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Bioisosterism: Interchange of 4-OH to 4-NH_2 in Vanillin or Homovanillin Ring of Capsaicinoids

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A series of 4-amino Capsaicin analogs **15**, **17** and **19** were prepared to investigate the bioisosteric effect of 4-amino group, and all these compounds exhibited moderate or weak potency from their analgesic test. From our previous results and others, 4-hydroxyl group as well as 3-methoxy substituent could be crucial for high analgesic activity. This biological result also shows that the activity is sensitive to alkyl chain length in hydrophobic region and the phenylacetic amides **19** are more active than the corresponding urea derivatives **17**.

Key words : Capsaicin, Analgesics, Bioisosteric Effect, Capsaicinoids

INTRODUCTION

Capsaicin is a pungent compound produced by chili peppers and related plants of the Capsicum family, and binds to receptors which was found primarily in polymodal nociceptors (LaHann and Farmer, 1983). Capsaicin initially stimulates polymodal nociceptors and subsequently inhibits them from responding to a variety of stimuli (Holzer, 1991; Buck and Burks, 1986). This biological study led that Capsaicin and its analogs could be useful as a novel class of analgesics. Recently there has been remarkable study in the development of new capsaicinoids through structural modification of Capsaicin. Sandoz Co. research group reported that vanillic urea **2** is one of active compounds in their *in vitro* analgesic assay (Wrigglesworth *et al.*, 1996). We also found that homovanillic amides **3** and **4** showed highly potent analgesic activity in mice test (Park *et al.*, 1991 and Baek *et al.*, 1997). However, these compounds also possess Capsaicin-like side effects, e.g. sedation, vasodilation, ptosis and decrease of respiration. Our major concern is how to reduce accompanied side effects from analgesia. Its problem has long been thought to be difficult to overcome. In the course of our continuing efforts in the development of a new type of analgesics, we became interested in 4-amino-3-methoxybenzyl analogs. They would be interesting compounds because amino group has been used frequently as a bioisoster of hydroxyl in medicinal chemistry. Moreover our preliminary study showed that 4-amino and 4-piperazinyl derivatives are not so potent, but display diminished side effects at the ED_{50} dosage (Park *et al.*, 1993). Therefore, we felt that further SAR study at C-4 with amino moiety is necessary, and decided to prepare 4-amino-3-methoxybenzyl derivatives.

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RESULTS AND DISCUSSION

In the previous our reports (Park *et al.*, 1991 and Baek *et al.*, 1997), we described the synthesis of homovanillic amides **3** and **4** by coupling of 4-hydroxy-3-methoxybenzoic acid with alkylamines. Synthesis of 4-amino version of vanillic or homovanillic derivatives **15**, **17**, and **19** could be accomplished as same manner from 3-methoxy-4-nitro derivatives **7** and **10**. Synthesis of benzylamine derivative **7** was started from the corresponding alcohol **5** by chlorination followed by azidation to provide **6** (Scheme 1). The azido group of **6** was reduced in the presence of nitro group with a selective method using 1,3-propanedithiol and Et_3N (Bayley *et al.*, 1978) to give **7**. 3-Methoxy-4-nitrophenylacetic acid (**10**) was prepared from 3-methoxybenzyl cyanide (**8**) by literature procedure (Gallacher *et al.*, 1995). The hydrophobic parts of **15**, **17** and **19** are the same groups as shown in **3** and **4**. Thus isocyanate **11**, amine **12** and acid **13** were coupled with benzylamine **7** or phenylacetic acid **10** (Scheme 2). DCC coupling of **7** with acid **13** gave **14** in 86% yield, and palladium catalyzed hydrogenation of **14** afforded the corresponding amine **15** in 95% yield. Urea derivatives **17a** and **17b** were obtained from couplings of **7** with isocyanates **11a** and **11b** followed by palladium catalyzed hydrogenation. Phenylacetic amide derivatives **19a**, **19b** and **19c** were afforded

