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

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After capsaicin (1), a pungent principle of *capsicums*, was known to act on a subset of peripheral sensory neuron, molecular approach toward more potent capsaicin agonists which are anticipated to be useful as novel analgesic agents has been extensively studied. 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.

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. 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. 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, the free amine 6 was obtained from the reduction of the cyano group in 5 with LiAlH₄. 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, 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 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 method and observed to be inactive (ED₅₀ > 50 μmol/kg). 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 identified with reactant.

To a suspension of LiAlH\(_4\) (1.6 g, 2.0 eq.) in anhydrous ether (200 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature and then quenched with 10% aqueous NaOH solution (200 mL), dried (\(\text{Na}_2\text{SO}_4\)), filtered, and concentrated to give 7 (1.37 g, 78%) as a yellow solid. mp 58 °C, IR (KBr) 3310, 1654, 1265 cm\(^{-1}\), \(^{1}H\) NMR (CDCl\(_3\)) \(\delta\) 3.87 (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 (CDCl\(_3\)) \(\delta\) 41.9, 53.1, 107.9, 118.5, 146.8, 148.3, 158.2, 164.4, Anal. Calcd for C\(_7\)H\(_6\)N\(_2\)O\(_2\)F: 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 (0.75 g, 4.20 mmol) in CH\(_2\)Cl\(_2\) (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 : hexane = 1 : 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\(_6\)) \(\delta\) 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\(_6\)) \(\delta\) 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 (0.8 g). IR (neat) 3267, 1654, 1265 cm\(^{-1}\), \(^{1}H\) NMR (CDCl\(_3\)) \(\delta\) 3.66 (d, 4H, -CH\(_2\), \(J = 6.1\) Hz), 6.93 (s, 1H, 3-py-H), 8.14 (d, 1H, 6-py-H, \(J = 6.7\) Hz). (E)-8-Methyl-6-nonoic Acid (11). This was prepared by following the procedure reported by H. Kaga et al.\(^{3}\) Yellow oil. IR (neat) 3409, 1706, 1265 cm\(^{-1}\), \(^{1}H\) NMR (CDCl\(_3\)) \(\delta\) 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\(_3\)-H), 2.32 (m, 1H, C\(_5\)-H), 2.36 (t, 2H, C\(_2\)-H), 5.35-5.38 (m, 2H, CH=CH). \(^{13}C\) NMR (CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_6\)-H), 2.26 (t, 2H, C\(_2\)-H), 3.98
A solution of reaction immediately work-up gave the free base, which was used for the coupling extraction with methylene chloride followed by general method; after the salt was dissolved in ammonia solution, 144.8, 157.4. Free base was obtained from the following H), 4.24 (s, 2H, -CH$_2$NH-), 5.34 (m, 2H, CH=CH), 6.21 (s, 1H, -OCH$_3$), 4.36 (d, 2H, -CH$_2$NH-, J = 2.1 Hz), 13C-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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References

9. Mouse tail flick test was performed at Center for Drug Discovery, University of Florida, U.S.A. according to the procedure described in reference 3a.