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Title: 4'-HYDROXYBENZYLAMINE DERIVATIVES HAVING ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY

Abstract
Novel 4'-hydroxybenzylamine derivatives, pharmaceutical compositions and methods of use thereof are the present invention. Utility is for the treatment of arthritis, asthma, Raynaud's disease, inflammatory bowel disorders, trigeminal or herpetic neuralgia, inflammatory eye disorders, psoriasis, dental pain, and headaches, particularly vascular headache, such as migraine, cluster, mixed vascular syndromes, as well as nonvascular, tension headaches.
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4'HYDROXYBENZYLAMINE DERIVATES HAVING ANTI-INFLAMMATORY
AND ANALGESIC ACTIVITY

BACKGROUND OF THE PRESENT INVENTION

The present invention is novel compounds, which
are derivatives of hydroxybenzylamine and as such are
related to capsaicin. The present compounds have
antiinflammatory activity for the treatment of
arthritis, asthma, Raynaud's disease, inflammatory
bowel disorders, trigeminal or herpetic neuralgia,
inflammatory eye disorders, psoriasis, and/or having
analgesic activity for the treatment of dental pain
and headache, particularly vascular headache, such as
migraine, cluster, and mixed vascular syndromes, as
well as nonvascular, tension headache. Thus, the
present invention is also a pharmaceutical
composition comprising the novel compounds together
with a pharmaceutically acceptable carrier or methods
of use of such compounds for treatment of the above
noted conditions.

Among known compounds are benzoic acid
derivations in which the derivative is limited to a
substituent having a (naphthoxy)isobutyramido
containing group and for which compounds an
antiphlogistic activity is disclosed. See U.S.
discloses N-(4-carboxybenzyl)acetamide in
"Quantitative Evaluation of the Inductive Effect,"
teaching to activity or utility for the compound is
indicated by Exner, et al.

Selected compounds related to capsaicin are
disclosed in a series of patents. Such disclosed
compounds have various amido, sulfonylamido or
amidosulfonyl and thioamido linkages in combination
with a benzyl or a benzyl analog moiety and may be
found in U.S. Patent No. 4,443,473, having a para-
hydroxybenzyl; 4,313,958, that has a para-
methoxybenzyl and claims the use of capsaicin; U.S.
Patent No. 4,460,602 having a para-hydroxybenzyl; U.S. Patent No. 4,401,663 having a para-hydroxy- or methoxybenzyl; European Patent Application No. 0,132,113 having a para-hydroxybenzyl; U.S. Patent No. 4,424,203 having a para-hydroxy- or, alkyloxy-benzyl; European Patent Application 0,132,114 having a para-hydroxy or alkoxybenzyl; European Patent Application 0,132,346 having a para-hydroxy or alkyloxy-benzyl and European Patent Application 0,132,115 having a para-hydroxybenzyl; as well as European Patent Application 0,149,544 and 0,149,545 both of which may have a para-hydroxybenzyl moiety. Of these European Patent Applications 0,132,115; 0,132,346; 0,132,113; 0,132,114; 0,132,115, 0,149,544 and 0,149,545 include a short chain acyl group on the benzyl moiety. Analgesia is disclosed as an activity for the compounds of the references. However, none of the references teach the compounds having the combination of moieties of the present invention.

Additionally, related benzoic acid and benzoic acid ester derivatives having antiinflammatory and analgesic activity are found in co-pending U.S. Application Serial No. 811,567 filed December 20, 1985 which refers to most of the above noted references. Therefore, U.S.S.N. 811,567 is hereby incorporated by reference.

**Detailed Description of Invention**

The novel compounds of the present invention have the following structural formula:
and pharmaceutically acceptable acid addition or base salts thereof; wherein:

(a) \( R_1 \) is (i) \( R \) wherein \( R \) is lower alkyl or \( NR'NR'' \) wherein \( R' \) and \( R'' \) are independently hydrogen or lower alkyl, (ii) halogen, (iii) trifluoromethyl, (iv) \( \text{NO}_2 \), (v) \( \text{SCH}_3 \), (vi) \( \text{SO}_2R' \) wherein \( R' \) is as defined above, (vii) \( \text{CO}_2R' \) wherein \( R' \) is as defined above, (viii) \( \text{NHCOR}' \) wherein \( R' \) is as defined above, (ix) \( \text{CN} \), or (x) 5-tetrazolyl;

(b) \( B \) is

\[
\begin{align*}
 & \text{(B}_1\text{)} \\
 & \text{(B}_2\text{)} \\
 & \text{(B}_3\text{)} \\
 & \text{(B}_4\text{)}
\end{align*}
\]
(c) X and Y are independently H or lower alkyl;
(d) R₂ is alkyl, alkenyl, alkynyl of 1 to 23 carbons, inclusive;
(e) Q is (i) R₃ wherein R₃ is lower alkyl or NR'NR" wherein R' and R" are independently as defined above; (ii) halogen; (iii) trifluoromethyl; (iv) NO₂; (v) SCH₃; (vi) SO₂R' wherein R' is independently as defined above; (vii) COR' wherein R' is independently as defined above; (viii) NHCOR' wherein R' is independently as defined above; (ix) CN; (x) tetrazolyl; (xi) imidazolyl; (xii) cyclohexyl; (xiii) phenyl; or (xiv)

