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(54) Fluorinated alkylamines and process for preparing same.

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Courier Press, Leamington Spa, England.

EP 0 000 036 B1

Fluorinated alkylamines and process for preparing same

Background of the Invention

The present invention is concerned with novel 1-fluoromethyl substituted alkylamines.

Various nonfluorinated substituted alkylamines such as histamine, 2-(3,4-dihydroxyphenyl) ethylamine (dopamine), tyramine, amphetamine and hydroxyamphetamine, are known. These compounds exhibit various physiological activities and have various clinical utilities (See D. M. Aviado "Sympathomimetic Drugs", Charles C. Thomas, Publisher, 1970). G.B. 976,353 discloses 1-trifluoromethylphenylalkylamines having anorectic properties. No 1-monofluoromethylalkylamines are suggested. U.S. 3,839,170 discloses α -CH₂F amines and amino acids and the process for direct replacement of a hydrogen atom with a F atom using fluoroxyperfluoroalkanes and fluoroxy-pentafluorosulfur in liquid or solid phase under specific reaction conditions. No 1-fluoromethylamines of the type disclosed in the present invention are suggested.

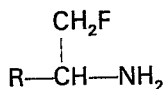
1-Fluoromethyl substituted alkyl amines have been discovered. These amines have decarboxylase inhibiting activity.

Summary of the Invention

1-Fluoromethyl substituted alkylamines and salts thereof.

Description of the Invention

An embodiment of the present invention is compounds having the formula



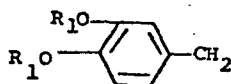
wherein R is a substituted C₁—C₄ alkyl group.

The pharmaceutically acceptable acid addition salts of the formula I compounds are also included. In general, the salts are those of the formula I base with a suitable organic or inorganic acid. Preferred inorganic acid salts are the hydrohalides e.g., hydrochlorides, hydroiodides, hydrobromides; the sulfates, and the phosphates. The hydrohalides, and especially the hydrochlorides, are more preferred.

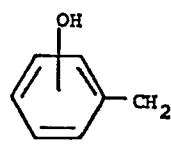
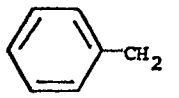
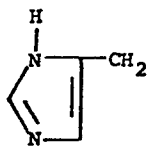
The formula I compounds have a chiral center and may occur in optically active forms i.e., as optical isomers. These isomers are designated conventionally by the symbols L and D, + and —, l and d, S and R or combinations thereof. Where the compound name or formula has no isomer designation, the name or formula includes the individual isomers, mixtures thereof and racemates.

The compounds having the S-isomer configuration are, in general preferred.

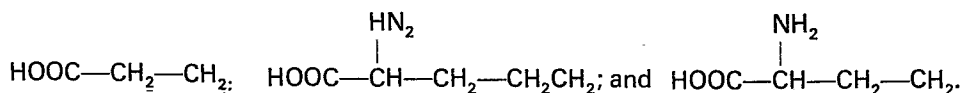
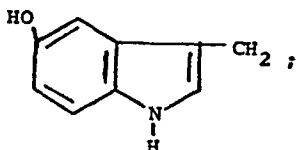
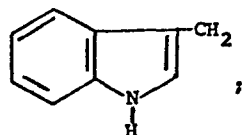
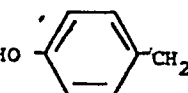
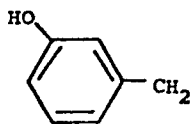
R is a substituted C₁—C₄ alkyl group exemplified by



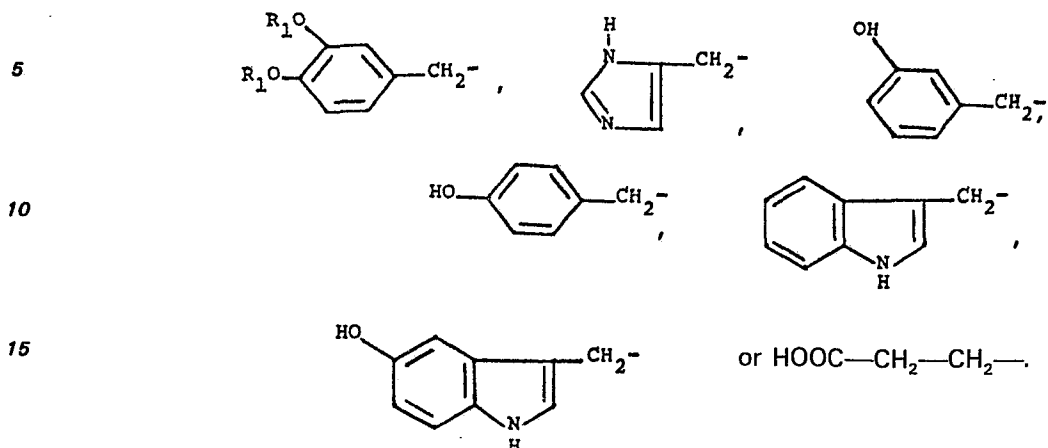
where R₁ is H or C₂—C₆ alkanoyl e.g., CH₃—CO, CH₃ (CH₂)₄—CO, (CH₃)₃C—CO and the like;



