H, *J* = 5.2 Hz), ^{13}C NMR ($CDCl_3$) δ 53.9, 114.1, 116.4, 117.5, 122.3, 148.4, 164.3.

4-Trifluoroacetylaminomethyl-2-methoxypyridine (7). To a solution of **6** (1.0 g, 75 mmol) in methylene chloride (100 mL) was slowly added trifluoroacetic anhydride (1.7 mL). After stirring for 1 h at room temperature, the reaction mixture was neutralized with 10% aqueous $NaHCO_3$ solution and then extracted with methylene chloride (3×50 mL). The organic layer was washed with water (2×50 mL), dried (Na_2SO_4), filtered, and concentrated to give **7** (1.37 g, 78%) as a yellow solid. mp 58 °C, IR (KBr) 3310, 1701, 1147 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H, -OCH_3), 4.34 (d, 2H, -CH_2, *J* = 6.0 Hz), 6.51 (s, 1H, 3-py-H), 6.67 (d, 1H, 5-py-H, *J* = 5.4 Hz), 7.98 (d, 1H, 6-py-H, *J* = 5.4 Hz), ^{13}C NMR ($CDCl_3$) δ 41.9, 53.1, 107.9, 118.5, 146.8, 148.3, 158.2, 164.4, Anal. Calcd for $C_9H_9N_2O_2F_3$: C, 46.16; H, 3.87; N, 11.96. Found: C, 46.00; H, 3.87; N, 11.87.

4-Trifluoroacetylaminomethyl-2-methoxypyridine-N-oxide (8). To a solution of **7** (0.98 g, 4.2 mmol) in CH_2Cl_2 (50 mL) was added m-chloroperbenzoic acid (70-75%, 1.8 g). After the resulting mixture was stirred for 12 h at room temperature, the organic solvent was removed. The residue was chromatographed on a silica gel column (ethyl acetate : hexane = 3 : 1) to give **8** (0.75 g, 72%) as a white solid. mp 180 °C, IR (KBr) 3159, 1724, 1211 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 3.98 (s, 3H, -OCH_3), 4.42 (d, 2H, -CH_2, *J* = 3.1 Hz), 6.93 (d, 1H, 5-py-H, *J* = 6.1 Hz), 7.16 (s, 1H, 3-py-H), 8.23 (d, 1H, 6-py-H, *J* = 6.1 Hz), 10.13 (br., 1H, -NH), ^{13}C NMR (DMSO-d_6) δ 41.4, 57.2, 108.1, 116.6, 137.0, 139.3, 156.4, 157.1, 158.0.

4-Aminomethyl-2-methoxypyridine-N-oxide (9). To a solution of **8** (0.75 g, 30 mmol) in water (10 mL) and methanol (40 mL) was added potassium carbonate (0.81 g). The reaction mixture was stirred for 5 h at room temperature and then concentrated. The residue was chromatographed on a silica gel column (methanol) to afford **9** (0.15 g, 32%) as a yellow oil. IR (KBr) 3418, 1176 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 2H, -CH_2), 4.02 (s, 3H, -OCH_3), 6.85 (dd, 1H, 5-py-H, *J* = 1.5, 6.7 Hz), 6.95 (s, 1H, 3-py-H), 8.14 (d, 1H, 6-py-H, *J* = 6.7 Hz).

(E)-8-Methyl-6-nonenoic Acid (11). This was prepared by following the procedure reported by H. Kaga *et al*..[7] Yellow oil. IR (neat) 3409, 1706, 1265 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 6H, $(CH_3)_2$), 1.42 (q, 2H, C_3-H), 1.63 (q, 2H, C_4-H), 2.02 (q, 2H, C_5-H), 2.32 (m, 1H, C_8-H), 2.36 (t, 2H, C_2-H), 5.35-5.38 (m, 2H, CH=CH), ^{13}C NMR ($CDCl_3$) δ 23.1, 24.2, 26.4, 26.8, 29.2, 34.0, 126.5, 138.0, 180.3.

