(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76489 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US00/15071

(22) International Filing Date: 31 May 2000 (31.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/138,550 10 June 1999 (10.06.1999) US

(71) Applicants *(for all designated States except US)*: **WARNER-LAMBERT COMPANY** [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). **YAMANOUCHI PHARMACEUTICAL COMPANY, LTD.** [JP/JP]; 17-1, Hasune 2-chome, Itabashi ku, Tokyo 174-8612 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AUGELLI-SZAFRAN, Corinne, Elizabeth** [US/US]; 2812 Aspen Ridge Drive, Ann Arbor, MI 48103 (US). **BARVIAN, Mark, Robert** [US/US]; 1037 Morningside Drive, Ann Arbor, MI 48103 (US). **BIGGE, Christopher, Franklin** [US/US]; 2400 Parkside Drive, Ann Arbor, MI 48105 (US). **GLASE, Shelly, Ann** [US/US]; 4468 Hillside Court, Ann Arbor, MI 48105 (US). **HACHIYA, Shunichiro** [JP/JP]; 202, 5-9, Ninomiya 2-chome, Tsukuba, Ibaraki 305-0051 (JP). **KEILY, John, Steven** [US/US]; 4230 Corte Facil, San Diego, CA 92130 (US). **KIMURA, Takenori** [JP/JP]; 701, 11-3, Umezone 2-chome, Tsukuba, Ibaraki 305-0045 (JP). **LAI, Yingjie** [CA/US]; 27H Reading Road, Edison, NJ 08817 (US). **SAKKAB, Annette, Theresa** [US/US]; 39790 Foxway Court, Northville, MI 48167 (US). **SUTO, Mark, James** [US/US]; 1442 Sandal Lane, La Jolla, CA 92037 (US). **WALKER, Lary, Craswell** [US/US]; 4890 North Ridgeside Circle, Ann Arbor, MI 48105 (US). **YASUNAGA, Tomoyuki** [JP/JP]; 13-18, Minami 3-chome, Ushiku-shi, Ibaraki 300-1222 (JP). **ZHUANG, Nian** [CN/US]; 5139 Blue Spruce Drive, Ypsilanti, MI 48197 (US).

(74) Agents: **RYAN, M., Andrea**; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

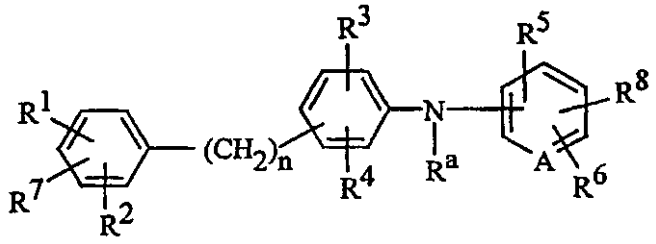
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS



(I)

(57) Abstract: The present invention provides a method of treating Alzheimer's disease using a compound of Formula (I). Also provided is a method of inhibiting the aggregation of amyloid proteins using a compound of the Formula (I) and a method of imaging amyloid deposits, as well as new compounds of Formula (I).

WO 00/76489 A2

METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS

FIELD OF THE INVENTION

This invention relates to a method of inhibiting amyloid protein aggregation and imaging amyloid deposits. More particularly, this invention relates to a method of inhibiting amyloid protein aggregation in order to treat Alzheimer's disease.

BACKGROUND OF THE INVENTION

Amyloidosis is a condition characterized by the accumulation of various insoluble, fibrillar proteins in the tissues of a patient. The fibrillar proteins that comprise the accumulations or deposits are called amyloid proteins. While the particular proteins or peptides found in the deposits vary, the presence of fibrillar morphology and a large amount of β-sheet secondary structure is common to many types of amyloids. An amyloid deposit is formed by the aggregation of amyloid proteins, followed by the further combination of aggregates and/or amyloid proteins.

The presence of amyloid deposits has been shown in various diseases, each with its particular associated protein, such as Mediterranean fever, Muckle-Wells syndrome, idiopathetic myeloma, amyloid polyneuropathy, amyloid cardiomyopathy, systemic senile amyloidosis, amyloid polyneuropathy, hereditary cerebral hemorrhage with amyloidosis, Alzheimer's disease, Down's syndrome, Scrapie, Creutzfeldt-Jacob disease, Kuru, Gerstmann-Straussler-Scheinker syndrome, medullary carcinoma of the thyroid, Isolated atrial amyloid, β_2-microglobulin amyloid in dialysis patients, inclusion body myositis, β_2-amyloid deposits in muscle wasting disease, Sickle Cell Anemia, Parkinson's Disease, and Islets of Langerhans diabetes Type II insulinoma.

Alzheimer's disease is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgement, and emotional stability that gradually leads to mental deterioration and ultimately death. Because Alzheimer's disease and related degenerative brain disorders are a major medical issue for an increasingly aging population, the need for new treatments and methods for diagnosing the disorders are needed.

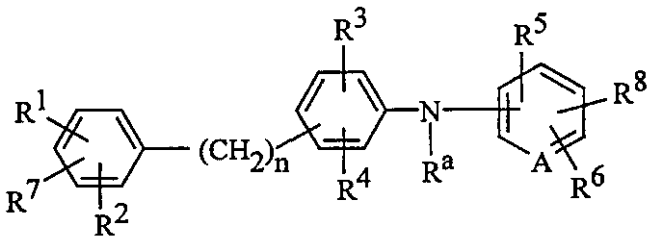
A simple, noninvasive method for detecting and quantitating amyloid deposits in a patient has been eagerly sought. Presently, detection of amyloid deposits involves histological analysis of biopsy or autopsy materials. Both methods have major drawbacks. For example, an autopsy can only be used for a postmortem diagnosis.

The direct imaging of amyloid deposits in vivo is difficult, as the deposits have many of the same physical properties (i.e., density and water content) as normal tissues. Attempts to image amyloid deposits directly using magnetic resonance imaging (MRI) and computer-assisted tomography (CAT) have been disappointing and have detected amyloid deposits only under certain favorable conditions. In addition, efforts to label amyloid deposits with antibodies, serum amyloid P protein, or other probe molecules has provided some selectivity on the periphery of tissues, but has provided for poor imaging of tissue interiors.

Thus, it would be useful to have a noninvasive technique for imaging and quantitating amyloid deposits in a patient. In addition, it would be useful to have compounds that inhibit the aggregation of amyloid proteins to form amyloid deposits.

SUMMARY OF THE INVENTION

The present invention provides a method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



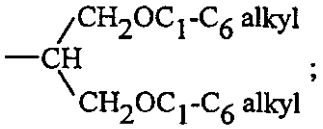
I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C(=O)C_1-C_6 alkyl;

n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, $-NH_2$, NR^bR^c, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NO_2$, $-OC_1$-C_{12} alkyl, -C_1-C_8 alkyl, $-CF_3$, -CN, $-OCH_2$ phenyl, $-OCH_2$-substituted phenyl, $-(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl, -CH=CH-phenyl, $-O(CH_2)_pNR^bR^c$, $-CNR^bR^c$, $-NHCR^b$, $-NH(CH_2)_pNR^bR^c$, $-N(C_1$-C_6alkyl$)(CH_2)_pNR^bR^c$,



;

R^8 is COOH, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, -C_1-C_6 alkyl, $-(CH_2)_m$-phenyl, or R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C_1-C_6 alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C_1-C_6 alkyl, $-CF_3$, or phenyl;

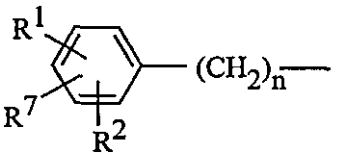
m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

In a preferred embodiment, the  group is attached at

the 4-position of the phenyl ring.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2; and

R^3 and R^4 are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

R^1 is halo;

R^2 is hydrogen or halo;

R^3, R^4, R^5, and R^6 are hydrogen; and

n is 2 to 5 inclusive.

In another preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2 or 3;

R^1 is $-NR^bR^c$; and

R^2, R^3, R^4, R^5, and R^7 all are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

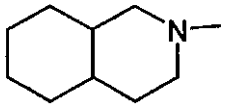
n is 2;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine, $-N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, $-CF_3$, phenyl, hydrogen, $-OCH_2$ phenyl,

$-O(CH_2)_3N(CH_3)_2$, -O phenyl, $-O(CH_2)_7CH_3$,

$-CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl,



, $-N[(CH_2)_3CH_3]_2$, substituted phenyl,

$-OCH_2$-substituted phenyl, pyrrozolyl, or $-N(phenyl)_2$.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 3, 4, or 5;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine or hydrogen.

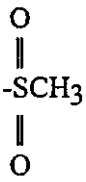
In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5, R^6, and R^8 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$,



imidazolyl, $-SCH_3$, -CN, fluorine, $-CH_3$, $-CF_3$, halogen,

$-NH-C_1-C_6$ alkyl, $-N(C_1-C_6alkyl)_2$, $-NH_2$, or pyrrolyl.

In a preferred embodiment of the method, in the compounds of Formula I

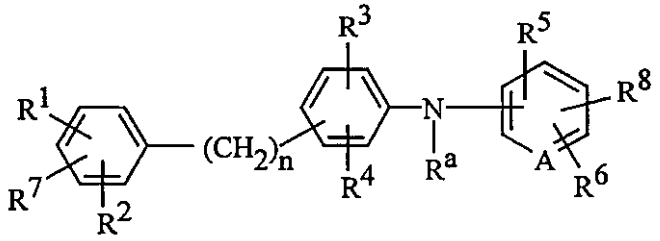
R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5 is $-CO_2H$.

Also preferred is a method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



I

wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

R^3 and R^4 are hydrogen;

R^1, R^7, and R^2 are independently chlorine, $-N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, $-CF_3$, phenyl, hydrogen, $-OCH_2$ phenyl, $-O(CH_2)_3N(CH_3)_2$, -O phenyl, $-O(CH_2)_7CH_3$, $-CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl, $-N[(CH_2)_3CH_3]_2$, substituted phenyl, $-OCH_2$-substituted phenyl, pyrazolyl, or $-N(phenyl)_2$;

R^5 and R^6 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$, imidazolyl, -CN, fluorine, $-CH_3$, $-CF_3$, or pyrrolyl;

or the pharmaceutically acceptable salts thereof.

In a preferred embodiment of the method, compounds of Formula I are

2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Aminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(4-Aminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid;

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-(4-{3-[4-(1H-Pyrrol-1-yl)phenyl]propyl}phenylamino)benzoic acid;

2-{4-[3-(4-Piperidin-1-ylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid;

2-{4-[3-(3-Piperidin-1yl-phenyl)-propyl]-phenylamino}-benzoic acid;

2-{4-[3-(4-[2-Diethylaminoethylamino]phenyl)-propyl]phenylamino}-benzoic acid;

2-{4-[2-(4-[Hydroxycarbonylmethylamino]phenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[2-(4-[2-Diethylaminoethylamino]phenyl)ethyl]phenylamino}-benzoic acid;

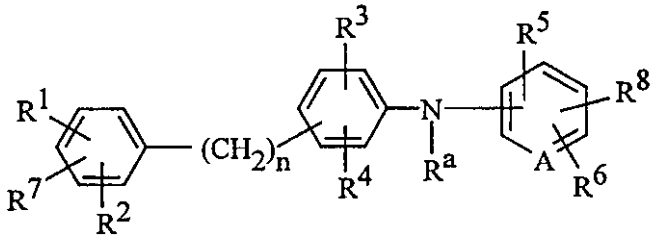
2-{4-[3-(4-Morpholinophenyl)propyl]phenylamino}-benzoic acid;

2-{4-[3-(4-Piperazinylphenyl)propyl]phenylamino}-benzoic acid; and

2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid.

The invention also provides the foregoing compounds wherein the benzoic acid portion is replaced with a pyridyl carboxylic acid, for example, 4-[4-(3,4-dichlorophenyl)phenylamino]-3-hydroxycarbonylpyridine.

Also provided is a method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



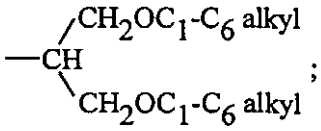
I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C($=O$)C_1-C_6 alkyl;

n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, -NH_2, NR^bR^c, -CO_2H, -CO_2C_1-C_6 alkyl, -NO_2, -OC_1-C_{12} alkyl, -C_1-C_8 alkyl, -CF_3, -CN, -OCH_2 phenyl, -OCH_2-substituted phenyl, -$(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl, -CH=CH-phenyl, -$O(CH_2)_pNR^bR^c$, -C($=O$)NR^bR^c, -NHC($=O$)R^b, -$NH(CH_2)_pNR^bR^c$, -N(C_1-C_6alkyl)$(CH_2)_pNR^bR^c$,



R^8 is COOH, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, $-C_1$-C_6 alkyl, $-(CH_2)_m$-phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C_1-C_6 alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, $-C_1$-C_6 alkyl, $-CF_3$, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2; and

R^3 and R^4 are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

R^3 and R^4 are hydrogen; and

n is 2 to 5 inclusive.

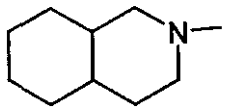
In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine, $-N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, $-CF_3$, phenyl, hydrogen, $-OCH_2$ phenyl, $-O(CH_2)_3N(CH_3)_2$, -O phenyl, $-O(CH_2)_7CH_3$, $-CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl,



, $-N[(CH_2)_3CH_3]_2$, substituted phenyl, $-OCH_2$-substituted phenyl, pyrazolyl, or $-N(phenyl)_2$.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 3, 4, or 5;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine or hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5 and R^6 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$, imidazolyl, -CN, fluorine, $-CH_3$, $-CF_3$, halogen, -NH-C_1-C_6 alkyl, $-N(C_1$-C_6alkyl$)_2$, $-NH_2$, or pyrrolyl.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

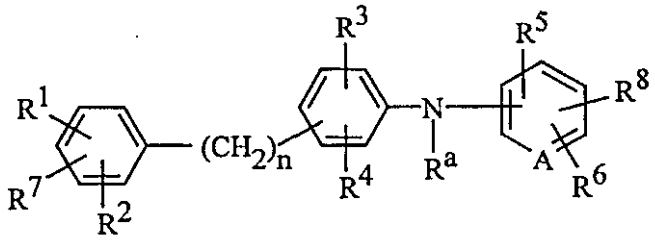
n is 2;

R^3 and R^4 are hydrogen; and

R^5 is $-CO_2H$.

Also provided is a preferred method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering

to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



I

wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

R^3 and R^4 are hydrogen;

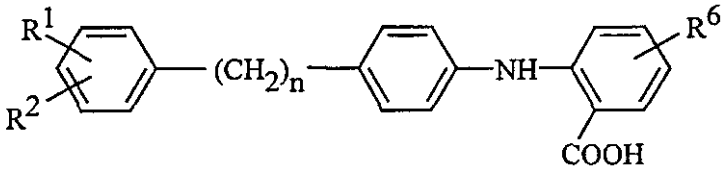
R^1, R^7, and R^2 are independently chlorine, $-N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, $-CF_3$, phenyl, hydrogen, $-OCH_2$ phenyl, $-O(CH_2)_3N(CH_3)_2$, -O phenyl, $-O(CH_2)_7CH_3$, $-CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl, $-N[(CH_2)_3CH_3]_2$, substituted phenyl, $-OCH_2$-substituted phenyl, pyrazolyl, or $-N(phenyl)_2$;

R^5 and R^6 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$, imidazolyl, -CN, fluorine, $-CH_3$, $-CF_3$, or pyrrolyl;

R^8 is COOH or tetrazolyl;

or the pharmaceutically acceptable salts thereof.

The most preferred compounds provided by the invention have Formula II



II

and pharmaceutically acceptable salts thereof,

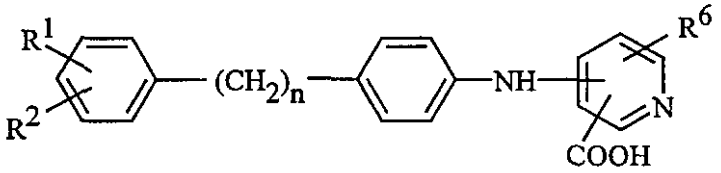
wherein:

R^1 is halo;

R^2 is H or halo; and

n and R^6 are as defined above in Formula I.

Another preferred group of compounds have Formula III



III

and pharmaceutically acceptable salts thereof,

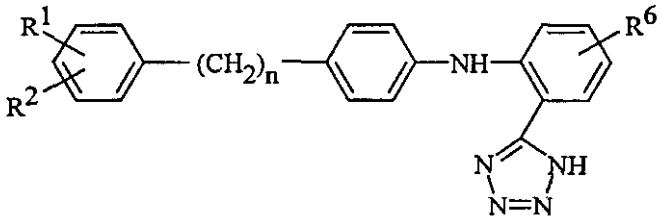
wherein:

R^1 is halo;

R^2 is H or halo; and

n and R^6 are as defined above in Formula I.

Another group of preferred invention compounds have Formula IV



IV

and pharmaceutically acceptable salts thereof,

wherein:

R^1 is halo;

R^2 is H or halo; and

n and R^6 are as defined above in Formula I.

In a preferred embodiment of the method, the novel compounds of Formula I are provided which are

2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid;

2-{4-[2-[-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4′-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; or

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

The present invention also provides the compounds:

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4′-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Aminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(4-Aminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid;

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Acetylaminophenyl)propyl]]phenylamino}benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-(4-{3-[4-(1H-Pyrrol-1-yl)phenyl]propyl}phenylamino)benzoic acid;

2-{4-[3-(4-Piperidin-1-ylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid;

2-{4-[3-(3-Piperidin-1yl-phenyl)-propyl]-phenylamino}-benzoic acid;

{5-[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid;

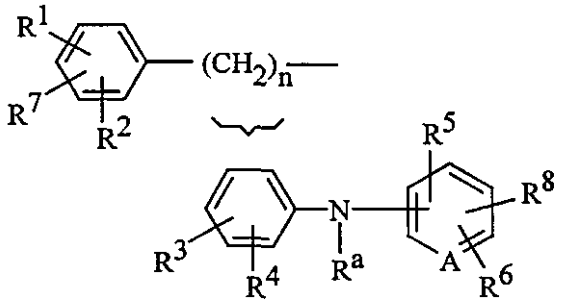
{5-[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid;

3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}propanoic acid;

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}butanoic acid; or

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

Also provided are the foregoing compounds wherein the terminal phenylalkyl group is attached at the 2- or 3-position of the central phenyl ring, i.e., compounds of the Formula Ia



Ia

Typical 2- and 3-substituted compounds are:

2-{3-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{2-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{3-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid;

2-{3-[3-(4-Di-n-propylaminophenyl)propyl]phenylamino}-benzoic acid;

2-{3-[3-(4-n-Propylaminophenyl)propyl]phenylamino}-benzoic acid;

2-{3-[3-(4-[2-Diethylaminoethylamino]phenyl)propyl]phenylamino}-benzoic acid;

2-{2-[3-(4-[Hydroxycarbonylmethylamino]phenyl)propyl]phenylamino}-benzoic acid;

2-{2-[2-(3-[2-Diethylaminoethylamino]phenyl)ethyl]phenylamino}-benzoic acid;

2-{3-[3-(4-Morpholinophenyl)propyl]phenylamino}-benzoic acid;

2-{3-[3-(4-Piperazinylphenyl)propyl]phenylamino}-benzoic acid;

2-{3-[2-(4-Chlorophenyl)ethyl]phenylamino}-benzoic acid;

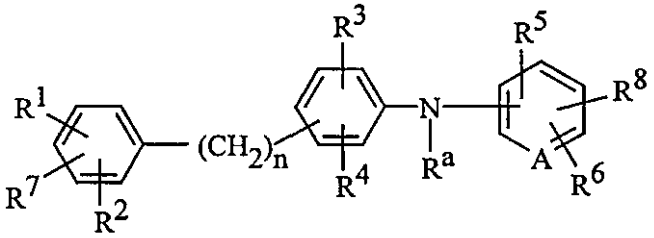
2-{3-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid; and

2-{4-[4-(4-{4-Methylpiperazinyl}phenyl)butyl]phenylamino}-benzoic acid.

Pharmaceutical formulations of the novel compounds admixed with a pharmaceutically acceptable diluent, carrier, or excipient are also provided.

Also provided is a method of imaging amyloid deposits, the method comprising:

a. introducing into a patient a detectable quantity of a labeled compound having the Formula I or a pharmaceutically acceptable salt thereof:



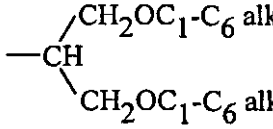
I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C($=O$)C_1-C_6 alkyl;

n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, -NH_2, NR^bR^c, -CO_2H, -CO_2C_1-C_6 alkyl, -NO_2, -OC_1-C_{12} alkyl, -C_1-C_8 alkyl, -CF_3, -CN, -OCH_2 phenyl, -OCH_2-substituted phenyl, -$(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl, -CH=CH-phenyl, -$O(CH_2)_pNR^bR^c$, -C($=O$)NR^bR^c, -NHC($=O$)R^b, -$NH(CH_2)_pNR^bR^c$, -$N(C_1$-C_6alkyl$)(CH_2)_pNR^bR^c$,



;

R^8 is COOH, tetrazolyl, -SO_2R^d, or -$CONHSO_2R^d$;

R^b and R^c are independently hydrogen, -C_1-C_6 alkyl, -$(CH_2)_m$-phenyl, or R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C_1-C_6

alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C_1-C_6 alkyl, -CF_3, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof;

b. allowing sufficient time for the labeled compound to become associated with amyloid deposits; and

c. detecting the labeled compound associated with the amyloid deposits.

In a preferred embodiment of the method, the patient has or is suspected to have Alzheimer's disease.

In a preferred embodiment of the method, the labeled compound is a radio labeled compound.

In a preferred embodiment of the method, the labeled compound is detected using MRI.

The present invention also provides the preferred compounds:

2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid;

and pharmaceutical formulations thereof.

Pharmaceutically acceptable acid addition salts, amides, and prodrugs of the foregoing compounds are also provided by this invention.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" means a straight or branched chain hydrocarbon having from 1 to 12 carbon atoms. Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, sec-butyl, pentyl, hexyl, octyl, decyl, and 1,1-dimethyloctyl.

Preferred alkyl groups are C_1-C_8 alkyl, and especially C_1-C_6 alkyl.

The term "alkoxy" means an alkyl group attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy, and isobutoxy. Preferred alkoxy groups are C_1-C_{12} alkoxy, and especially C_1-C_6 alkoxy.

The term "halogen" includes chlorine, fluorine, bromine, and iodine.

The term "substituted" means that one or more hydrogen atom in a molecule has been replaced with another atom or group of atoms. For example, substituents include halogen, especially chloro, -OH, $-CF_3$, $-NO_2$, $-NH_2$, $-NH(C_1\text{-}C_6\text{alkyl})$, $-N(C_1\text{-}C_6\text{alkyl})_2$, C_1-C_6 alkyl, $-OC_1$-C_6 alkyl, -CN, $-CF_3$, $-CO_2H$, and $-CO_2C_1$-C_6 alkyl.

The term "substituted phenyl" means a phenyl ring in which from 1 to 4 hydrogen atoms have been independently replaced with a substituent, preferably one selected from the list above. Typical "substituted phenyl" groups include 4-chlorophenyl, 3,4-dibromophenyl, 3-fluoro-4-methylphenyl, 3,4-dichlorophenyl, 3,4-methylenedioxyphenyl, and 4-dimethylaminophenyl.

The symbol "-" means a covalent bond.

Substituent groups represented by R^1, R^3, and R^5, for example, include amino(NR^bR^c) and acylamino ($-NHCOR^b$). R^b and R^c can be hydrogen, alkyl and phenylalkyl and substituted phenylalkyl, and typical NR^bR^c groups include methylamino, diethylamino, isobutyl-propylamino, benzylamino, and 3,4-dimethoxybenzylamino. Examples of acylamino groups include formamido, acetamido, 2-phenylacetamido, and 2-(3-nitrophenyl)acetamido. R^1, R^3, and R^5 can also be aminoalkoxy ($-O(CH_2)_pNR^bR^c$) such as N-methylaminomethoxy and 2-(N-benzylamino)ethoxy, as well as

aminoalkylamino (-NH(CH_2)$_p$$NR^bR^c$) such as 3-(dimethylamino)propylamino and 2-(N-ethyl-N-benzylamino)ethylamino. Substituent groups such as R^1, R^3, and R^5 additionally can be cyclic structures, for instance when NR^bR^c is part of the substituent group, and R^b and R^c are taken together with the nitrogen to which they are attached to form a cyclic ring selected from imidazole, pyrrole, piperidine, piperazine, 4-C_1-C_6 alkylpiperazine, morpholine, thiomorpholine, pyrazole, and decahydroisoquinoline.

Substituent groups such as R^1, R^2, R^5, R^6, and R^7 also can be -CH=CH-phenyl (i.e., styryl), phenoxy, O-substituted phenyl such as 3-iodophenoxy, 2,4,6-trihydroxyphenoxy, 2-fluoro-3-nitrophenoxy, as well as -O-benzyl and -O-substituted benzyl such as 2-trifluoromethylbenzyloxy and 4-aminobenzyloxy.

The term "pharmaceutically acceptable salt, ester, amide, and prodrug" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laureate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as, nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for

example, Berge S.M., et al., Pharmaceutical Salts, *J. Pharm. Sci.*, 66:1-19 (1977) which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, nontoxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods, for example by reacting a carboxylic acid of Formula I with an alcohol such as ethanol or benzyl alcohol.

Examples of pharmaceutically acceptable, nontoxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amides and C_1-C_2 dialkyl secondary amides are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the present invention can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds, as well as mixture thereof, including racemic mixtures, form part of this invention.

In the first step of the present method of imaging, a labeled compound of Formula I is introduced into a tissue or a patient in a detectable quantity. The compound is typically part of a pharmaceutical composition and is administered to the tissue or the patient by methods well-known to those skilled in the art.

In the methods of the present invention, a compound can be administered either orally, rectally, parenterally (intravenous, by intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for

example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft- and hard-filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable nonirritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

In a preferred embodiment of the invention, the labeled compound is introduced into a patient in a detectable quantity and after sufficient time has passed for the compound to become associated with amyloid deposits, the labeled compound is detected noninvasively inside the patient. In another embodiment of the invention, a labeled compound of Formula I is introduced into a patient, sufficient time is allowed for the compound to become associated with amyloid deposits, and then a sample of tissue from the patient is removed and the labeled compound in the tissue is detected apart from the patient. In a third embodiment of the invention, a tissue sample is removed from a patient and a labeled compound of Formula I is introduced into the tissue sample. After a sufficient amount of time for the compound to become bound to amyloid deposits, the compound is detected.

The administration of the labeled compound to a patient can be by a general or local administration route. For example, the labeled compound may be administered to the patient such that it is delivered throughout the body. Alternatively, the labeled compound can be administered to a specific organ or tissue of interest. For example, it is desirable to locate and quantitate amyloid

deposits in the brain in order to diagnose or track the progress of Alzheimer's disease in a patient.