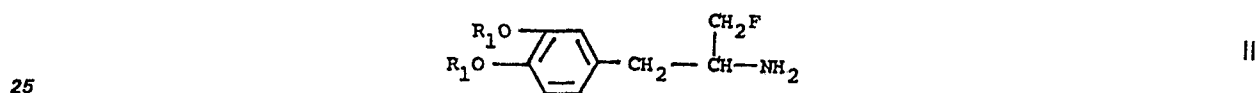
preferably



Preferred compounds of formula I are those where R is

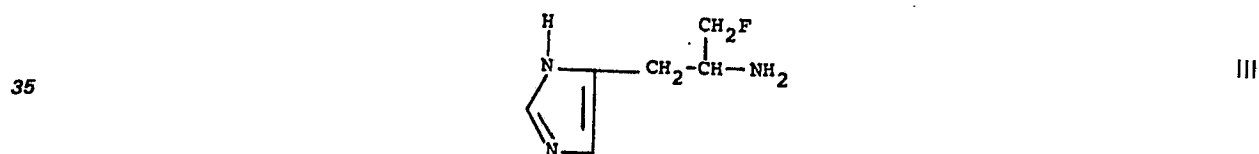


20 Compounds which are particularly preferred have the formula

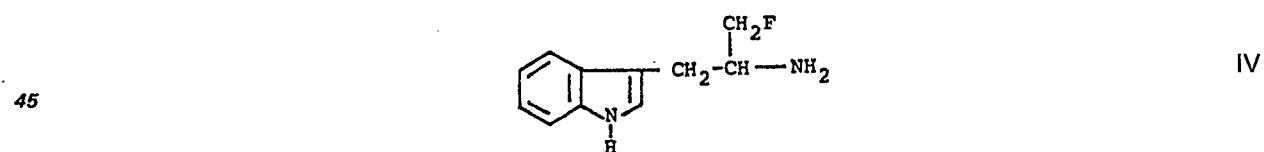


More preferred formula II compounds are those wherein R₁ is hydrogen; formula II compounds having the S-isomer configuration are especially preferred.

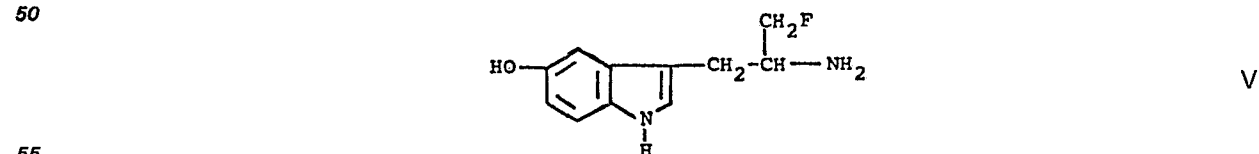
30 Another particularly preferred compound has the formula



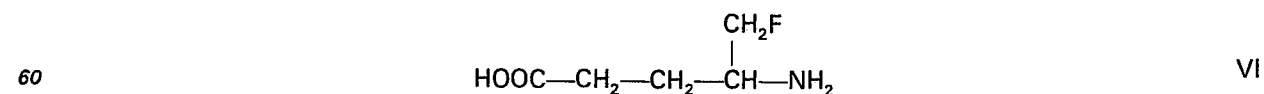
40 Another preferred compound has the formula



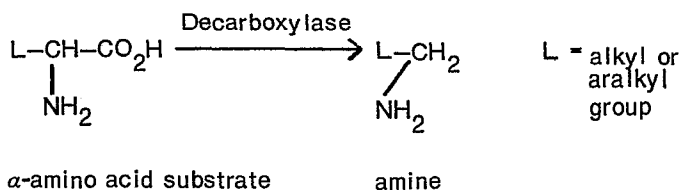
50 Another preferred compound has the formula



Still another preferred compound has the formula



The compounds of the present invention have potent decarboxylase inhibiting activity. Decarboxylases are enzymes which act on α -amino acid substrates, effecting decarboxylation to produce the corresponding amine. This action is illustrated by the following equation:



By inhibiting this decarboxylation, the biosynthetic pathway to a number of biologically significant amines can be modulated or inhibited with physiologically useful consequences. For example, α -fluoromethyl dopamine inhibits dopa decarboxylase and can be used in combination with dopa to potentiate the latter's usefulness in the treatment of Parkinson's disease.