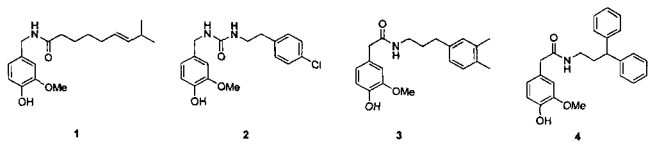
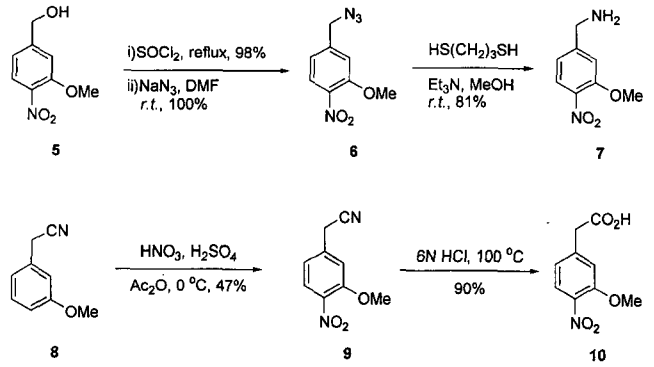


Fig. 1.



Scheme 1.

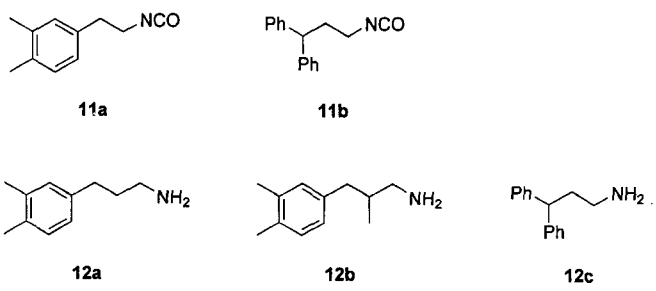
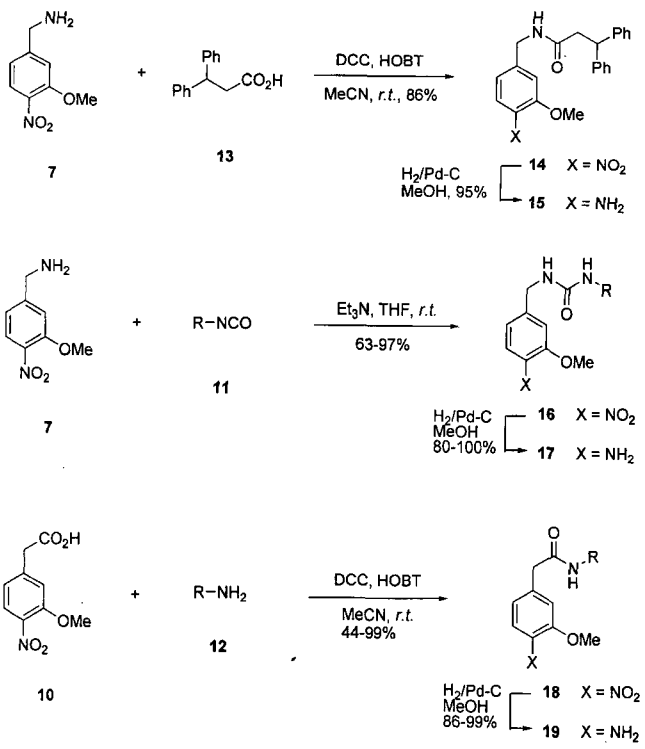


Fig. 2.

from **10** with amines **12a**, **12b** and **12c** by the same manner described for **15**.

