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Synthesis of Homovanillic Amide Derivatives and Their Analgesic Activity

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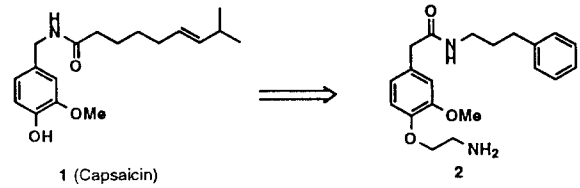
Capsaicin, *trans*-8-methyl-*N*-vanillyl-6-nonenamide **1**, is the primary pungent component in red pepper which is known to exhibit antinociceptive activity by interacting at a specific recognition site (receptor) expressed predominantly by primary afferent neurons (LaHann and Farmer, 1983). The actual existence of this receptor has been demonstrated by the specific binding of [^{3}H]resiniferatoxin, an ultrapotent capsaicin analog (Szallasi and Blumberg, 1990; Szallasi and Blumberg, 1991). Initial studies (Szolcsanyi and Jancso-Gabor, 1975; Szolcsanyi and Jancso-Gabor, 1976) and recent works by the groups at Procter & Gamble Co. (Janusz *et al.*, 1993) and Sandoz Co. (Walpole *et al.*, 1993) elaborated the structure-activity relationships for irritability and analgesic activity of capsaicin analogs, respectively.

In the previous reports (Park *et al.*, 1991, and 1993), we described the synthesis and analgesic effects of various homovanillic amides as analogs of capsaicin. In the study, we tried to enhance the analgesic activity of capsaicin by structural modification. Our study has been performed in three directions. First, the amide bond of capsaicin was transposed. Second, a phenyl ring was introduced to replace a double bond of capsaicin. Finally, aminoethylation was performed on 4-hydroxy group of capsaicin to improve oral bioavailability. These studies have led to *N*-(3-phenylpropyl)homovanillic amide **2** which has high analgesic activity.

Our continuing efforts in this area have focused on the introduction of various substituents on the phenyl ring of **2** as well as their pharmacological studies. We report herein the synthesis of homovanillic amide

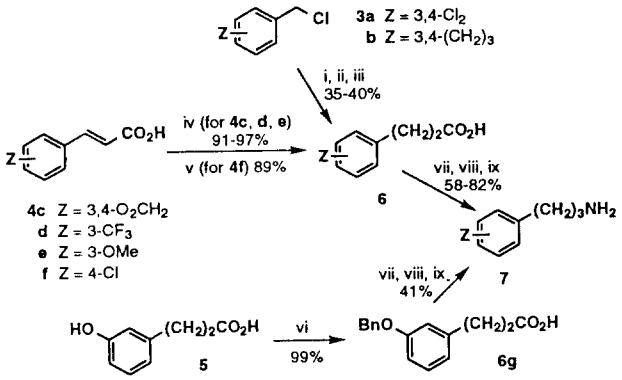


1 (Capsaicin) 2

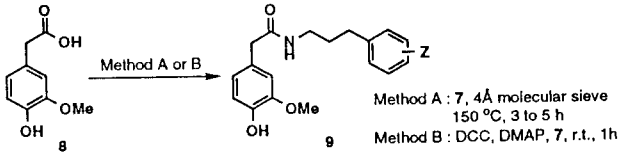
derivatives and their analgesic activity.

The various amines **7** used for preparation of homovanillic amide derivatives were prepared from readily available benzyl chlorides **3** or cinnamic acid derivatives **4** or **5** (Scheme 1). Either two-carbon homologation of benzyl chlorides **3** or hydrogenation of cinnamic acid derivatives (**4** or **5**) gave 3-arylpropionic acids **6** which were converted to corresponding amines **7**.

The next step of this work involved the preparation of amides **9** by coupling of these various amines **7** with homovanillic acid **8** (Scheme 2). The coupling was accomplished by either method of heating at 150°C for 3 to 5 hours in the presence of powdered 4Å molecular sieves in 80 to 90% yields (Method A, Cossy and Pale-Grosdemange, 1989) or DCC cou-



Scheme 1. (i) NaOEt, $CH_2(CO_2Et)_2$, EtOH, reflux, 4h (ii) NaOH, H_2O, reflux, 1h (iii) H_2SO_4, H_2O, 100°C, 12h (iv) H_2/Pd-C, MeOH, r.t., 3h (v) NH_2NH_2, $CuSO_4$, EtOH, r.t., 24h (vi) BnBr, K_2CO_3, acetone, reflux, 5h (vii) $SOCl_2$, reflux, 1h (viii) NH_3, H_2O-Et_2O, 0.5h (ix) LAH, THF, 0°C to reflux 1h



Scheme 2.

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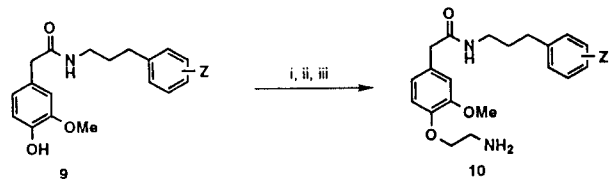

Scheme 3. (i) NaH, $BrCH_2CH_2Br$, THF, reflux, 24h, 47-67% (ii) NaN_3, $(n\text{-}Bu)_4NBr$, PhH, reflux, 7h, 80-95% (iii) H_2, Pd-C, MeOH, r.t., 3h, 65-92%

Table 1. Analgesic Activity of Homovanillic amide Derivatives **10**

Compound	Z	Coupling Method (**8** to **9**)	ED_{50} (mg/Kg) AA (*p.o.*)[a]	PBQ (*p.o.*)[b]
ketoprofen			3.61	
ibuprofen			91.2	
indomethacin			9.10	
aspirin			72.4	
2			2.50	2.58
10a	3,4-Cl_2	A	0.66	
10b	3,4-$(CH_2)_3$[c]	B		1.56
10c	3,4-(O_2CH_2)	A	0.80	
10d	3-CF_3	A	1.54	
10e	3-OMe	A	1.25	
10f	4-Cl	A	0.40	
10g	3-OBn	A	28.8	

[a]acetic acid induced writhing test (oral administration)
[b]phenylbenzoquinone induced writhing test (oral administration)
[c]3 to 1 mixture of 3,4-$(CH_2)_3$ and 2,3-$(CH_2)_3$

pling method over 70% yields (Method B).

Aminoethylation on phenolic hydroxy group of **9** was accomplished by three consequent steps (Scheme 3); (i) bromoethylation with 1,2-dibromoethane, (ii) azidation with NaN_3 and catalytic amount of $(n\text{-}Bu)_4NBr$, and (iii) reduction of azide to amine by catalytic hydrogenation.

The analgesic activity of the prepared compounds was evaluated by the acetic acid-induced or PBQ-induced writhing test by oral administration. The activity of most derivatives is higher than that of unsubstituted compound **2** and compounds with Cl-substituent (**10a** and **10f**) are the most potent. 3-OMe and 3-CF_3 substituted compounds (**10e** and **10d**) show almost equal activity, and they are much more active than 3-OBn derivative **10g**. It is interesting because OMe and OBn are electron donating groups, whereas CF_3 is a strong electron withdrawing group. Thus, it seems that the substituent of proper size on the phenyl ring is needed to show high analgesic activity, especially at 3 and/or 4 positions.

ACKNOWLEDGEMENT

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