The term "tissue" means a part of a patient's body. Examples of tissues include the brain, heart, liver, blood vessels, and arteries. A detectable quantity is a quantity of labeled compound necessary to be detected by the detection method chosen. The amount of a labeled compound to be introduced into a patient in order to provide for detection can readily be determined by those skilled in the art. For example, increasing amounts of the labeled compound can be given to a patient until the compound is detected by the detection method of choice. A label is introduced into the compounds to provide for detection of the compounds.

The term "patient" means humans and other animals. Those skilled in the art are also familiar with determining the amount of time sufficient for a compound to become associated with amyloid deposits. The amount of time necessary can easily be determined by introducing a detectable amount of a labeled compound of Formula I into a patient and then detecting the labeled compound at various times after administration.

The term "associated" means a chemical interaction between the labeled compound and the amyloid deposit. Examples of associations include covalent bonds, ionic bonds, hydrophilic-hydrophilic interactions, hydrophobic-hydrophobic interactions, and complexes.

Those skilled in the art are familiar with the various ways to detect labeled compounds. For example, magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT) can be used to detect radiolabeled compounds. The label that is introduced into the compound will depend on the detection method desired. For example, if PET is selected as a detection method, the compound must possess a positron-emitting atom, such as ^{11}C or ^{18}F.

Another example of a suitable label in a compound of Formula I is an atom such as ^{13}C, ^{15}N, or ^{19}F which can be detected using magnetic resonance imaging (MRI) which is also sometimes called nuclear magnetic resonance (NMR). In addition, the labeled compounds of Formula I may also be detected by MRI using paramagnetic contrast agents.

Another example of detection is electron paramagnetic resonance (EPR). In this case, EPR probes which are well-known in the art, such as nitroxides, can be used.

The imaging of amyloid deposits can also be carried out quantitatively so that the amount of amyloid deposits can be determined.

The present invention also provides a method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, by administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein inhibiting amount of a compound of Formula I. Those skilled in the art are readily able to determine an amyloid inhibiting amount by simply administering a compound of Formula I to a patient in increasing amounts until the growth of amyloid deposits is decreased or stopped. The rate of growth can be assessed using imaging or by taking a tissue sample from a patient and observing the amyloid deposits therein.

A patient in need of inhibition of the aggregation of amyloid proteins is a patient having a disease or condition in which amyloid proteins aggregate. Examples of such diseases and conditions include Mediterranean fever, Muckle-Wells syndrome, idiopathetic myeloma, amyloid polyneuropathy, amyloid cardiomyopathy, systemic senile amyloidosis, amyloid polyneuropathy, hereditary cerebral hemorrhage with amyloidosis, Alzheimer's disease, Down's syndrome, Scrapie, Creutzfeldt-Jacob disease, Kuru, Gerstmann-Straussler-Scheinker syndrome, medullary carcinoma of the thyroid, Isolated atrial amyloid, β_2-microglobulin amyloid in dialysis patients, inclusion body myositis, β_2-amyloid deposits in muscle wasting disease, and Islets of Langerhans diabetes Type II insulinoma.

Also provided by the present invention are compounds of Formula I wherein one or more atom in the compound has been replaced with a radioisotope (a labeled compound). The radioisotope can be any radioisotope. However, ^{3}H, ^{123}I, ^{125}I, ^{131}I, ^{11}C, and ^{18}F are preferred. Those skilled in the art are familiar with the procedure used to introduce a radioisotope into a compound. For example, a compound of Formula I wherein one carbon atom is ^{11}C or ^{14}C is readily prepared.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is sufficient. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any manner.

EXAMPLES

SYNTHESIS

Compounds of Formula I can be prepared by several routes as illustrated in Schemes 6 through 9. Schemes 1 through 5 show synthetic routes that can be used to obtain the desired starting amines (IV), (VIII), (XV), and (XXI).

In Scheme 1, the appropriately substituted aldehyde (I) and a nitrophenylacetic acid (II) yield olefin (III) when heated in piperidine at 150°C. Standard hydrogenation conditions, such as Raney nickel, give desired amine (IV).

Scheme 2 depicts the synthesis of amine (VIII) which contains a three methylene tether. Condensation of aldehyde (I) and nitro-ketone (V) in the presence of sodium hydroxide gives the desired alpha, beta-unsaturated ketone, which upon standard hydrogenation conditions (Raney nickel) gives (VII) and then Wolff-Kishner conditions yields the desired amine (VIII).

Scheme 3 is very similar to Scheme 2, except that the aldehyde (I) is condensed with a substituted aniline (IX).

Scheme 4 illustrates standard Wittig conditions in which the starting materials (XII) and (XIII) are obtained via aldol condensation and ylide chemistry, respectively. Reaction of aldehyde (XII) and bromophosphorane (XIII) in the

presence of a base, such as butyl lithium, gives diene (XIV). Standard reduction conditions (e.g., Raney nickel) of (XIV) yields the desired amine (XV).

Scheme 5 illustrates the synthesis of amine (XXI) which contains a 5-methylene tether. Wittig reaction of the bromophosporane (XVII), which is formed from the corresponding substituted bromide (XVI), and nitro aldehyde (XIX), obtained from Swern oxidation of the corresponding alcohol (XVIII), using a base (e.g., LHDMS) yields olefin (XX). Reduction of (XX) using standard conditions (Raney nickel) gives amine (XXI).

Scheme 6 illustrates one route to obtain compounds of Formula I. Either by Buchwald coupling (Method A) followed by saponification or utilizing the Ullman reaction (Method B), compounds of Formula I can be isolated from amines such as (IV), (VIII), and (XV). Compounds of Formula I that contain hydroxy groups, such as Examples 4 and 6, require demethylation of the hydroxy protecting groups with reagents such as boron tribromide in the final step of the synthesis.

Protecting groups will also be used when reactive functional groups such as amino and carboxylic acids are present, so as to avoid unwanted side reactions. Carboxy groups typically are converted to esters (e.g., tert-butyl, benzyl), and amino groups generally are acylated (e.g., acetyl or trimethylsilyl). These and other such protecting groups are well-known to organic chemists, and are fully described by Greene and Wuts in Protective Groups in Organic Synthesis, John Wiley and Sons, New York (2nd Ed. 1991). All citations are incorporated herein by reference.

Scheme 7 illustrates the synthesis of compounds of Formula I by reacting amines such as (IV), (VIII), and (XXI) with fluoro-nitro intermediate (XXIV), in the presence of a base (e.g., LHMDS or Et_3N) to give ester (XXV). This ester can then be saponified using standard conditions, such as sodium hydroxide.

In Scheme 8, amine (XV) can be coupled with readily available fluoro-substituted carboxylic acids [e.g., (XXVI) or (XXVII)] in the presence of various bases (such as DBU or triethylamine) to yield compounds of Formula I.

Scheme 9 depicts coupling of amine (VIII) with readily available methyl ester (XXVIII) in the presence of a base, such as imidazole, to give ester (XXIX).

This ester can then be saponified as usual to give compounds of Formula I.

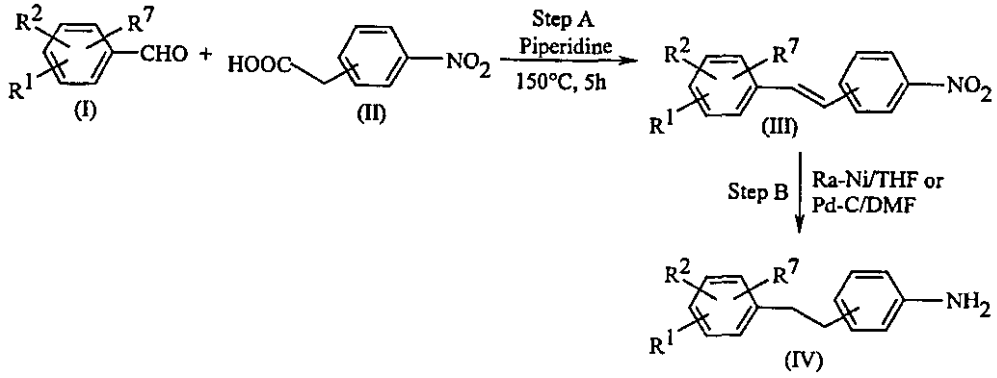
Scheme 10 illustrates the synthesis of fluoro-intermediate (XXIV) which is obtained by nitration of readily available methyl ester (XXX) to give (XXVIII). Treatment of (XXVIII) with potassium cyanide gives (XXIV).

In Scheme 11, the synthesis of compounds related to Example 18 is illustrated. Reaction of the potassium salts of ortho-substituted benzoic acids (XXVI) with substituted anilines (XXVII) in the presence of potassium carbonate and cupric acetate yields various iodo-substituted aminobenzoic acids (XXVIII). Reaction of (XXVIII) with substituted boronic acids and palladium chloride gives the desired substituted aminobenzoic acids (XXX).

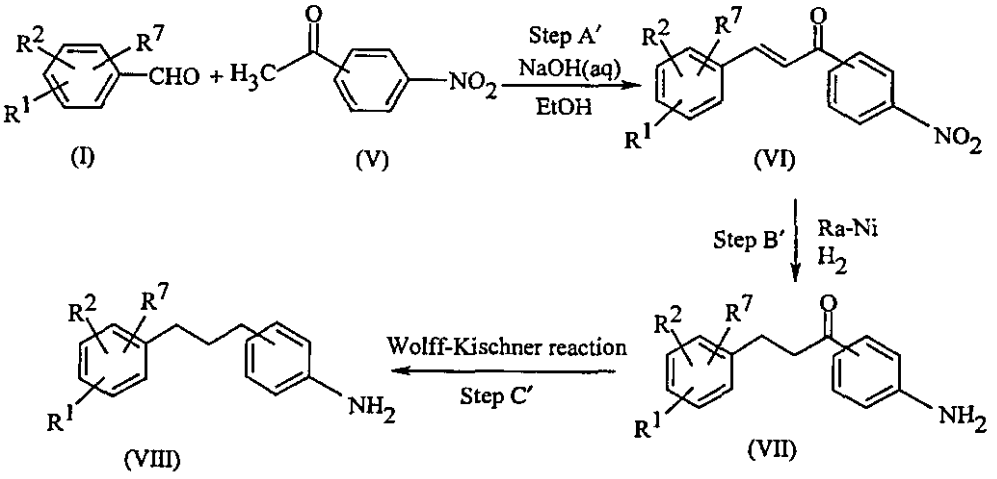
It should, of course, be recognized that several invention compounds of Formula I can be prepared from other compounds defined by Formula I, utilizing standard organic reactions such as oxidation, reduction, alkylation, condensation, elimination, and similar well-known synthetic processes. For example, compounds of Formula I wherein R^a is hydrogen are readily alkylated to form compounds wherein R^a is C_1-C_6 alkyl. Compounds wherein R^1 is NH_2 are readily acylated by reaction with an acid halide or acid anhydride to provide compounds wherein R^1 is -$NHCOR^b$. Similarly, compounds wherein R^1 is NO_2 are easily reduced to provide compounds wherein R^1 is NH_2. The benzoic acids (where R^8 is COOH) are readily converted to esters and amides, as well as salts and other prodrugs by routine processes. For example, the benzoic acid can be reacted with oxalylchloride to form the acid chloride, which then readily reacts with a sulfonamide such as methanesulfonamide to produce the corresponding invention compound where R^8 is -$CONHSO_2CH_3$.

Formation of Amines

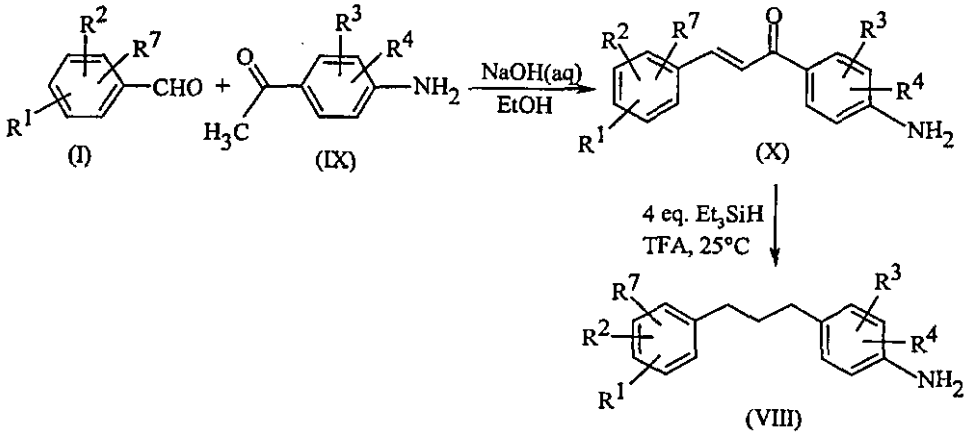
Scheme 1



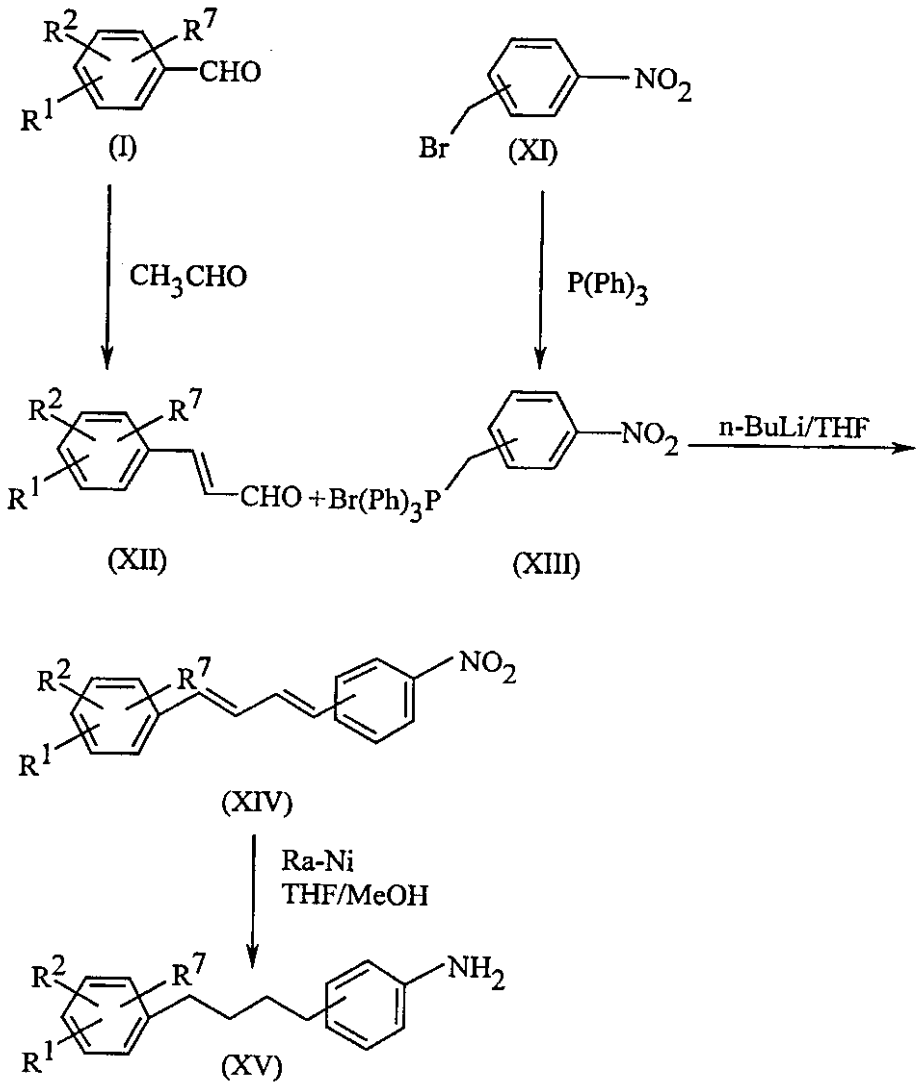
Scheme 2



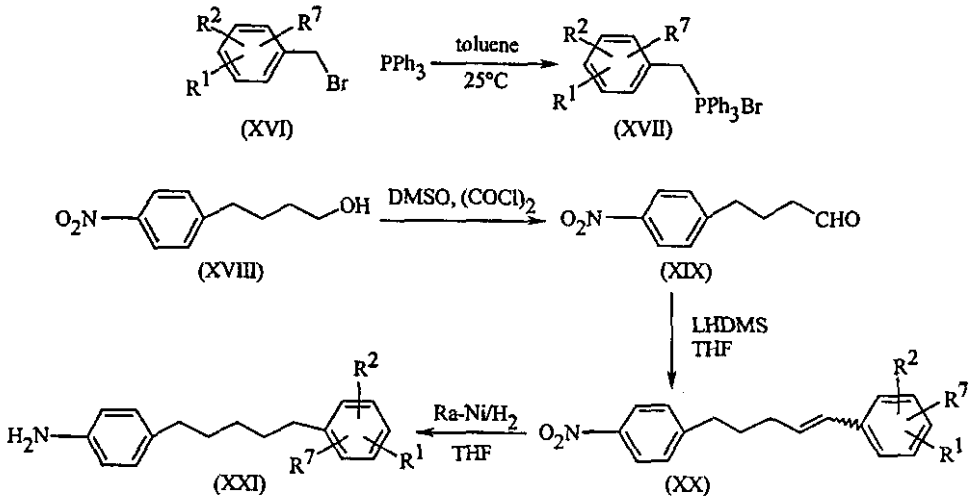
Scheme 3


R2
R7
CHO
R1
(I)
O
H3C
R3
R4
NH2
(IX)
NaOH(aq)
EtOH
(X)
4 eq. Et3SiH
TFA, 25°C
(VIII)

Scheme 4

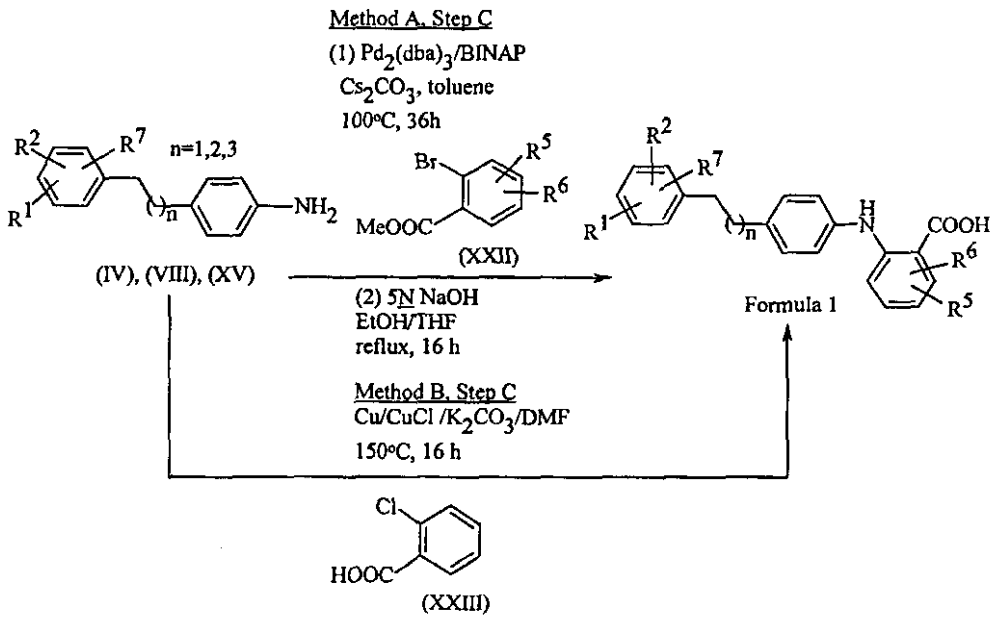

R2
R7
CHO
R1
(I)
CH3CHO
NO2
Br
(XI)
P(Ph)3
R2
R7
R1
CHO + Br(Ph)3P
NO2
n-BuLi/THF
(XII)
(XIII)
R2
R7
R1
NO2
(XIV)
Ra-Ni
THF/MeOH
R2
R7
R1
NH2
(XV)

Scheme 5

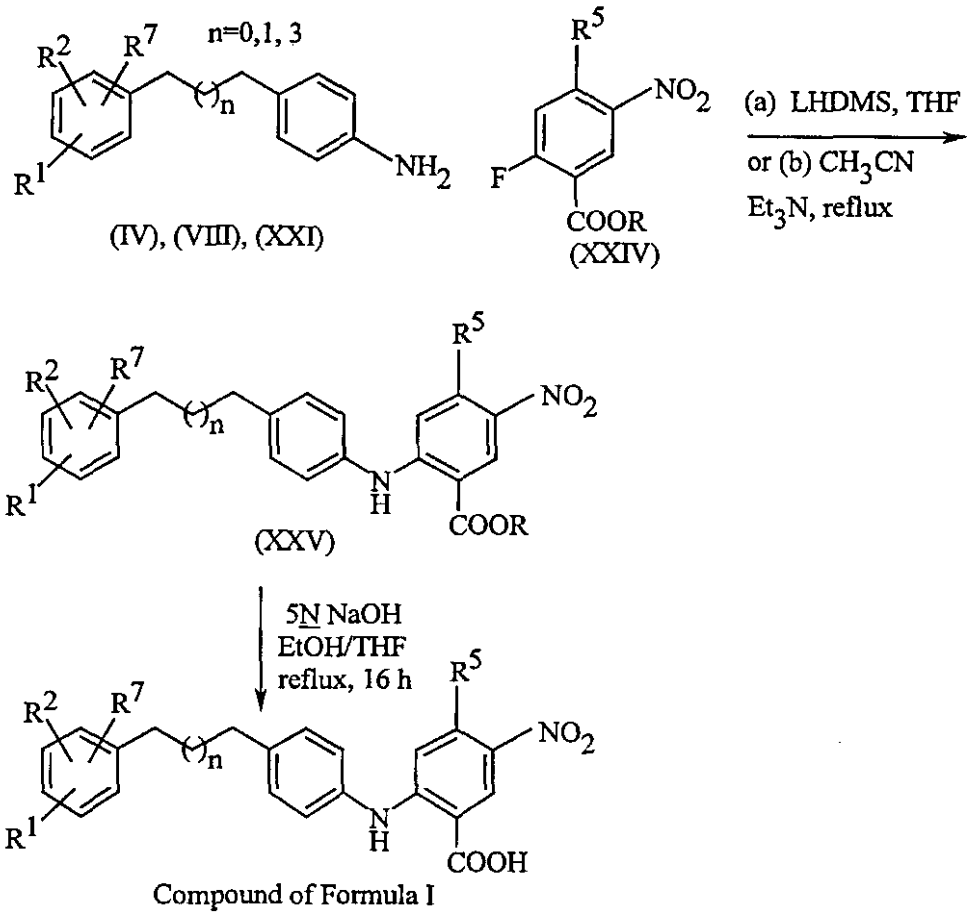


Coupling Routes

Scheme 6

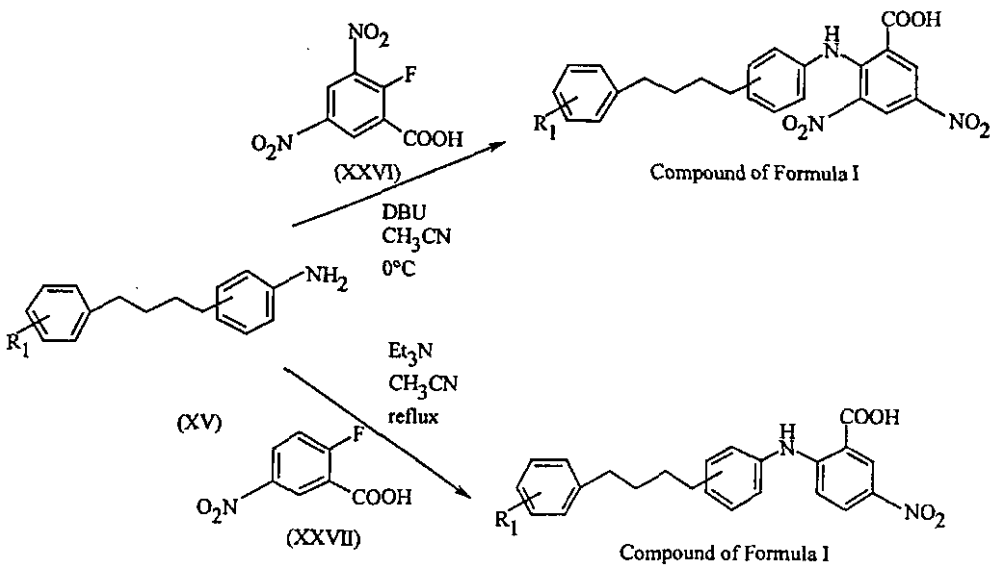


Scheme 7

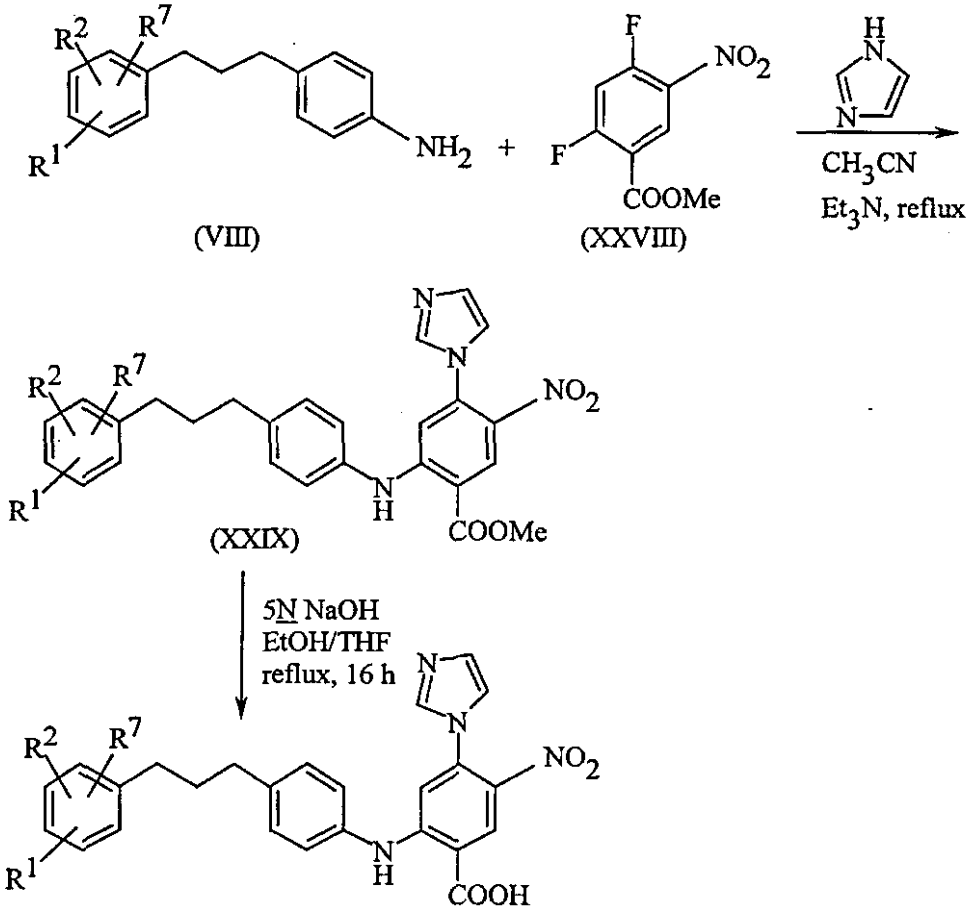


R is an ester forming group such as alkyl or benzyl.