The present compounds also are substantially specific in their decarboxylase inhibition activity, that is an α -fluoromethyl substituted alkylamine generally inhibits the decarboxylation of the corresponding non α -fluoromethyl- α amino acid. For example, α -fluoromethyl dopamine inhibits the decarboxylation of dopa; α -fluoromethyl histamine will inhibit the decarboxylation of histidine; 4-FM-GABA (4-fluoromethyl-4-amino-butyric acid) inhibits glutamic acid decarboxylase; etc.

Because of this specificity and potency as decarboxylase inhibitors, the present compounds are also useful as diagnostic tools to determine the presence and importance of the corresponding decarboxylase in relation to diseases or to the functioning of biological systems. For example, the role of catechol amines in certain CNS (central nervous system) functions can be studied by inhibiting their biosynthesis with an appropriate α -fluoromethyl-alkylamine; α -fluoromethyl-tryptamine displays antihypertensive activity; and the study and treatment of ulcers can be advanced through modulation of histamine biosynthesis using α -fluoromethyl histamine.

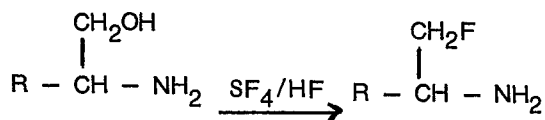
Representative compounds have been determined to have decarboxylase inhibiting activity using a conventional in-vitro assay.

A representative compound, S—(and R) 1 - fluoromethyl - 2(3,4 - dihydroxyphenyl)-ethylamine, also referred to as α -fluoromethyl dopamine, was found to effect a pressor response in rats. This indicates that some of the present compounds may also be useful for treating hypotension in humans.

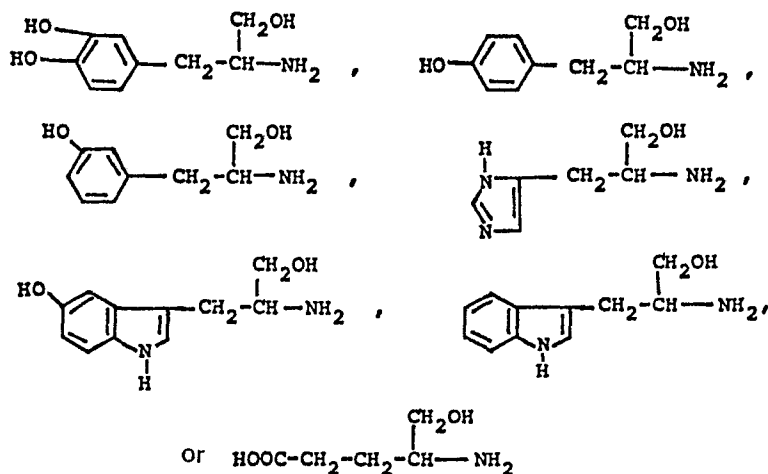
4-FM-GABA displays CNS activities, including sedative and antidepressant indications.

The compounds of the present invention may be prepared using any convenient method.

One such useful process involves the reaction of an α -hydroxymethyl substituted alkyl amine with SF_4 in liquid HF, as illustrated by the following equation:

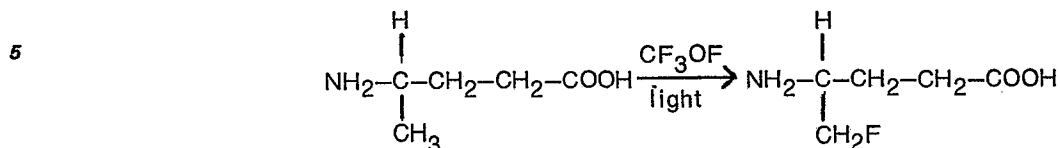


The starting compounds as



can be obtained according to ENz et al., Helv. Chim. Acta 29, 1048—1060 (1946). The reaction is generally carried out at temperatures ranging from about -80°C to about 20°C . This general reaction is also referred to as fluorodehydroxylation and is described in the Journal of Organic Chemistry 40, 3809—10 (1975).