The term "lower alkyl" means a hydrocarbon chain up to 4 carbon atoms such as methyl, ethyl, propyl, or butyl, and isomers thereof.
The terms alkyl, alkenyl, and alkynyl are divalent hydrocarbon straight or branched chains containing one or more single, double or triple carbon to carbon bonds, respectively.
Preferred embodiments of the present invention contain the R₁ substituent as shown in the following formula (II):
Preferred embodiments of the present invention contain the \( R_1 \) substituent as shown in the following formula (II):

\[
\begin{align*}
\text{OH} & \\
\text{R}_1 & \\
& \\
\text{X} & \\
& \\
\text{N-B-R}_2 & \\
& \text{Q}
\end{align*}
\]

wherein \( X, Y, B, R_2 \), and \( Q \) are all as defined above. More preferred embodiments of the present invention are compounds of formula II wherein \( B = B_1 \) and \( X, Y, R_2 \) and \( Q \) are as defined above. The most preferred embodiments of the present invention is the compound \( N-[(3\text{-chloro-4-hydroxyphenyl})\text{methyl}]\text{nonamide}, \)
\( N-[(4\text{-hydroxy-3-methylphenyl})\text{methyl}]\text{nonamide, or} \)
\( N-[(4\text{-hydroxy-3-(methylthio)phenyl})\text{methyl}]\text{nonamide.} \)
The preferred method of use is for treating headaches, particularly migraine headaches.

Examples of suitable acids for the preparation of the acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as acetic acid, benzoic acid, tartaric acid, fumaric acid, succinic acid, maleic acid, arginine acid, lactic acid, tartaric acid, and sulfonic acids such as methansulfonic acid, ethansulfonic acid, benzenesulfonic acid or p-toluenesulfonic acid.

The base salts of the present inventions include those safe for topical or systemic administration, such as sodium, potassium, calcium, magnesium, and ammonium salts or the like.
Generally, the preparation of the compounds of the present invention is represented by the following scheme:

\[
\text{OH} \quad \text{R₁} \quad \text{Hal-B-R₂-Q} \quad \rightarrow \quad \text{I}
\]

wherein R₁, X, Y, B, R₂, Q are as defined above and Hal is chloro, bromo, but preferably chloro.

The preparation uses standard synthetic techniques used in the examples or analogous to those used in the examples hereinafter. The starting materials for the preparation are readily available, known or can be prepared by known methods.

More specifically, preparation of the compounds of formula I wherein B is B₁ are analogous to those well known in the art using variations in conditions and having starting materials known or readily prepared within the skill of an ordinary artisan.

The compounds of formula I wherein B is B₂, B₃, B₄, B₅ or B₆ are likewise prepared by methods analogous to those well known in the art using variations in conditions and having starting materials known or readily prepared by an artisan. Such methods are shown as follows in Schemes I through V respectively as follows:
Scheme I

\[
\begin{align*}
\text{OH} & \quad \text{R}_1 \\
\text{X} & \quad \text{Y} \\
\text{NH} &
\end{align*}
\]

\[
\begin{align*}
+ & \quad \text{ClSO}_2\text{R}_2\text{Q} \\
\rightarrow & \quad \text{The compound of formula I wherein} \\
& \quad \text{B is } -\text{S}^- \cdot \\
& \quad \text{(B}_2\text{)}
\end{align*}
\]

Scheme II

\[
\begin{align*}
\text{OH} & \quad \text{R}_1 \\
\text{X} & \quad \text{Y} \\
\text{NH} &
\end{align*}
\]

\[
\begin{align*}
+ & \quad \text{OCNR}_2\text{Q} \\
\rightarrow & \quad \text{The compound of formula I wherein} \\
& \quad \text{B is } -\text{C-NH}^- \cdot \\
& \quad \text{(B}_3\text{)}
\end{align*}
\]
Scheme III

\[
\text{OH} \quad \begin{array}{c}
\text{R}_1 \\
\text{Y} \\
\text{X} \\
\text{NH}
\end{array} + \text{SCNR}_2Q
\]

or

\[
\text{OH} \quad \begin{array}{c}
\text{R}_1 \\
\text{Y} \\
\text{X} \\
\text{N} \\
\text{C} \\
\text{N}
\end{array} + \text{P}_2\text{S}_5
\text{I}_3
\]

(or other phosphorus-sulfur agent such as Lawesson's reagent)

or

\[
\text{OH} \quad \begin{array}{c}
\text{R}_1 \\
\text{Y} \\
\text{X} \\
\text{NH}
\end{array} + \text{CS}_2 \xrightarrow{\text{MeI}} \text{OH} \quad \begin{array}{c}
\text{R}_1 \\
\text{Y} \\
\text{X} \\
\text{N} \\
\text{C} \\
\text{SMe}
\end{array} + \text{QR}_2\text{NH}_2
\]
Scheme IV

\[
\text{OH} \quad \text{R}_1 \quad \text{Cl}_2\text{CO} \quad \text{(base)} \quad \text{OH} \\
\text{Y} \quad \text{X} \quad \text{NCO}
\]

or

\[
\text{OH} \quad \text{R}_1 \quad \text{Cl}_{\text{C-OR}_2}\text{Q} \quad \text{(base)} \quad \text{QR}_2\text{OH}
\]