Scheme 8


NO2
F
O2N
COOH
(XXVI)
DBU
CH3CN
0°C
NH2
R1
Et3N
CH3CN
reflux
(XV)
F
O2N
COOH
(XXVII)
H
N
COOH
R1
O2N
NO2
Compound of Formula I
H
N
COOH
R1
NO2
Compound of Formula I

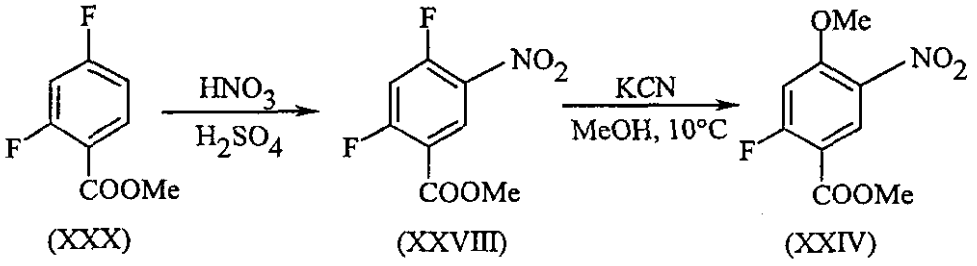
Scheme 9



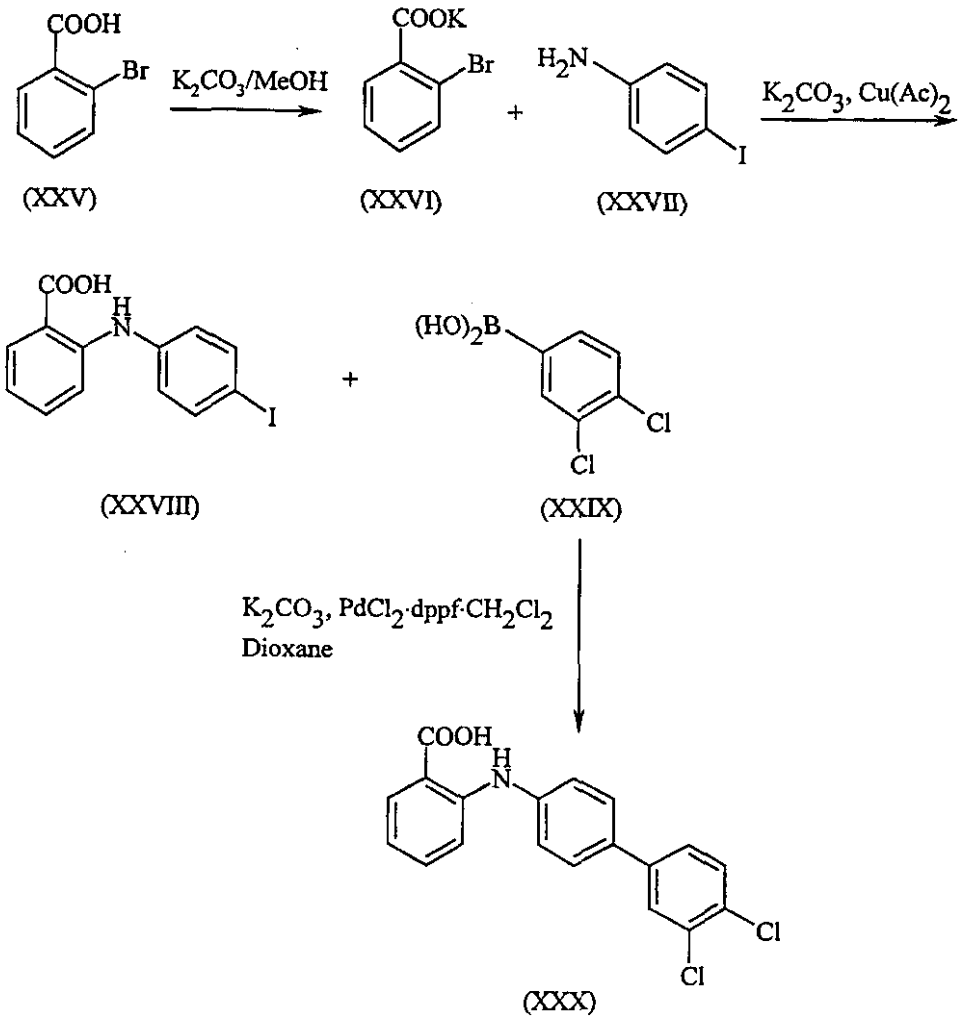
Compound of Formula I

Synthesis of Fluoro-Intermediate

Scheme 10



Scheme 11


COOH
Br
K_2CO_3/MeOH
COOK
Br
H_2N
I
K_2CO_3, $Cu(Ac)_2$
(XXV)
(XXVI)
(XXVII)
COOH
H
N
I
$(HO)_2B$
Cl
Cl
(XXVIII)
(XXIX)
K_2CO_3, $PdCl_2$·dppf·CH_2Cl_2
Dioxane
COOH
H
N
Cl
Cl
(XXX)

EXAMPLE 1

Preparation of 2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid

Step A (Scheme 1): Preparation of 1,2-Dichloro-4-[2-(4-nitrophenyl)ethenyl]-benzene

A mixture of *p*-nitrophenylacetic acid (51.23 g, 0.28 mol) and 3,4-dichlorobenzaldehyde (49.50 g, 0.28 mol) in piperidine (50 mL) was heated to 150-160°C for 5 hours under a N_2 atmosphere. After cooling the reaction mixture, the precipitate was triturated in boiling methanol (MeOH) (50 mL) and then cooled to -5°C for 12 hours. The crystalline precipitate was filtered off, rinsed with cold MeOH and dried at room temperature in a vacuum oven overnight to yield an orange solid, 22.71 g (0.077 mol, 27%) of the desired product.
mp 190-191°C.
MS:294.9 (M^+).

Step B (Scheme 1): Preparation of 4-[2-(3,4-Dichlorophenyl)ethyl]benzenamine

A sample of 1,2-dichloro-4-[2-(4-nitrophenyl)ethenyl]benzene (98.0 g, 0.33 mol) in tetrahydrofuran (THF) (1.6 L) was reduced in the presence of Raney Nickel (Ra-Ni) (20 g) at 25°C to 40°C (ΔP = 13.5 psi) under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give an orange solid, 85.0 g (0.32 mol, 95.8%) of the desired product.
mp 68-70°C.
MS: 266.1 (M^+).

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid

Method A

A mixture of 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (28.37 g, 106.59 mmol), methyl 2-bromobenzoate (19.10 g, 88.82 mmol), cesium carbonate (40.52 g, 124.35 mmol), tris(dibenzylideneacetone-dipaladium(0) (2.44 g, 2.67 mmol) and (*S*)-(2,2′-bis(di-p-tolylphosphino-1,1′-binaphthyl (98%, (*S*)-tol-BINAP) (2.71 g, 4.00 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (300 mL)

was heated to 100°C for 34 hours under N_2. After cooling to room temperature, the reaction mixture was diluted with ether, filtered through celite and rinsed thoroughly with ether. The filtrate was evaporated to dryness to give a brown residue (68 g). The resulted residue was dissolved in ethanol (EtOH) (50 mL) and THF (100 mL), and then 5N NaOH (aq.) (200 mL) was added, and the mixture was refluxed for 16 hours. The solvent was removed in vacuum. The residue was acidified with concentrated HCl to pH 3. The resulting precipitate was collected by filtration, triturated with boiling MeOH-H_2O (4:1) and dried in a vacuum at room temperature for 16 hours to give Example 1, an orange solid (31.95 g, 0.083 mol, 77.6%). mp 175.0-177.0°C.

Analysis for $C_{21}H_{17}N_1O_2Cl_2$: Calcd: C, 65.30; H, 4.44; N, 3.63.

Found: C, 65.40; H, 4.54; N, 3.50.

Method B

A mixture of 2-chlorobenzoic acid (5.4 g, 0.034 mol), 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (10.0 g, 0.037 mol), anhydrous potassium carbonate (16.9 g, 0.12 mol), copper powder (4.94 g, 0.077 mol), and copper(I) chloride (0.37 g, 0.0037 mol) in dry dimethylformamide (DMF) (85 mL) was heated to reflux for 24 hours at 150°C. The reaction mixture was poured into hot H_2O (150 mL) and heated to 90°C on a hot plate. Charcoal was added, and this mixture was stirred at 90°C for 5 minutes. The warm brown mixture was filtered through filter paper. The cooled filtrate was then acidified with concentrated HCl (pH 1), and the precipitate was collected by filtration, triturated with boiling MeOH-H_2O (1:2) and dried under vacuum at room temperature for 16 hours to give Example 1, an orange solid (2.3 g, 0.006 mol, 17.5%). mp 165.0-173.0°C.

Analysis for $C_{21}H_{17}N_1O_2Cl_2$: Calcd: C, 65.30; H, 4.44; N, 3.63.

Found: C, 65.68; H, 4.58; N, 3.60.

EXAMPLE 2

Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester

A mixture of 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (600 mg, 2.25 mmol), 2-bromo-5-nitrobenzoic acid methyl ester (489 mg, 1.88 mmol), cesium carbonate (857 mg, 2.62 mmol), tris(dibenzylideneacetone-dipaladium(0) (51 mg, 0.056 mmol) and (*S*)-(2,2′-bis(di-p-tolylphosphino-1,1′-binaphthyl (98%, (*S*)-tol-BINAP) (58 mg, 0.085 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (16 mL) was heated to 100°C for 12 hours under N_2. After cooling, the reaction mixture was diluted with ether, filtered through celite and rinsed thoroughly with ether. The filtrate was evaporated to dryness to give a brown residue. Purification by flash chromatography (silica gel, 5% EtOAc/hexane) yielded 540 mg (1.21 mmol, 64%) of the desired product. mp 107-108°C.

Analysis for $C_{22}H_{18}N_2Cl_2O_4$: Calcd: C, 59.34; H, 4.07; N, 6.29.

Found: C, 59.03; H, 4.04; N, 5.99.

Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

A solution of 2-{4-[2-(3,4-dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester (340 mg, 0.76 mmol) and 1N NaOH (aq.) (4.0 mL) in EtOH (4.0 mL) and THF (4.0 mL) was heated to reflux for 16 hours. The solvent was removed in vacuum. The residue was diluted with H_2O and acidified with concentrated HCl to pH 1. The mixture was then extracted with methylene chloride, dried (Na_2SO_4), filtered and concentrated in vacuo to yield a yellow solid, 329 mg (0.76 mmol, 100%) of the desired product. mp 214-217°C.

Analysis for $C_{21}H_{16}N_2Cl_2O_4$: Calcd: C, 58.49; H, 3.74; N, 6.50.

Found: C, 58.24; H, 3.81; N, 6.28.

EXAMPLE 3

Preparation of 2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

To a cooled (-78°C) solution of 4-[2-(3,4-dichloro-phenyl)-ethyl]phenylamine (0.836 g, 3.14 mmol) in THF (20 mL), LHDMS (6.28 mL, 1 M in THF, 6.28 mmol) was added dropwise. The reaction mixture was allowed to stir at -78°C for 10 minutes. A solution of 2-flouro-4-methoxy-5-nitrobenzoic acid methyl ester (0.72 g, 3.14 mmol) in THF (30 mL) was added dropwise, and this solution was stirred for 30 minutes at -78°C. The reaction mixture was allowed to gradually warm to room temperature and stir for 2 hours under a N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (EtOAc), and acidified with 5N HCl (pH 3). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to yield a brown residue. To a solution of this residue in EtOH (20 mL) and THF (40 mL), 5N NaOH (50 mL) was added, and the mixture was refluxed for overnight. The solvent was removed in vacuum, and the residue was acidified with concentrated HCl (pH 3). The precipitate was collected by filtration, triturated with boiling MeOH-H_2O (1:1), and dried in a vacuum oven for 16 hours to give Example 3, an orange solid (0.70 g, 1.51 mmol, 48%). mp 208-209°C. Analysis for $C_{22}H_{18}N_2O_5Cl_2$: Calcd: C, 57.28; H, 3.93; N, 6.07. Found: C, 57.43; H, 3.69; N, 5.86.

EXAMPLE 4

Preparation of 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,2-Dimethoxy-4-[2-(4-nitrophenyl)ethenyl]-benzene

The title compound was prepared from *p*-nitrophenylacetic acid (25.0 g, 0.14 mol), and 3,4-dimethoxybenzaldehyde (21.0 g, 0.14 mol) in piperidine (5 mL) using the procedure described in Example 1, Step A, to yield a yellow solid, 13.4 g (0.047 mol, 34%) of the desired product. mp: 133-134°C. Analysis of $C_{16}H_{15}N_1O_4$: Calcd: C, 67.36; H, 5.30; N, 4.91. Found: C, 66.81; H, 5.27; N, 4.84.

Step B (Scheme 1): Preparation of 4-[2-(3,4-Dimethoxy-phenyl)ethyl]-phenylamine

1,2-Dimethoxy-4-[2-(4-nitrophenyl)ethenyl]benzene (12.1 g, 0.042 mol) was reduced in the presence of 10% Pd-C (2.0 g) in dimethylformamide (DMF) (120 mL) at 25°C under a hydrogen atmosphere. The reaction mixture was concentrated in vacuo to give a solid. The solid was recrystallized from MeOH (400 mL) to yield a white crystalline product, 6.8 g (0.026 mol, 63%) of the desired product. mp 115-116°C.

Analysis for $C_{16}H_{19}N_1O_2$: Calcd: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.60; H, 7.39; N, 5.35.

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dimethoxy-phenyl)ethyl]-phenylamino}benzoic acid

The title compound was prepared from 4-[2-(3,4-dimethoxy-phenyl)-ethyl]phenylamine (9.25 g, 0.036 mol), 2-chlorobenzoic acid (5.2 g, 0.036 mol), anhydrous potassium carbonate (15.0 g, 0.11 mol), copper powder (0.45 g, 0.007 mol), and a catalytic amount of copper(I) chloride in dry DMF (75 mL) using the procedure described in Example 1, Step C, Method B. After crystallization with MeOH/H_2O, 4.5 g (0.012 mol, 33%) of the desired product was obtained. mp: 137-139°C.

Analysis for $C_{23}H_{23}N_1O_4$: Calcd: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.47; H, 6.03; N, 3.78.

Step D: Preparation of 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid

To a solution of 2-{4-[2-(3,4-dimethoxy-phenyl)-ethyl]phenylamino}-benzoic acid (0.28 g, 0.74 mmol) in CH_2Cl_2 (20 mL), BBr_3 (3.5 mL, 1M in CH_2Cl_2, 3.5 mmol) was added at room temperature under a N_2 atmosphere. The reaction mixture was allowed to stir at room temperature for 2 hours and then poured into ice water (50 mL). This mixture was extracted with EtOAc, and the organic layer was washed two times with water, dried (Na_2SO_4), filtered and

concentrated in vacuo to yield 0.24 g (0.69 mmol, 93%) of the desired product. mp 215-217°C.

Analysis for $C_{21}H_{19}NO_4$: Calcd: C, 72.19; H, 5.48; N, 4.00. Found: C, 71.80; H, 5.46; N, 3.99.

EXAMPLE 5

Preparation of 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,1-Dibutylamino-4-[2-(4-nitrophenyl)ethenyl]benzene

The title compound was prepared from *p*-nitrophenylacetic acid (9.92 g, 0.055 mol) and 4-dibutylamino-benzaldehyde (14.32 g, 0.055 mol) in piperidine (5 mL) using the procedure described in Example 1, Step A. This procedure yielded a red solid, 4.12 g (0.012 mol, 16%) of the desired product.

MS: 352.2. (M^+); 353.2. (MH^+).

Step B (Scheme 1): Preparation of 4-[2-(4,4-Dibutylaminophenyl)ethyl]-phenylamine

The title compound was prepared from 1,1-dibutylamino-4-[2-(4-nitrophenyl)ethenyl]benzene (4.10 g, 11.63 mmol) and Ra-Ni (2.0 g) in MeOH (100 mL) at 21°C to 32°C (ΔP = 3.6 psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a colorless oil, 3.49 g (10.76 mmol, 92.6%) of the desired product.

MS: 325.3 (MH^+).

Step C (Scheme 6): Preparation of 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}-benzoic acid

The title compound was prepared from 2-chlorobenzoic acid (1.46 g, 9.36 mmol), 4-[2-(4,4-dibutylaminophenyl)ethyl]phenylamine (3.31 g, 10.20 mmol), anhydrous potassium carbonate (4.27 g, 30.88 mmol), copper powder (1.25 g, 19.65 mmol), and copper(I) chloride (0.092 g, 0.93 mmol) in dry DMF (30 mL) using the procedure described in Example 1, Step C, Method B.

This procedure yielded a 0.39 g (0.87 mmol, 8.6%) of the desired product. mp 115-117°C.

Analysis for $C_{29}H_{36}N_2O_2$: Calcd: C, 78.34; H, 8.16; N, 6.30. Found: C, 78.15; H, 8.07; N, 6.10.

EXAMPLE 6

Preparation of 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,2,3-Trimethoxy-5-[2-(4-nitrophenyl)ethenyl]benzene

The title compound was prepared from *p*-nitrophenylacetic acid (18.6 g, 0.10 mol), 3,4,5-trimethoxy-benzaldehyde (19.6 g, 0.10 mol) and piperidine (5 mL) using the procedure described in Example 1, Step A. This procedure yielded a solid, 13.0 g (0.041 mol, 41%) of the desired product. mp:192-195°C.

Step B (Scheme 1): Preparation of 4-[2-(3,4,5-Trimethoxy-phenyl)ethyl]-phenylamine

The title compound was prepared from 1,2,3-trimethoxy-5-[2-(4-nitrophenyl)ethenyl]benzene (9.5 g, 0.03 mol) and Ra-Ni (1.0 g) in THF (50 mL) at 21-26°C (ΔP = 9.6 psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a tan powder, 6.6 g (0.023 mol, 74%) of the desired product. mp 91-93°C.

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]phenylamino}-benzoic acid methyl ester

The title compound was prepared from 4-[2-(3,4,5-trmethoxyphenyl)-ethyl]phenylamine (0.75 g, 2.61 mmol), methyl 2-bromobenzoate (0.47 g, 2.17 mmol), cesium carbonate (0.99 g, 3.04 mmol), tris(dibenzylideneacetone-dipaladium(0) (0.06 g, 0.065 mmol) and (*S*)-(-0-2,2′-bis(di-p-tolylphosphino-1,1′-binaphthyl (98% (*S*)-Tol-BINAP) (0.066 g, 0.098 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (100 mL) using the procedure described in Example 1, Step C, Method A to yield a yellow oil, 0.69 g (1.63 mmol, 76%) of the desired product.

Analysis for $C_{25}H_{27}N_1O_5$: Calcd: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.53; H, 6.24; N, 3.14.

Preparation of 2-{4-[2-(3,4,5-Trimethoxy-phenyl)ethyl]phenylamino}-benzoic acid

To a solution of 2-{4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenylamino}-benzoic acid methyl ester (0.62 g, 1.47 mmol) in THF-EtOH (2:1, 6 mL), 1N NaOH solution (4 mL) was added, and the reaction mixture was heated to reflux for 5 hours. The reaction mixture was then concentrated in vacuo to remove the organic solvent. The residue was acidified with concentrated HCl (pH 3). This precipitate was collected by filtration, triturated with boiling MeOH-H_2O (4:1) and dried in vacuum at room temperature for 16 hours to give the title compound as a white solid, 0.59 g (1.45 mmol, 98.5%). mp 146.0-147.0°C.
Analysis for $C_{24}H_{25}N_1O_5$: Calcd: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.54; H, 6.43; N, 3.15.

Step D: Preparation of 2-{4-[2-(3,4,5-Trihydroxyphenyl)ethyl]phenylamino}-benzoic acid

The title compound was prepared from 2-{4-[2-(3,4,5-trimethoxy-phenyl)-ethyl]phenylamino}benzoic acid (0.50 g, 1.23 mmol) in CH_2Cl_2 (40 mL) and BBr_3 (10 mL, 1M in CH_2Cl_2, 10.0 mmol) using the procedure described in Example 4, Step D. This procedure yielded a green solid, 0.25 g (0.68 mmol, 65%) of the desired product. mp: 160.0-162.0°C.
Analysis for $C_{21}H_{19}N_1O_5 \cdot 1.44\ H_2O$: Calcd: C, 64.46; H, 5.64; N, 3.58.
Found: C, 64.07; H, 5.27; N, 3.39.

EXAMPLE 7

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

Step A′ (Scheme 2): Preparation of 3-(3,4-Dichlorophenyl)-1-(4-nitro-phenyl)propenone

Sodium hydroxide (7.3 g, 0.18 mol) was dissolved in water (80 mL) and 95% EtOH (80 mL) and cooled to 10°C with an ice-H_2O bath. 3,4-Dichlorobenzaldehyde (31.8 g, 0.18 mol) was added in one portion. After the addition, the mixture was warmed to 15°C. 1-(4-Nitrophenyl)ethanone (30.0 g, 0.18 mol) was added at this temperature with rigorous stirring. After stirring for 5 minutes, the reaction mixture was diluted with 95% EtOH (300 mL). The resulting tan mixture was stirred at room temperature for 30 minutes, then stirred with an ice-H_2O bath underneath the flask for 2 hours. The light brown solid was filtered off, washed with H_2O, and air-dried. The solid was dissolved in hot THF (1.5 L) and treated with charcoal. The resulting mixture was filtered off, and the filtrate was diluted with 95% EtOH (500 mL). This solution was filtered and oven-dried (40°C) to yield a light brown solid, 38.56 g (0.12 mol, 66%) of the title compound. mp 220-223°C.

Analysis for $C_{15}H_9Cl_2NO_3$: Calcd: C, 55.93; H, 2.82; Cl, 22.01; N, 4.35. Found: C, 55.79; H, 2.93; Cl, 22.16; N, 4.32.

Step B′ (Scheme 2): Preparation of 1-(4-Amino-phenyl)-3-(3,4-dichlorophenyl)propan-1-one

3-(3,4-Dichlorophenyl)-1-(4-nitro-phenyl)propenone (34.56 g, 0.11 mol) was reduced in the presence of Ra-Ni (3.0 g) in THF (250 mL) at 20°C to 32°C (ΔP = 33.4 psi) under a hydrogen atmosphere. The reaction mixture was concentrated in vacuo and recrystallized from MeOH (100 mL) to give a light yellow solid, 23.5 g (0.080 mol, 75%) of the desired product. mp 127-129°C.

Analysis for $C_{15}H_{13}Cl_2NO$: Calcd: C, 61.24; H, 4.45; N, 4.76; Cl, 24.10. Found: C, 60.91; H, 4.60; N, 4.70; Cl, 23.98.

Step C′ (Scheme 2): Preparation of 4-[3-(3,4-Dichlorophenyl)propyl]phenylamine

A mixture of 1-(4-aminophenyl)-3-(3,4-dichlorophenyl)propan-1-one (20.0 g, 0.068 mol), NH_2NH_2-H_2O (16 mL), and KOH (85%, 5.6 g) in ethylene

glycol (160 mL) was heated to reflux under a N_2 atmosphere for 16 hours. After cooling to room temperature, the reaction mixture was poured into ice-H_2O and extracted with CH_2Cl_2 (2 L). The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford an oil. Purification by flash chromatography (silica gel, CH_2Cl_2) yielded an oil,14.00 g (0.05 mol, 73%) of the desired product.

Analysis for $C_{15}H_{15}Cl_2N$: Calcd: C, 64.30; H, 5.40; N, 4.99; Cl, 25.31. Found: C, 64.21; H, 5.59; N, 5.24; Cl, 24.87.

Preparation of 2,4-Difluoro-5-nitrobenzoic acid methyl ester

Fuming nitric acid 90% (8.5 mL, 0.19 mol) was added with gentle stirring to concentrated sulfuric acid 98% (125 mL) in a 1 L beaker. After stirring for 10 minutes at room temperature, 2,4-difluorobenzoic acid methyl ester (21.9 g, 0.127 mol) was added dropwise. After the addition, the reaction mixture was allowed to stir gently for 40 minutes at room temperature. The reaction mixture was then poured into ice-H_2O (1 L) and stirred for 10 minutes. The mixture was extracted with EtOAc. The layers were separated, and the organic layer was washed sequentially with 1N NaCl, saturated $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford a yellow residue. This residue was washed with 10% EtOAc/hexane, filtered, and dried to yield a pale yellow solid, 29.0 g (0.133 mol, 82%). mp 78-80°C.

Analysis for $C_8H_5F_2NO_4$: Calcd: C, 44.25; H, 2.32; N, 6.45. Found: C, 44.18; H, 2.39; N, 6.14.

Preparation of 2-Fluoro-4-methoxy-5-nitrobenzoic acid methyl ester

A mixture of sodium metal (1.27 g, 0.055 mol) and MeOH (250 mL) was stirred at 0°C for 10 minutes. This solution was added to a solution of 2-fluoro-5-nitrobenzoic acid methyl ester (10.0 g, 0.046 mol) in MeOH (250 mL), and the mixture was stirred for 20 minutes at 0°C to 5°C. The reaction mixture was then allowed to warm to room temperature and stir for 2 hours. The mixture was then filtered to give an off-white precipitate. Recrystallization with $CHCl_3$ (70 mL)

yielded an off-white crystalline solid, 1.825 g (0.008 mol, 17%) of the title compound.

Analysis for $C_9H_8F_1N_1O_5$: Calcd: C, 47.17; H, 3.52; N, 6.11. Found: C, 47.09; H, 3.47; N, 6.00.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester

A mixture of 4-[3-(3,4-dichloro-phenyl)propyl]phenylamine (0.94 g, 3.3 mmol), 2-fluoro-4-methoxy-5-nitro-benzoic acid methyl ester (0.75 g, 3.3 mmol), and Et_3N (0.46 mL) in CH_3CN (30 mL) was heated to reflux for 120 hours. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to give a solid. Recrystallization with MeOH yielded 0.67 g (1.37 mmol, 42%) of the desired product.

Analysis for $C_{24}H_{22}N_2Cl_2O_5 \cdot 0.42H_2O$: Calcd: C, 58.01; H, 4.63. N, 5.64; Found: C, 57.61; H, 4.51; N, 5.94.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

To a solution of 2-{4-[3-(3,4-dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester (0.30 g, 0.061 mol) in THF (5 mL), 1N NaOH (aq.) (2.5 mL) was added, and the mixture was stirred for 36 hours at room temperature. The solvent was removed, and the residue was acidified with concentrated HCl to pH 3. The precipitate was collected by filtration and dried in vacuum for 16 hours. Recrystallization with MeOH gave the title compound as an orange solid 0.21 g (0.043 mol, 70%). mp 200-201°C.

Analysis for $C_{23}H_{20}N_2O_5Cl_2 \cdot 0.2H_2O$: Calcd: C, 57.68; H, 4.29; N, 5.85; Cl, 14.81. Found: C, 57.71; H, 4.34; N, 5.58; Cl, 14.56.