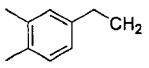
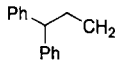
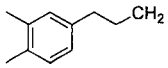
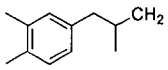
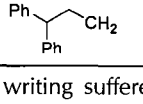
The analgesic activity of the prepared compounds was evaluated by the acetic acid induced writhing test at the Pharmaceutical Screening Laboratory of Korea Research Institute of Chemical Technology. The inhibition data of writhing suffered by the test group were compared with those of the control group, and the results are shown in Table I. Analgesic effect of the amide **15** and the urea **17b** are very weak. This result is consistant with the previous result that the aliphatic chain length between hydrogen bonding species and aromatic ring in hydrophobic part influences strongly in analgesic effect (Park *et al.*, 1991). In general three-carbon length is optimal. Therefore, the weak activity of **15** and **17b**, which have two- and four-carbon lengths is acceptable. In other hands, the urea **17a** has moderate activity, and phenylacetic amides **19** are most active in this series.

In summary, we prepared 4-amino capsaicinoid analogs to investigate the bioisosteric effect of 4-hydroxyl group and all of these compounds show moderate or weak analgesic activity from *in vivo* test. Thus, from our previous results (Lim *et al.*, 1996) and others



Scheme 2.

Table I. *In vivo* analgesic activity evaluated by acetic acid induced writing test

Compound	R	% Inhibition[a]		
		1 mg/kg	4 mg/kg	40 mg/kg
15				22
17a				70
17b				NA[b]
19a			15	100
19b				100
19c		NA[b]	96	100

[a]The number of writing suffered by the test group was compared with that of the control group.
[b]No activity was observed.

(Walpole *et al.*, 1993 and Janusz *et al.*, 1993), 4-hydroxyl group as well as 3-methoxy substituent could be crucial for high analgesic activity. This biological result also shows that the activity might be sensitive to alkyl chain length in hydrophobic region and

phenylacetic amides **19** were more active than the corresponding urea derivatives **17**.

MATERIALS AND METHODS

All reactions carried out N_2 atmosphere unless otherwise noted. MeCN and CH_2Cl_2 were distilled from CaH_2 prior to use. Organic extracts or filtrates were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography was performed with Merck-EM Type 60 (230~400 mesh) Silica Gel (flash). ^1H NMR spectra were measured by Varian Gemini 200 MHz spectrometer. Chemical shifts were reported in ppm (δ) relative to TMS as internal standard. Mass spectrometric data determined by use of the electron impact (EIMS) method were reported as *m/z* (relative intensity). Melting points were uncorrected.

3-Methoxy-4-nitrobenzyl azide (6)

A solution of 3-methoxy-4-nitrobenzyl alcohol (5.0 g, 27.3 mmol) and $SOCl_2$ (4.9 g, 41.0 mmol) was heated at reflux temperature for 12 h. The mixture was diluted with CH_2Cl_2 and then washed with aqueous $NaHCO_3$ followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 3-methoxy-4-nitrobenzylchloride (5.4 g, 98%) as a solid: mp 65~66°C; ^1H NMR ($CDCl_3$) δ 3.97 (s, 3H, OCH_3), 4.58 (s, 2H, CH_2Cl), 7.01 (dd, *J*=8.2, 1.9 Hz, 1H, ArH), 7.11 (d, *J*=1.9 Hz, 1H, ArH), 7.83 (d, *J*=8.2 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 201 (M^+, 47), 166 (M^+-Cl, 5), 154 (100), 105 (77), 89 (62), 77 (58).

A solution of the 3-methoxy-4-nitrobenzylchloride (2.3 g, 11.4 mmol) and NaN_3 (0.80 g, 12.5 mmol) in DMF (10 mL) was stirred at *r.t.* for 4 h. DMF was removed under high vacuum and water was added. The mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **6** (2.6 g, 100%) as an oil: ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2N_3), 6.91~7.04 (m, 2H, ArH), 7.81 (d, *J*=8.2 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 208 (M^+, 59), 207 (21), 166 (21), 133 (30), 107 (50), 77 (100), 63 (80).

