Title: PROCESS FOR THE PREPARATION OF 0-[4-(4-PYRIDINYL)BUTYL]-TYROSINE DERIVATIVES AS FIBRINOGEN RECEPTOR ANTAGONISTS

R¹-\text{\text{-}}(\text{CH}_2)_m\text{-}O\text{-}\text{NH}_2\text{-}SO_2\text{-}R^4
\text{CO}_2\text{H} \quad (I)

Abstract

The invention is a highly efficient synthesis for making compounds of formula (I), wherein R¹ is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the heteroatoms are N; or NR², wherein R² is H or C₁₀ alkyl; m is an integer from two to six; and R⁴ is aryl, C₁₀ alkyl, or C₄ alkyl.
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TITLE OF THE INVENTION
PROCESS FOR THE PREPARATION OF 0-[4-(4-PIPERIDINYL)BUTYL]-TYROSINE DERIVATIVES AS FIBRINOGEN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION
United States Serial No. 750,647, filed August 30, 1991, describes fibrinogen receptor antagonists, and procedures for preparing fibrinogen receptor antagonists, which are prepared according to the procedure of the present invention. In particular, the compound:

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{HO}_2C & \quad \text{NHSO}_2n-\text{Bu}
\end{align*}
\]
is prepared according to an 11-step procedure involving the formation of potentially hazardous NaH/DMF for ether formation, which required a chromatographic purification.


Beumel et al., Synthesis (1974), 43; Screttas et al., Chimia (1970), 109; and Osuch et al., Chimia (1956), 1723, describe a procedure for metallation of 4-picoline.


SUMMARY OF THE INVENTION

The invention is a highly efficient synthesis for making compounds of the formula:

\[ R^1-(CH_2)_m-O-\text{NHSO}_2R^4 \]

\[ \text{CO}_2H \]

wherein:

- \( R^1 \) is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the heteroatoms are N; or NR\(^6\), wherein \( R^6 \) is H or C\(_{1-10}\) alkyl;

- \( m \) is an integer from two to six; and

- \( R^4 \) is aryl, C\(_{1-10}\) alkyl, or C\(_{4-10}\) aralkyl.
DETAILED DESCRIPTION OF THE INVENTION

The invention is a process for preparing fibrinogen receptor antagonists of the formula:

\[
R^1-(CH_2)_m-O-\begin{array}{c}
| \\
\text{SO}_2\text{R}^4 \\
\text{CO}_2\text{H}
\end{array}
\]

wherein

- \( R^1 \) is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the hetero atoms are \( N \); or \( NR^6 \) wherein \( R^6 \) is \( C_{1-10} \) alkyl;
- \( m \) is an integer from two to six; and
- \( R^4 \) is aryl, \( C_{1-10} \) alkyl, or \( C_{4-10} \) aralkyl,

according to the procedure whereby

\[
\begin{align*}
R^1-\text{CH}_3 & \xrightarrow{1)} \text{n-BuLi} \xrightarrow{2)} \text{Br(CH}_2)_{m+1}\text{OR} \quad \xrightarrow{(1)} \quad \text{R'}(\text{CH}_2)_{m}\text{OR} \\
(1) & \quad (2)
\end{align*}
\]
methylated $R^1$ is reacted with $n$BuLi, before quenching with a straight chain alkyl group having $\text{Br}$ at one end and OR at the other end, to yield (2), wherein $R$ is tetrahydropyran;

\[
\begin{align*}
(2) & \xrightarrow{1) \text{HCl/EtOH}} (3) \\
\end{align*}
\]

(2) is aged, first in hydrogen chloride gas in ethanol, and then neutralized in triethylamine/tetrahydrofuran, to form (3); and

\[
\begin{align*}
(3) + \text{HO-} & \xrightarrow{1) \text{Ph}_3\text{P, (i-PrO}_2\text{CN)}_2 \text{THF}} \xrightarrow{2) \text{LiOH, THF, MeOH, H}_2\text{O}} (4) \\
\end{align*}
\]

(3) is combined with (4) to yield (5) after ester hydrolysis.
Preferably, when

\[ R^1 \text{ is pyridine,} \]

\[ R'(CH_2)_m \text{--O--} \text{--NH--SO_2R}^4 \]
\[ \text{CO}_2\text{H} \]

(5)

is selectively hydrogenated using Pd/C in acetic acid

\[ 1) \text{H}_2, \text{Pd/C, AcOH} \rightarrow \text{to yield} \]
\[ 2) \text{HCl} \]

\[ \text{HN--(CH}_2_\text{m--O--} \text{--NH--SO}_2\text{R}^4 \]
\[ \text{CO}_2\text{H} \]

\[ \cdot \text{HCl} \]