EXAMPLE 8

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid methyl ester

A mixture of 2,4-difluoro-5-nitrobenzoic acid methyl ester (1.63 g, 7.5 mmol), imidazole (0.56 g, 8.25 mmol), and Et_3N (1.14 mL, 8.25 mmol) in CH_3CN (50 mL) was stirred for 16 hours at room temperature. To this deep orange solution, 4-[3-(3,4-dichlorophenyl)propyl]phenylamine (2.10 g, 7.5 mmol) and triethylamine (Et_3N) (1.14 mL, 8.25 mmol) was added, and the mixture was heated to reflux for overnight. The reaction mixture was cooled and concentrated in vacuo to afford a residue. This residue was diluted with CH_2Cl_2 and washed with a saturated K_2HCO_3 solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude oil. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 1.0 g (1.90 mmol, 25%) of the desired product.

MS: 524.1 (M^+).

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-1-yl-5-nitrobenzoic acid

The title compound was prepared from 2-{4-[2-[-(3,4-dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid methyl ester (1.0 g, 1.9 mmol), 1N NaOH (2.0 mL) in THF (30 mL) using the procedure described in Example 8. This procedure yielded an orange solid, 0.30 g (0.6 mmol, 32%) of the desired product.

Analysis for $C_{25}H_{20}Cl_2N_4O_4 \cdot 0.2H_2O$: Calcd: C, 58.31; H, 3.99; N, 10.88; Cl, 13.89. Found: C, 58.34; H, 4.07; N, 10.73; Cl, 13.41.

EXAMPLE 9

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}-benzoic acid

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid methyl ester

The title compound was prepared from 4-[3-(3,4-dichlorophenyl)propyl]-phenylamine (600 mg, 2.14 mmol), 2-bromobenzoic acid methyl ester (380 mg, 1.78 mmol), cesium carbonate (812 mg, 2.49 mmol), tris(dibenzylideneacetone-dipaladium(0) (49 mg, 0.053 mmol) and (*S*)-(2,2′-bis(di-p-tolylphosphino-1,1′-binaphthyl (98%, (*S*)-tol-BINAP) (54 mg, 0.080 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (15 mL) using the procedure described in Example 2, Step C. This procedure yielded an yellow oil, 0.61 g (1.47 mmol, 69%) of the desired product.

MS: 414 (M^+), 416 (MH^+).

Analysis for $C_{23}H_{21}Cl_2O_2N \cdot 0.4\ H_2O$: Calcd: C, 65.25; H, 5.23; N, 3.30.

Found: C, 65.76; H, 5.18; N, 3.10.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid

The title compound was prepared from 2-{4-[3-(3,4-dichlorophenyl)-propyl]phenylamino}benzoic acid methyl ester (0.41 g, 0.99 mmol), 1N NaOH (4.0 mL) in EtOH (4 mL) and THF (4 mL) using the procedure described in Example 2. This procedure yielded a yellow solid, 0.32 g (0.80 mmol, 81%) of the desired product. mp 120-126°C.

Analysis for $C_{22}H_{19}Cl_2O_2N_1 \cdot 0.75\ H_2O$: Calcd: C, 64.04; H, 5.00; N, 3.39.

Found: C, 64.17; H, 4.69; N, 3.18.

EXAMPLE 10

Preparation of 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid

Preparation of (*trans*)-3-(3,4-Dichlorophenyl)-2-propenal

A mixture of 3,4-dichlorobenzaldehyde (140.0 g, 0.8 mol) and acetaldehyde (300 mL) was cooled to 5°C. Potassium hydroxide (5.1 g, 0.091 mol) was dissolved in hot MeOH (40 mL), and the resulting solution was

added to the above cooled mixture while maintaining the internal temperature at 25°C to 30°C. The mixture was allowed to stir in ice-H_2O bath for 40 minutes and then treated with acetic anhydride (400 mL). After the addition, the mixture was heated to 100°C with stirring for 30 minutes and then cooled to 30°C. To this mixture, 12N HCl/H_2O (102 mL/1.2 L) was added, and the resulting mixture was heated to reflux for 30 minutes and then cooled to room temperature. This heterogeneous mixture was filtered and washed with H_2O to afford a brown solid. The crude product was dissolved in EtOAc and washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. Recrystallization from hexane/EtOAc (9:1) yielded 76.5 g (0.38 mol, 48%) of the title compound. mp: 91-93°C. Analysis for $C_9H_6Cl_2O$: Calcd: C, 53.77; H, 3.01; Cl, 35.27. Found: C, 53.75; H, 3.10; Cl, 35.58.

Preparation of (*trans*), (*trans*)-1,2-Dichloro-4-[4-(4-nitrophenyl)-1,3-butadienyl]benzene

A mixture of 4-nitro-benzyl bromide (200.0 g, 0.93 mol) and triphenylphosphine (244.0 g, 0.93 mol) in $CHCl_3$ (1.5 L) was heated to reflux for overnight. The reaction mixture was cooled to room temperature, concentrated in vacuo to remove $CHCl_3$ and then suspended in Et_2O and stirred rigorously. The suspension was filtered, and the off-white solid was washed with Et_2O, dried at 80°C for 16 hours to give 433.0 g (0.91 mol, 98%) of bromo[(4-nitrophenyl)methyl]triphenylphosphorane .A solution of bromo[(4-nitrophenyl)methyl]triphenylphosphorane (100.0 g, 0.23 mol) in dry THF (500 mL) was cooled to 5°C. n-Butyl lithium (n-BuLi) (2.4 M, 96 mL, 0.23 mol) was added dropwise to maintain the temperature between 5°C to 10°C. The cooling bath was then removed, and the reaction mixture was allowed to warm to room temperature. After 4 hours, a solution of (trans)-3-(3,4-dichlorophenyl)-2-propenal (36.2 g, 0.18 mol) in THF (100 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate was concentrated in vacuo to give a residue. Purification

by flash chromatography (silica gel, 20% EtOAc/hexane) yielded 16.0 g (0.05 mol, 28%) of the desired product. mp 125-135°C.

Analysis for $C_{16}H_{11}Cl_2NO_2$: Calcd: C, 60.02; H, 3.46; N, 4.37, Cl, 22.15. Found: C, 59.77; H, 3.47; N, 4.40; Cl, 22.39.

Preparation of 4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamine

The title compound was prepared from (*trans*), (*trans*)-1,2-dichloro-4-[4-(4-nitrophenyl)-1,3-butadienyl]benzene (15.42 g, 0.048 mol), Ra-Ni (1 g) at 20°C to 26°C (ΔP = 19.3 psi) under a hydrogen atmosphere in THF (75 mL) and MeOH (75 mL) using the procedure described in Example 1, Step B. This procedure yield a solid, 10.97 g (0.037 mol, 78%) of the desired product. mp 50-52°C.

Analysis of $C_{16}H_{17}N_1Cl_2$: Calcd: C, 65.32; H, 5.82; N, 4.76. Found: C, 65.43; H, 5.84; N, 4.61.

Preparation of 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid

The title compound, mp 98-105°C, was prepared from 4-[4-(3,4-dichlorophenyl)butyl]phenylamine (0.50 g, 1.7 mmol), 2-chlorobenzoic acid (0.24 g, 1.56 mmol), anhydrous potassium carbonate (0.71 g, 5.15 mmol), copper powder (0.21 g, 3.28 mmol), and copper(I) chloride (0.015 g, 0.15 mmol) in dry DMF (5 mL) using the procedure described in Example 1, Step C, Method B.

EXAMPLE 11

Preparation of 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid

A mixture of 2-fluoro-5-nitrobenzoic acid (1.85 g, 0.01 mol), 4-[4-(3,4-dichlorophenyl)butyl]-phenylamine (2.94 g, 0.01 mol) and Et_3N (2.80 mL) in acetonitrile (110 mL) was heated to reflux for 48 hours. The reaction mixture was cooled and concentrated in vacuo to remove the solvent. The residue was dissolved in CH_2Cl_2 and washed with diluted HCl. The organic layer was dried (Na_2SO_4), concentrated in vacuo to give a crude solid. Purification by flash

chromatography (silica gel, CH_2Cl_2) yielded 1.40 g (0.003 mol, 30%) of the desired product.

Analysis for $C_{23}H_{19}N_2O_4Cl_2$: Calcd: C, 60.27; H, 4.18; N, 6.11; Cl, 14.47. Found: C, 60.16; H, 4.41; N, 6.09; Cl, 15.69.

EXAMPLE 12

Preparation of 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid

To a cooled (0°C) solution of 4-[4-(3,4-dichlorophenyl)butyl]-phenylamine (1.47 g, 5.0 mmol) and DBU (0.75 mL, 7.5 mmol) in acetonitrile (25 mL), a solution of 2-fluoro-2,5-dinitrobenzoic acid (1.15 g, 5.0 mmol) in acetonitrile (15 mL) was added dropwise. After stirring for 30 minutes at 0°C, the reaction mixture was neutralized with dilute HCl and extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo to afford a crude residue. Recrystallization with EtOH yielded a bright orange solid, 2.06 g (4.1 mmol, 82%) of the title compound.

Analysis for $C_{23}H_{19}Cl_2N_3O_6$: Calcd: C, 54.77; H, 3.80; N, 8.33; Cl, 14.06. Found: C, 54.68; H, 4.00; N, 8.12; Cl, 13.81.

EXAMPLE 13

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid

Preparation of Bromo[(3,4-dichlorophenyl)methyl]triphenylphosphorane

A mixture of 4-bromomethyl-1,2-dichlorobenzene (2.40 g, 0.01 mol), and triphenylphosphine (5.24 g, 0.02 mol) in toluene (30 mL) was stirred for 16 hours at room temperature. The solid was filtered, rinsed with toluene, and oven-dried at room temperature to yield a white powder, 3.95 g (0.0078 mol, 78%) of the desired product.

^1H NMR [dimethylsulfoxide (DMSO):ppm] :7.89-7.61 (m, 15H), 7.50 (d, J=8.3 Hz, 1H), 7.04 (t, J=2.3 Hz, 1H), 6.97 (m, 1H), 5.20 (d, J=15.9 Hz, 2H).

Preparation of 4-(4-Nitrophenyl)butyraldehyde

To a cooled solution (-70°C) of oxalyl chloride (2.0 M in CH_2Cl_2, 14.1 mL, 28.2 mmol), dimethylsulfoxide (DMSO) (4.40 g, 56.32 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The resulting reaction mixture was then stirred for 30 minutes at -70°C under a nitrogen atmosphere. A solution of 4-(4-nitrophenyl)butan-1-ol (5.00 g, 25.6 mmol) in CH_2Cl_2 (3 mL) was added dropwise, and the reaction mixture was stirred for 1 hour at -70°C. Et_3N (16 mL, 115 mmol) was added, and the reaction mixture was then allowed to gradually warm to room temperature and stir for 30 minutes. The mixture was then quenched with H_2O and extracted with EtOAc. The organic layers were washed with 0.1N HCl solution, H_2O, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a lightly brown oil. Purification by flash chromatography (silica gel, 50% EtOAc/hexane) yielded 3.20 g (16.56 mmol, 65%) of the desired product.

^1H NMR (DMSO:ppm): 9.75 (s, 1H), 8.12 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.3 Hz, 2H), 2.72 (t, J=7.7 Hz, 2H), 2.47 (t, J=7.1 Hz, 2H), 1.94 (m, 2H).

Preparation of 1,2-Dichloro-4-[5-(4-nitrophenyl)-1-pentenyl]benzene

A solution of bromo[(3,4-dichlorophenyl)methyl]triphenylphosphorane (3.95 g, 7.9 mmol) in dry THF (20 mL) was cooled to 0°C. LHDMS (1.0 M/THF, 9 mL, 9.0 mol) was added dropwise to maintain the temperature at 0°C. After stirring for 30 minutes, a solution of 4-(4-nitro-phenyl)butyraldehyde (1.45 g, 7.5 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to warm to room temperature within 2 hours. The mixture was then quenched with H_2O and extracted with EtOAc. The organic layers were washed with 0.1N HCl solution, H_2O, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a lightly brown oil. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 2.5 g (7.4 mmol, 99%) of the desired product.

MS: 335 (M^+), 337 (MH^+).

Preparation of 4-[5-(3,4-Dichlorophenyl)pentyl]phenylamine

The title compound was prepared from 1,2-dichloro-4-[5-(4-nitrophenyl)-1-pentenyl]benzene (2.5 g, 7.4 mmol), Ra-Ni (1 g) in THF (50 mL) at 25°C to 40°C (ΔP = 9.9 psi) using the procedure described in Example 1, Step B. This procedure yielded 1.06 g (3.4 mmol, 46%) of the desired product.

^{1}H NMR (DMSO:ppm): 7.45 (d, *J*=8.3 Hz, 1H), 7.41 (d, *J*=2.2 Hz, 1H), 7.12 (m, 1H), 6.74 (d, *J*=8.3 Hz, 2H), 6.40 (d, *J*=8.3 Hz, 2H), 4.73 (s, 2H), 2.50 (t, *J*=7.7 Hz, 2H), 2.31 (t, *J*=7.6 Hz, 2H), 1.6-1.5 (m, 4H), 1.5-1.4 (m, 2H).

Preparation of 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-5-nitrobenzoic acid

To a cooled (-78°C) solution of 4-[5-(3,4-dichlorophenyl)pentyl]-phenylamine (0.231 g, 0.75 mmol) in THF (2 mL), LHDMS (2.25 mL, 1 M in hexane, 2.25 mmol) was added dropwise. The reaction mixture was allowed to stir at -78°C for 10 minutes. A solution of 2-fluoro-5-nitrobenzoic acid (0.139 g, 0.75 mmol) in THF (2 mL) was added dropwise, and this solution was stirred for 30 minutes at -78°C. The reaction mixture was allowed to gradually warm to room temperature and stir for 2 hours under N_2 atmosphere. The reaction mixture was diluted with EtOAc, and acidified with 1N HCl (pH 3). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to yield a brown residue. Purification by flash chromatography (silica gel, 2% MeOH/CH_2Cl_2) then recrystallization with MeOH yielded 265 mg (0.56 mmol, 75%) of the desired product. mp 147-148°C.

Analysis for $C_{24}H_{22}Cl_2N_2O_4 \cdot 0.37H_2O$: Calcd: C, 60.05; H, 4.77; N, 5.84. Found: C, 59.67; H, 4.64; N, 5.51.

EXAMPLE 14

Preparation of 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[5-(3,4-dichlorophenyl)pentyl]phenylamine (231 mg, 0.75 mmol), LHDMS (6.28 mL, 1 M in THF, 6.28 mmol) and 2-fluoro-4-methoxy-5-nitrobenzoic acid methyl ester (172 g, 0.75 mmol) in THF (5 mL) using the procedure described in Example 13. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 145 mg (0.28 mmol, 37%) of the desired product.

MS: 515.2 (M^+), 517.2 (MH^+).

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

The title compound was prepared from 2-{4-[5-(3,4-dichlorophenyl)-pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester (145 mg, 0.28 mmol) and 1N NaOH (aq.) (0.56 mL) in THF (1.2 mL) using the procedure described in Example 2. Purification by flash chromatography (silica gel, 10% MeOH/CH_2Cl_2), then recrystallization with MeOH yielded 58 mg (0.12 mmol, 41%) of the desired product. mp 192-193°C.

Analysis for $C_{25}H_{24}Cl_2N_2O_5$: Calcd: C, 59.65; H, 4.81; N, 5.56.

Found: C, 59.29; H, 4.58; N, 5.36.

EXAMPLE 15

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[3-(3,4-dichlorophenyl)propyl]-phenylamine (420 mg, 1.50 mmol), 2-bromobenzoic acid methyl ester (310 mg,

1.25 mmol), cesium carbonate (569 mg, 1.75 mmol), tris(dibenzylideneacetone-dipaladium(0) (34 mg, 0.037 mmol) and (*S*)-(2,2′-bis(di-p-tolylphosphino-1,1′-binaphthyl (98%, (*S*)-tol-BINAP) (38 mg, 0.056 mmol) (Ligand/Pd=1.5) in anhydrous toluene (15 mL) using the procedure described in Example 2, Step C. This procedure yielded an orange solid 0.51 g (1.11 mmol, 74%) of the desired product. mp 117-118°C.

MS: 457.1 (M^+); 459.1 (MH^+)

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid

The title compound was 2-{4-[3-(3,4-dichlorophenyl)-propyl]phenylamino}-5-nitrobenzoic acid methyl ester (0.50 g, 1.09 mmol), 2N NaOH (5.0 mL) in EtOH (2 mL) and THF (4 mL) using the procedure described in Example 2. This procedure yielded an orange solid, 0.49 g (1.10 mmol, 100%) of the desired product. mp 153-155°C.

MS: 443.2 (M^+), 445.2 (MH^+)

EXAMPLE 16

Preparation of 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

Preparation of 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[2-(3,4-dimethylphenyl)ethyl]-benzenamine (1.0 g, 4.43 mmol), 2-bromo-5-nitrobenzoic acid methyl ester (0.96 g, 3.69 mmol), cesium carbonate (1.68 g, 5.17 mmol), tris(dibenzylideneacetone-dipaladium(0) (101 mg, 0.11 mmol) and (*S*)-(2,2′-bis(di-p-tolylphosphino-1,1′-binaphthyl (98%, (*S*)-tol-BINAP) (113 mg, 0.17 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (32 mL) using the procedure described in Example 2, step C. This procedure yielded an yellow solid, 1.31 g (3.24 mmol, 73%) of the desired product. mp 115-117°C.

MS: 405 (M^+)

Analysis for $C_{24}H_{24}O_4N_2 \cdot 0.25\ H_2O$: Calcd: C, 71.27; H, 5.98; N, 6.93.
Found: C, 70.48; H, 6.03; N, 6.85.

Preparation of 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

The title compound was prepared 2-{4-[2-(3,4-dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester (1.12 g, 2.76 mmol), 1N NaOH (50 mL) in EtOH (50 mL) and THF (50 mL) using the procedure described in Example 2. This procedure yielded a yellow solid, 1.03 g (2.63 mmol, 81%) of the desired product. mp 214-216°C.

Analysis for $C_{23}H_{22}O_4N_2 \cdot 0.25\ H_2O$: Calcd: C, 69.99; H, 5.74; N, 7.18.
Found: C, 69.90; H, 5.82; N, 6.81.

EXAMPLE 17

Preparation of 2-[[4-[2-(4-Chloro-3-trifluromethylphenyl)ethyl]phenyl]amino-benzoic acid

Step A (Scheme 1): Preparation of *trans*-1-Chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene

A mixture of p-nitrophenylacetic acid (51.85 g, 0.29 mol) and 4-chloro-3-trifluoromethylbenzaldehyde (47.85 g, 0.23 mol) in piperidine (19.5 g, 0.23 mol) was heated under N_2 atmosphere to 150°C to160°°C for 1 hour. The reaction mixture was cooled to 80°C to 100°°C and refluxing *i*-PrOH (150 mL) was added. The mixture was continued to cool to room temperature and then placed under refrigeration for 5 hours. The crystalline precipitate was filtered off, rinsed with cold *i*-PrOH, and dried at room temperature in a vacuum oven overnight to yield *trans*-1-chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene as an orange solid, 22.53 g (68.75 mmol, 30%). mp 173-174°C.

MS: 327.0 (M^+)

Step B (Scheme 1): Preparation of 4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]-benzenamine

The title compound was prepared from *trans*-1-chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene (22.53 g, 0.069 mol) and Ra-Ni (22 g) in THF (0.5 L) at 18°C to 29°C ($\Delta P = 20.5$ psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a white solid, 20.0 g (66.73 mmol, 97%) of the desired product. mp 62-64°C.

MS: 298.1 (M^+)

Preparation of 2-[[4-[2-(4-Chloro-3-trifluromethylphenyl)ethyl]phenyl]-aminobenzoic acid

To a cold solution of 4-[2-(4-chloro-3-trifluoromethylphenyl)ethyl]-benzenamine (4.33 g, 14.45 mmol) in THF (50 mL) at -78°C, was added LHMDS (43.35 mL, 43.35 mmol) (1M/THF) dropwise. Allowed the reaction mixture to stir for 10 minutes at -78°C. A solution of 2-fluorobenzoic acid (2.02 g, 14.45 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 2 hours at -78°C, then warmed to room temperature and let stir for additional 3 hours. The reaction mixture was concentrated *in vacuo* (40°C) to remove the organic solvent. This residue was acidified to pH 3 with 3N HCl (aq.). This precipitate was collected by filtration, rinsed with 10% HCl (40 mL), and dried in vacuum for overnight to give as a pale solid , 4.3 g (10.24 mmol, 70%) of the desired product. mp 150-152°C.

Analysis for $C_{22}H_{17}O_2N_1ClF_3 \cdot 0.59\ H_2O$: Calcd: C, 61.39; H, 4.26; N, 3.25. Found: C, 61.01; H, 4.34; N, 3.30.

EXAMPLE 18

Preparation of 2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid

Preparation of o-Bromobenzoic acid potassium salt

To a solution of o-bromobenzoic acid (201.03 g, 1.0 mol) in MeOH (500 mL), K_2CO_3 (69 g, 1.0 mol) was added. The mixture was concentrated to give the desired product (239.1 g, 1.0 mol, 100%).

Preparation of 2-[(4-Iodophenyl)amino] benzoic acid

A mixture of o-bromobenzoic acid potassium salt (47.8 g, 0.2 mol), 4-iodoaniline (43.8 g, 0.2 mol), K_2CO_3 (13.8 g, 0.1 mol), and cupric acetate (2.87 g, 6%) in diglyme (100 mL) was heated to reflux for 30 minutes. The reaction mixture was diluted with H_2O (1.0 L) and filtered. The filtrate was acidified with diluted AcOH. The resulting precipitate was collected by filtration, washed with H_2O and dried in a vacuum at 50°C for 16 hours. Recrystallization from EtOAc gave the desired product, a solid (29.7 g, 0.087 mol, 44%). mp 205-206°C.

Analysis for $C_{13}H_{10}N_1O_2I$: Calcd: C,45.05; H, 2.97; N, 4.13. Found: C, 45.05; H, 2.97; N, 3.92.

Preparation of 2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid

A mixture of 3,4-dichlorophenylboronic acid (880 mg, 2.3 mmol), 2-[(4-iodophenyl)amino]benzoic acid (339 mg, 1 mmol), $PdCl_2$·dppf·CH_2Cl_2 [1,1′-bis(diphenylphosphino)ferrocene palladium (II) chloride, complexed with dichloromethane (1:1)] (67 mg, 0.082 mmol), K_2CO_3 (829 mg, 6 mmol), and H_2O (2 mL) in dioxane (15 mL) was heated to reflux for 1 hour. The reaction mixture was diluted with EtOAc and filtered. The filtrate was treated with 1N HCl, washed with H_2O, brine, dried (Na_2SO_4), and concentrated in vacuum to give a yellow solid. Purification by flash chromatography (silica gel, 10% MeOH/CH_2Cl_2) yielded 272 mg (0.76 mmol, 76%) of the desired product. mp >220°C.

Analysis for $C_{19}H_{13}O_2N_1Cl_2$: Calcd: C, 63.23; H, 3.71; N, 3.88.

Found: C, 62.95; H, 3.73; N, 3.63.

By following the general procedures described above, the following additional invention compounds were prepared:

EXAMPLE 19

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid

MS: 403 (M^+).

Analysis for $C_{26}H_{30}N_2O_2 \cdot 0.40$ mol H_2O: Calcd: C, 69.31; H, 6.87; N, 6.12.

Found: C, 69.29; H, 7.04; N, 6.35.

EXAMPLE 20

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid. mp 150-153°C.

MS: 376 (M^+).

EXAMPLE 21

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino}benzoic acid. mp 164-167°C.

MS: 376 (M^+).

Analysis for $C_{22}H_{20}N_2O_4 \cdot 2.20$ mol H_2O: Calcd: C, 63.51; H, 5.91; N, 6.73.

Found: C, 63.56; H, 5.45; N, 6.46.

EXAMPLE 22

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid. mp 110-112°C.

MS: 347 (M^+1^+).

EXAMPLE 23

2-{4-[3-(3-Aminophenyl)propyl]phenylamino}benzoic acid. mp 109°C.

MS: 333 (M^+1^+).

EXAMPLE 24

2-{4-[2-(4-Aminophenyl)phenylamino}benzoic acid. mp 198-201°C.

MS: 333 (M^+1^+).

Analysis for $C_{21}H_{20}N_2O_2 \cdot 0.1$ mol H_2O: Calcd: C, 75.47; H, 6.09; N, 8.38.

Found: C, 75.32; H, 6.12; N, 8.27. Found: C, 75.32; H 6.12; N, 8.27.

EXAMPLE 25

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride. mp 176-177°C

MS: 417 (M^+1^+).

Analysis for $C_{27}H_{32}N_2O_2$: Calcd: C, 71.59; H, 7.34; N, 6.18; Cl, 7.83. Found: C, 71.31; H, 7.24; N, 6.19; Cl, 7.74.

EXAMPLE 26

2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride monohydrate

MS: 389 (M^+1^+).

Analysis for $C_{25}H_{28}N_2O_2 \cdot HCl \cdot H_2O$: Calcd: C, 67.78; H, 7.05; N, 6.32; Cl, 8.00. Found: C, 67.83; H, 7.01; N, 6.30; Cl, 7.75.

EXAMPLE 27

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino}benzoic acid

MS: 431 (M^+1^+).

Analysis for $C_{28}H_{34}N_2O_2 \cdot 0.2\ H_2O$: Calcd: C, 77.46; H, 7.99; N, 6.45. Found: C, 77.43; H, 7.86; N, 6.40.

EXAMPLE 28

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino}benzoic acid. mp 115-117°C.

MS: 374 (M^+), 375 (M^+1^+).

Analysis for $C_{24}H_{26}N_2O_2 \cdot 0.1\ H_2O$: Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.57; H, 7.21; N, 7.47.

EXAMPLE 29

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid. mp 133°C.

MS: 375 (M^+1^+).

Analysis for $C_{24}H_{26}N_2O_2 \cdot 0.1\ H_2O$: Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.62; H, 7.06; N, 7.36.

EXAMPLE 30

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic acid

MS: 431 (M^+1^+).

Analysis for $C_{28}H_{34}N_2O_2$: Calcd: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.02; H, 8.17; N, 6.50.

EXAMPLE 31

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino}benzoic acid.

mp 95.5-97.5°C.

Analysis for $C_{35}H_{32}N_2O_2$: Calcd: C, 82.00; H, 6.29; N, 5.46. Found: C, 81.81; H, 6.58; N, 5.44.

EXAMPLE 32

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino}benzoic acid

MS: 403 (M^+1^+).

Analysis for $C_{26}H_{30}N_2O_2 \cdot 0.1\ H_2O$: Calcd: C, 77.23; H, 7.53; N, 6.93. Found: C, 77.14; H, 7.82; N, 6.88.

EXAMPLE 33

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino}benzoic acid. mp 182-184°C.

MS: 333 (M^+1^+).

Analysis for $C_{21}H_{20}N_2O_2 \cdot 0.25\ H_2O$: Calcd: C, 74.87; H, 6.13; N, 8.43. Found: C, 74.86; H, 6.16; N, 8.32.

EXAMPLE 34

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino}benzoic acid

MS: 375 (M^+1^+).

Analysis for $C_{24}H_{26}N_2O_2 \cdot 0.1\ H_2O$: Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.52; H, 7.22; N, 7.49.

EXAMPLE 35

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino}benzoic acid. mp 224°C.