The compound of formula I wherein B is \(-\text{C-O-}\) 
\((B_5)\)
Scheme V

\[
\text{OH} \quad \text{R}_1 \quad \text{Y} \quad \text{NH}
\]

\[
\text{Cl-C-OR}_2\text{Q}
\]

(Base)

\[
\text{OH} \quad \text{R}_1 \quad \text{Y} \quad \text{NCS}
\]

(catalytic base)

\[
\text{OH} \quad \text{R}_1 \quad \text{Y} \quad \text{NCO}-\text{R}_2\text{Q}
\]

QR\text{OH}/base

\[
\text{OH} \quad \text{R}_1 \quad \text{Y} \quad \text{NCS}
\]

CH\text{I}

\[
\text{OH} \quad \text{R}_1 \quad \text{Y} \quad \text{S} \quad \text{C-SCH}_3
\]

Examples of suitable oxygen protecting groups are benzyl, t-butyldimethylsilyl, ethoxyethyl, and the like. Protection of an N-H containing moiety is necessary for some of the processes described herein for the preparation of compounds of this invention. Suitable nitrogen protecting groups are benzyl, triphenylmethyl, trialkylsilyl, trichloroethylcarbamate, trichloroethoxycarbonyl, vinylloxycarbamate, and the like.

Under certain circumstances it is necessary to protect two different oxygens with dissimilar protecting groups such that one can be selectively removed while leaving the other in place. The benzyl and t-butyldimethylsilyl groups are used in this way; either is removable in the presence of the other, benzyl being removed by catalytic hydrogenolysis, and t-butyldimethylsilyl being removed by reaction with, for example, tetra-n-butyrammonium fluoride.

In the process described herein for the preparation of compounds of this invention the requirements for protective groups are generally well recognized by one skilled in the art of organic chemistry, and accordingly the use of appropriate protecting is necessarily implied by the processes of
the charts herein, although not expressly illustrated.

The present invention is also pharmaceutical compositions for treating pain, inflammation or migraine comprising an analgesic, antiinflammatory, or antimigraine effective amount of a compound of formula I as defined above or their pharmaceutically acceptable base or acid addition salts and a pharmaceutically acceptable carrier. Such compositions may be one of a broad range of known forms for topical or systemic administration.

The methods of use are for the treatment in mammals, particularly in humans, of various conditions such as enumerated above either for diseases known as inflammatory or for pain and for migraine. An ordinarily skilled physician would recognize such conditions. The compounds of formula I are active in animal tests which are generally recognized as predictive for antiinflammatory, analgesic or antimigraine activity. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically acceptable dosage forms by conventional methods known to the pharmaceutical art. In general a preferred method of administration is, however, by oral dosage forms.

The compounds of formula I can be administered in such unit oral dosage forms as tablets, capsules, pills, powders, or granules. They may also be administered rectally or vaginally in such forms as suppositories or bougies. They may also be introduced parenterally, (e.g., subcutaneously, intravenously, or intramuscularly), using forms known to the pharmaceutical art. Finally, the compounds of formula I can be administered topically using forms known to the pharmaceutical art for application through the skin, by nasal application or in the eye.
An effective but nontoxic amount of the compound of formula I or the salts thereof is employed in treatment. The dosage regimen for treating inflammation, pain or, particularly migraine, by the compounds of formula I and their salts as described above is selected in accordance with a variety of factors including the type, age, weight, sex, and medical condition of the subject, the severity of the inflammation, pain and particularly migraine, the route of administration and the particular compound employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

Initial dosages of the compounds of the invention are ordinarily in the area of 0.1 mg/kg up to at least 100 mg/kg per dose orally, preferably 0.5 to 30 mg/kg orally are given. Each dose is given from one to four times daily or as needed. When other forms of administration are employed equivalent doses are administered.

Generally, the activity for use as described above for the novel compounds of the present invention is shown as an ED_{50} for illustrative compounds of formula I when administered in a test essentially as described by Koster et al. [Fed. Proc., Vol. 18 (1959), p. 412] in which the peritoneal injection of acetic acid to mice provokes repeated stretching and twisting movements which persist for more than 6 hrs. Analgesics prevent or suppress these syndromes which are considered to be an exteriorization of a diffuse abdominal pain.
The results are expressed as mg/kg which amount produces the desired inhibition of stretching or "writhing" in 50 percent of a population.

The protocol and the results are particularly as follows:

ANTIWRITHING TEST IN MICE (AW) TEST PROTOCOL

The purpose of this test is to evaluate drugs for analgesic activity.

METHOD

SUBJECTS Subjects are male Swiss-Webster mice (25-35 g).