Another useful method for preparation of α -fluoromethyl-substituted amines involves photofluorination, e.g.:



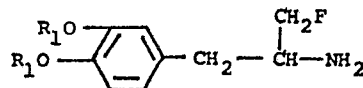
This process was described generally in J. Am. Chem. Soc. 98, 5591 (1976) and ibid. 92, 7494 (1970).

An acid addition salt of a compound of the present invention may be prepared by conventional treatment of the α -fluoromethyl-substituted amine with a useful acid generally in a suitable solvent.

A single enantiomer of the present compounds may be obtained by (1) resolving the fluoromethyl-substituted amine racemate using conventional resolution techniques or (2) resolving the precursor α -hydroxymethyl-substituted amine using conventional resolution techniques and then fluoro-dehydroxylating the precursor enantiomer. A conventional resolution technique may involve formation of a salt of the appropriately substituted amine with an optically active acid and subsequently recovering the specific enantiomer from the salt.

Compounds of the formula

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where R_1 is $\text{C}_2 - \text{C}_8$ alkanoyl are prepared by acylating the corresponding compound where R_1 is hydrogen, in an acid medium to prevent acylation of the amino group. In general, conventional acylating agents and conditions are employed.

The following examples illustrate preparation of representative compounds of the present invention. All temperatures are in $^\circ\text{C}$. Melting points are determined in open capillary and are uncorrected.

Example 1

Synthesis of *R*- α -Fluoromethyl-Dopamine-HCl

35 a) Preparation of *R*- α -Hydroxymethyl-Dopamine-HCl

Four and 55/100 g of sodium borohydride is suspended by stirring (magnetic stirring bar) with 250 ml of tetrahydrofuran (THF). To the stirred suspension there is added 6.7 g of CaCl_2 (powder), the mixture stirred for 30 minutes at room temperature, then refluxed under stirring for 90 minutes. To the $\text{Ca}(\text{BH}_4)_2$ solution thus obtained, a solution of 10.2 g of methyl ester of *D*-DOPA (DOPA = 3,4-dihydroxy-phenylalanine) in 55 ml of THF is admixed. After 15 minutes at room temperature, the suspension is refluxed with continued stirring for 5-1/2 hours. (Note: The whole operation described above was conducted under a protective blanket of dry N_2 gas.) The solvent is evaporated in vacuo and methanol (300 ml) is added with caution. After the gas evolution ceases, the solvent is removed by distillation in vacuo, fresh methanol is added again, the HCl gas is passed in until saturation. Solvent is removed again by evaporation in vacuo and the whole $\text{CH}_3\text{OH}/\text{HCl}$ treatment is repeated. (These treatments split the borate complex formed in the reduction as well as removing the methyl borate). The residue is dissolved in H_2O , 109 ml of 0.55M aq. H_2SO_4 is added and the mixture aged at 5°C overnight. The $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ is then removed by filtration, washed with water (10 ml) and isopropanol (2×30 ml). The combined filtrates were evaporated in vacuo to dryness, the solid residue is stirred with isopropanol (100 ml) for 1/2 h., filtered, cake washed with isopropanol (2×30 ml), the combined filtrates evaporated to dryness in vacuo. This crude product is further purified by elution chromatography (cation-exchange resin column made of 0.95 1 AG50-X-8 resin, 200/400 mesh U.S. Bureau of Standards, Standard Screen Sieves 1919; H form). Effluent is monitored by LKB UVICORD II UV monitor. Elution is as follows:

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0.4M aq. HCl, containing 7.5% methanol: 5 l.
0.6M aq. HCl, containing 10% methanol: 4.8 l.
0.7M aq. HCl, containing 10% methanol: 2.1 l.
1.0M aq. HCl, containing 10% methanol: 4.0 l.

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Elution rate: 0.6 l/hour.

The product is located by the UV absorption monitor, which is connected with a chart recorder. The UV absorbing peak is released by the last solvent listed. The appropriate fractions are combined and evaporated to dryness in vacuo, to deliver the hydrochloride of *R* - α - hydroxymethyl -

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dopamine. For final purification this is recrystallized from isopropanol, to give crystalline product, m.p. 159—160°C. $[\alpha]_D$: $19.5 \pm 0.5^\circ$ (c, 1 in 1M aq. HCl).