MS: 375 (M^+1^+).

EXAMPLE 36

2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid. mp 213-215°C.

MS: 375 (M^+1^+).

EXAMPLE 37

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride. mp 189-193°C.

MS: 417 (M^+1^+).

Analysis for $C_{27}H_{32}N_2O_2 \cdot HCl$: Calcd: C, 71.58; H, 7.34; N, 6.18; Cl, 7.83.

Found: C, 71.48; H, 7.35; N, 6.10; Cl, 7.66.

EXAMPLE 38

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride. mp 175-180°C.

MS: 445 (M^+).

Analysis for $C_{29}H_{36}N_2O_2 \cdot HCl$: Calcd: C, 72.40; H, 7.75; N, 5.82; Cl, 7.37.

Found: C, 72.61; H, 7.95; N, 5.78; Cl, 7.23.

EXAMPLE 39

2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid. mp 176-178°C.

MS: 389 (M^+1^+).

EXAMPLE 40

2-{4-[3-(3-Acetylaminophenyl)propyl]phenylamino}benzoic acid. mp 140-145°C.

MS: 389 (M^+1^+).

EXAMPLE 41

2-{4-[2-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride. mp 166-171°C.

MS: 389 (M^+1^+).

Analysis for $C_{25}H_{28}N_2O_2 \cdot HCl$: Calcd: C, 70.66; H, 6.88; N, 6.59; Cl, 8.34. Found: C, 70.48; H, 6.89; N, 6.57; Cl, 18.39.

EXAMPLE 42

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid monohydrochloride. mp 187-193°C.

MS: 401 (M^+1^+).

Analysis for $C_{26}H_{28}N_2O_2 \cdot HCl$: Calcd: C, 71.46; H, 6.69; N, 6.41; Cl, 8.11. Found: C, 71.28; H, 6.73; N, 6.35; Cl, 8.30.

EXAMPLE 43

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid

MS: 431 (M^+1^+).

Analysis for $C_{28}H_{34}N_2O_2$: Calcd: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.91; H, 8.03; N, 6.43.

EXAMPLE 44

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid

MS: 459 (M^+1^+).

Analysis for $C_{30}H_{38}N_2O_2$: Calcd: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40; H, 8.50; N, 6.19.

EXAMPLE 45

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid

MS: 459 (M^+1^+).

Analysis for $C_{30}H_{38}N_2O_2$: Calcd: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40; H, 8.43; N, 6.11.

EXAMPLE 46

2-(4-{3-[4-(1H-Pyrrol-1-yl)phenyl]propyl}phenylamino)benzoic acid.

mp 131-136°C.

MS: 397 (M^+1^+).

Analysis for $C_{26}H_{24}N_2O_2 \cdot 0.2\ H_2O$: Calcd: C, 78.05; H, 6.15; N, 7.00. Found: C, 77.95; H, 6.17; N, 7.08.

EXAMPLE 47

2-{4-[3-(4-Piperidin-1-ylphenyl)propyl]phenylamino}benzoic acid

MS: 415 (M^+1^+).

Analysis for $C_{27}H_{30}N_2O_2 \cdot 0.2\ H_2O$: Calcd: C, 77.55; H, 7.33; N, 6.70. Found: C, 77.37; H, 7.35; N, 6.63.

EXAMPLE 48

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid.

mp 57-62°C.

MS: 431 (M^+1^+).

Analysis for $C_{27}H_{30}N_2O_3 \cdot 0.3\ H_2O$: Calcd: C, 74.39; H, 7.07; N, 6.43. Found: C, 74.23; H, 6.97; N, 6.27.

EXAMPLE 49

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid. mp 236-239°C.

MS: 375 (M^+).

EXAMPLE 50

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}benzoic acid.

mp 137°C.

MS: 417 (M^+1^+).

EXAMPLE 51

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid

MS: 389 (M^+1^+).

Analysis for $C_{25}H_{28}N_2O_2 \cdot 0.2\ H_2O$: Calcd: C, 76.58; H, 7.30; N, 7.14. Found: C, 76.61; H, 7.29; N, 7.03.

EXAMPLE 52

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid

MS: 389 (M^+1^+).

Analysis for $C_{25}H_{28}N_2O_2 \cdot 0.1\ H_2O$: Calcd: C, 76.93; H, 7.28; N, 7.18. Found: C, 76.85; H, 7.44; N, 7.06.

EXAMPLE 53

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid.

mp 171-177°C.

MS: 401 (M^+1^+).

Analysis for $C_{26}H_{28}N_2O_2 \cdot 0.2\ H_2O$: Calcd: C, 77.27; H, 7.08; N, 6.93. Found: C, 77.09; H, 6.97; N, 6.96.

EXAMPLE 54

2-{4-[3-(3-Piperidin-1yl-phenyl)-propyl]-phenylamino}-benzoic acid.

mp 59-61°C.

MS: 415 (M^+1^+).

Analysis for $C_{27}H_{30}N_2O_2 \cdot 0.3\ H_2O$: Calcd: C, 77.22; H, 7.34; N, 6.67. Found: C, 77.18; H, 7.25; N, 6.49.

EXAMPLE 55

{5-[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid. mp 222-224°C.

MS: 391 (M^+1^+).

EXAMPLE 56

{5-[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid. mp >250°C.

MS: 377 (M^+1^+).

Analysis for $C_{18}H_{20}N_2O_3S_2 \cdot 0.4\ H_2O$: Calcd: C, 56.34; H, 5.46; N, 7.30; S, 16.71. Found: C, 56.27; H, 5.18; N, 7.31; S, 16.74.

EXAMPLE 57

3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}propanoic acid. mp 214-215°C.

MS: 405 (M^+1^+).

EXAMPLE 58

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}butanoic acid. mp 152-154°C.

MS: 417 (M^-1^+), 418 (M^+), 419 (M^+1^+).

Analysis for $C_{21}H_{26}N_2O_3S_2 \cdot 0.2\ H_2O$: Calcd: C, 59.74; H, 6.30; N, 6.64; S, 15.19. Found: C, 59.59; H, 6.16; N, 6.52; S, 15.38.

EXAMPLE 59

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]phenylamino}-5-methyl-benzoic acid. mp 98-99°C.

MS: 414 (M^+).

EXAMPLE 60

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-methanesulfonamide was prepared by reacting the product from Example 9 with methanesulfonamide. mp 53-61°C.

Analysis for $C_{23}H_{22}Cl_2N_2O_3S \cdot 0.13\ H_2O$: Calcd: C, 57.58; H, 4.68; N, 5.84. Found: C, 57.20; H, 4.66; N, 5.51.

EXAMPLE 61

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid. mp 214-216°C.

Analysis for $C_{23}H_{22}N_2O_4 \cdot 0.25\ H_2O$: Calcd: C, 69.99; H, 5.74; N, 7.18. Found: C, 69.90; H, 5.82; N, 6.81.

EXAMPLE 62

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid. mp 239-244°C.

MS: 439 (MH^+).

EXAMPLE 63

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid. mp 207-209°C.

Analysis for $C_{22}H_{16}ClF_3N_2O_4$: Calcd: C, 56.85; H, 3.47; N, 6.03.

Found: C, 56.75; H, 3.71; N, 5.83.

EXAMPLE 64

5-Amino-2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid was prepared by reacting the product from Example 2 with hydrogen gas in the presence of Raney nickel. mp 137-142°C.

Analysis for $C_{21}H_{18}Cl_2N_2O_2 \cdot 0.96$ mol THF: Calcd: C, 63.94; H, 4.72; N, 6.00.

Found: C, 64.33; H, 4.91; N, 6.35.

EXAMPLE 65

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid. mp 198-202°C.

Analysis for $C_{21}H_{18}N_2O_4 \cdot 0.11\ H_2O$: Calcd: C, 69.22; H, 5.04; N, 7.69.

Found: C, 69.59; H, 5.27; N, 7.22.

EXAMPLE 66

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid. mp 148-150°C.

Analysis for $C_{22}H_{17}F_4NO_2$: Calcd: C, 65.51; H, 4.25; N, 3.47. Found: C, 65.51; H, 4.13; N, 3.46.

EXAMPLE 67

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid mp 203-208°C.

Analysis for $C_{21}H_{16}F_2N_2O_4$: Calcd: C, 63.32; H, 4.05; N, 7.03. Found: C, 62.94; H, 4.37; N, 6.87.

EXAMPLE 68

{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-[2-(1H-tetrazol-5-yl)-phenyl]-amine was prepared as described in Example 1, using a tetrazole fluoro intermediate that was synthesized from commercially available 2-fluorobenzonitrile and sodium azide under standard reaction conditions. mp 129 shrink, 152-157°C.

Analysis for $C_{21}H_{17}Cl_2N_5 \cdot 0.15$ EtOAc·0.15 Hexane: Calcd: C, 61.80; H, 4.64; N, 16.12. Found: C, 61.61; H, 4.28; N, 15.83.

EXAMPLE 69

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid. mp 190-193°C.

Analysis for $C_{22}H_{16}F_4N_2O_4$: Calcd: C, 58.93; H, 3.60; N, 6.25. Found: C, 58.69; H, 3.42; N, 6.57.

EXAMPLE 70

2-(4-Phenethyl-phenylamino)-benzoic acid. mp 173-182°C.

Analysis for $C_{21}H_{19}NO_2$: Calcd: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.42; H, 5.97; N, 4.47. Found: C, 79.59; H, 6.03; N, 4.50.

EXAMPLE 71

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-fluoro-benzoic acid. mp 180-182°C.

Analysis for $C_{21}H_{16}Cl_2FNO_2 \cdot 0.06\ H_2O$: Calcd: C, 62.23; H, 4.01; N, 3.46. Found: C, 61.83; H, 4.04; N, 3.29.

EXAMPLE 72

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid.

mp 168-171°C.

Analysis for $C_{20}H_{16}Cl_2N_2O_2$: Calcd: C, 62.03; H, 4.16; N, 7.23.

Found: C, 62.11; H, 4.17; N, 7.07.

EXAMPLE 73

2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 192.5-194.5°C.

Analysis for $C_{21}H_{17}ClN_2O_4$: Calcd: C, 63.56; H, 4.32; N, 7.06. Found: C, 63.83; H, 4.62; N, 6.79.

EXAMPLE 74

2-{4-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 210-212°C.

Analysis for $C_{21}H_{17}ClN_2O_4 \cdot 0.26\ H_2O$: Calcd: C, 62.82; H, 4.40; N, 6.98.

Found: C, 62.51; H, 4.34; N, 6.58.

EXAMPLE 75

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid.

mp 153-160°C.

Analysis for $C_{22}H_{19}Cl_2NO_2 \cdot 0.61\ H_2O$: Calcd: C, 64.25; H, 4.96; N, 3.41.

Found: C, 63.87; H, 4.64; N, 3.55.

EXAMPLE 76

2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 236-238°C.

EXAMPLE 77

2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 200.5-202.5°C.

Analysis for $C_{21}H_{16}Cl_2N_2O_4$: Calcd: C, 58.49; H, 3.74; N, 6.50.
Found: C, 58.33; H, 3.67; N, 6.29.

EXAMPLE 78

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid. mp 130-132°C.

Analysis for $C_{22}H_{16}Cl_2F_3NO_2$: Calcd: C, 58.17; H, 3.55; N, 3.08.
Found: C, 58.25; H, 3.65; N, 3.05.

EXAMPLE 79

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid. mp >260°C.

EXAMPLE 80

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dimethylamino-benzoic acid. mp 75-80°C.

EXAMPLE 81

2-{4-[2-(3,5-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid. mp 191-194°C. Analysis for $C_{21}H_{17}Cl_2NO_2$: Calcd: C, 65.30; H, 4.44; N, 3.63. Found: C, 65.38; H, 4.29; N, 3.52.

EXAMPLE 82

2-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid was prepared according to Example 1 using a decahydroisoquinoline aldehyde which was prepared from trans-decahydroisoquinoline and para-fluorobenzaldehyde under standard reaction conditions. mp 203-206°C.
Analysis for $C_{30}H_{34}N_2O_2 \cdot 0.12\ H_2O$: Calcd: C, 78.89; H, 7.56; N, 6.13.
Found: C, 78.49; H, 7.58; N, 5.90.

The following examples are prepared according to the foregoing methods, or by utilizing standard combinatorial synthetic methodology by reacting halo substituted benzoate esters with a substituted aniline to form the corresponding

diarylamine, followed by saponification to the benzoic acid of Formula I. The reactions are carried out on 0.15 mmol scale as follows. Solutions of each halo benzoate reactant (0.18 M) in toluene are placed in 2 dram reaction vials. Each aniline reactant is dissolved in anhydrous toluene to give 0.15 M solutions. A Distriman pipet is used to add 1 mL (0.15 mmol, 1 eq) of each halo benzoate solution to the appropriate vials containing 1 mL (0.18 mmol, 1.2 eq) of the aniline reactants. A catalyst solution is prepared by dissolving 0.025 M of $Pd_2(dba)_3$ (dipalladium-tridibenzylidene acetone) and 0.075 M of BINAP (2,2′-bis(diphenylphosphino)-1,1′-binapthyl) in toluene, and 0.25 mL of the catalyst solution is added to each reaction vial. A base, generally cesium carbonate (68 mg, 0.21 mmol, 1.40 eq) is added to each reaction vial, and the vials are capped and placed in a shaker oven and heated at 100°C for 48 hours. The reaction mixtures are then cooled, and the reaction solvents are removed by evaporation. The solid residue is suspended in 400 µL of ethyl acetate and filtered to remove all catalyst. The filtrates are concentrated to dryness by evaporation to provide compounds of Formula I, wherein the benzoic acid portion is esterified (e.g., benzyl or methyl ester). The esters are dissolved in 500 µL of THF/ethanol (1:1 v/v) to which is added 300 µL of 5 M sodium hydroxide. The solutions are shaken for 5 hours at 60°C and then cooled and concentrated to dryness by evaporation of the solvents to provide the desired compounds of Formula I. Typical compounds prepared by this method are as follows. The structure of the compounds are generally confirmed by mass spectral analysis.

EXAMPLE 83

2-(3′,5′-Dichloro-3-methyl-biphenyl-4-ylamino)-benzoic acid

MS: 371; MW: 372.2495.

EXAMPLE 84

2-(3′,5′-Dibromo-3-methyl-biphenyl-4-ylamino)-benzoic acid

MS: 459; MW: 461.1515.

EXAMPLE 85

2-(4-1,3-Benzodioxol-5-yl-2-methyl-phenylamino)-benzoic acid

MS: 347; MW: 347.3683.

EXAMPLE 86

2-(2,2′,4′-Trichloro-biphenyl-4-ylamino)-benzoic acid

MS: 391; MW: 392.6678.

EXAMPLE 87

2-(2-Chloro-3′,4′-difluoro-biphenyl-4-ylamino)-benzoic acid

MS: 359; MW: 359.7578.

EXAMPLE 88

2-(3′-Bromo-2-chloro-biphenyl-4-ylamino)-benzoic acid

MS: 401; MW: 402.6737.

EXAMPLE 89

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid

EXAMPLE 90

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 91

3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 92

5-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid

EXAMPLE 93

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 94

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,5-dimethoxy-benzoic acid

EXAMPLE 95

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 96

3-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 97

5-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-isophthalic acid

EXAMPLE 98

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 99

4-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid

EXAMPLE 100

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 101

2-{4-[2-(3-Methoxy-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 102

2-{4-[2-(3-Bromo-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 103

2-{4-[2-(3-Fluoro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 104

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 105

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid

EXAMPLE 106

2-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2,3-dihydro-1H-isoindol-5-ylamino]-benzoic acid

EXAMPLE 107

2-{4-[2-(3-Fluoro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 108

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-nitro-benzoic acid

EXAMPLE 109

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid

EXAMPLE 110

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-6-nitro-benzoic acid

EXAMPLE 111

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-benzoic acid

EXAMPLE 112

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 113

{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenyl}-(2-methoxy-5-nitro-phenyl)-amine

EXAMPLE 114

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 115

3-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid

EXAMPLE 116

2-{4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 159-161°C.

EXAMPLE 117

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monosodium; mp 107-108°C.

EXAMPLE 118

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monopotassium; mp >200°C.

EXAMPLE 119

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid calcium salt (1:1); mp >220°C.

EXAMPLE 120

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoate-2-hydroxy-1,1-bis-hydroxymethyl-ethyl-ammonium; mp 185-187°C.

EXAMPLE 121

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-methoxy-benzoic acid; mp 155-158°C.

EXAMPLE 122

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 184-185°C.

EXAMPLE 123

2-{3-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 155-157°C.

EXAMPLE 124

2-{3-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 182-184°C.

EXAMPLE 125

2-{4-[2-(2,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 180-181°C.

EXAMPLE 126

2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 140-143°C.

EXAMPLE 127

2-{4-[2-(2-Hydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 218-219°C.

EXAMPLE 128

2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 152-154°C.

EXAMPLE 129

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-benzoic acid; mp 200-202°C.

EXAMPLE 130

2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 181-183°C.

EXAMPLE 131

3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 137-138°C.

EXAMPLE 132

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 214-215°C.

EXAMPLE 133

2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 146-147°C.

EXAMPLE 134

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 153-154°C.

EXAMPLE 135

2-{4-[5-(3,4-Dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid; mp 106-108°C.

EXAMPLE 136

2-{4-[2-(4-{2-Hydroxycarbonylphenylamino}phenyl)ethyl]-phenylamino}-benzoic acid; MS 451 (M^{-1}).

EXAMPLE 137

2-(3′,5′-Dichloro-biphenyl-4-ylamino)-benzoic acid; mp >220°C.

EXAMPLE 138

4-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-2-methoxy-5-nitro-benzoic acid; mp 74-78°C.

EXAMPLE 139

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-5-fluoro-benzoic acid; mp 122-123°C.

EXAMPLE 140

5-Amino-2-{4-[5-(3,4-dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid; mp 182-184°C.

EXAMPLE 141

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-C,C,C-trifluoro-methanesulfonamide; MS 531 (M^-).

EXAMPLE 142

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-benzenesulfonamide; MS 539.

EXAMPLE 143

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid; mp 190-192°C. MS 453 (M^{-1}).

EXAMPLE 144

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid; mp 264-266°C.

EXAMPLE 145

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-trifluoromethyl-benzoic acid; mp 134-136°C; MS 454 (M^+).

EXAMPLE 146

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid; MS 454 (M^+).

EXAMPLE 147

2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-5-dimethylamino-benzoic acid; mp 128-131°C.

EXAMPLE 148

2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-benzoic acid; MS 400 (M^+).

EXAMPLE 149

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dipropylamino-benzoic acid; MS 485 (M^+).

EXAMPLE 150

5-Dibutylamino-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid; MS 513 (M^+).

EXAMPLE 151

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-diethylamino-benzoic acid; mp 106-110°C.

EXAMPLE 152

2,2′-[1,2-Ethanediylbis (4,1-phenyleneimino)]bis-benzoic acid

EXAMPLE 153

4-[3-[4-(Diethylamino)phenyl]propyl]-N-(2-methoxy-5-nitrophenyl)-benzinamine

EXAMPLE 154

2-{3-[2-(4-Chlorophenyl)ethyl]phenylamino}-benzoic acid

EXAMPLE 155

2-{3-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid

EXAMPLE 156

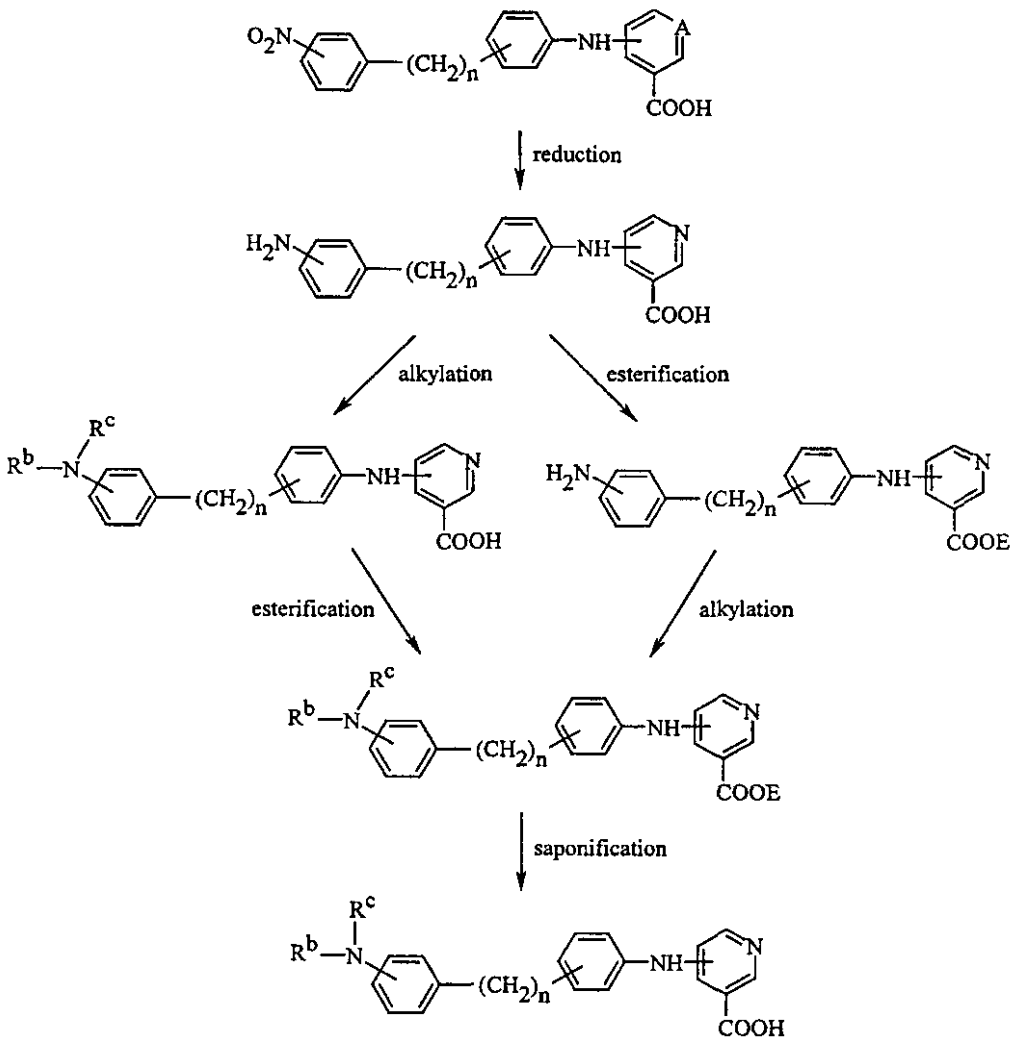
2-{3-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid

EXAMPLE 157

2-{3-[3-(4-Di-n-propylaminophenyl)propyl]phenylamino}-benzoic acid

The following Examples 158-163 illustrate the use of invention compounds as starting materials and intermediates in the synthesis of other invention compounds and derivatives. The examples illustrate reduction of nitro groups to amino groups, alkylation of amino group, and esterification of carboxylic acid groups. These reactions are depicted in the following generalized Scheme 12.

Scheme 12



where R^b and R^c are as defined above, and E is an ester forming group such as C_1-C_6 alkyl (e.g., methyl, 2,2,2-trichloroethyl), benzyl, diphenylmethyl, or the like.

EXAMPLE 158

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid

To a slurry of 4-[3-(4-nitrophenyl)propyl]aniline (4.08 g, 15.9 mmol) and 2-bromobenzoic acid (3.52 g, 17.5 mmol) in i-PrOH (100 mL) was added

$Cu(OAc)_2$ (87 mg, 0.478 mmol) and KOAc (3.44 g, 35.0 mmol) at room temperature. The resulting mixture was allowed to heat under reflux for 23 hours, then cooled to room temperature. After removing the solvent under reduced pressure, the residue was diluted with water (100 mL) and basified with aqueous 1.0 M-NaOH solution to pH 9.0. The aqueous layer was washed with Et_2O (20 mL, twice) and acidified with aqueous 1.0 M-HCl solution to pH 3.0. The precipitate formed was filtered by suction and dried at 60°C in vacuo, affording the title compound as a beige solid (5.75 g, 96% yield). mp 150-153°C.

MS (Fab): 376 (MH^+).

EXAMPLE 159

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid

To a solution of 2-{4-[3-(4-nitrophenyl)propyl]phenylamino}benzoic acid (Example 158) (3.0 g, 7.97 mmol) in DMF (40 mL) was added 10% Pd-C (300 mg) at room temperature under argon atmosphere. Hydrogen gas (1 atm) was introduced into the flask and the mixture was stirred for 14 hours at room temperature. The reaction mixture was filtered through a Celite pad to remove Pd-C and concentrated in vacuo. The residue was diluted with MeOH (ca. 50 mL) and concentrated in vacuo. This operation was repeated 3 times to remove any trace of DMF. The residue was diluted with MeOH again, and insoluble stuff was removed by filtration. Removing the solvent of the filtrate in vacuo afforded an oil, which was diluted with CH_3CN (50 mL) and added dropwise water (100 mL) slowly. The precipitate formed was filtered and dried at 60°C in vacuo, affording the title compound as a white solid (2.34 g, 85% yield). mp 110-112°C.

MS (Fab): 347 (MH^+).

EXAMPLE 160

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid methyl ester

To a solution of 2-{4-[3-(4-aminophenyl)propyl]phenylamino}benzoic acid (Example 159) (2.34 g, 6.75 mmol) in MeOH (50 mL) was added concentrated H_2SO_4 (1.0 mL) at room temperature. The mixture was stirred under reflux for 3.0 days. The reaction was quenched with Et_3N (10 mL) at 5°C, and the

solvent was removed under reduced pressure. The residue was diluted with water (20 mL) and extracted with Et_2O (20 mL, 4 times). The combined ether layer was washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purification by column chromatography afforded crude title compound as a yellow amorphous material (2.59 g). This material was used without further purification.

EXAMPLE 161

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid methyl ester and 2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid methyl ester

To a solution of the crude ester described above (2.59 g, ca. 6.75 mmol) and CH_3CHO (2.0 mL, 35.1 mmol) in CH_3CN (50 mL) was added $NaBH_3CN$ (1.70 g, 27.0 mmol) at 5°C, and the suspension was stirred for 30 minutes while the pH was monitored and aqueous 1.0 M-HCl solution was added to maintain the mixture moderately acidic (pH 3.0-4.0). The reaction mixture was allowed to warm up to room temperature over 1.0 hour and then basified with aqueous 1.0 M-NaOH solution to pH 9.0. The reaction mixture was concentrated under reduced pressure to remove CH_3CN, and the resulting aqueous solution was acidified with aqueous 1.0 M-HCl solution to pH 3.0. The aqueous solution was extracted with $CHCl_3$ (20 mL, 3 times), and the combined extract was washed with brine (5 mL). After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and purified by column chromatography (silica gel 60N, n-hexane/$CHCl_3$/Et_3N 50:98:2). First eluted was the dialkylated product as a yellow amorphous material (1.07 g, 38%).

MS (Fab): 417 (MH^+).

Subsequently eluted was the monoalkylated product as a yellow amorphous material (0.79 g, 30%).

MS (Fab): 389 (MH^+).