DRUGS A compound of formula I is dissolved or suspended in physiological saline containing 2% Emulphor.

Suspensions are subjected to ultrasonication for three minutes. Drug doses are expressed as the active moiety and are normally administered to mice (10, 30, and 100 mg/kg IP, SC, PO, or IM) in a volume of 10 ml/kg, 1 hr prior to testing; ICV doses (in μg/kg) are administered in a volume of 0.5 ml/kg, 5 min prior to testing. Animals dosed PO are fasted for 16 hours prior to dosing. Groups of eight mice are tested with each dose or the vehicle solution (control group).

PROCEDURE Mice are treated with a dilute solution of acetic acid (0.6%, 10 ml/kg IP) which elicits writhing. In four successive trials, one pair of mice from each treatment group is placed in one of four adjacent clear plexiglas chambers (4 in x 4 in x 4 in). This allows the simultaneous observation of four pairs of
mice representing all treatments and controls throughout the test. Writhing movements (abdominal contractions, stretching of the torso and hind legs, and concave arching of the back) are counted for five minutes commencing seven minutes after acetic acid administration.

DATA ANALYSIS Drug effects on acetic acid-induced writhing are expressed as percent suppression of writhing relative to the vehicle-treated control group run in parallel with treated animals. The writhing tallies from pairs of animals are summed for each treatment and are divided by the summed writhing in the control group. The ED\textsubscript{50}s for suppression of writhing are determined by non-linear regression analysis.

TABLE

Antiwrithing Results

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<td>1\textsuperscript{1}</td>
<td>11.8 mg/kg ± 0.9292</td>
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<td>3.4 mg/kg ± 0.8215</td>
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<td>1.2 mg/kg ± 0.7746</td>
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<td>22.0 mg/kg ± 0.8220</td>
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<td>13.0 mg/kg ± 0.8987</td>
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<td>30</td>
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<tr>
<td>1\textsuperscript{7}</td>
<td>9.4 mg/kg ± 0.8355</td>
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<tr>
<td>1\textsuperscript{8}</td>
<td>1.3 mg/kg ± 0.8184</td>
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<tr>
<td>1\textsuperscript{9}</td>
<td>8.0 mg/kg</td>
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DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following Preparations will further illustrate the invention, without limiting it thereto.

Preparations

The preparation of the compound of formula I\textsuperscript{1} is generally illustrated as follows:

\[
\begin{align*}
\text{HO} & \quad \text{CN} & \quad \text{CN} & \quad \text{NH}_2 \\
\text{Ia.} & \quad \text{OEt} & \quad \text{OEt} & \quad \text{Ib.} \\
\text{I'} & \quad \text{HO} & \quad \text{NH} & \quad \text{CO} & \quad \text{CH}_2 \text{CH}_2 & \text{CH}_2 \\
\end{align*}
\]

Preparation of I\textsubscript{a}.

To a mixture of 4-hydroxybenzonitrile (50.00 g, 0.420 mol) and ethyl vinyl ether (82 ml, 0.86 mol) in chloroform (420 ml) is added concentrated hydrochloric acid (0.5 ml). The reaction mixture becomes warm, and a solution forms. The reaction is stirred at ambient temperature for 15 hours, and washed with 1 N NaOH (4 x 200 ml) and saturated NaCl (200 ml). After drying over MgSO\textsubscript{4}, the dark oil is purified by distillation (Bp 120°C; 1.0 mm Hg). Yield: 58.37 g (72.7%).
Preparation of Ib.

A solution of Ia (57.87 g, 0.303 mol) in tetrahydrofuran (125 ml) is added dropwise to a mechanically stirred, ice cooled suspension of lithium aluminum hydride (23.50 g, 0.619 mol) in tetrahydrofuran (615 ml). The resulting greenish mixture is refluxed for 15 hours, cooled in an ice bath and quenched by the dropwise addition of H₂O (23.5 ml), .5 N NaOH (24 ml), and H₂O (24 ml). To the resulting greyish mixture is added 5 N NaOH until the mixture is white, and no grey material remains. The reaction is filtered through celite, and the filtrate evaporated in vacuo. The residue is partitioned between ethyl ether (1000 ml) and H₂O (350 ml). The ether layer is washed with saturated NaCl, and dried over K₂CO₃. Evaporation of the solvent gave the product as a cloudy yellow oil. Yield: 59.52 g (97.9%). Used as is in next step.

Preparation of I': Nonamide, N-[(4-hydroxyphenyl)-methyl]-

A solution of nonanoyl chloride (20.0 ml, 0.111 mol) in tetrahydrofuran (70 ml) is added dropwise to a stirred solution of Ib (20.02 g, 0.103 mol) and triethylamine (16.0 ml, 0.115 mol) in tetrahydrofuran (175 ml) at +5°C. The reaction is stirred at room temperature for 3 hours and evaporated in vacuo. The residue is taken up in methylene chloride and washed with 1 N HCl, H₂O, saturated NaHCO₃, H₂O, and brine. After drying over MgSO₄, the solution is evaporated, and the residue is taken up in tetrahydrofuran (400 ml) and 1 N HCl (135 ml). After stirring for one hour the reaction is evaporated, and the residue taken up in chloroform, washed with 1 N HCl, saturated NaHCO₃, and brine. After drying over MgSO₄ the solution is evaporated to a yellow solid. Recrystallization from isopropyl ether gives the
product of formula I' as a light yellow solid.
Yield: 19.83 g (73.4%); mp 86-87.5°C.