3-Methoxy-4-nitrobenzylamine (7)

To a solution of **6** (2.10 g, 10 mmol) in MeOH (0.2 M solution) was added 1,3-propanedithiol (1.10 g, 40 mmol) and Et_3N (4.0 g, 40 mmol). After stirring at *r.t.* for 24 h, the mixture was concentrated *in vacuo*. 1N NaOH solution was added and the mixture was extracted with CH_2Cl_2. Normal work up gave **7** (1.5 g, 80%) as solid: mp 49~50°C; ^1H NMR ($CDCl_3$) δ 1.49 (s, 2H, NH_2), 3.95 (s, 2H, CH_2NH_2), 3.96 (s, 3H, OCH_3), 6.95 (dd, *J*=8.3 Hz, 1H, ArH), 7.10 (d, *J*=1.5 Hz, 1H, ArH), 7.84 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 182 (M^+, 32), 136 (90), 134 (50), 105 (61), 79 (100), 77 (71).

4-Amino-3-methoxyphenylacetic acid (10)

^1H NMR ($CDCl_3$) δ 3.72 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 6.98 (dd, *J*=8.1, 1.5 Hz, 1H, ArH), 7.04 (d, *J*=1.5 Hz, 1H, ArH), 7.86 (d, *J*=8.1 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 211 (M^+, 43), 181 (33), 120 (82), 105 (100).

2-(3,4-Dimethylphenyl)ethyl isocyanate (11a)

A mixture of 2-(3,4-dimethylphenyl)ethyl amine HCl salt (1.20 g, 6.5 mmol) and diphosgene (1.30 g, 6.6 mmol) in toluene (20 mL) was heated at reflux temperature for 2 h. The mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give quantitative amount of **11a** as a crude liquid, which was used for next step without further purification: ^1H NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.82 (t, *J*=7.12 Hz, 2H, CH_2-CH_2NCO), 3.47 (t, *J*=7.1 Hz, 2H, CH_2NCO), 6.96~7.10 (m, 3H, ArH); EIMS *m/z* (rel. intensity) 175 (M^+, 34), 119 (100), 91 (32), 77 (14).

3,3-Diphenylpropylisocyanate (11b)

Reaction of 3,3-diphenylpropylamine (0.40 g, 1.9 mmol) and diphosgene (0.37 g, 0.23 ol) in toluene (10 mL) was carried out for 2 h as described for **11a**, which provided quantitative amount of **11b**: ^1H NMR ($CDCl_3$) δ 2.29~2.36 (m, 2H, $CH_2CH(Ph)_2$), 3.24 (t, *J*=6.6 Hz, 2H, CH_2NCO), 4.05 (t, *J*=7.7 Hz, 1H, $CH(Ph)_2$), 7.14~7.33 (m, 10H, ArH); EIMS *m/z* (rel. intensity) 237 (M^+, 7), 193 (27), 167 (100), 165 (64), 152 (33).

1-[2-(3,4-Dimethylphenyl)ethyl]-3-(3-methoxy-4-nitrobenzyl)urea (16a)

To a solution of **7** (1.20 g, 6.5 mmol) and Et_3N (0.7 g, 7.2 mmol) in THF (30 mL) was added a solution of **11a** (1.10 g, 6.5 mmol) in THF (20 mL), and the mixture was stirred at *r.t.* for 13 h. Saturated $NaHCO_3$ solution was added and then the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give **16a** (2.24 g, 97%) as a solid: mp 146~147°C; ^1H NMR ($CDCl_3$) δ 2.17~2.28 (m, 2H, NCH_2CH_2), 2.72 (t, *J*=6.8 Hz, 2H, NHCH2CH2), 3.90 (s, 3H, OCH_3), 4.33 (d, *J*=6.2 Hz, 2H, $ArCH_2NH$), 4.62 (br t, 1H, NH), 4.95 (br t, 1H, NH), 6.83~7.05 (m, 5H, ArH), 7.76 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 357 (M^+, 3), 324 (9), 193 (7), 132 (100), 119 (34).