EXAMPLE 162

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid

To an emulsion of 2-{4-[3-(4-diethylaminophenyl)propyl]phenylamino}-benzoic acid methyl ester (1.68 g, 4.03 mmol) in EtOH (50 mL) was added aqueous 3 M-KOH solution (4.0 mL, 12.0 mmol) at room temperature, then the mixture was allowed to heat under reflux for 40 minutes. The reaction mixture was cooled to room temperature and neutralized with aqueous 1.0 M-HCl solution to pH 9.0. The mixture was concentrated under reduced pressure to remove EtOH, and the resulting aqueous solution was extracted with $CHCl_3$ (50 mL, 3 times). The combined extract was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purification by column chromatography (silica gel 60N, conc NH_4OH/MeOH/$CHCl_3$ 0.2:2:100 to 0.5:5:100) afforded a yellow oil. This oil was diluted with acetone, and the solution was concentrated under reduced pressure at room temperature to give the title compound as an amorphous solid (1.62 g, 99% for 0.2 hydrate).

MS (Fab): 403 (MH^+).

Analysis for $C_{26}H_{30}N_2O_2 \cdot 0.20\ H_2O$: Calcd: C, 76.89; H, 7.54; N, 6.90.

Found: C, 76.73; H, 7.67; N, 7.10.

EXAMPLE 163

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid

The title compound was prepared from 2-{4-[3-(4-ethylaminophenyl)-propyl]phenylamino}benzoic acid methyl ester (from Example 161), EtOH (10 mL), and 3 M-KOH solution (1.0 mL) using the procedure described in Example 162. This procedure yielded a yellow solid, 253 mg of the desired product (90% for 0.1 hydrate).

MS (Fab): 375 (MH^+).

Analysis for $C_{24}H_{26}N_2O_2 \cdot 0.10\ H_2O$: Calcd: C, 76.61; H, 7.02; N, 7.44.

Found: C, 76.62; H, 7.06; N, 7.36.

BIOLOGICAL EXAMPLES

Representative compounds of Formula I have been evaluated in several in vitro and in vivo assays which are well-established as indicative of clinical usefulness in treating Alzheimer's disease.

AMYLOID ASSAYS

BASSR (Beta-Amyloid Self-Seeding Radioassay)

An assay for inhibitors of self-seeded amyloid fibril growth

Materials:

Stock Solutions:

Assay Buffer - 50 mM sodium phosphate, pH 7.5, 100 mM NaCl, 0.02% NaN_3, 1 M urea (filter and store at 4°C).

Soluble Aβ(1-40) peptide (Bachem, Torrance, CA) - 2.2 mg/mL in deionized H_2O (stored in aliquots at -20°C, keep on ice when thawed) will self-seed after 1 week storage. Typically, the solution should be stored until no lag phase is seen in the assay.

^{125}I-labeled Aβ (1-40) - 150K-350K cpm/μL in 100% acetonitrile - 0.1% trifluoroacetic acid (TFA) - 1% β-mercaptoethanol (aliquots stored at -20°C). ^{125}I-labeled Aβ(1-40) can be made in accordance with the procedure set forth by H. LeVine, III in *Neurobiol. Aging,* **16**, 755, (1995), which is hereby incorporated by reference, or this reagent may be purchased from Amersham, Arlington Heights, Illinois.

Final assay conditions: 30 μM soluble Aβ(1-40) in deionized water in assay buffer + 20K-50K cpm ^{125}I-labeled Aβ(1-40) per assay. Compound to be tested is dissolved in dimethylsulfoxide (DMSO), typically 5 to 50 mM stock, such that the final concentration of DMSO is <1% v/v in the assay.

Assay: Reaction mixture for 50 assays (on ice) is comprised of 0.1 to 0.2 µL of ^{125}I-labeled A*^{125}I-labeled Aβ* (1-40) + 1 µL of soluble *Aβ* (1-40) + 13.5 µL assay buffer per assay. The following are the amounts of the components of the reaction mixture sufficient for 50 assay wells:

5-10 µL ^{125}I-labeled *Aβ* (1-40) dried down
675 µL assay buffer
50 µL soluble *Aβ* (1-40)

Assay Method

1) Prepare reaction mixture above by mixing components and storing on ice.
2) Pipet 14.5 µL of reaction mixture into each of 50 wells on a polypropylene U-bottom 96-well microtiter plate on ice. (Costar 3794).
3) Add 1.7 µL of diluted compound to be tested to each well in a column of eight, including solvent control. Serial 3-fold dilutions from 1 mM (100 µM final) in assay buffer - urea = 7 dilutions + zero. Each 96-well plate can therefore accommodate 11 samples + 1 Congo Red control (0.039-5 µM final in 2-fold steps).
4) Seal the plate with aluminum film (Beckman 538619) and incubate for 10 minutes on ice.
5) Raise the temperature to 37°C and incubate for 3 to 5 hours (depending on the lot of the peptide).
6) Remove the aluminum film and add 200 µL/well of ice cold assay buffer with urea, collecting the radiolabeled fibrils by vacuum filtration through 0.2 µm pore size GVWP filters in 96-well plates (Millipore MAGV N22, Bedford, MA). Determine the radioactivity of the filters using standard methods well-known to those skilled in the art.

BASST (Beta-Amyloid Self-seeding, ThioflavinT)

An assay for inhibitors of self-seeded amyloid fibril growth

METHODS:

Materials:

Stock Solutions:

Assay Buffer - 50 mM sodium phosphate, pH 7.5, 100 mM NaCl, 0.02% NaN_3, 1 M urea (filter and store at 4°C)

Soluble Aβ (1-40) - 2.2 mg/mL in deionized H_2O (store in aliquots at -20°C, keep on ice when thawed) will self-seed after 1 week storage. Typically, the solution should be stored until no lag phase is seen in the assay.

Final assay conditions: 30 μM soluble *Aβ* (1-40) in deionized water in assay buffer. Compound to be tested is dissolved in DMSO, typically 5 to 50 mM stock, such that the final concentration of DMSO is <1% v/v in the assay.

Assay: Reaction mixture for 50 assays (on ice) comprised of 1 μL of soluble *Aβ* (1-40) + 13.5 μL assay buffer per assay. The following are the amounts of the components of the reaction mixture that result in each of the 50 assay wells:

50 μL soluble *Aβ* (1-40)

675 μL assay buffer

Assay Method

1) Prepare the reaction mix above by mixing the components and storing on ice.
2) Pipet 14.5 μL of reaction mixture into each of 50 wells of a polystyrene U-bottom 96-well microtiter plate (Corning 25881-96) on ice.
3) Add 1.7 μL of diluted compound to be tested to each well in a column of eight, including solvent control. Serial 3-fold dilutions from 1 mM (100 μM final) in assay buffer - urea = 7 dilutions + zero. Each 96-well plate can therefore accommodate 11 samples + 1 Congo Red control (0.039-5 μM final in 2-fold steps).
4) Seal the plate with aluminum film and incubate for 10 minutes on ice.
5) Raise the temperature to 37°C and incubate for 3 to 5 hours (depends on the lot of the peptide).
6) Remove the aluminum film and add 250 μL/well of 5 μM thioflavin T (ThT) [T-3516, Sigma-Aldrich] in 50 mM glycine-NaOH, pH 8.5. Read

fluorescence on a plate reader (ex = 440 nm/20 nm ; em = 485 nm/20 nm) within 5 minutes.

BAPA (Beta-Amyloid Peptide Aggregation)

This assay is used to provide a measure of inhibition by a compound against the aggregation behavior of the beta amyloid peptide.

The purpose of this assays is to provide a higher volume method of assaying the amount of beta amyloid aggregation using an endpoint assay based on filtration. In this assay, hexafluoroisopropanol (HFIP) is used to break down the initial amyloid peptide to a monomer state and use a concentration of 33 μM which is high enough so that aggregation will occur at pH 6.0 in several hours.

METHODS:

β-Amyloid Peptide Aggregation, pH 6.0 (BAPA)

In a 96-well plate (Costar 3794), we add 25 μL 50 mM Phosphate Buffer, pH 6.0, 10 μL 0.5 mg/mL Aβ (1-40) peptide in 20% HFIP + 0.1 μL/assay radioiodinated ^{125}I Aβ (1-40) [^{125}I Aβ(1-40)], and 1 μL of the compound to be tested starting at 50 mM with a concentration of DMSO <1%. Then, we incubate for 2 to 4 hours at room temperature. We stop the reaction with 200 μL of 50 mM phosphate buffer, pH 6.0, and filter it through a 0.2 μm 96-well filter plate (Millipore MAGU N22). We wash the filter plate with 100 μL of the same phosphate buffer. Aggregation was detected on a Microbeta counter after impregnating the filters with Meltilex (1450-441) and is corrected for background.

BATYM ASSAY

METHODS:

Required Aβ (1-42) (California Peptide) was dried from its hexafluoroisopropanol (HFIP) stock solution. The Aβ (1-42) was dissolved in dimethylsulfoxide (DMSO) and then mixed with phosphate buffered saline (PBS) (pH 7.4). The mixed Aβ (1-42) solution was filtered with a 0.2 μm Omnipore membrane syringe filter (Millipore, Bedford, MA). The compound to be tested in DMSO (50 times concentrate) was put into each well (0.5 μL/well) of a 96-well

plate. The Aβ (1-42) solution was added into each well (24.5 μL/well). The plate was centrifuged at 1,000 g for 5 minutes and incubated at 37°C for 1 day (Aβ 1-42; final concentration 100 μM).

After incubation Thioflavin T (ThT) (30 μM) solution in glycine-NaOH buffer (pH 8.5, 50 mM) was added into each well (250 μL/well), fluorescence was measured (ex = 440/20 nm, em = 485/20 nm) using a fluorescence plate reader. The inhibitory activity was calculated as the reduction of fluorescence with the following formula:

Inhibition (%) ={(F(Aβ)-F(Aβ+compound)}/{F(Aβ)-F(solvent + compound)} × 100

The IC_{50}s were calculated by a curve fitting program using the following equation. The data were obtained from two different experiments in triplicate.

Inhibition(x) = 100-100/ $\{1+(x/IC_{50})^n\}$,

x = Concentration of tested compound (M),

IC_{50} = (M),

n = Hill coefficient.

Representative compounds of Formula I have exhibited inhibitory activities (IC_{50}) ranging from 0.1 μM to greater than 100 μM in the foregoing assays.

The results of these assays for specific and representative compounds of the present invention are shown in Table 1 below.

Table 1. β-Amyloid Inhibitory Activity of Compounds of Formula I

Example No.	BASSR (IC_{50} = μM)	BASST (IC_{50} = μM)	BATYM (IC_{50} = μM)	BAPA (IC_{50} = μM)
1	10 (P), >100 (P) (6×), >100 (Q), >100 (R), >100 (S), 52 (T) >100 (Z)	2, 4, 30,10 (P) 3(Q) >100 (R) 11 (S), 11 (T) 6(Z)	50, 58.8 (P) 57.8 (Q)	60 (P), >100 (P) 86 (Q), >60 (R), >60 (S), 11 (T)
2	2.2, 4.1, 4.1, 12, 4.5	1, 1.5 (P)	6.52 (P)	70 (P)
3	4.5, 5, 5 (all 3 V-shaped) (P) 15 (ppt), 5 (Q)	2 (P) 3 (Q)	11.7 (P)	>60 (P)
4	30, >100 (3×)	3, 4, 8	26.3, 30.7	67
5	70, >100	4.5	10	74
6	15, 21, 20, 40	4, 1, 3	21.5	>60
7	18, 13, 12, 20	2	8.83	39
8	15, 15, 18, 15	3, >100	7.17	
9	20 (ppt), 30, 52, 40 (P)	1, 2 (P)	20.1, 28.2 (P) 38.6 (R)	75 (P)
10	70, 50	4	75.7	67
11	18 (ppt), 20 (ppt), 20 (2×), >100 (P) >100, 21, 30 (Q)	1, 1, 3 (P) 1, 0.8 (Q)	5.62 (P) 6.78 (Q)	23 (P) 9 (Q)
12	20 (4×)	1, 1	3.93	>60
13	21, >100, 20 (ppt), 15 (ppt), >100	0.9	6.41	6
14	18 (ppt), 8, 6 (ppt), 7 (ppt)	1.0	10.9	>10 (V-shaped)
15	100 (3×) P 100, 16 (V-shaped) 12, 15, 11 (Q)	1 (P) 1.2 (Q)	8.52 (P) 7.26 (Q) 7.07 (Q)	>60 (P) 7 (Q)

Table 1. β-Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC_{50} = μM)	BASST (IC_{50} = μM)	BATYM (IC_{50} = μM)	BAPA (IC_{50} = μM)
16	18, 7.5, 10 (P) 70, 32, 42 (Q)	3, 0, 3 (P) 1.1, 0.8, 0.6 (Q)	12 (P) 10.3 (Q)	13 (P)
17	>100 (ppt) (3×)	6.2	64.5	>60 (Q), 41 (R)
18	>100 (5×) (P)	30, >100 (P)	>100 (P)	9, >40, 53 (P), 12
19	3, 4, >100, 2.2	>100, 1, 1, 1.5	31.0, 34.0	>60, 43
20	4.2	6	68.6	22
21	3	4	62.7	26
22	3	9	>100	24
23	20	2	>100	17
24	>100	20	>100	91
25	>100	4	21.1	47
26	>100	1	>100	57
27	>100	3	19.8	74
28	>100	5	42.3	27
29	>100	4	38.1	30
30	30, 20	4, 2	75.3	38
31	>100	1	22.6	86
32	>100	1	29.2	96
33	>100	>100	>100	>10
34	45	3	45.0	48
35	>100	100	>100	154
36	>100	>100	>100	149
37	>100	0.8	30.2	25
38	20, 10 (V)	3	23.4	184
39	>100	20	>100	21
40	>100	3.0	>100	53
41	>100	5	49.7	42
42	>100	2	55.6	30
43	>100	0.3	24.2	63
44	>100	1	26.5	52
45	>100	1	21.5	32
46	>100	6	34.3	
47	>100	2	38.2	
48	25	10	>100	
49	>100	>100	>100	
50	>100	>100	>100	
51	85	0.8	39.1	

Table 1. β-Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC_{50} = μM)	BASST (IC_{50} = μM)	BATYM (IC_{50} = μM)	BAPA (IC_{50} = μM)
52	75	0.5	36.5	
53	>100	0.3	30.0	
54	>100	0.4	43.9	
55	12	2	5.1	101
56	>100	3	11.5	30
57	4.8	1.5	4.0	50
58	3.5	1	5.1	60
59	>100	>100	>100	3
60	>100	3	40.7	8
61	18, 7.5, 10	3, 0.3	12	13
62	>100	1.5	8.98	
63	15, 15, 18 (ppt)	1	9.43	45
64	>100	5	35	>100
65	60, 80	1.5	15.9	>100 (V-shaped)
66	>100 (ppt), >100 (ppt)	2.1	50.1	>100
67	41	4	13.3	>60
68	>100, >100	1	>100	110
69	2 (V-shaped), 3.5 (ppt)	0.8	11.7	58
70	20, 100	10	>100	65
71	>100	3		>60
72	40, 15, 12	2, 2.5	74.8	>60, >60
73	25, 35, 40	0.3	9.43	>60
74	6, 18, 19, 18	0.3, 0.5	8.36	>60
75	>100	2.2	46.2	>60
76	3	0.5	8.59	>60
77	18, 15	8, 0.3	9.49	>60
78	70	0.1	>100	8
79	3.1, 50, 38, 70, 70, 30, 40	1, 0.3, 0.3, 0.3	9.14	51
80	>100	4	24.8	>60
81	>100	15	48.4	73
82	>100, >100, >100	2, 0.3, 0.3		
83	>100	>100		9, 47, 29
84	>100	>100		5, 40, 21
85	>100	18		8, 77, 45

Table 1. β-Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC_{50} = μM)	BASST (IC_{50} = μM)	BATYM (IC_{50} = μM)	BAPA (IC_{50} = μM)
86	40	18		>10, 89, 37
87	>100	50		>10, 15, 32
88	>100	10		>10, 37, 27
116	>100, >100	18, 30		96
117	>100	3	61.3	>100
118	>100, >100	6		>60
119	>100	3		>60
120	>100	3		>60
121	>100, >100	1		
122	>100	2	>100	>60
123	>100 (3 ×), 14	3, 3	70.8	
	4, 18, >100,	3.2, 4 (Q)	85.2 (Q)	>60 (Q)
	>100 (Q)			
124	>100	10	62.7	
125	82	10	>100	80
126	>100, >100	4, 5	84	63
	30, 100 (Q)	10, 4 (Q)	73.9 (Q)	>60 (Q)
127	>100 (ppt)	10	>100	67
128	>100 (ppt) (4 ×)	10, 41, 6	75	60
	11, >100 (3 ×)			
	15, 20, 10, 7.5 (Q)	7, 3, 3 (Q)	>60 (Q)	>60 (Q)
	15, >100 (3 ×) Q			
129	1 (V-shaped) (2	10, 3, 2, 2	>100	>102
	×)			
	>100 (ppt)			
130	>100 (3 ×)	2, >100, 50	47.5	238
131	>100	10	93.5	>60
132	>100	10	>100	60
133	>100	>100	>100	>60
134	>100	2	36.5	>60
135	>100	1.2	31.2	>60
136	>100	3	>100	53
137	>100, >100	3		52
141	>100	7	56.7	>50
142	>100	2.1	26.9	55
143	>100 (4 ×)	40, 30	>100	2, >60, >60
144	15, 25	40	>100	114

Table 1. β-Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC_{50} = μM)	BASST (IC_{50} = μM)	BATYM (IC_{50} = μM)	BAPA (IC_{50} = μM)
145	10, 40, 30	4	56.8	9
146	>100	30	>100	>60
147	>100	10	93.4	>60
148	>100		>100	
149	>100	>100	>100	>60
150	>100	10	>100	76
151	>100, >100	5, >100	>100	108
154	>100	3, 30	70.8	
155	>100	3	44.6	
156			27.8	
157			25.9	

A letter in parentheses after particular value indicates the particular synthetic lot of the compound tested. The terms "P," "Q," "R," "S," "T," and "Z" designate different lots of the same compound. For example, 10 (P) indicates that compound tested was from Lot P. If no lot is specified, the lot of the compound was Lot P.

The abbreviation "ppt" means precipitate and indicates that a precipitate formed at the indicated concentration. In addition, the term "V-shaped" means that inhibition was observed followed by precipitation.

A value followed by a number and × (i.e., 4×) means that the compound was tested four times, and each time the result was the same.

The invention compounds have also shown good activity in standard in vivo assays commonly used to evaluate agents to treat diseases related to aggregation of amyloid proteins, especially Alzheimer's disease and other amyloidoses. In one assay, amyloid protein is induced into the spleen of mice by subcutaneous injections of silver nitrate, Freund's complete adjuvant, and an intravenous injection of amyloid enhancing factor. Silver nitrate is administered each day through Day 11. Test compounds are administered to the mice daily starting on Day 1 through Day 11. On Day 12, the animals are sacrificed, and the spleens are removed, histologically prepared, stained with Congo red, and the percent area of the spleen occupied by birefringent, Congo red-stained amyloid is

quantitated microscopically. Invention compounds evaluated in this test have inhibited splenic amyloid deposition by up to 70% relative to untreated controls.

Another in vivo assay in which the invention compounds have been evaluated uses transgenic mice. The mice bear a human β-amyloid precursor protein transgene with a prion promoter and are described by Hsiao et al., "Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice," *Science* 1966;274:99-102. These transgenic mice develop β-amyloid deposits at about 9 months of age. By 15 months, diffuse and compact senile plaques are abundant, primarily in the neocortex, olfactory bulb, and hippocampus. Invention compounds are administered orally to the mice beginning at the age of 8 months (just prior to the onset of amyloid deposits) and continuing for several months (up to about age 14-18 months). The animals are then sacrificed, and the brains are removed. The amount of amyloid in the brain is quantitated both histologically and biochemically. Invention compounds evaluated in this model have inhibited amyloid accumulation in the cortex and hippocampus by up to 49% relative to untreated controls.

The above data establishes that representative invention compounds are active in standard assays used to measure inhibition of protein aggregation. The compounds exhibit excellent specificity, for example, as shown in the BASST assay, as well as the BATYM and BAPA assays. The compounds are thus useful to clinically inhibit amyloid protein aggregation and to image amyloid deposits for diagnostic use. The compounds will be used in the form of pharmaceutical formulations, and the following examples illustrate typical compositions.

EXAMPLE 164

Tablet Formulation

Ingredient	Amount
Compound of Example 1	50 mg
Lactose	80 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

The compound of Example 1 is mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended in 6 mL of water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet. The tablets are administered to a patient at the rate of 1 to 4 each day for prevention of amyloid protein aggregation and treatment of Alzheimer's disease.

EXAMPLE 165

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 20.0 g of Compound No. 19 (Example 19). The mixture is stirred and the pH is adjusted to 5.5 with hydrochloric acid. The volume is adjusted to 1000 mL with water for injection. The solution is sterilized, filled into 5.0 mL ampoules, each containing 2.0 mL (40 mg of Compound No. 19), and sealed under nitrogen. The solution is administered by injection to a patient suffering from medullary carcinoma of the thyroid and in need of treatment.

EXAMPLE 166

Patch Formulation

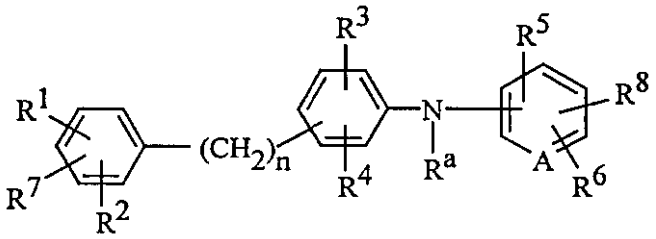
Ten milligrams of 2-{4-[3-(3,4-dichlorophenyl)propyl]phenylamino} benzoic acid is mixed with 1 mL of propylene glycol and 2 mg of acrylic-based polymer adhesive containing a resinous cross-linking agent. The mixture is applied to an impermeable backing (30 cm^2) and applied to the upper back of a patient for sustained release treatment of amyloid polyneuropathy.

The invention and the manner and process of making and using it, are now described in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

CLAIMS

What is claimed is:

1. A method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



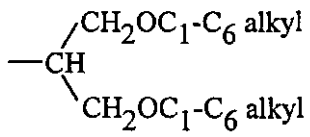
I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C(=O)C_1-C_6 alkyl;

n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, $-NH_2$, NR^bR^c, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NO_2$, $-OC_1$-C_{12} alkyl, -C_1-C_8 alkyl, $-CF_3$, -CN, $-OCH_2$ phenyl, $-OCH_2$-substituted phenyl, $-(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl, -CH=CH-phenyl, $-O(CH_2)_pNR^bR^c$, $-C(=O)NR^bR^c$, $-NHC(=O)R^b$, $-NH(CH_2)_pNR^bR^c$, $-N(C_1$-C_6alkyl$)(CH_2)_pNR^bR^c$,



;

R^8 is COOH, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, -C_1-C_6 alkyl, $-(CH_2)_m$-phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl,

imidazolyl, piperazinyl, 4-C_1-C_6 alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C_1-C_6 alkyl, -CF_3, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

2. The method of Claim 1 wherein

R^a is hydrogen;

n is 2; and

R^3 and R^4 are hydrogen.

3. The method of Claim 1 wherein

R^a is hydrogen;

R^3 and R^4 are hydrogen; and

n is 2 to 5 inclusive.

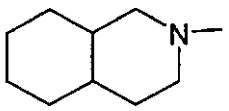
4. The method of Claim 1 wherein

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine, -$N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, -CF_3, phenyl, hydrogen, -OCH_2 phenyl, -$O(CH_2)_3N(CH_3)_2$, -O phenyl, -$O(CH_2)_7CH_3$, -$CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl,



, -$N[(CH_2)_3CH_3]_2$, substituted phenyl, -OCH_2- substituted phenyl, pyrrozolyl, or -N(phenyl)$_2$.

5. The method of Claim 1 wherein

R^a is hydrogen;

n is 3, 4, or 5;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine or hydrogen.

6. The method of Claim 1 wherein

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5, R^6, and R^8 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$, imidazolyl, -CN, fluorine, $-CH_3$, $-CF_3$, halogen, $-NH-C_1-C_6$ alkyl, $-N(C_1-C_6alkyl)_2$, $-NH_2$, or pyrrolyl.

7. The method of Claim 1 wherein

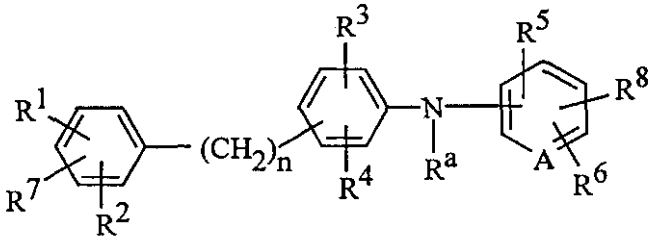
R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5 is $-CO_2H$.

8. A method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



I

wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

R^3 and R^4 are hydrogen;

R^1, R^7, and R^2 are independently chlorine, -$N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, -CF_3, phenyl, hydrogen, -OCH_2 phenyl, -$O(CH_2)_3N(CH_3)_2$, -O phenyl, -$O(CH_2)_7CH_3$, -$CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl, -$N[(CH_2)_3CH_3]_2$, substituted phenyl, -OCH_2-substituted phenyl, pyrazolyl, or -$N(phenyl)_2$;

R^5 and R^6 are independently hydrogen, -CO_2H, -NO_2, -OCH_3, imidazolyl, -CN, fluorine, -CH_3, -CF_3, or pyrrolyl;

R^8 is COOH or tetrazolyl;

or the pharmaceutically acceptable salts thereof.

9. The method of Claim 1 wherein the compound of Formula I is:

2-[[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

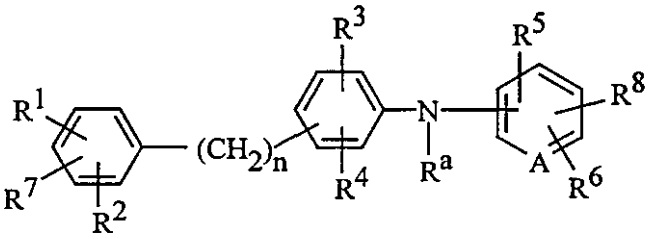
2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; or

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

10. A method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



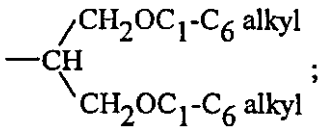
I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C($=O$)C_1-C_6 alkyl;

n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, $-NH_2$, NR^bR^c, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NO_2$, $-OC_1$-C_{12} alkyl, -C_1-C_8 alkyl, $-CF_3$, -CN, $-OCH_2$ phenyl, $-OCH_2$-substituted phenyl, $-(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl, -CH=CH-phenyl, $-O(CH_2)_pNR^bR^c$, -C($=O$)NR^bR^c, -NHC($=O$)R^b, $-NH(CH_2)_pNR^bR^c$, $-N(C_1$-C_6alkyl$)(CH_2)_pNR^bR^c$,



;

R^8 is COOH, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, -C_1-C_6 alkyl, $-(CH_2)_m$-phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C_1-C_6 alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C_1-C_6 alkyl, -CF_3, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

11. The method of Claim 10 wherein

R^a is hydrogen;

n is 2; and

R^3 and R^4 are hydrogen.