The preparation of a compound of formula I² is generally as follows:

```
  \begin{align*}
    &\text{I} \\
    &\downarrow \\
    &\text{I}^2 \text{ wherein } X \text{ is Cl} \\
    &\downarrow \\
    &\text{I}^3 \text{ wherein } X \text{ is Br} \\
\end{align*}
```

Preparation of I². Nonamide, N-[(3-chloro-4-hydroxyphenyl)methyl]-

A solution of chlorine (2.8 g) in chloroform (90 ml) is added dropwise to a stirred solution of the compound of formula I' (5.00 g, 0.019 mol) in chloroform (300 ml) until all of the compound of formula I' is consumed. The reaction is washed with 1 N HCl, H₂O, and saturated NaCl, and dried over MgSO₄. After evaporation, the resulting oil is chromatographed (Silica gel; 70:25:5 chloroform: hexanes:tetrahydrofuran), and placed under high vacuum for 15 hours. The resulting solid is collected, washed with hexanes, and dried in vacuo. Yield: 2.90 g (51.3%); mp 64-66°C.
Preparation of I₃. Nonamide, N-[(3-bromo-4-hydroxy-phenyl)methyl]-

A solution of bromine (2.55 g, 0.016 mol) in chloroform (100 ml) is added dropwise to an ice cooled, stirred solution of a compound of formula I' (4.00 g, 0.0152 mol) in chloroform (225 ml). The reaction is allowed to stir for 15 hours, is evaporated, and chromatographed (silica gel; 75:20:5 chloroform:hexanes:tetrahydrofuran). Yield: 3.43 g (66.0%); mp 72-74°C.

Preparation of I₄. Nonamide, N-[(4-hydroxy-3-nitro-phenyl)methyl]-

A solution of concentrated nitric acid (1.02 g, 0.0113 mol) in acetic acid (10 ml) is added dropwise to a stirred, ice cooled solution of a compound of the formula I' (3.00 g, 0.0114 mol) in acetic acid (60 ml). After stirring for 30 minutes the reaction is evaporated and the residue flash chromatographed (silica gel; 3:1 hexanes:ethyl acetate). The product is recrystallized from cyclohexanes. Yield: 2.19 g (62.3%); mp 95.5-97°C.

Preparation of I₅. Nonamide, N-[(3-amino-4-hydroxy-phenyl)methyl]-

A solution of the compound of formula I' (2.65 g, 8.59 mmol) in methanol/tetrahydrofuran (50/50; 100 ml) is hydrogenated over Raney nickel (0.3 g) at 50 psi. The solution is evaporated and the residue recrystallized from hexanes/ethyl acetate. Yield: 1.58 g (65.5%); mp 141-143°C.

The preparation of the compounds of the formula I₆ and of the formula I₇ is generally illustrated as follows:
Preparation of VIa.

To a stirred solution of 3-methyl-p-anisaldehyde (10.00 g, 0.0666 mol) and methoxyamine hydrochloride (5.90 g, 0.0706 mol) in methanol (333 ml) is added, dropwise, 1 N NaOH (73 ml). After stirring for 5 days at room temperature, the reaction is evaporated, and the residue partitioned between chloroform and water. The water layer is extracted twice more with chloroform, and the chloroform extracts are combined and washed with 1 N HCl, H₂O, saturated NaHCO₃, H₂O, and saturated NaCl. After drying over MgSO₄, the solution is evaporated to a colorless oil. The product of formula VIa obtained as an oil having a yield of 11.48 g (96.2%) is used as is in the next step.

Preparation of VIb.

A solution of product of formula VIa (5.91 g, 0.0330 mol) in MeOH/NH₃ (saturated, 100 ml) is hydrogenated over Raney nickel (2.0 g, washed with MeOH) at 50 psi. The solution is evaporated and flash chromatographed (silica gel; 95:5:0.5
chloroform:methanol:ammonium hydroxide) to yield a compound of the formula V1b as a yellow oil. Yield: 4.39 g (86.7%).

Preparation of V1c.

5 A solution of nonanoyl chloride (2.45 g, 0.0139 mol) in tetrahydrofuran (25 ml) is added dropwise to a stirred, ice cooled solution of compound V1b as prepared above (2.00 g, 0.0132 mol) and triethylamine (2.0 ml, 0.0143 mol) in tetrahydrofuran (75 ml).

After stirring for 3 hours, the reaction is evaporated, and the residue taken up in methylene chloride (100 ml). The solution is washed with H2O, 1 N HCl, H2O, saturated NaHCO3, H2O, and saturated NaCl. After drying over MgSO4 the evaporated product is flash chromatographed (silica gel; 3:1 hexanes:ethyl acetate) to yield a compound of the formula V1c as a white solid. Yield: 2.71 g (70.3%).