b) *Preparation of R- α -Fluoromethyl-Dopamine-HCl*

- 5 One g of the product obtained under a) is charged into a KEL-F (Registered Trade Mark) reactor. HF gas is passed in while the reactor is immersed in a dry-ice-acetone bath, until a solution with 30 ml volume forms. The cooling bath is removed and the solvent evaporated by passing through a stream of N_2 gas. The residue thus obtained represents the HF salt of *R- α -hydroxymethyl-dopamine*. This is redissolved by condensing into the reactor HF again by cooling it in a dry-ice-acetone bath and passing
- 10 in HF gas until a solution with volume 50 ml forms. SF_4 gas (1.5 ml, measured as liquid at $-78^\circ C$) is passed in then under continuous cooling and stirring and the solution left standing overnight, while the reactor is being kept in the cooling bath, but without replenishing dry ice. The solvent is removed the next morning by passing through a stream of N_2 and the residue is redissolved in 2.5 M aq. HCl (25 ml), evaporated to dryness and the residue purified by elution chromatography on a column made of cation-
- 15 exchange resin (190 ml of Dowex 50 AG50-X-8, (Registered Trade Mark) 200/400 mesh U.S. Bureau of Standards, Standard Screen Sieves 1919). Elution with water, followed by 0.5M aq. HCl with 5% methanol (2 l), followed by 0.6M aq. HCl with 10% methanol (4 l). UV absorption of the effluent is followed by LKB UVICORD II recording UV monitor. The effluent fractions containing UV absorbing material are evaporated to dryness in vacuo to deliver *R- α -fluoromethyl-dopamine-HCl*. 0.6 g of this
- 20 crude product is dissolved in isopropanol (4 ml), treated with DARCO G-60 (Registered Trade Mark) then 26 ml of ethyl acetate is added. The crystalline product is recrystallized once more in a similar manner, to give 0.545 g of pure HCl salt, m.p. 152—3°C $[\alpha]_D$: 18.4 ± 0.5 (C, 1 in 1M aq. HCl).

Example 2

25 *Synthesis of S- α -Fluoromethyl-Dopamine-HCl*

- S- α -Fluoromethyl dopamine-HCl* is synthesized in an entirely analogous manner as described in example 1 for the *R* isomer; however to obtain the *S* isomer, the methyl ester of *L-DOPA* is employed as starting material. The intermediate *S-hydroxymethyl dopamine* has a melting point of 159—60°C; $[\alpha]_D$: $-20.1 \pm 0.5^\circ$ (C, 1 in 1M aq. HCl). The *S- α -fluoromethyl-dopamine-HCl* obtained from this
- 30 fluorodehydroxylation, has a m.p. = 151—3°C, $[\alpha]_D$: $-19.2 \pm 0.5^\circ$ (C, 1 in 1M aq. HCl).

Example 3

Synthesis of R- α -Fluoromethyl-Histamine

- One g of *D-histidinol* is placed into a KEL-F reactor; the reactor is immersed into a dry-ice-acetone
- 35 cooling bath and HF gas is passed in until a volume of 40 ml collects. SF_4 gas is passed in (2.0 ml, measured as liquid, at $-78^\circ C$) and the mixture kept at $-78^\circ C$ for 5 hours. The cooling bath is removed and the solvent evaporated by passing N_2 gas through it. The residue is dissolved in cc. aq. HCl (15 ml), the solution is evaporated to dryness in vacuo to yield substantially pure *R- α -fluoromethyl-histamine* hydrochloride-hydrofluoride salt. For transformation into the dihydrochloride salt, this product is
- 40 dissolved in water and charged onto a cation-exchange resin column Dowex 50-X-8 (resin, H^+ form). The column is washed first with H_2O until the effluent becomes neutral, then the product is eluted with 4M aq. HCl (275 ml). This effluent is evaporated to dryness to deliver substantially pure *R- α -fluoromethyl-histamine* dihydrochloride. This is recrystallized by dissolving it in 40 ml of boiling ethanol 2BA, concentrating this solution by evaporation in vacuo to 15 ml volume and cooled (ice-bath) for 2
- 45 hours. The crystals formed are collected by filtration and dried in vacuo to give *R- α -fluoromethyl-histamine* dihydrochloride, m.p. 181—2°.

Example 4

Synthesis of S- α -fluoromethyl-Histamine

- 50 *S- α -Fluoromethyl histamine-HCl* is prepared from *L-histidinol* via the method described in Example 3 for *R- α -fluoromethyl-histamine-2HCl*, m.p. = 182—83°C.
- The free amines are obtained from the hydrochloride salts by conventional neutralization.