12. The method of Claim 10 wherein

R^a is hydrogen;

R^3 and R^4 are hydrogen; and

n is 2 to 5 inclusive.

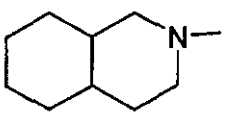
13. The method of Claim 10 wherein

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine, -$N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, -CF_3, phenyl, hydrogen, -OCH_2 phenyl, -$O(CH_2)_3N(CH_3)_2$, -O phenyl, -$O(CH_2)_7CH_3$, -$CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl,



, -$N[(CH_2)_3CH_3]_2$, substituted phenyl, -OCH_2-substituted phenyl, pyrazolyl, or -$N(phenyl)_2$.

14. The method of Claim 10 wherein

R^a is hydrogen;

n is 3, 4, or 5;

R^3 and R^4 are hydrogen; and

R^1, R^2, and R^7 are independently chlorine or hydrogen.

15. The method of Claim 10 wherein

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5 and R^6 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$, imidazolyl, -CN, fluorine, $-CH_3$, $-CF_3$, halogen, $-NH-C_1-C_6$ alkyl, $-N(C_1-C_6alkyl)_2$, $-NH_2$, or pyrrolyl.

16. The method of Claim 10 wherein

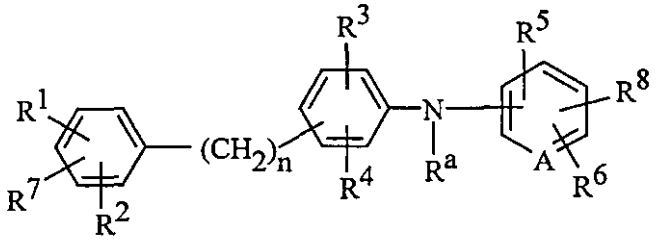
R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^8 is $-CO_2H$.

17. A method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



I

wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

R^3 and R^4 are hydrogen;

R^1, R^7, and R^2 are independently chlorine, -$N(CH_2CH_3)_2$, -OH, CH_3-, fluorine, -CF_3, phenyl, hydrogen, -OCH_2 phenyl, -$O(CH_2)_3N(CH_3)_2$, -O phenyl, -$O(CH_2)_7CH_3$, -$CH(CH_2OCH_2CH_3)_2$, pyrrolyl, -CH=CH-phenyl, -$N[(CH_2)_3CH_3]_2$, substituted phenyl, -OCH_2-substituted phenyl, pyrazolyl, or -$N(phenyl)_2$;

R^5 and R^6 are independently hydrogen, -CO_2H, -NO_2, -OCH_3, imidazolyl, -CN, fluorine, -CH_3, -CF_3, or pyrrolyl;

R^8 is COOH or tetrazolyl;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

18. The method of Claim 17 wherein the compound of Formula I is:

2-[[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4′-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; or

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

19. The compounds:

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid; or

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid.

20. The compounds:

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid.

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid; or

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid.

21. The compounds:

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid; or

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid.

22. The compounds:

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Aminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(4-Aminophenyl)phenylamino}benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid;

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid monohydrochloride;

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-(4-{3-[4-(1H-Pyrrol-1-yl)phenyl]propyl}phenylamino)benzoic acid;

2-{4-[3-(4-Piperidin-1-ylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid;

2-{4-[3-(3-Piperidin-1yl-phenyl)-propyl]-phenylamino}-benzoic acid;

{5-[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid;

{5-[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid;

3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}propanoic acid;

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}butanoic acid;

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]phenylamino}-5-methyl-benzoic acid;

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-methanesulofnamime;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitro-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

5-Amino-2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-[2-(1H-tetrazol-5-yl)-phenyl]-amine;

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid;

2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid;

2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dimethylamino-benzoic acid;

2-{4-[2-(3,5-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(3′,5′-Dichloro-3-methyl-biphenyl-4-ylamino)-benzoic acid;

2-(3′,5′-Dibromo-3-methyl-biphenyl-4-ylamino)-benzoic acid;

2-(4-1,3-Benzodioxol-5-yl-2-methyl-phenylamino)-benzoic acid;

2-(2,2′,4′-Trichloro-biphenyl-4-ylamino)-benzoic acid;

2-(2-Chloro-3′,4′-difluoro-biphenyl-4-ylamino)-benzoic acid;

2-(3′-Bromo-2-chloro-biphenyl-4-ylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,5-dimethoxy-benzoic acid;

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

3-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

4-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3-Methoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Bromo-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Fluoro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid;

2-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2,3-dihydro-1H-isoindol-5-ylamino]-benzoic acid; or

2-{4-[2-(3-Fluoro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid.

23. The compounds:

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid; or

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid.

24. The compounds:

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4′-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

25. 2-[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid or a pharmaceutically acceptable salt thereof.

26. 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}benzoic acid or a pharmaceutically acceptable salt thereof.

27. A compound which is selected from:

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-nitro-benzoic acid;

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid;

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-benzoic acid;

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenyl}-(2-methoxy-5-nitro-phenyl)-amine;

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-nitro-benzoic acid;

3-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monosodium;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monopotassium;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid calcium salt (1:1);

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoate-2-hydroxy-1,1-bis-hydroxymethyl-ethyl-ammonium;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{3-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{3-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(2,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(2-Hydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-benzoic acid;

2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid;

2-(3′,5′-Dichloro-biphenyl-4-ylamino)-benzoic acid;

4-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-2-methoxy-5-nitro-benzoic acid;

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-5-fluoro-benzoic acid;

5-Amino-2-{4-[5-(3,4-dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid;

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-C,C,C-trifluoro-methanesulfonamide;

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-benzenesulfonamide;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-5-dimethylamino-benzoic acid;

2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dipropylamino-benzoic acid;

5-Dibutylamino-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

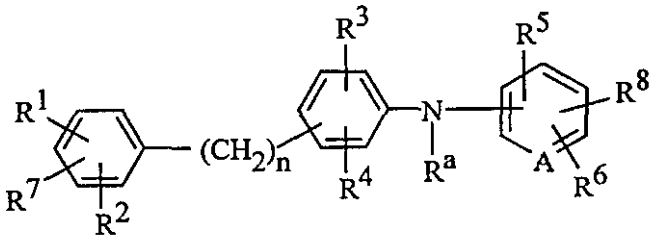
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-diethylamino-benzoic acid;

2,2'-[1,2-Ethanediylbis (4,1-phenyleneimino)]bis-benzoic acid; and

4-[3-[4-(Diethylamino)phenyl]propyl]-N-(2-methoxy-5-nitrophenyl)-benzinamine

28. A method of imaging amyloid deposits, the method comprising:

a. introducing into a patient a detectable quantity of a labeled compound having the Formula I or a pharmaceutically acceptable salt thereof:



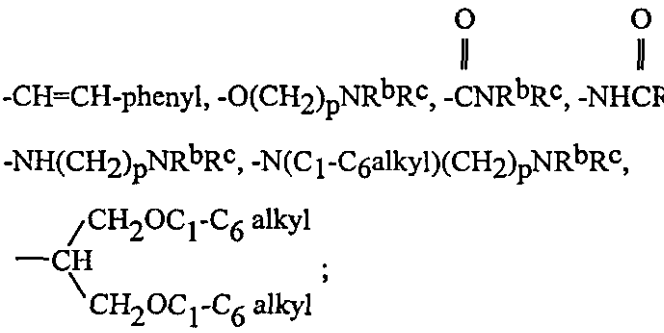
I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C(=O)C_1-C_6 alkyl;

n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, $-NH_2$, NR^bR^c, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NO_2$, $-OC_1$-C_{12} alkyl, -C_1-C_8 alkyl, $-CF_3$, -CN, $-OCH_2$ phenyl, $-OCH_2$-substituted phenyl, $-(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl,



-CH=CH-phenyl, $-O(CH_2)_pNR^bR^c$, $-CNR^bR^c$, $-NHCR^b$, $-NH(CH_2)_pNR^bR^c$, $-N(C_1$-C_6alkyl$)(CH_2)_pNR^bR^c$,

;

R^8 is COOH, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, -C_1-C_6 alkyl, $-(CH_2)_m$-phenyl, or R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C_1-C_6 alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C_1-C_6 alkyl, $-CF_3$, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

b. allowing sufficient time for the labeled compound to become associated with amyloid deposits; and

c. detecting the labeled compound associated with the amyloid deposits.

29. The method of Claim 28 wherein the patient has or is suspected to have Alzheimer's disease.

30. The method of Claim 28 wherein the labeled compound is a radio labeled compound.

31. The method of Claim 28 wherein the labeled compound is detected using MRI.

32. The compounds:

2-[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; and

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid.

33. A pharmaceutical formulation comprising a compound of Claim 19 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

34. A pharmaceutical formulation comprising a compound of Claim 20 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

35. A pharmaceutical formulation comprising a compound of Claim 21 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

36. A pharmaceutical formulation comprising a compound of Claim 22 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

37. A pharmaceutical formulation comprising a compound of Claim 23 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

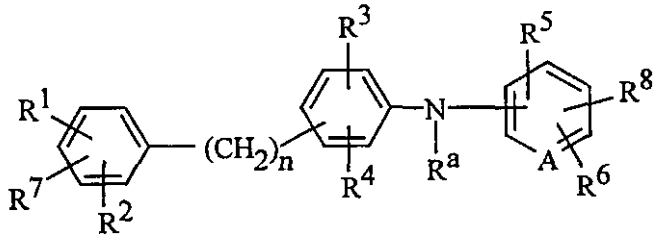
38. A pharmaceutical formulation comprising a compound of Claim 24 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

39. A pharmaceutical formulation comprising a compound of Claim 25 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

40. A pharmaceutical formulation comprising a compound of Claim 26 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

41. A pharmaceutical formulation comprising a compound of Claim 32 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

42. A compound of Formula I.



I

wherein

R^a is hydrogen, C_1-C_6 alkyl, or -C(C_1-C_6 alkyl);

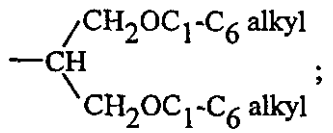
n is 0 to 5 inclusive;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, -OH, $-NH_2$, NR^bR^c, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, $-NO_2$, $-OC_1$-C_{12}

alkyl, -C_1-C_8 alkyl, -CF_3, -CN, -OCH_2 phenyl, -OCH_2-substituted phenyl, -$(CH_2)_m$-phenyl, -O-phenyl, -O-substituted phenyl,

-CH=CH-phenyl, -$O(CH_2)_pNR^bR^c$, -CNR^bR^c, -$NHCR^b$,

-$NH(CH_2)_pNR^bR^c$, -$N(C_1$-C_6alkyl$)(CH_2)_pNR^bR^c$,



;

R^8 is COOH, tetrazolyl, -SO_2R^d, or -$CONHSO_2R^d$;

R^b and R^c are independently hydrogen, -C_1-C_6 alkyl, -$(CH_2)_m$-phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C_1-C_6 alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C_1-C_6 alkyl, -CF_3, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2, when adjacent to one another, can be methylene-dioxy;

or the pharmaceutically acceptable salts thereof.

43. A pharmaceutical formulation comprising a compound of Claim 42 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
A61K 31/195
A61K 31/415 A61K 31/40
A61K 31/47 A61K 31/425
A61K 31/445 A61K 31/41
A61K 31/36 A61P 25/28
C07D233/54 C07D295/12
C07D207/327 C07D277/36

[12]发明专利申请公开说明书

[21]申请号 00808672.9

[43]公开日 2002年11月6日

[11]公开号 CN 1378446A

[22]申请日 2000.5.31 [21]申请号 00808672.9

[30]优先权

[32]1999.6.10 [33]US [31]60/138,550

[86]国际申请 PCT/US00/15071 2000.5.31

[87]国际公布 WO00/76489 英 2000.12.21

[85]进入国家阶段日期 2001.12.7

[71]申请人 华纳一兰伯特公司

地址 美国新泽西州

共同申请人 山之内制药株式会社

[72]发明人 C·E·奥吉利一沙弗兰
M·R·巴维安 C·F·比格
S·A·格拉斯 八谷俊一郎
J·S·基利 木村武德 赖英杰
A·T·沙克 M·J·苏托
L·C·沃克 安永智之

庄 埝

[74]专利代理机构 上海专利商标事务所

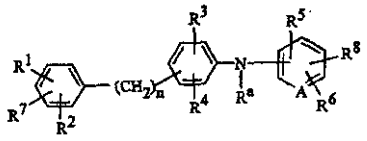
代理人 陈剑华

权利要求书19页 说明书88页 附图0页

[54]发明名称 抑制淀粉样蛋白聚集和使淀粉样沉积物成象的方法

[57]摘要

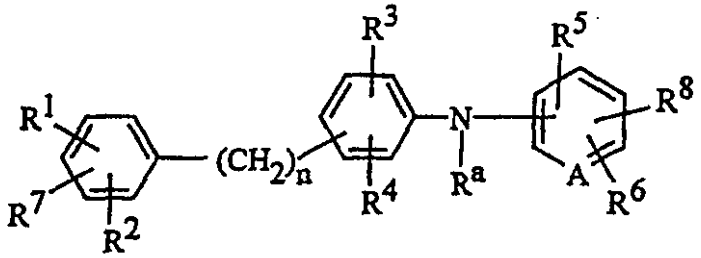
本发明提供一种用式I化合物治疗阿尔茨海默病的方法;本发明还提供一种用式I化合物抑制淀粉样蛋白聚集的方法和一种将淀粉样沉积物成象的方法以及新颖的式I化合物。



I

ISSN1008-4274

1. 治疗阿尔茨海默病的方法，该方法包括将治疗有效量的式 I 化合物或其药用盐给药于阿尔茨海默病患者：



I

式中，

R^a 为氢、C_1-C_6 烷基或-CO-C_1-C_6 烷基；

n 为 0－5；

R^1、R^2、R^3、R^4、R^5、R^6 和 R^7 独立地表示氢、卤素、-OH、$-NH_2$、NR^bR^c、-COOH、$-CO_2C_1$-C_6 烷基、$-NO_2$、$-OC_1$-C_{12} 烷基、$-C_1$-C_8 烷基、$-CF_3$、-CN、$-OCH_2$ 苯基、$-OCH_2$-取代的苯基、$-(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、$-O(CH_2)_pNR^bR^c$、$-CO-NR^bR^c$、$-NHCO-R^b$、$-NH(CH_2)_pNR^bR^c$、$-N(C_1$-C_6 烷基$)(CH_2)_pNR^bR^c$、$-CH(CH_2OC_1$-C_6 烷基$)_2$；

R^8 为 COOH、四唑基、$-SO_2R^d$ 或 $-CONHSO_2R^d$；

R^b 和 R^c 独立地表示氢、$-C_1$-C_6 烷基、$-(CH_2)_m$-苯基或 R^b 和 R^c 与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4－C_1-C_6 烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环；

R^d 为氢、$-C_1$-C_6 烷基、$-CF_3$ 或苯基；

m 为 0－5；

p 为 1－5；

A 为 CH 或 N；

R^1 和 R^2 在彼此相邻时可以是甲二氧基。

2. 如权利要求 1 所述的方法，其中，

R^a 为氢；

n 为 2；

R^3 和 R^4 为氢。

3. 如权利要求 1 所述的方法，其中，

R^a 为氢；

R^3和R^4为氢;

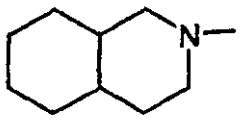
n为2-5。

4. 如权利要求1所述的方法，其中，

R^a为氢;

n为2;

R^3和R^4为氢;

R^1、R^2和R^7独立地表示氯、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、  、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N(苯基)_2$。

5. 如权利要求1所述的方法，其中，

R^a为氢;

n为3、4或5;

R^3和R^4为氢;

R^1、R^2和R^7独立地表示氯或氢。

6. 如权利要求1所述的方法，其中，

R^a为氢;

n为2;

R^3和R^4为氢;

R^5、R^6和R^8独立地表示氢、$-CO_2H$、$-NO_2$、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$、卤素、$-NH-C_1-C_6$烷基、$-N(C_1-C_6烷基)_2$、$-NH_2$或吡咯基。

7. 如权利要求1所述的方法，其中，

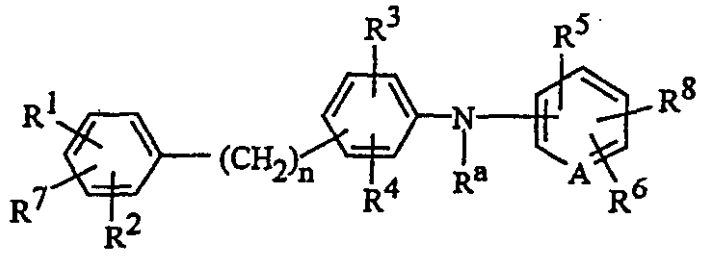
R^a为氢;

n为2;

R^3和R^4为氢;

R^5为$-CO_2H$。

8. 治疗阿尔茨海默病的方法，该方法包括将治疗有效量的式I化合物或其药用盐给药于阿尔茨海默病患者:



I

式中，

R^a为氢；

n为1-5；

R^3和R^4为氢；

R^1、R^2和R^7独立地表示氯、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O-苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N(苯基)_2$；

R^5和R^6独立地表示氢、$-CO_2H$、$-NO_2$-、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$或吡咯基；

R^8为COOH或四唑基。

9. 如权利要求1所述的方法，其中，所述式I化合物是

2-〔〔4-〔2-(3,4-二氯苯基)乙基〕苯基〕氨基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔4-(3,4-二氯苯基)乙基〕苯氨基}-4-甲氧基-5-硝基苯甲酸；

2-{4-〔2-(3,4-二羟基苯基)乙基〕苯氨基}苯甲酸；

2-{4-〔2-(4-二丁基氨基苯基)乙基〕苯氨基}苯甲酸；

2-{4-〔2-(3,4,5-三羟基苯基)乙基〕苯氨基}苯甲酸；

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}-4-甲氧基-5-硝基苯甲酸；

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}-4-咪唑-1-基-5-硝基苯甲酸；

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}苯甲酸；

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}苯甲酸；

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}-3,5-二硝基苯甲酸；

2-{4-〔5-(3,4-二氯苯基)戊基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔5-(3,4-二氯苯基)戊基〕苯氨基}-4-甲氧基-5-硝基苯甲酸；

2－〔4－(3,4－二氯苄基)苯氨基〕苯甲酸;

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氟苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}苯甲酸;

2－〔4－(2－联苯－4－基乙基)苯氨基〕－5－硝基苯甲酸;

5－硝基－2－(4－苯乙基苯氨基)苯甲酸;

2－(4－苯乙基苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲氧基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}对苯二甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲基苯甲酸;

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}间苯二甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲磺酰基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－咪唑－1－基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－硝基苯甲酸;

5－氰基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4,6－二氟苯甲酸;

6－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－2,3－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3,5－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－吡咯－1－基苯甲酸;

2－{4－〔2－(4－苄氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3－二甲基氨基丙氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－（4－辛氧基苯基）乙基〕苯氨基}苯甲酸;

2－（4－{2－〔4－（2－乙氧基－1－乙氧基甲基乙基）苯基〕乙基}苯氨基）苯甲酸;

2－{4－〔2－（4－吡咯－1－基苯基）乙基〕苯氨基}苯甲酸;

2－{4－〔2－（4－苯乙烯基苯基）乙基〕苯氨基}苯甲酸;

2－{4－〔2－（4－二丁基氨基苯基）乙基〕苯氨基}苯甲酸;

2－{4－〔2－（4'－乙基联苯－4－基）乙基〕苯氨基}苯甲酸;

2－{4－〔2－（4－辛基苯基）乙基〕苯氨基}苯甲酸;

2－（4－{2－〔3－（3,5－二氯苯氧基）苯基〕乙基}苯氨基）苯甲酸;

2－（4－{2－〔4－（2－氯－6－氟－苄氧基）苯基〕乙基}苯氨基）苯甲酸;

2－{4－〔2－（4－吡唑－1－基苯基）乙基〕苯氨基}苯甲酸;

2－{4－〔2－（4－二苯基氨基苯基）乙基〕苯氨基}苯甲酸;

2－（4－{2－〔4－（3,4－二氯苄氧基）苯基〕乙基}苯氨基）苯甲酸;

2－{4－〔2－（3,4－二氯苯基）乙基〕苯氨基}－5－氨基苯甲酸;

2－{4－〔2－（3,4－二氯苯基）乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－（3,4－二氯苯基）〕苯氨基}－5－硝基苯甲酸;

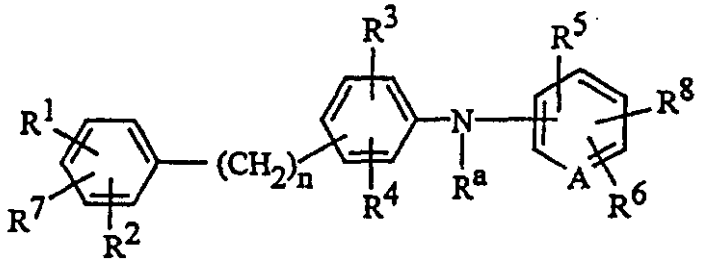
2－{4－〔3－（3,4－二氯苯基）丙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－（3,4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸;

2－〔〔4－〔2－（4－氯－3－三氟甲基苯基）乙基〕苯基}氨基苯甲酸;

2－〔4－（3,4－二氯苯基）苯基〕氨基苯甲酸。

10. 抑制淀粉样蛋白聚集成淀粉样沉积物的方法，该方法包括将淀粉样蛋白聚集抑制量的式I化合物或其药用盐给药于需要抑制淀粉样蛋白聚集的患者:



I

式中，

R^a为氢、C_1-C_6烷基或-CO-C_1-C_6烷基;

n为0－5;

R^1、R^2、R^3、R^4、R^5、R^6和R^7独立地表示氢、卤素、-OH、-NH_2、NR^bR^c、-COOH、-CO_2C_1-C_6烷基、-NO_2、-OC_1-C_{12}烷基、-C_1-C_8烷基、-CF_3、-CN、

$-OCH_2$苯基、$-OCH_2$-取代的苯基、$-(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、$-O(CH_2)_pNR^bR^c$、$-CO-NR^bR^c$、$-NHCO-R^b$、$-NH(CH_2)_pNR^bR^c$、$-N(C_1-C_6$烷基$)(CH_2)_pNR^bR^c$、$-CH(CH_2OC_1-C_6$烷基$)_2$;

R^8为 COOH、四唑基、$-SO_2R^d$或$-CONHSO_2R^d$;

R^b和R^c独立地表示氢、$-C_1-C_6$烷基、$-(CH_2)_m$-苯基或R^b和R^c与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4-C_1-C_6烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环;

R^d为氢、$-C_1-C_6$烷基、$-CF_3$或苯基;

m 为 0-5;

p 为 1-5;

A 为 CH 或 N;

R^1和R^2在彼此相邻时可以是甲二氧基。

11. 如权利要求 10 所述的方法，其中，

R^a为氢;

n 为 2;

R^3和R^4为氢。

12. 如权利要求 10 所述的方法，其中，

R^a为氢;

R^3和R^4为氢;

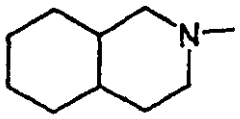
n 为 2-5。

13. 如权利要求 10 所述的方法，其中，

R^a为氢;

n 为 2;

R^3和R^4为氢;

R^1、R^2和R^7独立地表示氯、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O 苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、  、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N($苯基$)_2$。

14. 如权利要求 10 所述的方法，其中，

R^a为氢;

n 为 3、4 或 5;

R^3和R^4为氢;

R^1、R^2和R^7独立地表示氟或氢。

15. 如权利要求10所述的方法，其中，

R^a为氢;

n为2;

R^3和R^4为氢;

R^5和R^6独立地表示氢、$-CO_2H$、$-NO_2$、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$、卤素、$-NH-C_1-C_6$烷基、$-N(C_1-C_6$烷基$)_2$、$-NH_2$或吡咯基。

16. 如权利要求10所述的方法，其中，

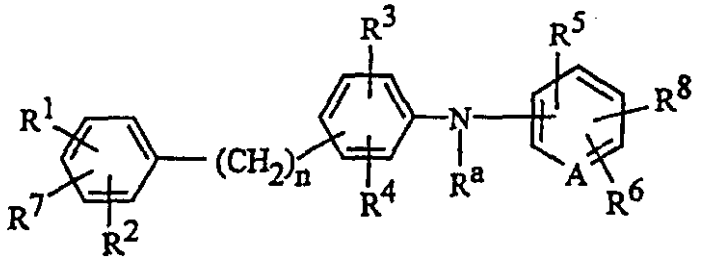
R^a为氢;

n为2;

R^3和R^4为氢;

R^8为$-CO_2H$。

17. 抑制淀粉样蛋白聚集成淀粉样沉积物的方法，该方法包括将淀粉样蛋白聚集抑制量的式I化合物或其药用盐给药于需要抑制淀粉样蛋白聚集的患者:



I

式中，

R^a为氢;

n为1-5;

R^3和R^4为氢;

R^1、R^2和R^7独立地表示氟、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O-苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N($苯基$)_2$;

R^5和R^6独立地表示氢、$-CO_2H$、$-NO_2-$、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$或吡咯基;

R^8为COOH或四唑基;

A为CH或N;

R^1和R^2在彼此相邻时可以是甲二氧基。

18. 如权利要求17所述的方法，其中，所述式I化合物是：

2-〔〔4-〔2-(3,4-二氯苯基)乙基〕苯基〕氨基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔4-(3,4-二氯苯基)乙基〕苯氨基}-4-甲氧基-5-硝基苯甲酸；

2-{4-〔2-(3,4-二羟基苯基)乙基〕苯氨基}苯甲酸；

2-{4-〔2-(4-二丁基氨基苯基)乙基〕苯氨基}苯甲酸；

2-{4-〔2-(3,4,5-三羟基苯基)乙基〕苯氨基}苯甲酸；

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}-4-甲氧基-5-硝基苯甲酸；

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}-4-咪唑-1-基-5-硝基苯甲酸；

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}苯甲酸；

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}苯甲酸；

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}-3,5-二硝基苯甲酸；

2-{4-〔5-(3,4-二氯苯基)戊基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔5-(3,4-二氯苯基)戊基〕苯氨基}-4-甲氧基-5-硝基苯甲酸；

2-〔4-(3,4-二氯苄基)苯氨基〕苯甲酸；

2-{4-〔2-(3,4-二甲基苯基)乙基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-硝基苯甲酸；

2-{4-〔2-(4-氯-3-三氟甲基苯基)乙基〕苯氨基}苯甲酸；

2-〔4-(2-联苯-4-基乙基)苯氨基〕-5-硝基苯甲酸；

5-硝基-2-(4-苯乙基苯氨基)苯甲酸；

2-(4-苯乙基苯氨基)苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-甲氧基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}对苯二甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-甲基苯甲酸；

4-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}间苯二甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-甲磺酰基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-咪唑-1-基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-6-硝基苯甲酸；

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-4-硝基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－硝基苯甲酸;

5－氯基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4,6－二氟苯甲酸;

6－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－2,3－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3,5－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－吡咯－1－基苯甲酸;

2－{4－〔2－(4－苄氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3－二甲基氨基丙氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(2－乙氧基－1－乙氧基甲基乙基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡咯－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯乙烯基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4'－乙基联苯－4－基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔3－(3,5－二氯苯氧基)苯基〕乙基}苯氨基)苯甲酸;

2－(4－{2－〔4－(2－氯－6－氟－苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡唑－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二苯基氨基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3,4－二氯苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－〔〔4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯基〕氨基苯甲酸;

2－〔4－(3,4－二氯苯基)苯基〕氨基苯甲酸.