Preparation of 76. Nonamide, N-[(4-hydroxy-3-methylphenyl)methyl]-

20 A solution of boron tribromide in methylene chloride (1.0 M, 30 ml, 30 mmol) is added dropwise to a stirred solution of the compound of formula V1c as prepared above (2.41 g, 8.26 mmol) in chloroform (50 ml) under nitrogen. After stirring at room temperature for 30 minutes, the solution is refluxed for ten minutes, and then cooled to 5°C in an ice bath. The reaction is quenched with methanol (20 ml), and evaporated. The residue is taken up in chloroform (100 ml) and washed with H2O, 1 N HCl, H2O, saturated NaHCO3, H2O, and saturated NaCl. After drying over MgSO4 the product is flash chromatographed (silica gel; 2:1 hexanes:ethyl acetate) to yield an oil which solidified on standing. Recrystallized from hexanes/ethyl acetate
to give the product of formula \( \text{I}^6 \). Yield: 1.55 g (67.6%); mp 64-66°C.

**Preparation of VIIa.**

A solution of 3-fluoro-4-methoxybenzaldehyde (15.00 g, 97.3 mmol) in methanol (300 ml) is added to a stirred, ice cooled solution of methoxyamine hydrochloride (8.40 g, 101 mmol) and 1 N NaOH (105 ml, 105 mmol) in methanol (180 ml). After stirring at room temperature for 16 hours, the solution is evaporated, and the residue partitioned between ethyl ether and water. The ether layer is washed with saturated NaHCO₃, dried over K₂CO₃, and evaporated to yellowish-white crystalline plates. Recrystallization from hexanes gives the compound of formula VIIa. Yield: 15.10 g (84.7%); mp 52-55°C.

**Preparation of VIIb.**

A solution of the compound of formula VIIa as prepared above (15.00 g, 81.9 mmol) in MeOH/NH₃ (saturated, 150 ml) is hydrogenated over Raney nickel (5 g) at 50 psi. The resulting cloudy solution is evaporated and vacuum distilled to give a product of the formula VIIb (Bp 95°C at 0.8 mm Hg). Yield: 11.88 g (93.2%).

**Preparation of VIIc.**

A solution of nonanoyl chloride (6.0 ml, 32.6 mmol) in tetrahydrofuran (25 ml) is added to a stirred, ice cooled solution of the compound of formula VIIb as prepared above (5.00 g, 32.2 mmol) and triethylamine (4.6 ml, 33.0 mmol) in tetrahydrofuran (100 ml) under nitrogen. The stirred reaction is warmed to room temperature, evaporated, and the residue partitioned between 1 N HCl and chloroform. The aqueous layer is extracted once with chloroform, and the chloroform extracts combined.
After washing the extracts with 1 N HCl, H₂O, saturated NaHCO₃, H₂O, and saturated NaCl, the product having the formula VIIc is evaporated as a white solid. Yield: 8.79 g (92.3%); mp 83-85°C.

Preparation of I₇. Nonamide, N-[(3-fluoro-4-hydroxyphenyl)methyl]-

A solution of boron tribromide in methylene chloride (1.0 M, 49 ml, 49 mmol) is added dropwise to a stirred solution of the compound of formula VIIc as prepared above (4.00 g, 13.5 mmol) in chloroform (80 ml) under a nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solution is refluxed for ten minutes, and then cooled to +5°C. The reaction is quenched with methanol (32 ml), and evaporated. The residue is flash chromatographed (silica gel; 70:25:5 chloroform:hexanes:tetrahydrofuran) to yield a compound of the formula I₇ as a white solid. Yield: 3.02 g (79.3%); mp 51-53°C.

The preparation of the compound of formula I₈ is generally illustrated as follows:

![Chemical Structures](image-url)
Preparation of VIIIa.

A solution of 3-bromo-4-methoxybenzaldehyde (20.00 g, 93.0 mmol) and concentrated hydrochloric acid (1 ml) in methanol (400 ml) is stirred at room temperature for 48 hours. After evaporation of the solvents the residue is partitioned between chloroform and water, and the organic layer washed with saturated NaHCO₃, H₂O, and saturated NaCl. After drying over K₂CO₃, the solution is evaporated, and the resulting oil vacuum distilled to give the product of formula VIIIa. Yield: 21.12 g (87.0%); Bp 110°C (0.8 mm Hg).

Preparation of VIIIb.