The synthesis of the invention uses inexpensive starting materials, and employs the Mitsunobu reaction to effect the ether formation in high yield and simple purification procedure. The prior art reaction employs a potentially hazardous NaH/DMF mixture to effect the ether formation in low yield, which required a chromatographic purification.
Preferably, the invention is a highly efficient synthesis for making

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{HO}_2C & \quad \text{NH} \quad \text{S} \\
\text{O} & \quad \text{O}
\end{align*}
\]

The six-step synthesis employs 4-picoline, as a latent form of piperidine, which eliminates the need for protection. 0-alkylation of a tyrosine derivative under Mitsunobu condition followed by saponification of the methyl ester, extractive removal of the Mitsunobu by-products, and recrystallizations provide the coupled product in high yield and purity. Selective hydrogenation of the pyridine ring is achieved by using 10% Pd/C in AcOH at 70°C.
EXAMPLE 1

1) n-BuLi
2) Br

1) HCl/EtOH
2) Et₃N/THF

HCl salt
free base
1-5 + 1-6

1) Ph₃P, (i-PrO₂CN)₂, THF
2) LiOH, THF, MeOH, H₂O

1-7 R=Me
1-8 R=H

1-8
1) H₂, Pd/C, AcOH
2) HCl

1-9

HCl
Preparation of N-n-Butanesulfonyl-(L)-tyrosine methyl ester (1-6)

A 50 L four-neck round bottom flask equipped with a mechanical stirrer, condenser, nitrogen inlet, HCl trap, heating unit and a thermometer probe was purged with nitrogen overnight and then charged with (L)-tyrosine methyl ester HCl salt (1304 g, 5.628 mol), CH₃CN (16 L), pyridine (994.3 g, 12.57 mol) and n-butanesulfonyl chloride (924.83 g, 5.906 mol). The mixture was heated at 65°C for 20 h. The solvent was removed in a batch concentrator under house vacuum at 40°C over 1-2 days. The resulting black oil was washed with 10% KHSO₄ (8.5 L) and the mixture extracted with methylene chloride (4 x 8 L). The organic was filtered through 2.9 kg MgSO₄ (top) and 1.3 kg flash-grade SiO₂ (bottom) in a sinter glass funnel. Evaporation of the filtrate gave ~1021 g solid (purity = 90 A%). The solid was dissolved in toluene (5L) with heating and the batch was aged at ambient temperature for 5 h and then filtered. The filter cake was washed with toluene (2L) and dried to give 857.5 g (48%) of 1-6 as an off-white solid. mp 70-71°C; [α]D⁻²⁵ = -27.0° (c 0.967, MeOH); MS(EI) m/z 315 (M+).

¹H NMR (CD₃OD) δ 7.06 (d, J = 7.7 Hz, 2H), 6.72 (d, J = 7.7 Hz), 4.10 (ABq, J = 9.6, 5.1 Hz, 1H), 3.02 (ABq, J = 13.7, 5.1 Hz, 1H), 2.73 (ABq, J = 13.7, 9.6 Hz, 1H), 2.61 (t, J = 7.9 Hz, 2H), 1.41 (m, 2H), 1.33 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H).

Preparation of 4-(4-Pyridinyl)butanol (1-5)

A 12 L four-neck round bottom flask equipped with a mechanical stirrer, condenser, addition funnel with side-arm and a thermometer probe was purged with nitrogen overnight. THF (2.4 L) and 4-picoline (322.5 g, 3.46 mol) were added and the batch was cooled to −40°C. A solution of n-butyllithium (2.69 L of 1.56 M solution, 4.21 mol) in hexane was added slowly while keeping the internal temperature ≤−30°C. The addition took about 1 h to give an orange solution with some precipitate. The batch was warmed to ambient temperature, aged for four hours and then cooled to −20°C. A solution of 2-(3-bromopropoxy)-tetrahydropyran (850.0 g, 3.81 mol) in dry THF (450 mL) was added slowly via an addition funnel, maintaining the batch temperature at ≤−5°C, and then the batch was aged at ambient temperature overnight. Ice water (3 L) was added and the mixture was extracted with ethyl acetate (1 × 2 L, 1 × 1.5 L, 1 × 1 L). The combined organic layers were washed with water (4 L) and then concentrated to give ~874 g of crude 1-3 as an oil, which is used directly in the next step.

