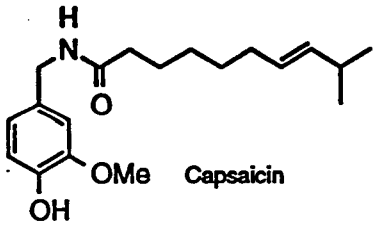
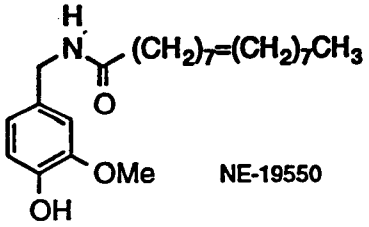
Development of Non-Narcotic Analgesic Agents

Park, No-Sang
Korea Research Institute of Chemical Technology
P. O. Box 9, Daedeogdanji, Daejeon, KOREA 305-606

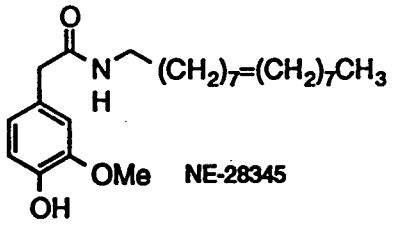
Capsaicin [N-(4-hydroxy-3-methoxybenzyl)-*trans*-8-methyl-6-nonenamide], a pungent principle of red pepper, is known to induce analgesia. Though it has shown remarkable pharmacological activity, the toxicity and side effects inhibited its wider application. The interest has been renewed by the emergence of its agonists, resineferatoxin and ruthenium red. Recently, few successful capsaicinoids including Olvanil(NE-19550), NE-28345, and NE-21610 were reported.



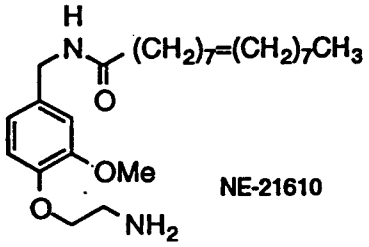
Capsaicin



NE-19550



NE-28345



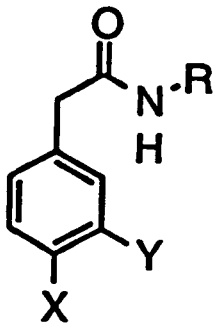
NE-21610

Our earlier studies showed that the transposition of amide fuctionality improved analgesic activity. Introduction of alkyl-substituted phenylalkylamine instead of unsaturated alkylamines played a crucial role, possibly due to increased lipophilicity. The *p*-hydroxyphenylacetamides showed strong analgesic activity in mice by *s.c.* administration, but also displayed side effects typically observed in case of capsaicin. The activity decreased sharply when administrered orally.

Chemistry

Most of the arakylamines required for preparation of phenylacetamide derivatives were prepared from readily available benzyl chorides or cinnamic acid derivatives, except halogenated phenylpropylamines. The condensation of the amines and 3-substitued 4-hydroxyphenylacetic acids was performed by simply heating a mixture of acid, amine, and powdered 4 A^0molecular sieves at about 150℃ for 3-5 hours to provide the amines in 80-90% yields except 3-nitro derivatives which were prepared by way of acid chlorides.

The aminoethylation of phenolic hydroxyl group was accomplished in three step sequence: bromoethylation, azide substitution, hydrogenolysis. For 3-nitro derivatives, the azide was reduced by triphenylphosphine-mediated hydrolysis followed by chromatographic separation.



$X = OH, OCH_2CH_2NH_2, N(CH_2CH_2)_2NH$
$Y = OMe, OH, F, Cl, NH_2, NO_2$
$R = (CH_2)_nAr \ (n = 2, 3, 4, 5)$

Various derivatives with 4-amino group were also prepared. 3-Hydroxy or 3-methoxy derivatives were obtained by nitration and reduction of 3-substituted phenylacetamides. The nitration did not proceed cleanly, giving the desired nitro compounds in about 30% yields. 4-Amino group was transformed to

acetamide, glycolic amide, glycinamide, urea, thiourea and piperazine. Introduction of piperazine was accomplished by reacting 4-amino derivatives with *bis*(2-chloroethyl)amine in toluene.

3-Hydroxy-4-aminoethoxy derivative was prepared from 3-benzyloxy-4-hydroxyphenyl-acetic acid which was obtained by partial protection and separation of ethyl 3,4-dihydroxy-phenylacetate. Benzoxazolineacetic acid was prepared from 3-hydroxyphenylacetamide by nitration, catalytic hydrogenation, amidation with Cbz-Glycyl chloride, and acid catalyzed cylization-dehydration followed by hydrogenolysis of Cbz protection group.

Pharmacology

The analgesic activities of the synthesized compounds were evaluated by acetic acid-induced writhing test and phenyl-1,4-benzoquinone (PBQ)-induced writhing test in mice. The results are shown on Table I, and included for comparison are activities of antipyretic and narcotic analgesics. *p*-Hydroxycetamides gave ED_{50} values of 0.1-10mg/kg(i.p.). The 4-aminoethoxylated phenylacetamides exhibit analgesic and antiinflammatory effects by *p.o.* similar to those *p*-hydroxyacetamides by *s.c.* with much less toxicity observed. This class of compounds displayed stronger analgestic activities compared to classical antipyretics. Among the tested compounds, KR-25018 and KR-24041 were comparable to morphine and significantly superior to other reference drugs.

The methylene chain length (n=1-5) does not affect much on the activity though the activity is higher with n of 3. The position of methyl substituents on phenyl ring of aralkyl part of the amide also plays a role in enchancing the activity with methyl groups on meta and/or para position of phenyl ring preferred.