A solution of the compound of formula VIIIa as prepared above (15.00 g, 57.4 mmol) in anhydrous tetrahydrofuran (150 ml) is added dropwise to a stirred suspension of magnesium turnings (1.41 g, 58.0 mmol) in anhydrous tetrahydrofuran (45 ml) under a nitrogen atmosphere. (Several drops of ethylene dibromide are added to initiate the reaction.) The reaction mixture is refluxed for 2 hours, cooled to room temperature, and a solution of methyl disulfide (5.41 g, 57.4 mmol) in anhydrous tetrahydrofuran (75 ml) is added dropwise. The solution is refluxed for 2 hours, and cooled to 10°C. To the reaction mixture is added 20% NH₄Cl (260 ml) while keeping the temperature below 20°C. The resulting biphasic mixture is extracted with ethyl ether (2 x 150 ml). The etheral extracts are combined, washed with brine, and dried over MgSO₄. After evaporation, the crude product is flash chromatographed (silica gel; 4:1 hexanes:ethyl acetate). The purified product is taken up in tetrahydrofuran and stirred with 3 N HCl (25 ml) for ten minutes. The solution is evaporated, and the residue partitioned between H₂O (50 ml) and ethyl ether (50 ml). The water layer is extracted
once more with ether (50 ml) and ethereal extracts combined. After washing with saturated NaCl and drying over MgSO₄, the solution is evaporated to give a product of the formula VIIIb as a thick, yellow oil. Yield: 4.19 g (40.0%).

**Preparation of VIIIc.**

To an ice cold, stirred solution of methoxyamine hydrochloride (3.03 g, 36.3 mmol) in methanol (65 ml) is added, dropwise, 1 N NaOH (40 ml). To this is then added a solution of a compound of the formula VIIIb as prepared above (6.40 g, 35.1 mmol) in methanol (110 ml). The reaction solution is stirred at room temperature for 15 hours, and then evaporated. The residue is partitioned between chloroform and water. The water layer is extracted once more with chloroform, and the combined chloroform extracts are washed with H₂O, 1 N HCl, H₂O, saturated NaHCO₃, H₂O, and saturated NaCl. After drying over MgSO₄, the solution is evaporated, and the crude product of formula VIIIc flash chromatographed (silica gel; 5:1 hexanes:ethyl acetate). Yield: 6.12 g (82.8%).

**Preparation of VIIIId.**

A solution of trifluoroacetic acid (10.94 ml, 142 mmol) in tetrahydrofuran (15 ml) is added dropwise to a stirred suspension of sodium borohydride (5.37 g, 142 mmol) in tetrahydrofuran (140 ml) under a nitrogen atmosphere while keeping the temperature between 17 and 22°C. To the resulting solution is then added a solution of a compound of the formula VIIIc as prepared above (6.00 g, 28.4 mmol) in tetrahydrofuran (15 ml). The reaction mixture is stirred at ambient temperature for 2 hours, and then refluxed for 2 hours. After cooling to 5°C, the mixture is carefully quenched
with water (20 ml) while keeping the temperature below 10°C. The resulting mixture is evaporated to near dryness, and the residue partitioned between 1 N NaOH and methylene chloride. The water layer is extracted twice more with methylene chloride. The organic extracts are combined and washed with 1 N NaOH, H₂O, and saturated NaCl. After drying over K₂CO₃, the filtered solution is acidified with 6 N HCl in isopropyl alcohol. The milky solution is evaporated, and the residue triturated with ethyl ether. The solid product of the formula VIIIId is filtered, washed with ether, and dried in vacuo then recrystallized from methanol/ethyl ether. Yield: 4.26 g (68.3%); mp 232-234°C.

Preparation of VIIIe

A solution of nonanoyl chloride (3.4 ml, 18.5 mmol) in tetrahydrofuran (25 ml) was added dropwise to a stirred, ice cold, solution of a compound of the formula VIIIId as prepared above (3.80 g, 17.4 mmol) and triethylamine (5.4 ml, 38.7 mmol) in 1-methyl-2-pyrrolidone (75 ml) under a nitrogen atmosphere while keeping the temperature less than 15°C. The reaction is stirred at room temperature for 63 hours, poured into 500 ml H₂O, and extracted with ethyl acetate (5 x 100 ml). The organic extracts are combined, washed with 1 N HCl, H₂O, saturated NaHCO₃, H₂O, saturated NaCl, and dried over MgSO₄. Evaporation yields a product of the formula VIIe as a white solid. Yield: 3.96 g (70.8%); mp 96-97°C.

Preparation of 1. Nonamide, N-[(4-hydroxy-3-(methylthio)phenyl)methyl]-

A 1.0 M solution of boron tribromide in methylene chloride (39 ml, 39 mmol) is added dropwise to a stirred solution of a compound of the formula
VIIIe as prepared above (3.38 g, 10.4 mmol) in chloroform (70 ml) under a nitrogen atmosphere. The mixture is stirred at room temperature for 30 minutes, refluxed for 40 minutes and stirred at room temperature for 15 hours. The ice cooled reaction is quenched with methanol (40 ml). After evaporation, the residue is taken up in chloroform (100 ml) and washed with 1 N HCl, H₂O, and saturated NaCl. After drying over MgSO₄, the product of the formula I⁸ is evaporated and flash chromatographed (70:23:7 chloroform:hexanes:tetrahydrofuran). The resulting thick oil crystallized on standing under high vacuum. Yield: 2.60 g (80.4%); mp 69.5-71.5°C.