Example 5

55 *Synthesis of (S)- α -fluoromethyl-tryptamine*

- S(L)-Tryptophanol* (0.7 g, 3.7 mmoles) was placed in a Kel-F reactor, cooled in a dry ice-acetone bath ($-78^\circ C$) and approximately 20 ml of anhydrous HF was condensed with stirring at $-78^\circ C$. Sulfur tetrafluoride (approx. 1.5 ml, 26 mmoles) was added with stirring at $-78^\circ C$ over a 15-minute period. The reaction mixture was stirred for 30 minutes at $-78^\circ C$ and then the HF was blown off with a fast
- 60 stream of N_2 over a 2.5-hr. period at $-78^\circ C$. The dark residue was dissolved in 25 ml 3N HCl and evaporated to dryness at $25^\circ C$, in vacuo. The residue was dissolved in 10 ml H_2O , basified with 2.5N NaOH, and the separated amine was extracted with 2×50 ml ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to dryness in vacuo at room temperature. The crude product (4 spots, by TLC on silica gel plates developed with ethyl acetate-methanol-water 85:10:5) was
- 65 chromatographed on silica gel H (E. Merck, 120g.) using ethyl acetate-methanol-water 88:10:2 as the

elution solvent. The desired product (S)- α -fluoromethyl-tryptamine, was contained in fractions No. 31—60 (12 ml each). They were combined and evaporated to dryness to yield S- α -fluoromethyl-tryptamine characterized as the tartrate salt, by 300 MHz ^1H NMR, mass spectroscopy and microanalysis.

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Example 6

Synthesis of R- α -Fluoromethyl-tryptamine

Employing the procedure described in Example 5, but using R(D)-tryptophanol as starting material, R- α -fluoromethyl-tryptamine is obtained.

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Example 7

Synthesis of R,S-4-Fluoromethyl-4-Amino-butyric Acid

Eleven and 7/10 g of 4-methyl-4-aminobutyric acid is placed in a KEL-F reactor and dissolved in 200 ml of liquid HF; then CF_3OF gas is passed in while the reactor is immersed in a dry-ice/acetone cooling bath. The solution is irradiated (through a window on the top) by a 2500 W ultraviolet light source. (See J. of Am. Chem. Soc. 98, 5591-93 (1976) and ibid 92, 7494 (1970) for a general description of photofluorination).

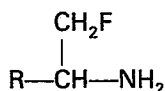
First, 3 ml liquid C_3OF is allowed to evaporate and passed into the solution during a 70 minute period, followed by another 40 min. period with irradiation. Two additional 2 ml (liq.) increments of CF_3OF are passed into the reaction mixture with continuing irradiation, each in a time period of about 2 hours. The liquid HF is then removed by a stream of nitrogen gas. The residue is dissolved in 50 ml of 2.5 N aq. HCl and evaporated to dryness in vacuo. This treatment is repeated. The residue thus obtained is dissolved in 270 ml of water; 270 ml of conc. aq. HCl is added and the solution refluxed for 16 hours, then evaporated to dryness in vacuo, redissolved in 100 ml of water and chromatographed on a column of cation-exchange resin. 3 l of AG-50-X-8 (200—400 mesh, U.S. Bureau of Standards, Standard Screen Sieves 1919) resin is employed in the H^+ form. Elution: 18 liters of water, followed by 0.4 N aq. HCl. The effluent is monitored by UVICORD Model III ultra-violet absorption monitor, filter 206 nm. 22 ml fractions are collected. Fractions 410—610 are combined and evaporated to dryness in vacuo to deliver 4 - fluoromethyl - 4 - amino-butyric acid hydrochloride. For liberation of the acid, the 4-FM-GABA.HCl is dissolved in water and passed through an AG-50-X-8 ion-exchange resin column (100 ml of resin). The column is first washed with water, then eluted with 2 N aq. NH_4OH . Evaporation of the NH_4OH solution in vacuo gives R,S - 4 - fluoromethyl - 4 - amino butyric acid. It is recrystallized from H_2O /isopropanol and characterized by C—H—N—F analysis and ^1H and ^{19}F NMR spectroscopy.

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Claims

1. A compound of the formula

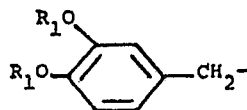
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wherein R is a substituted C_1 — C_4 alkyl group.