1-Oxo-2-methoxypyridyl-8-methyl-6-*trans*-nonenamide (10). The mixture of **9** (0.10 g, 64 mmol), (E)-acid **11** (0.12 g, 69 mmol), DCC (0.12 g, 58 mmol), and a catalytic amount of DMAP in methylene chloride (25 mL) was stirred for 8 h at room temperature. After filtration of the precipitate, the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (ethyl acetate : methanol = 1 : 1) to give **10** (98 mg, 52%) as a yellow oil. IR (KBr) 3267, 1654, 1265 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 6H, -$(CH_3)_2$), 1.43 (q, 2H, C_3-H), 1.64 (q, 2H, C_4-H), 1.98 (q, 2H, C_5-H), 2.04 (m, 1H, C_8-H), 2.26 (t, 2H, C_2-H), 3.98

(s, 3H, -OCH_3), 4.36 (d, 2H, -CH_2NH-, J = 6.0 Hz), 5.35-5.38 (m, 2H, CH=CH), 6.78 (d, 2H, 3,5-py-H, J = 6.6 Hz), 8.09 (d, 1H, 6-py-H, J = 5.5 Hz), 8.12 (br., 1H, -NH-), ^{13}C NMR ($CDCl_3$) δ 22.6, 25.2, 29.3. 30.9, 32.2, 36.2, 41.7, 57.2, 107.1, 116.3, 126.3, 138.0, 139.2, 141.9, 157.9, 173.7.

4-Aminomethyl-1-hydroxy-2-pyridone (12). A solution of **8** (150 mg, 6.4 mmol) in acetyl chloride (20 mL) was refluxed for 1 h and then concentrated. The resulting yellow residue dissolved in water (20 mL) was stirred for 14 h at room temperature. After the solvent was evaporated, the crude 1-hydroxy-2-pyridone derivative was obtained as a white solid, which was dissolved in small amount of methanol-water-c-HCl (1 : 2 : 2, 20 mL) again and then refluxed for 17 h. After the reaction mixture was concentrated, the yellow precipitate was recrystallized from ethanol-water to give the HCl salt form of **12** (54 mg, 48%) as a yellow solid. mp 230 °C, IR (KBr) 3427, 1650 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 3.90 (s, 2H, CH_2), 6.35 (d, 1H, 3-py-H, J = 5.0 Hz), 6.60 (s, 1H, 5-py-H), 7.94 (d, 1H, 6-py-H, J = 7.2 Hz), 8.50 (br., 3H, -NH_3^+), ^{13}C NMR (DMSO-d_6) δ 104.1, 118.1, 136.0, 144.8, 157.4. Free base was obtained from the following method; after the salt was dissolved in ammonia solution, extraction with methylene chloride followed by general work-up gave the free base, which was used for the coupling reaction immediately

N-Hydroxy-2-oxopyridyl-8-methyl-6-trans-nonenamide (2). A solution of **10** (70 mg, 2.0 mmol) in acetyl chloride (6 mL) was refluxed for 1 h and then neutralized with 10% aqueous $NaHCO_3$ solution. The aqueous solution was extracted with methylene chloride (3 × 10 mL). The organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated. The resulting yellow residue dissolved in small amount of acetone and water was stirred for 8 h at room temperature. The precipitate was filtered and then dried to give **2** (50 mg, 71%) as a slightly yellow solid. mp 107 °C, IR (KBr) 3410, 3279, 1639 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 6H, $(CH_3)_2$), 1.35 (q, 2H, C_3-H), 1.64 (q, 2H, C_4-H), 1.98 (q, 2H, C_5-H), 2.15 (m, 1H, C_8-H), 2.27 (t, 2H, C_2-H), 4.24 (s, 2H, -CH_2NH-), 5.34 (m, 2H, CH=CH), 6.21 (s, 1H, 5-py-H), 6.40 (s, 1H, 3-py-H), 7.00 (br., 1H, -NH-), 7.64 (d, 1H, 6-py-H, J = 2.1 Hz), ^{13}C-NMR ($CDCl_3$) δ 19.5, 20.8, 21.7, 22.6, 24.5, 30.2, 30.4, 92.9, 107.1, 115.8, 123.3, 124.5, 126.4, 141.8, 176.8.

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