1-(3,3-Diphenylpropyl)-3-(3-methoxy-4-nitrobenzyl) urea (16b)

Reaction of **7** (0.35 g, 1.9 mmol), **11b** (0.45 mg, 1.9 mmol) and Et_3N (0.23 g, 2.8 mmol) in THF was carried

out as described for **16a**, which provided **16b** (0.50 g, 63%) as a solid: mp 154~155°C; ^{1}H NMR ($CDCl_3$) δ 2.26 (q, *J*=7.6 Hz, 2H, $C\underline{H}_2CH(Ph)_2$), 3.09~3.19 (m, 2H, $NHC\underline{H}_2CH_2$), 3.87 (s, 3H, OCH_3), 3.94 (t, *J*=7.8 Hz, 1H, $C\underline{H}(Ph)_2$), 4.32 (d, *J*=6.2 Hz, 2H, $ArC\underline{H}_2NH$), 4.43 (br t, 1H, NH), 4.69 (br t, 1H, NH), 6.85 (dd, *J*= 8.3, 1.5 Hz, 1H, ArH), 6.95 (d, *J*=1.5 Hz, 1H, ArH), 7.15~7.26 (m, 10H, ArH), 7.77 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 419 (M^+, 56), 239 (28), 194 (70), 193 (100).

N-(3-Methoxy-4-nitrobenzyl)-3,3-diphenylpropionamide (14)

To a solution of **7** (0.30 g, 1.6 mmol), **13** (0.37 g, 1.6 mmol) and HOBT (0.24 g, 1.8 mmol) in MeCN (20 mL) was added DCC (0.37 g, 1.8 mmol), and the mixture was stirred at *r.t.* for 2 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (EtOAc:n-hexane=2:1) to provide **14** (0.55 g, 86%) as a solid: mp 129~130°C; ^{1}H NMR ($CDCl_3$) δ 2.97 (d, 2H, *J*=7.8 Hz, $C\underline{H}_2CH(Ph)_2$), 3.81 (s, 3H, OCH_3), 4.32 (d, *J*=5.9 Hz, 2H, CH_2NHCO), 4.59 (t, *J*= 7.8 Hz, 1H, $CH(Ph)_2$), 5.74 (br t, 1H, NH), 6.35 (dd, *J*= 8.3, 1.5 Hz, 1H, ArH), 6.75 (d, *J*=1.5 Hz, 1H, ArH), 7.15~7.30 (m, 10H, ArH), 7.64 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 390 (M^+, 53), 223 (100), 180 (26), 167 (88).

N-[3-(3,4-Dimethylphenyl)propyl]-2-(3-methoxy-4-nitrophenyl)acetamide (18a)

A solution of **10** (0.60 g, 2.84 mmol), **12a** (0.60 g, 2.84 mmol) and HOBT (0.42 g, 3.1 mmol) in MeCN (20 mL) was added DCC (0.64 g, 3.1 mmol), and the mixture was stirred at *r.t.* for 1 h. Saturated $NaHCO_3$ solution was added and then the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (EtOAc:n-hexane=1:1) to provide **18a** (1.0 g, 99%) as a solid: mp 95~98°C; ^{1}H NMR ($CDCl_3$) δ 1.80 (quint, *J*=7.7 Hz, 2H, $CONHCH_2C\underline{H}_2$), 2.23 (s, 6H, $2CH_3$), 2.55 (t, *J*=7.7 Hz, 2H, $CH_2C\underline{H}_2Ar$), 3.28 (q, *J*=7.1 Hz, 2H, $CONHC\underline{H}_2$), 3.53 (s, 2H, $C\underline{H}_2CONH$), 3.96 (s, 3H, OCH_3), 5.45 (br s, 1H, NH), 6.84~7.05 (m, 5H, ArH), 7.85 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 356 (M^+, 25), 339 (19), 146 (64), 131 (100), 119 (85).