To a solution of crude 1-3 (873 g) in ethanol (3.5 L) was added a solution of HCl gas (278 g, 7.61 mol) in ethanol (2.5 L). The mixture was stirred at ambient temperature for 3 h, then concentrated under vacuum. The resulting oil was dissolved in warm isopropanol (700 mL) and ethanol (50 mL), then with mechanical stirring isopropyl acetate (1.2 L) was added slowly. The mixture was aged for 18 h at ambient temperature, cooled (with
ice water) and filtered under nitrogen. The filter cake was washed with isopropyl acetate (3 x 500 mL) and vacuum-dried under nitrogen to give ~280 g of 1-4.

To a mixture of compound 1-4 (280 g) in dry THF (2 L) was added slowly a solution of triethylamine (166 g, 1.64 mol) in THF (400 mL). The mixture was stirred for 2 h, filtered and the filter cake (triethylamine hydrochloride) was washed with THF (2 x 500 mL). The filtrate was evaporated to dryness under vacuum to give 200 g compound 1-5 in 40% overall yield from 4-picoline.

1-4: mp 153-154°C; MS(CI) m/z 151 (M⁺ - HCl).

1H NMR (CD3OD) δ 1.63 (m, 2H), 1.89 (m, 2H), 2.99 (t, J = 7.8 Hz, 2H), 3.60 (t, J = 6.2 Hz, 2H), 7.98 (d, J = 6.5 Hz, 2H), 8.72 (d, J = 6.5 Hz, 2H);

13C NMR (CD3OD) δ 27.3, 32.9, 36.7, 62.2, 128.6, 142.1, 166.6.

Anal. Calcd for C9H14NOCl: C, 57.60; H, 7.52; N, 7.46; Cl, 18.89. Found: C, 57.65; H, 7.34; N, 7.33; Cl, 19.17.

Preparation of N-(n-Butanesulfonfyl)-O-(4-(4-pyridinyl)butyl)-(L)-tyrosine (1-8)

To a dry 5 L three-neck round bottom flask equipped with a mechanical stirrer, nitrogen inlet and a thermometer probe containing a solution of N-n-butanesulfonfyl-(L)-tyrosine methyl ester (400.3 g, 1.268 mol) and triphenylphosphine (417.5 g, 1.595 mol) in THF (600 mL) was slowly added a solution of 4-(4-pyridinyl)-butanol (207.0 g, 1.37 mol) and diisopropyl azodicarboxylate (319.9 g, 1.582 mol) in
THF (475 mL) via a 1-L addition funnel over 3.5 h. The temperature was maintained at 23-26°C using a water bath. The mixture was allowed to stir for additional 30 min, then hexane (1.1 L) and methylene chloride (60 mL) were added. The resulting mixture was loaded onto sand (1 kg, on top)/Silica Gel 60 (3 kg) in a 5 L sintered glass funnel, eluted with 1:1 hexanes/THF (32 L), and collected 2-L fractions. Fractions 1-8 were combined and the precipitate Ph₃PO was filtered. The filter cake was washed with 1:1 hexanes/THF (300 mL). The filtrate was concentrated to give 1051 g of crude methyl ester 1-7 as an oil.

To a solution of 1-7 (1051 g) in THF/MeOH/H₂O (3:1:1, 5 L) was added slowly solid LiOH•H₂O (108.5 g, 2.58 mol) at 25-29°C over 30 min. The mixture was aged for 1.5 h and then quenched by adding DI water (4 L) and conc. HCl (125 mL) to give a final pH 10.4. The mixture was diluted with water (4 L) and extracted with isopropyl acetate (4 x 3 L) and the combined organic layer was back-extracted with 0.1 N NaOH (3 L). The combined aqueous layer was acidified to pH 4.5 using conc. HCl (100 mL) and then extracted with methylene chloride (3 x 4 L). The methylene chloride extracts were filtered through sand (1 kg, on top)/Silica Gel 60 (3 kg) in a 5 L sintered glass funnel, then eluted with ethyl acetate (4 L), ethyl acetate/methanol/acetic acid (12 L/0.6 L/60 mL) and ethyl acetate/methanol/acetic acid (28.1 L/3.5 L/350 mL), and collected in 4-L fractions. The product-enriched fractions 4-8 were combined and evaporated to dryness to give 466 g wet solid. The solid was recrystallized
from isopropyl alcohol (6 L) by warming to 50°C first and then cooling slowly to ambient temperature with stirring overnight. The slurry was filtered, washed with isopropyl alcohol (2 x 200 mL) and air-dried to give 305 g (55%) of 1-8.