In a similar manner using corresponding starting materials the compound of formula I⁹ which is nonanamide, N-[(3-amino-4-hydroxyphenyl)methyl]- was prepared, mp 141-143°C.
CLAIMS

1. A compound of the formula:

\[
\begin{align*}
\text{OH} & \quad \text{R}_1 \\
\text{Y} & \quad \text{N-B-R}_2-\text{Q}
\end{align*}
\]

and pharmaceutically acceptable acid addition or base salts thereof; wherein:

(a) \( \text{R}_1 \) is (i) \( \text{R} \) wherein \( \text{R} \) is lower alkyl or \( \text{NR}'\text{R}'' \) wherein \( \text{R}' \) and \( \text{R}'' \) are independently hydrogen or lower alkyl, (ii) halogen,

(iii) trifluoromethyl, (iv) \( \text{NO}_2 \), (v) \( \text{SCH}_3 \),

(vi) \( \text{SO}_2\text{R}' \) wherein \( \text{R}' \) is as defined above,

(vii) \( \text{CO}_2\text{R}' \) wherein \( \text{R}' \) is as defined above,

(viii) \( \text{NHCOR}' \) wherein \( \text{R}' \) is as defined above, (ix) \( \text{CN} \), or (x) 5-tetrazolyl;

(b) \( \text{B} \) is

\[
\begin{align*}
\text{O} & \\
\text{C} & \\
\text{B}_1
\end{align*}
\]

\[
\begin{align*}
\text{O} & \\
\text{S} & \\
\text{B}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \\
\text{C-\text{NH}} & \\
\text{B}_3
\end{align*}
\]

\[
\begin{align*}
\text{S} & \\
\text{C-\text{NH}} & \\
\text{B}_4
\end{align*}
\]
(c) X and Y are independently H or lower alkyl;
(d) R₂ is alkylenyl, alkenylenyl, alkynylenyl of 1 to 23 carbons, inclusive;
(e) Q is (i) R₃ wherein R₃ is lower alkyl or NR'R'' wherein R' and R'' are independently as defined above; (ii) halogen; (iii) trifluoromethyl; (iv) NO₂; (v) SCH₃; (vi) SO₂R' wherein R' is independently as
defined above; (vii) COR' wherein R' is independently as defined above; (viii) NHCOR' wherein R' is independently as
defined above; (ix) CN; (x) tetrazolyl; (xi) imidazolyl; (xii) cyclohexyl; (xiii) phenyl; or

(xiv)

2. A compound according to Claim 1 having the
formula:
wherein X, Y, B, R₁, R₂ and Q are as defined above.

3. A compound according to Claim 2 wherein B is B₁.

4. A compound according to Claim 3 wherein R₂ is an alkylenyl chain of 3 to 11 carbons, inclusive.

5. A compound according to Claim 4, and being N-[(4-hydroxyphenyl)methyl]nonamide.

6. A compound according to Claim 4, and being N-[(3-chloro-4-hydroxyphenyl)methyl]nonamide.

7. A compound according to Claim 4, and being N-[(3-bromo-4-hydroxyphenyl)methyl]nonamide.

8. A compound according to Claim 4, and being N-[(4-hydroxy-3-nitrophenyl)methyl]nonamide.

9. A compound according to Claim 4, and being N-[(3-amino-4-hydroxyphenyl)methyl]nonamide.

10. A compound according to Claim 4, and being N-[(4-hydroxy-3-methylphenyl)methyl]nonamide.

11. A compound according to Claim 4, and being N-[(3-fluoro-4-hydroxyphenyl)methyl]nonamide.

13. A pharmaceutical composition for treating inflammation, pain or migraine comprising an antiinflammatory, analgesic or antimigraine effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

14. A method of reducing inflammation in mammals suffering therefrom which comprises administering to such mammal an effective amount of a compound of Claim 1.

15. A method for treating pain in mammals suffering therefrom which comprises administering to such mammal an analgesic effective amount of a compound of Claim 1.

16. A method for treating headaches in mammals suffering therefrom which comprises administering to such mammal an antiheadache effective amount of a compound of Claim 1.

17. A process for the preparation of a compound of Claim 1 which comprises contacting a compound of the formula

```
OH  R_1
   |
   X
Y  NH
```
and a compound of the formula

$$\text{Hal-B-R}_2\text{-Q, OCNR}_2\text{Q, or SCNR}_2\text{Q,}$$

wherein Hal is bromo, chloro or iodo and $R_1$, $X$, $Y$, $B$, $R_2$ and $Q$ are as defined above; to obtain a compound of formula I and, alternatively, further reacting the compound of formula I to obtain nontoxic pharmaceutically acceptable salts thereof.
**INTERNATIONAL SEARCH REPORT**

**I. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) or to both National Classification and IPC:

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**II. FIELDS SEARCHED**

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**III. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>DE, A, 2106816 (I.C.I.) 19 August 1971, see page 31, claims 1, 13</td>
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* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed
  - "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
  - "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  - "Z" document member of the same patent family

**IV. CERTIFICATION**

Date of the Actual Completion of the International Search: 8th July 1988

Date of Mailing of this International Search Report: 05 AUG 1988

International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 8702886
SA 19617

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 29/07/88. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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