N-1-[3-(3,4-Dimethylphenyl)-2-methylpropyl]-2-(3-methoxy-4-nitrophenyl)acetamide (18b)

Reaction of **10** (0.50 g, 2.4 mmol), **12b** (0.42 g, 2.4 mmol), HOBT (0.35 g, 2.6 mmol) and DCC (0.54 g, 2.6 mmol) in MeCN (20 mL) was carried out as described for **18a** to provide **18b** (0.73 g, 72%) as a solid: mp 100~101°C; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, *J*=6.6 Hz, 3H, $CH(C\underline{H}_3)CH_2$), 1.86~2.04 (m, 1H, $C\underline{H}(CH_3)CH_2$), 2.22 (s, 6H, $2CH_3$), 2.35~2.56 (m, 2H, $CH(CH_3)C\underline{H}_2Ph$), 3.16 (t, *J*=6.6 Hz, 2H, $CONHC\underline{H}_2$), 3.50 (s, 2H, $C\underline{H}_2CONH$), 3.94 (s, 3H, OCH_3), 5.44 (br s, 1H, NH), 6.82~7.26 (m, 5H, ArH), 7.82 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 371 (M^+, 20), 224 (16), 160 (75), 145 (100), 119 (33).

N-(3,3-Diphenylpropyl)-2-(3-methoxy-4-nitrophenyl)acetamide (18c)

Reaction of **10** (0.30 g, 1.4 mmol), **12c** (0.30 g, 1.4 mmol), HOBT (0.21 g, 1.5 mmol) and DCC (0.32 g, 1.5 mmol) in MeCN (20 mL) was carried out as described for **18a** to provide **18c** (0.25 g, 44%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.25 (q, *J*=7.6 Hz, 2H, $CONHCH_2C\underline{H}_2$), 3.18~3.28 (m, 2H, $CONHC\underline{H}_2$), 3.44 (s, 2H, $C\underline{H}_2CONH$), 3.87 (t, *J*=7.6 Hz, 1H, $CH(Ph)_2$), 3.92 (s, 3H, OCH_3), 5.36 (br s, 1H, CONH), 6.82 (dd, *J*=8.3, 1.5 Hz, 1H, ArH), 6.97 (d, *J*=1.5 Hz, 1H, ArH), 7.12~7.30 (m, 10H, ArH), 7.80 (d, *J*=8.3 Hz, 1H, ArH); EIMS *m/z* (rel. intensity) 404 (M^+, 50), 387 (16), 224 (33), 207 (41), 167 (100).

Typical procedure for palladium catalyzed hydrogenation

A mixture of **14** (0.50 g, 1.3 mmol) and 10% Pd/C (0.05 g) in MeOH (20 mL) was stirred under H_2-Balloon. The mixture was passed through a celite pad and the filtrate was concentrated *in vacuo*, which was purified by column chromatography (EtOAc:n-hexane=2:1) to provide **15** (0.44 g, 95%) as a solid.

N-(3-Amino-4-nitrobenzyl)-3,3-diphenylpropionamide (15)

mp 114~115°C; ^{1}H NMR ($CDCl_3$) δ 2.89 (d, *J*=7.8 Hz, 2H, $C\underline{H}_2CH(Ph)_2$), 3.74 (s, 3H, OCH_3), 4.16 (d, *J*=5.4 Hz, 2H, $C\underline{H}_2NHCO$), 4.60 (t, *J*=7.8 Hz, 1H, $C\underline{H}(Ph)_2$), 5.44 (br t, 1H, NH), 6.45 (dd, *J*=7.8, 1.7 Hz, 1H, ArH), 6.48 (d, *J*=1.7 Hz, 1H, ArH), 6.55 (d, *J*=7.8 Hz, 1H, ArH), 7.16~7.27 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 43.3, 43.6, 47.3, 55.4, 110.2, 114.6, 120.4, 126.4, 127.7, 127.9, 128.5, 135.4, 143.6, 147.2, 170.6; EIMS *m/z* (rel. intensity) 360 (M^+, 55), 193 (45), 165 (26), 150 (38), 136 (100).