**HPLC Assay:** product 1-8, 99.5% area; RT = 6.76 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min; linear gradient 10 to 90% A over 10 min, A = CH₃CN, B = 0.1% aqueous H₃PO₄.

mp 137-138°C; [α]²⁵D = -14.7° (c 0.91, MeOH); MS(Cl) m/z 435 (MH⁺).

¹H-NMR (CD₃OD) δ 0.86 (t, J=7.3Hz, 3H), 1.33 (hex, J=7.3Hz, 2H), 1.68 (m, 2H), 1.83 (m, 2H), 2.82 (m, 2H), 3.06 (A of ABX, J_{AB}=13.9Hz, J_{AX}=6.3Hz, 1H), 3.16 (B of ABX, J_{BA}=13.9Hz, J_{BX}=5.0Hz, 1H), 3.90 (t, J=5.7Hz, 2H), 4.32 (X of ABX, J_{XA}=6.3Hz, J_{XB}=5.0Hz, 1H), 6.72 (d, J=8.6Hz, 2H), 7.17 (d, J=8.6Hz, 2H), 7.33 (d, J=6.3Hz, 2H), 8.49 (d, J=6.3Hz, 2H);

¹³C-NMR (CDCl₃) δ 13.5, 21.5, 25.4, 26.5, 28.6, 35.1, 38.9, 53.0, 57.9, 67.0, 114.3, 125.0, 128.7, 130.8, 145.9, 155.8, 157.7, 175.0;

Anal. Calcd for C₂₂H₃₀O₅S₂N₂:
  C, 60.81; H, 6.96; N, 6.45; S, 7.38.

Found:  C, 60.53; H, 6.88; N, 6.26; S, 7.65.
Preparation of N-(n-butanesulfonyl)-O-(4-(4-piperidinyl)butyl)-(L)-tyrosine, hydrochloride, monohydrate (1-9)

Pyridine 1-8 (274.6 g, 0.632 mol) and 10% Pd/C (27.5 g, 10 wt%) in acetic acid (2.75 L) was hydrogenated in a stainless steel vessel at 40 psi and 70°C until complete uptake of hydrogen was observed (4-6 h). The reaction mixture was filtered through a pad of Solka-Floc (280 g; prewashed with 1 L acetic acid) and then washed with acetic acid (1 L). The filtrate was concentrated to a thick oil containing approximately 285 g acetic acid, then DI water (4.125 L) was added to give a concentration of 1 g/15 mL 7% acetic acid in water and the resulting slurry was stirred at 50°C for 1 hour and at ambient temperature for 18 hours. The solid was collected on
a sintered glass funnel, washed with DI water (3 x 350 mL) and dried under vacuum with nitrogen sweep to give 238.4 g (86%) of free base of 1-9 as a white solid.

HPLC Assay: free base of 1-9, 99.5 area %, RT=6.94 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min; linear gradient 20 to 70% A over 12 min, A=CH$_3$CN, B=0.1% aqueous H$_3$PO$_4$. mp 223-225°C; [$\alpha$]$^25_D$= -14.7° (c 0.91, MeOH).

$^1$H-NMR (CD$_3$OD) δ 0.88 (t, J=7.3Hz, 3H), 1.33 (m, 6H), 1.58 (m, 5H), 1.76 (m, 2H), 1.81 (m, 2H), 2.77 (t, J=7.5, 2H), 2.80 (m, 1H), 2.88 (m, 2H), 3.03 (B of ABX, J$_{BA}$=13.9Hz, J$_{BX}$=4.6Hz, 1H), 3.30 (m, 2H), 3.90-4.0 (m, 3H), 6.80 (d, J=8.5Hz, 2H), 7.18 (d, J=8.5Hz, 2H). Anal. Calcd for C$_{22}$H$_{37}$O$_5$N$_2$S:

C, 59.84; H, 8.40; N, 6.34; S, 7.24.
Found: C, 59.98; H, 8.40; N, 6.40; S, 7.24.

To a rapidly stirred suspension of free base of 1-9 (24.64 g, 55.93 mol) and isopropyl acetate (1 L) was added concentrated hydrochloric acid (10 mL) dropwise. The temperature remained at 19°C throughout addition. The mixture was then stirred at room temperature (19°C) for a further 6 hours. The product was isolated by filtration under nitrogen. The solid product was washed with isopropyl acetate (2x100 mL) and suction-dried under nitrogen overnight to afford 27.1 g (98%) of 1-9.