The substituent on meta position of phenylacetic acid portion also affects the activity. Presence of fluorine or methoxy group (X = F or OCH_3) caused enhancement of activity compared to hydrogen or chlorine. This indicates that an electronic factor of the substituent on the phenyl group, rather than a

steric factor, influences the activity. Though the ED_{50} values of some of fluoro derivatives are lower than those of corresponding methoxy derivatives, the dose-response curves of fluoro derivatives are relatively flat compared to those of methoxy derivatives.

The analgesic activities were confirmed by other tests, *e.g.*, Randall-Selitto test[10], tail-flicktest, hot-plate test, and tail-pinch test. Tail-flick test and hot-plate test suggested that KR-25018 was more effective than morphine and also behaved as a central analgesic.

Some aspects of toxicity were also studied. The LD_{50}/ED_{50} values for mice were at least 1,800 for tested compounds. Dimethyl derivatives exhibit much lower toxicity than their corresponding monomethyl derivatives. The derivatives did not show mutagencity in the Ames test. They displayed some side effects, like sedation and ptosis, which were not seen at ED_{50}.

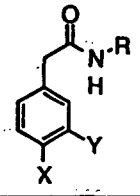


Table I. Analgesic Activities of Synthetic Capsaicinoids

KR-	Y	X	R	acetic acid (*s. c.*)	acetic acid (*p. o.*)	PBQ (*p. o.*)
25007	OH	OH	Octyl	0.32	9.0	
25012	OMe	$OCH_2CH_2NH_2$	Octyl	0.13	0.54	2.20
21034	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$		2.5	2.58
21033	OMe	$OCH_2CH_2NH_2$	$(CH_2)_4Ph$		0.20	4.69
21021	OMe	$OCH_2CH_2NH_2$	$(CH_2)_5Ph$		0.79	
26004	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Cl_2		0.66	
24041	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3-Me		0.07	5.31
21036	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3-CF_3		1.54	
21049	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3-Et		0.69	
21050	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3-*n*-Pr		1.7	1.86
24033	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-4-Me		1.03	
25018	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2		0.08	0.43
24037	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,5-Me_2		4.6	2.15
21029	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-$(OMe)_2$		NE	
21035	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-(O_2CH_2)		0.8	4.22
24047	OMe	$OCH_2CH_2NH_2$	$(CH_2)_4Ph$-3-Me		1.54	
21025	OMe	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2		0.77	3.71
25023	OMe	$OCH_2CH_2NH_2$	$(CH_2)_4Ph$-3,4-Me_2		1.44	
24051	OMe	OCH_2CH_2NHMe	$(CH_2)_3Ph$-3,4-Me_2			0.68
21054	OMe	$OCH_2CH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2			NE
25041	OMe	$N(CH_2CH_2)_2NH$	$(CH_2)_3Ph$-3,4-Me_2			P
25017	H	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2		3.98	
25016	F	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2		2.95	
25015	Cl	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2		4.78	
27004	NH_2	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2			22.1
27008	NO_2	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2			21.1
26012	OH	$OCH_2CH_2NH_2$	$(CH_2)_3Ph$-3,4-Me_2			0.49

The values given are ED_{50} values in mg/Kg.

They displayed some side effects, like sedation and ptosis, which were not seen at ED_{50}. They were not shown for larger animals (rats, rabbits, and dogs) even at higher doses. The analgestic effect of KR-25018 was independent of the motor impairment by rotor-rod test.

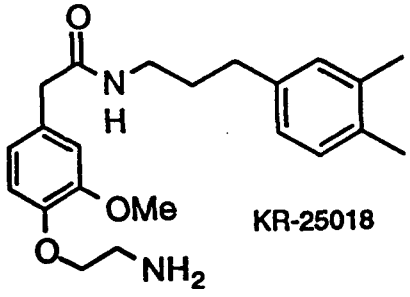
Table 2. Acute Toxicities of Synthetic Capsaicinoids

Test Drugs	ED_{50} (mg/Kg)	LD_{50} (mg/Kg)		Therapeutic Index
		Male	Female	(LD_{50}/ED_{50})
KR-25018	0.08	224	364	2,800/4,600
KR-24041	0.07	125	125	1,800/1,800

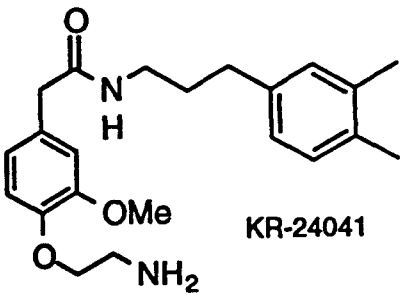
ED_{50} values are by A.A. writhing test(p.o.)

The compounds were non-narcotic by narcotic antagonist study and opioid receptor binding study. The apparent half-lives of analgesic activity after oral administration were 6 hours as assessed by acetic acid-induced writhing tests.

A new class of compounds were synthesized by transposition of amide bond, introduction of substituents on aryl portion, and modification of alkyl portion of capsaicin. N-Arylalkyl-4-(2-aminoethoxy)phenylacetamide derivatives had high analgesic and antiinflammatory activities and their pharmacological aspects were studied. The most interesting derivative of the series was N-{3-(3,4-dimethylphenyl)propyl}-4-(2-aminoethoxy)-3-methoxyphenylacetamide (KR-25018) and N-{3-(3-methylphenyl)propyl}-4-(2-aminoethoxy)-3-methoxyphenylacetamide(KR-24041).



KR-25018



KR-24041

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