1-(4-Amino-3-methoxybenzyl)-3-[2-(3,4-dimethylphenyl)ethyl]urea (17a)

Yield 100%; mp 113~114°C; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 6H, $2CH_3$), 2.67 (t, *J*=7.0 Hz, 2H, $NHCH_2C\underline{H}_2$), 3.30~3.40 (m, 2H, $CONHC\underline{H}_2$), 3.78 (s, 3H, OCH_3), 4.15 (d, *J*=5.5 Hz, 2H, $ArC\underline{H}_2NHCO$), 4.58 (br t, 1H, NH), 4.72 (br t, 1H, NH), 6.55~6.66 (m, 3H, ArH), 6.83~7.03 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.2,

19.7, 35.8, 41.7, 44.7, 55.4, 109.9, 114.6, 120.1, 126.0, 129.0, 129.7, 130.0, 134.5, 135.3, 136.4, 136.7, 147.4, 158.0; EIMS *m/z* (rel. intensity) 327 (M^+, 38), 195 (19), 179 (18), 136 (100).

1-(4-Amino-3-methoxybenzyl)-3-(3,3-diphenylpropyl) urea (17b)

Yield 80%; mp 140~141°C; ^{1}H NMR ($CDCl_3$) δ 2.20 (q, *J*=7.3 Hz, 2H, $C\underline{H}_2CH(Ph)_2$), 2.82 (s, 2H, NH2), 3.08 (q, *J*=6.6 Hz, 2H, $CONHC\underline{H}_2$), 3.78 (s, 3H, OCH_3), 3.86 (t, *J*=7.9 Hz, 1H, $CH(Ph)_2$), 4.14 (d, *J*=5.4 Hz, 2H, $ArC\underline{H}_2NHCO$), 4.44 (br s, 1H, NH), 4.61 (br s, 1H, NH), 6.49 (d, *J*=8.0 Hz, 1H, ArH), 6.68 (d, *J*=1.8 Hz, 1H, ArH), 6.76 (dd, *J*=8.0, 1.8 Hz, 1H, ArH), 7.10~7.27 (m, 10H, ArH).

2-(4-Amino-3-methoxyphenyl)-*N*-[3-(3,4-dimethylphenyl) propyl]acetamide (19a)

Yield 86%; mp 183~185°C; ^{1}H NMR (DMSO-d_6) δ 1.64 (quint, J=7.3 Hz, 2H, $CONHCH_2C\underline{H}_2$), 2.16 (s, 6H, $2CH_3$), 2.46 (t, *J*=7.7 Hz, 2H, CH_2Ar), 2.97~3.03 (m, 2H, $CONHC\underline{H}_2$), 3.33 (s, 2H, $C\underline{H}_2CONH$), 3.79 (s, 3H, OCH_3), 5.43 (br s, 1H, NH), 6.72~7.02 (m, 6H, ArH), 8.07 (br t, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 18.9, 19.4, 31.0, 32.0, 38.2, 42.2, 55.6, 112.3, 118.6, 121.2, 125.6, 127.2, 129.3, 129.5, 131.3, 133.2, 135.8, 138.9, 149.0, 170.1; EIMS *m/z* (rel. intensity) 326 (M^+, 14), 136 (100), 122 (17), 105 (6).

2-(4-amino-3-methoxyphenyl)-*N*-1-[3-(3,4-Dimethyl-phenyl)-2-methylpropyl]acetamide (19b)

Yield 99%; ^{1}H NMR ($CDCl_3$) δ 0.78 (d, *J*=6.8 Hz, 3H, $CH(C\underline{H}_3)CH_2$), 1.74~1.83 (m, 1H, $C\underline{H}(CH_3)CH_2$), 2.21 (s, 6H, $2CH_3$), 2.22 (dd, *J*=13.5, 7.9 Hz, 1H, $CH(CH_3)C\underline{H}_2Ar$), 2.47 (dd, *J*=13.5, 6.2 Hz, 1H, $CH(CH_3)C\underline{H}_2Ar$), 3.04~3.14 (m, 2H, $CONHC\underline{H}_2$), 3.45 (s, 2H, CH_2CO), 3.82 (s, 3H, OCH_3), 5.45 (br s, 1H, NH), 6.60~6.98 (m, 5H, ArH), 7.00 (d, *J*=7.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.5, 19.2, 19.7, 35.4, 40.4, 43.6, 44.9, 55.4, 111.4, 115.1, 122.0, 124.8, 126.3, 129.5, 130.3, 134.0, 135.4, 136.3, 137.5, 147.6, 171.8; EIMS *m/z* (rel. intensity) 340 (M^+, 24), 179 (3), 136 (100), 121 (29).