HPLC Assay: 1-9, 99.8 area%; RT=6.79 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min;
linear gradient 10 to 90% A over 10 min, A=CH$_3$CN, B=0.1% aqueous H$_3$PO$_4$; or 1-9, 99.8 area%, RT=6.94 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min; linear gradient 20 to 70% A over 12 min, A=CH$_3$CN, B=0.1% aqueous H$_3$PO$_4$.

Chiral HPLC: L-isomer, >99.9%; RT=10 min; D-isomer, <0.1%; RT=8.5 min; ULTRON-ES-OVM column, 4.6 mm x 25 cm, 5 m, with guard column; 270 nm; 0.7 mL/min; isocratic, 90% Buffer (6 g ammonium formate adjusted to pH 4.1 with formic acid), 10% MeOH. mp 87-88°C, mp2 131-132°C; [α]$^2_{D}$=−14.4° (c 0.92, MeOH);

$^1$H-NMR (CD$_3$OD) δ 0.84 (t, J=7.3Hz, 3H), 1.23 (hex, J=7.3Hz, 2H), 1.30-1.70 (m, 9H), 1.75 (m, 2H), 1.95 (m, 2H), 2.64 (t, J=7.4, 2H), 2.77 (A of ABX, J$^A_{AB}$=13.9Hz, J$^A_{AX}$=9.8Hz, 1H), 2.95 (m, 2H), 3.11 (B of ABX, J$^B_{BA}$=13.9Hz, J$^B_{BX}$=4.6Hz, 1H), 3.47 (m, 2H), 3.95 (t, J=6.2Hz, 2H), 4.09 (X of ABX, J$^X_{XX}$=9.8Hz, J$^X_{XB}$=4.6Hz, 1H), 6.84 (d, J=8.6Hz, 2H), 7.18 (d, J=8.6Hz, 2H).

$^{13}$C-NMR (CD$_3$OD) δ 14.0, 22.5, 24.0, 26.5, 30.0, 30.4, 34.8, 36.8, 39.0, 45.3, 54.1, 59.4, 68.7, 115.5, 130.4, 131.7, 159.6, 175.2.

IR (Nujol, cm$^{-1}$) 3520, 3208, 3166, 2800-2300, 1727, 1610, 1595, 1324, 1256, 1141, 1119, 829.

HRMS calc'd for C$_{22}$H$_{37}$N$_2$O$_5$S 441.2423, found 441.2423 (M$^+$-H$_2$O-HCl).

Anal. Calc'd for C$_{22}$H$_{39}$O$_6$ClN$_2$S:

C, 53.37; H, 7.94; N, 5.66; Cl, 7.16; S, 6.48.

Found: C, 53.56; H, 8.04; N, 5.62; Cl, 7.36; S, 6.53.
WHAT IS CLAIMED IS:

1. A process for preparing compounds of the following formula:

\[
R' - (\text{CH}_2)_m \text{-O}- \begin{array}{c}
\text{NHSO}_2R'^4 \\
\text{CO}_2\text{H}
\end{array}
\]

wherein:
- \( R'^1 \) is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the heteroatoms are N; or NR^6, wherein R^6 is C_{1-10} alkyl;
- \( m \) is an integer from two to six; and
- \( R'^4 \) is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl,

according to the process steps whereby

1) \( R'^1 \text{-CH}_3 \)

1) n-BuLi

(1)

2) Br(\text{CH}_2)_m, OR

(2)

methylated \( R'^1 \) is reacted with nBuLi, before quenching with a straight chain alkyl group having Br at one end and OR at the other end, to yield (2), wherein R is tetrahydropyran;
(2) is aged, first in hydrogen chloride gas in ethanol, and then neutralized in triethylamine/tetrahydrofuran and to yield (3); and

(3) is combined with (4) to yield (5).
2. A process according to Claim 1, wherein \( R^1 \) is pyridine, and

\[
\begin{align*}
\text{HN}(\text{CH}_2)_m & \quad \text{O} \quad \text{NH}_2\text{SO}_2R^4 \\
& \quad \text{CO}_2\text{H}
\end{align*}
\]

(5)

is selectively hydrogenated using Pd/C in acetic acid to yield

\[
\begin{align*}
\text{HN}(\text{CH}_2)_m & \quad \text{O} \quad \text{NH}_2\text{SO}_2R^4 \\
& \quad \text{CO}_2\text{H}
\end{align*}
\]
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER
   (If several classification symbols apply, indicate all)

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

Int.Cl. 5 C07D211/22; C07D213/30

II. FIELDS SEARCHED

Classification System

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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
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IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Bernd Kessler
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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82