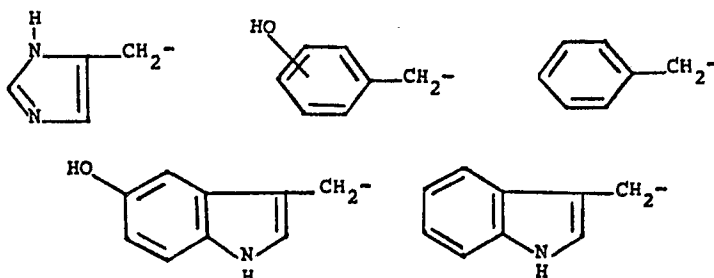
2. Pharmaceutically acceptable acid addition salts of the Claim 1 compounds.
3. A compound of Claim 1 having the S-isomer configuration.
4. A compound of Claim 1 wherein said substituted alkyl group is

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wherein R_1 is H or C_2 — C_6 alkanoyl

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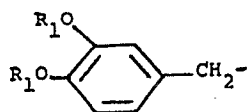


où R est un groupe alcoyle en C₁ à C₄ substitué.

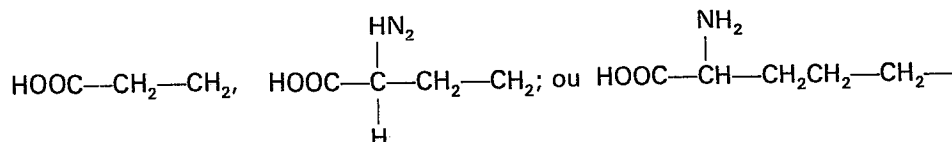
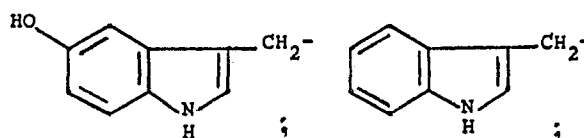
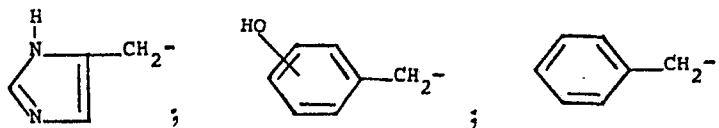
2. Sels d'addition acides pharmaceutiquement acceptables des composés de la revendication 1.

3. Composé de la revendication 1 ayant la configuration isomérique S.

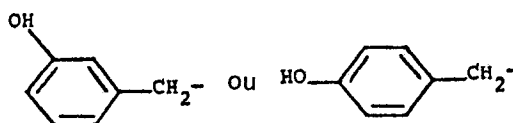
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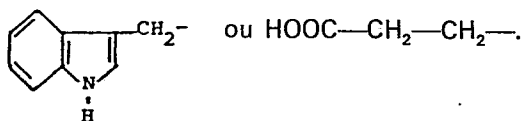
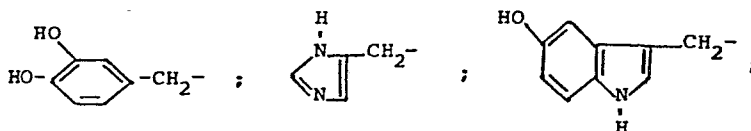
où R₁ représente H ou un alcanoyle en C₂ à C₆,



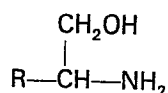
5. Composé des revendications 3 ou 4 où ledit groupe alcoyle substitué est



6. Composé de la revendication 3 où ledit groupe alcoyle substitué est



7. Procédé de préparation des composés de la revendication 1 qui comprend la fluorodéshydroxylation d'un composé de formule

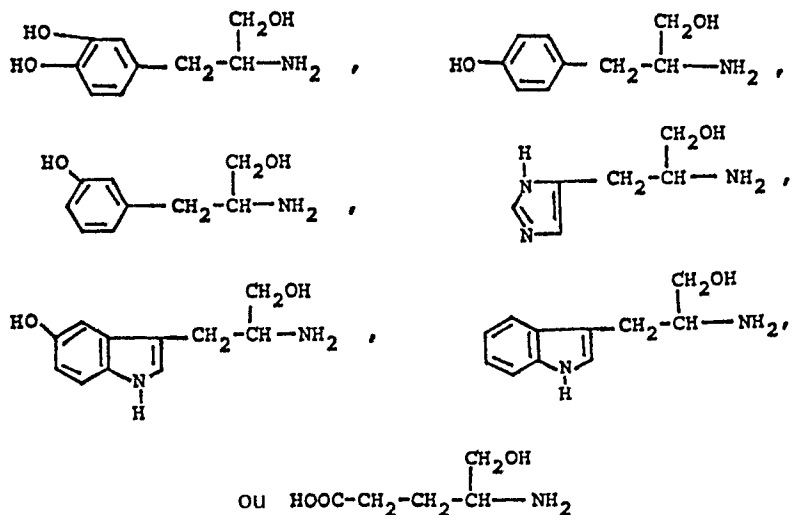


VII

où R est un groupe alcoyle en C₁ à C₄ substitué.