2-(4-Amino-3-methoxyphenyl)-*N*-(3,3-diphenylpropyl) acetamide (19c)

Yield 86%; 210°C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.14~2.22 (m, 2H, $C\underline{H}_2CH(Ph)_2$), 2.89~2.99 (m, 2H, $CONHC\underline{H}_2$), 3.43 (s, 2H, $C\underline{H}_2CONH$), 3.85 (s, 3H, OCH_3), 3.97 (t, *J*=7.7 Hz, 1H, $CH(Ph)_2$), 6.87~7.38 (m, 13H, ArH), 8.26 (br t, 1H, CONH), 9.90 (br s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ 34.5, 37.4, 42.2, 47.8 56.0, 113.1, 119.2, 121.3 123.3, 126.1, 127.5, 128.4, 137.8, 144.6, 151.8, 169.6; EIMS *m/z* (re. intensity) 347 (M^+, 25), 165 (4), 136 (100), 135 (44), 56 (18).

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REFERENCES CITED

Baek, G. H., Jung, Y. S., Cho, S. J., Seong, C. M. and Park, N. S., Homovanillic amide derivatives as capsaicin analogs and their analgesic activity. *Arch. Pharm. Res.*, 20, 659-661 (1997).

Bayley, H., Standring, D. N. and Knowles, J. R., Propane-1,3-dithiol: a selective reagent for the efficient reduction of alkyl and aryl azides to amines. *Tetrahedron Lett.*, 39, 3633-3634 (1978).

Buck, S. H. and Burks, T. F. The neuropharmacology of capsaicin: review of some recent observations. *Pharmacological Reviews*, 38, 179-226 (1986).

Gallacher, G., Smith, C. Z. and Hawkes, G. E., Synthesis of a homovanillic acid immunogen that incorporates an isostric group designed to generate antibodies with improved specificaity. *Biogenic Amines*, 11, 49-62 (1995).

Holzer, P. Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacological Reviews*, 43, 143-201 (1991).

LaHann, T. R. and Farmer, R. W., Antinociceptive actions of capsacin in rodents. *Proc. West. Pharmacol. Soc.*, 26, 145-149 (1983).

Lim, H.-J., Jung, Y. S., Ha, D.-C., Seong, C.-M., Lee, J.-C., Choi, J., Choi, S. W., Han, M.-S., Lee, K.-S. and Park, N.-S., Synthesis of homavanillic amide derivatives and their analgesic activity. *Arch. Pharm. Res.*, 19, 246-247 (1996).

Park, N.-S., Ha, D.-C, Choi, J.-K., Kim, H.-S., Lim, H.-J. and Lee, B.-Y., N-Aralkylated 4-(2-aminoethoxy) phenylacetamide derivatives as potent analgesic and antiinflammatory agents. *Korean J. of Med. Chem.*, 1, 36-43 (1991).

Park, N.-S., Choi, J.-K., Kim, H.-S., Lee, B.-Y. and Ha, D.-C., Pain reducing effects of 4-amino and 4-(1-piperazinyl) phenylacetamide derivatives. *Korean J. of Med. Chem.*, 3, 116-123 (1993).

Walpole, C. S. J., Wrigglesworth, R., Bevan, S. J., Campbell, E. A., Dray, A., James, I. F., Perkins, M. N., Reid, D. J. and Winter, J., Analogues of capsaicin with agonist activity as novel analgesic agents; structure-activity studies. 1. The aromatic "A-region". *J. Med. Chem.*, 36, 2362-2372 (1993).

Wrigglesworth, R., Walpole, C. S. J., Bevan, S., Campbell, E. A., Dray, A., Hughes, G. A., James, I., Masdin, K. J. and Winter, J., Analogues of capsaicin with agonist activity as novel analgesic agents: structure-activity studies. 4. Potent, orally active analgesics. *J. Med. Chem.*, 39, 4942-4951 (1996).