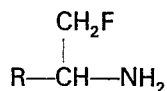
8. Procédé de la revendication 7 où ledit composé de formule VII est

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Patentansprüche

1. Verbindung mit der Formel

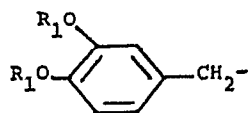


worin R eine substituierte C₁—C₄-Alkylgruppe ist.

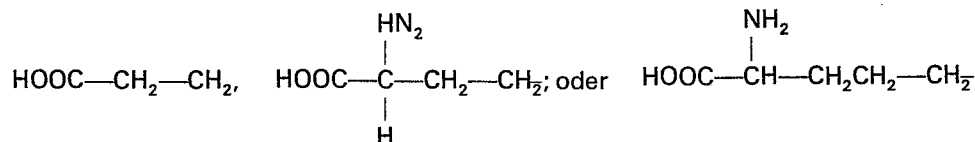
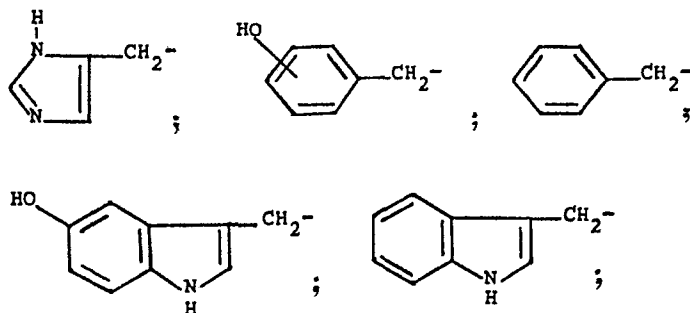
2. Pharmazeutisch brauchbare Säureadditionssalze der Verbindungen des Anspruchs 1.

3. Verbindung nach Anspruch 1 mit der Konfiguration des S-Isomeren.

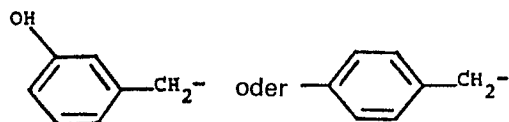
4. Verbindung nach Anspruch 1, in der die substituierte Alkylgruppe



worin R₁ H oder C₂—C₆-Alkanoyl ist,

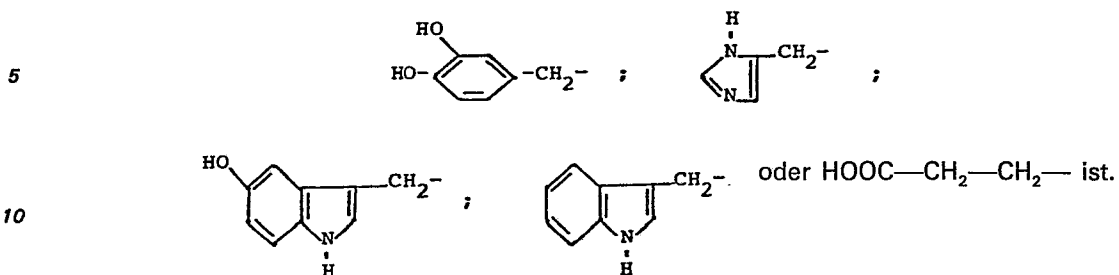


5. Verbindung nach Anspruch 3 oder 4, worin die substituierte Alkylgruppe

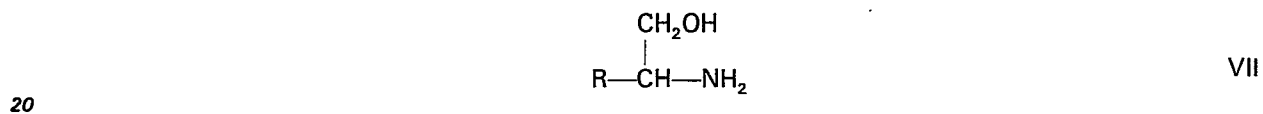


ist.

6. Verbindung nach Anspruch 3, worin die substituierte Alkylgruppe



7. Verfahren zur Herstellung von Verbindungen nach Anspruch 1 durch Fluordehydroxylieren
15 einer Verbindung mit der Formel



worin R eine substituierte C_1-C_4 -Alkylgruppe ist.

8. Verfahren nach Anspruch 7, worin die Verbindung der Formel VII