19. 下述化合物:

2－{4－〔4－(3,4－二氯苯基)乙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸;

2－{4－〔2－(3,4－二羟基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4,5－三羟基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸;

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸;

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}苯甲酸.

20. 下述化合物:

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－3,5－二硝基苯甲酸;

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸;

2－〔4－(3,4－二氯苄基)苯氨基〕苯甲酸;

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}苯甲酸;

2－〔4－(2－联苯－4－基乙基)苯氨基〕－5－硝基苯甲酸;

5－硝基－2－(4－苯乙基苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－氨基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)〕苯氨基}－5－硝基苯甲酸.

21. 下述化合物:

2－(4－苯乙基苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲氧基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}对苯二甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}间苯二甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲磺酰基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－咪唑－1－基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－硝基苯甲酸;

22. 下述化合物:

5－氯基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4,6－二氟苯甲酸;

6－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－2,3－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3,5－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－三氟甲基苯甲酸;

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－硝基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－硝基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－氨基苯基)苯氨基}苯甲酸;

2－{4－〔2－(4－二丙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐一水和物;

2－{4－〔3－(3－二丙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二甲基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－乙氨基苯基)丙基〕苯氨基}苯甲酸;

2－(N－{4－〔3－(4－二乙基氨基苯基)丙基〕苯基}－N－乙氨基)苯甲酸;

2－{4－〔2－(3－二苄基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－二甲基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－（4－乙酰氨基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（3－乙酰氨基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（3－二丙基氨基苯基）乙基〕苯氨基}苯甲酸一盐酸盐；

2－{4－〔2－（3－二丁基氨基苯基）乙基〕苯氨基}苯甲酸一盐酸盐；

2－{4－〔3－（4－乙酰氨基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（3－乙酰氨基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔2－（3－二乙基氨基苯基）乙基〕苯氨基}苯甲酸一盐酸盐；

2－{4－〔2－（3－哌啶－1－基苯基）乙基〕苯氨基}苯甲酸一盐酸盐；

2－{4－〔3－（4－二丙基氨基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（4－二丁基氨基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（3－二丁基氨基苯基）丙基〕苯氨基}苯甲酸；

2－（4－{3－〔4－（1H－吡咯－1－基）苯基〕丙基}苯氨基）苯甲酸；

2－{4－〔3－（4－哌啶－1－基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（4－二乙基氨基甲酰基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（4－羧基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（4－二乙基氨基甲基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（4－丙氨基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（3－丙氨基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（4－吡咯烷－1－基苯基）丙基〕苯氨基}苯甲酸；

2－{4－〔3－（3－哌啶－1－基苯基）丙基〕苯氨基}苯甲酸；

{5－〔（1－丁基－1，2，3，4－四氢－6－喹啉基）亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸；

{5－〔（1－丁基－2，3－二氢－1H－吲哚－5－基）亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸；

3－{5－〔（1－丁基－1，2，3，4－四氢喹啉－6－基）亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}丙酸；

4－{5－〔（1－丁基－1，2，3，4－四氢喹啉－6－基）亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸；

2－{4－〔3－（3，4－二氯苯基）丙基〕苯氨基}－5－甲基苯甲酸；

N－（2－{4－〔3－（3，4－二氯苯基）丙基〕苯氨基}苯甲酰基）甲磺酰胺；

2－{4－〔2－（3，4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸；

2－〔4－（2－联苯－4－基乙基）苯氨基〕－5－硝基苯甲酸；

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

5－氨基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基)苯甲酸;

5－硝基－2－(4－苯乙基苯氨基)苯甲酸;

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

{4－〔2－(3,4－二氯苯基)乙基〕苯基}－〔2－(1H－四唑－5－基)苯基〕胺;

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－(4－苯乙基苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－氯苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}烟酸;

2－{4－〔2－(3－氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(4－氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲基苯甲酸;

2－{4－〔2－(2－氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(2,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－三氟甲基苯甲酸;

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－二甲基氨基苯甲酸;

2－{4－〔2－(3,5－二氯苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔(4aS,8aR)－4－(八氢异喹啉－2－基)苯基〕乙基}苯氨基)苯甲酸;

2－(3',5'－二氯－3－甲基联苯－4－基氨基)苯甲酸;

2－(3',5'－二溴－3－甲基联苯－4－基氨基)苯甲酸;

2－(4－1,3－苯并间二氧杂环戊烯－5－基－2－甲基苯氨基)苯甲酸;

2－(2,2',4'－三氯联苯－4－基氨基)苯甲酸;

2－(2－氯－3',4'－二氟联苯－4－基氨基)苯甲酸;

2－(3'－溴－2－氟联苯－4－基氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

3－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

5－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}间苯二甲酸

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4,5－二甲氧基苯甲酸;

2－{4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基}－3－硝基苯甲酸;

3－{4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基}苯甲酸;

5－{4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基}间苯二甲酸;

2－{4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基}苯甲酸;

4－(4－{2－〔(4aS,8aR)－4－(八氢异喹啉－2－基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}－5－甲氧基苯甲酸;

2－{4－〔2－(3－甲氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－溴苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－氟苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲氧基苯甲酸;

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}烟酸 ;

2－〔2－(4－氟－3－三氟甲基苯基)－2,3－二氢－1H－异吲哚－5－基氨基〕苯甲酸;

2－{4－〔2－(3－氟－4－甲基苯基)乙基〕苯氨基}苯甲酸.

23. 下述化合物:

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－吡咯－1－基苯甲酸;

2－{4－〔2－(4－苄氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3－二甲基氨基丙氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(2－乙氧基－1－乙氧基甲基乙基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡咯－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯乙烯基苯基)乙基〕苯氨基}苯甲酸.

24. 下述化合物:

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4'－乙基联苯－4－基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔3－(3,5－二氯苯氧基)苯基〕乙基}苯氨基)苯甲酸;

2－(4－{2－〔4－(2－氯－6－氟－苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡唑－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二苯基氨基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3,4－二氯苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－氨基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－〔4－(3,4－二氯苯基)苯基〕氨基苯甲酸.

25. 2－〔4－〔2－(3,4－二氯苯基)乙基〕苯基〕氨基苯甲酸或其药用盐.

26. 2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酸或其药用盐.

27. 化合物，选自:

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}－5－硝基苯甲酸;

4－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

4－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}－3－甲氧基苯甲酸;

2－{4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基}－5－甲氧基苯甲酸;

{4－〔2－(3－氯－4－甲基苯基)乙基〕苯基}－(2－甲氧基－5－硝基苯基)胺;

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}－3－硝基苯甲酸;

3－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二甲氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸一钠;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸一钾;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸钙盐(1:1);

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸2－羟基－1,1－二羟甲基乙铵;

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－5－甲氧基苯甲酸;

2－{4－〔2－(3,4－二氟苯基)乙基〕苯氨基}苯甲酸;

2－{3－〔2－(4－氯苯基)乙基〕苯氨基}苯甲酸;

2－{3－〔2－(3,4－二甲基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(2,4－二甲氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(2－氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(2－羟基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－氯苯基)乙基〕苯氨基}苯甲酸;

2－〔4－(2－联苯－4－基乙基)苯氨基〕苯甲酸;

2－{4－〔2－(2,4－二氯苯基)乙基〕苯氨基}苯甲酸;

3－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基)苯甲酸;

2－{4－〔2－(3,4,5－三甲氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}苯甲酸;

2－(3',5'－二氯联苯－4－基氨基)苯甲酸;

4－{4－〔3－(3,4－二氯苯基)乙基〕苯氨基}－2－甲氧基－5－硝基苯甲酸;

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}－5－氟苯甲酸;

5－氨基－2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}苯甲酸;

N－(2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酰基)－C,C,C－三氟甲磺酰胺;

N－(2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酰基)苯磺酰胺;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}间苯二甲酸

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－三氟甲基苯甲酸;

2－({4－〔2－(3,4－二氯苯基)乙基〕苯基}甲氨基}－5－二甲基氨基苯甲酸;

2－({4－〔2－(3,4－二氯苯基)乙基〕苯基}甲氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－二丙基氨基苯甲酸;

5－二丁基氨基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

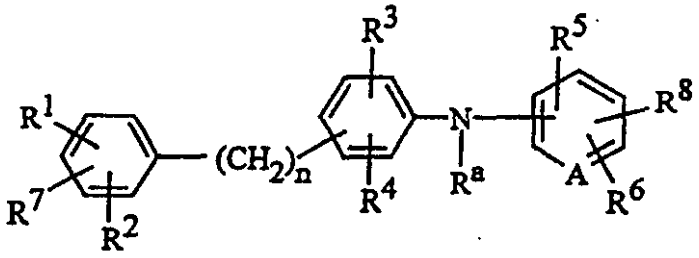
2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－二乙基氨基苯甲酸;

2,2'－〔1,2－乙二基二(4,1－亚苯基亚氨基)〕二-苯甲酸;

4－〔3－〔4－(二乙基氨基)苯基〕丙基)－N－(2－甲氧基－5－硝基苯基)苯胺.

28. 将淀粉样沉积物成象的方法，该方法包括:

a. 将可检测量的式 I 的标记化合物或其药用盐导入患者：



I

式中，

R^a 为氢、C_1-C_6 烷基或-CO-C_1-C_6 烷基；

n 为 0－5；

R^1、R^2、R^3、R^4、R^5、R^6 和 R^7 独立地表示氢、卤素、-OH、$-NH_2$、NR^bR^c、-COOH、$-CO_2C_1$-C_6 烷基、$-NO_2$、$-OC_1$-C_{12} 烷基、$-C_1$-C_8 烷基、$-CF_3$、-CN、$-OCH_2$ 苯基、$-OCH_2$-取代的苯基、$-(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、$-O(CH_2)_pNR^bR^c$、$-CO-NR^bR^c$、$-NHCO-R^b$、$-NH(CH_2)_pNR^bR^c$、$-N(C_1$-C_6 烷基$)(CH_2)_pNR^bR^c$、$-CH(CH_2OC_1$-C_6 烷基$)_2$；

R^8 为 COOH、四唑基、$-SO_2R^d$ 或 $-CONHSO_2R^d$；

R^b 和 R^c 独立地表示氢、$-C_1$-C_6 烷基、$-(CH_2)_m$-苯基或 R^b 和 R^c 与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4－C_1-C_6 烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环；

R^d 为氢、$-C_1$-C_6 烷基、$-CF_3$ 或苯基；

m 为 0－5；

p 为 1－5；

A 为 CH 或 N；

R^1 和 R^2 在彼此相邻时可以是甲二氧基；

b. 让标记化合物以足够的时间与淀粉样沉积物结合；

c. 检测与淀粉样沉积物结合的标记化合物。

29. 如权利要求 28 所述的方法，其中，患者患有或被怀疑患有阿尔茨海默病。

30. 如权利要求 28 所述的方法，其中，所述标记化合物是放射性标记的化合物。

31. 如权利要求 28 所述的方法，其中，所述标记化合物用 MRI 检测。

32. 下述化合物：

2－〔4－〔2－（3,4－二氯苯基）乙基〕苯基〕氨基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酸 ;

2－〔4－〔2－(4－氟－3－三氟甲基苯基)乙基〕苯基〕氨基苯甲酸;

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}苯甲酸。

33. 药剂，包含权利要求 19 的化合物和与之相配的药用稀释剂、赋形剂或载体。

34. 药剂，包含权利要求 20 的化合物和与之相配的药用稀释剂、赋形剂或载体。

35. 药剂，包含权利要求 21 的化合物和与之相配的药用稀释剂、赋形剂或载体。

36. 药剂，包含权利要求 22 的化合物和与之相配的药用稀释剂、赋形剂或载体。

37. 药剂，包含权利要求 23 的化合物和与之相配的药用稀释剂、赋形剂或载体。

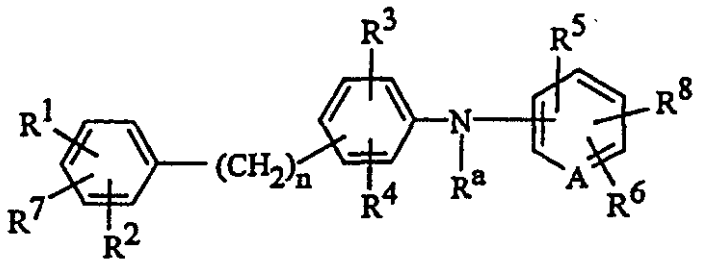
38. 药剂，包含权利要求 24 的化合物和与之相配的药用稀释剂、赋形剂或载体。

39. 药剂，包含权利要求 25 的化合物和与之相配的药用稀释剂、赋形剂或载体。

40. 药剂，包含权利要求 26 的化合物和与之相配的药用稀释剂、赋形剂或载体。

41. 药剂，包含权利要求 32 的化合物和与之相配的药用稀释剂、赋形剂或载体。

42. 式 I 化合物或其药用盐:



I

式中，

R^a 为氢、C_1-C_6 烷基或-CO-C_1-C_6 烷基;

n 为 0－5;

R^1、R^2、R^3、R^4、R^5、R^6 和 R^7 独立地表示氢、卤素、-OH、-NH_2、NR^bR^c、

-COOH、-CO_2C_1-C_6烷基、-NO_2、-OC_1-C_{12}烷基、-C_1-C_8烷基、-CF_3、-CN、-OCH_2苯基、-OCH_2-取代的苯基、-$(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、-$O(CH_2)_pNR^bR^c$、-CO-NR^bR^c、-NHCO-R^b、-$NH(CH_2)_pNR^bR^c$、-N(C_1-C_6烷基)$(CH_2)_pNR^bR^c$、-$CH(CH_2OC_1$-C_6烷基$)_2$;

R^8为COOH、四唑基、-SO_2R^d或-$CONHSO_2R^d$;

R^b和R^c独立地表示氢、-C_1-C_6烷基、-$(CH_2)_m$-苯基或R^b和R^c与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4-C_1-C_6烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环;

R^d为氢、-C_1-C_6烷基、-CF_3或苯基;

m为0-5;

p为1-5;

A为CH或N;

R^1和R^2在彼此相邻时可以是甲二氧基。

43. 药剂，包含权利要求42的化合物和与之相配的药用稀释剂、赋形剂或载体。

抑制淀粉样蛋白聚集和使淀粉样沉积物成象的方法

发明领域

本发明涉及抑制淀粉样的蛋白聚集和使淀粉样沉积物成象的方法。更具体地说，本发明涉及抑制淀粉样蛋白聚集以治疗阿尔茨海默病。

发明背景

淀粉样变性是一种以各种不溶性原纤蛋白在患者组织中积聚为特征的疾病。包含积聚物或沉积物的原纤蛋白被称作淀粉样蛋白。虽然沉积物中发现的具体蛋白或肽有所不同，但原纤形态学和大量β-片状二级结构则是许多类型的淀粉样变性所共同存在的。淀粉样沉积物通过淀粉样蛋白的聚集、然后通过聚集物和/或淀粉样蛋白的进一步结合而形成。

多种疾病已显示有淀粉样沉积物的存在，它们有其特定的关联蛋白，这些疾病例如有布氏杆菌病、Muckle-Wells 氏综合征、自发性淀粉样变性、淀粉样多神经病、淀粉样心肌病、全身性老年性淀粉样变性、具有淀粉样变性的遗传性小脑出血、阿尔茨海默病、唐氏先天愚征、绵羊瘙痒病、痉挛性假硬化症、苦鲁病、Gerstmann-Straussler-Scheinker 氏综合征、甲状腺髓样癌，透析患者中的单独心房淀粉样蛋白、β_2-微球蛋白淀粉样蛋白，包涵体肌炎、肌肉消耗性疾病中的β_2-淀粉样沉积物、镰形细胞贫血、帕金森氏病和胰岛糖尿病 II 型胰岛瘤。

阿尔茨海默病是一种退化性大脑病症，其临床特征是，记忆、认知、推理、判断和情绪稳定性的进行性丧失，逐渐导致精神衰退，最终死亡。由于阿尔茨海默病和相关的退化性大脑病症是日益老化的人口的主要医学问题，因此，需要新的疾病的诊断和治疗方法。

人们一直努力寻求一种简便的非损伤性的对患者的淀粉样沉积物进行检测和定量的方法。目前，对淀粉样沉积物的检测包括活组织检查或尸体解剖材料的组织学分析。二种方法都有重大缺陷。例如，尸体解剖只能用于死后诊断。

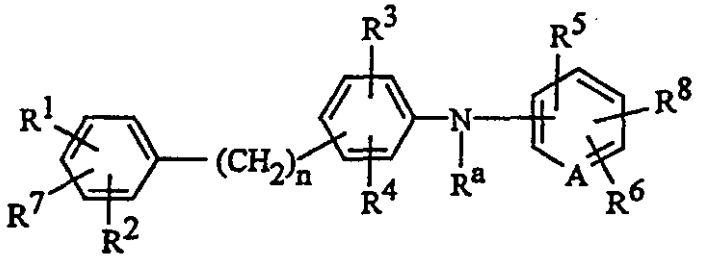
将体内淀粉样沉积物直接成象很困难，因为沉积物与正常的组织有许多相同的物理特性，即，密度和含水量。以往的直接用磁共振（MRI）和计算机辅助段层摄影法（CAT）将淀粉样沉积物成象的尝试令人失望，只能在某些顺利

条件下检测出淀粉样沉积物。此外，用抗体、血清淀粉样淀粉样 P 蛋白或其它探测分子将淀粉样沉积物标记的努力在组织周边方面提供了一些选择性，但对组织内部的成象性差。

因此，一种非损伤性的对患者的淀粉样沉积物进行成象和定量的方法将是有用的。此外，可抑制淀粉样蛋白聚集成淀粉样沉积物的化合物将是有用的。

发明的概述

本发明提供一种治疗阿尔茨海默病的方法，该方法包括将治疗有效量的式 I 化合物或其药用盐给药于阿尔茨海默病患者：



I

式中，

R^a 为氢、C_1-C_6 烷基或-CO-C_1-C_6 烷基；

n 为 0－5；

R^1、R^2、R^3、R^4、R^5、R^6 和 R^7 独立地表示氢、卤素、-OH、$-NH_2$、NR^bR^c、-COOH、$-CO_2C_1$-C_6 烷基、$-NO_2$、$-OC_1$-C_{12} 烷基、$-C_1$-C_8 烷基、$-CF_3$、-CN、$-OCH_2$ 苯基、$-OCH_2$-取代的苯基、$-(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、$-O(CH_2)_pNR^bR^c$、$-CO-NR^bR^c$、$-NHCO-R^b$、$-NH(CH_2)_pNR^bR^c$、$-N(C_1$-C_6 烷基$)(CH_2)_pNR^bR^c$、$-CH(CH_2OC_1$-C_6 烷基$)_2$；

R^8 为 COOH、四唑基、$-SO_2R^d$ 或 $-CONHSO_2R^d$；

R^b 和 R^c 独立地表示氢、$-C_1$-C_6 烷基、$-(CH_2)_m$-苯基或 R^b 和 R^c 与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4－C_1-C_6 烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环；

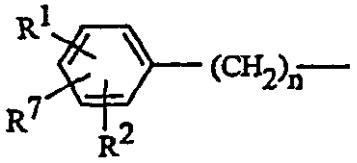
R^d 为氢、$-C_1$-C_6 烷基、$-CF_3$ 或苯基；

m 为 0－5；

p 为 1－5；

A 为 CH 或 N；

R^1 和 R^2 在彼此相邻时可以是甲二氧基。

在一较佳实施方式中，  基团连接在苯环的4位。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

n为2；

R^3和R^4为氢。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

R^1为卤素；

R^2为氢或卤素；

R^3、R^4、R^5和R^6为氢；

n为2-5。

在本发明方法的另一较佳实施方式中，在式I化合物中，

R^a为氢；

n为2或3；

R^1为$-NR^bR^c$；

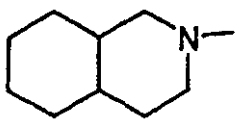
R^2、R^3、R^4、R^5和R^7均为氢。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

n为2；

R^3和R^4为氢；

R^1、R^2和R^7独立地表示氯、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、  、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N(苯基)_2$。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

n为3、4或5；

R^3和R^4为氢；

R^1、R^2和R^7独立地表示氟或氢。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

n为2；

R^3和R^4为氢；

R^5、R^6和R^8独立地表示氢、$-CO_2H$、$-NO_2$、$-OCH_3$、咪唑基、$-SO_2-CH_3$、-CN、氟、$-CH_3$、$-CF_3$、卤素、$-NH-C_1-C_6$烷基、$-N(C_1-C_6$烷基$)_2$、$-NH_2$或吡咯基。

在本发明方法的一较佳实施方式中，在式I化合物中，

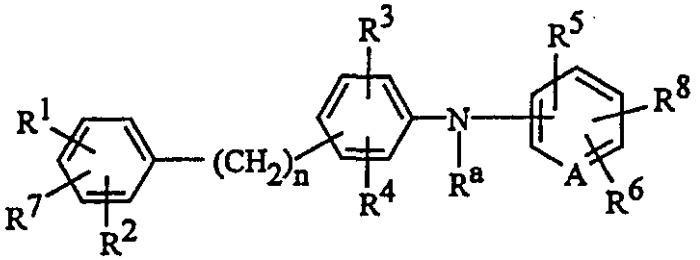
R^a为氢；

n为2；

R^3和R^4为氢；

R^5为$-CO_2H$.

在本发明的治疗阿尔茨海默病的方法中，最好将治疗有效量的具有以下定义的式I化合物或其药用盐给药于阿尔茨海默病患者：



I

式中，

R^a为氢；

n为1-5；

R^1、R^2和R^7独立地表示氟、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O-苯基、$-O(CH_2)_7CH_3$、

$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N(苯基)_2$；

R^5和R^6独立地表示氢、$-CO_2H$、$-NO_2$-、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$或吡咯基。

在本发明方法的较佳实施方式中，式I化合物是

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔4－(3,4－二氯苯基)乙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－{4－〔2－(3,4－二羟基苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(3,4,5－三羟基苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸；

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酸；

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}苯甲酸；

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－3,5－二硝基苯甲酸；

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－〔4－(3,4－二氯苄基)苯氨基〕苯甲酸；

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}苯甲酸；

2－〔4－(2－联苯－4－基乙基)苯氨基〕－5－硝基苯甲酸；

5－硝基－2－(4－苯乙基苯氨基)苯甲酸；

2－(4－苯乙基苯氨基)苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲氧基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}对苯二甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲基苯甲酸；

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}间苯二甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲磺酰基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－咪唑－1－基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－硝基苯甲酸;

5－氰基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4,6－二氟苯甲酸;

6－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－2,3－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3,5－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－吡咯－1－基苯甲酸;

2－{4－〔2－(4－苄氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3－二甲基氨基丙氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(2－乙氧基－1－乙氧基甲基乙基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡咯－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯乙烯基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4'－乙基联苯－4－基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔3－(3,5－二氯苯氧基)苯基〕乙基}苯氨基)苯甲酸;

2－(4－{2－〔4－(2－氯－6－氟－苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡唑－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二苯基氨基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3,4－二氯苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－氨基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－〔〔4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯基}氨基苯甲酸;

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－硝基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－硝基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二丙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐一水和物;

2－{4－〔3－(3－二丙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二甲基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－乙氨基苯基)丙基〕苯氨基}苯甲酸;

2－(N－{4－〔3－(4－二乙基氨基苯基)丙基〕苯基}－N－乙氨基)苯甲酸;

2－{4－〔2－(3－二苄基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－二甲基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－乙酰氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－乙酰氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－二丙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(3－二丁基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔3－(4－乙酰氨基苯基)丙基〕苯氨基}苯甲酸;

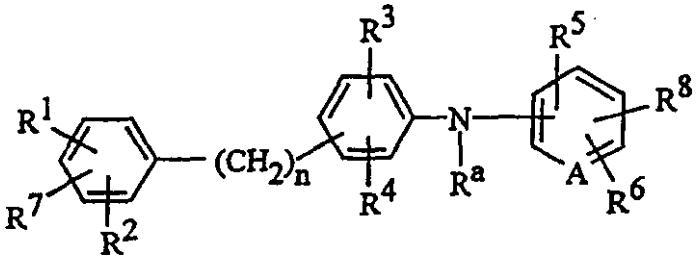
2－{4－〔3－(3－乙酰氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二乙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(3－哌啶－1－基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;
2－{4－〔3－(4－二丙基氨基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－二丁基氨基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(3－二丁基氨基苯基)丙基〕苯氨基}苯甲酸;
2－(4－{3－〔4－(1H－吡咯－1－基)苯基〕丙基}苯氨基)苯甲酸;
2－{4－〔3－(4－哌啶－1－基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－二乙基氨基甲酰基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－羧基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－二乙基氨基甲基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－丙氨基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(3－丙氨基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－吡咯烷－1－基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(3－哌啶－1－基苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－〔2－二乙基氨基乙基氨基〕苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔2－(4－〔羟基羰基甲氨基〕苯基)乙基〕苯氨基}苯甲酸;
2－{4－〔2－(4－〔2－二乙基氨基乙氨基〕苯基)乙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－吗啉代苯基)丙基〕苯氨基}苯甲酸;
2－{4－〔3－(4－哌嗪基苯基)丙基〕苯氨基}苯甲酸;
2－〔4－(3,4－二氯苯基)苯氨基〕苯甲酸.

本发明还提供上述式I中苯甲酸部分被吡啶基羧酸取代的化合物，例如，4－〔4－(3,4－二氯苯基)苯氨基〕－3－羟基羰基哌啶.

本发明还提供抑制淀粉样蛋白聚集成淀粉样沉积物的方法，该方法包括将淀粉样蛋白聚集抑制量的式I化合物或其药用盐给药于需要抑制淀粉样蛋白聚集的患者:



I

式中，

R^a为氢、C_1-C_6烷基或-CO-C_1-C_6烷基;

n 为 0－5;

R^1、R^2、R^3、R^4、R^5、R^6和 R^7独立地表示氢、卤素、-OH、$-NH_2$、NR^bR^c、-COOH、$-CO_2C_1$-C_6烷基、$-NO_2$、$-OC_1$-C_{12}烷基、$-C_1$-C_8烷基、$-CF_3$、-CN、$-OCH_2$苯基、$-OCH_2$-取代的苯基、$-(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、$-O(CH_2)_pNR^bR^c$、$-CO-NR^bR^c$、$-NHCO-R^b$、$-NH(CH_2)_pNR^bR^c$、$-N(C_1$-C_6烷基$)(CH_2)_pNR^bR^c$、$-CH(CH_2OC_1$-C_6烷基$)_2$;

R^8为 COOH、四唑基、$-SO_2R^d$或$-CONHSO_2R^d$;

R^b和 R^c独立地表示氢、$-C_1$-C_6烷基、$-(CH_2)_m$-苯基或 R^b和 R^c与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4－C_1-C_6烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环;

R^d为氢、$-C_1$-C_6烷基、$-CF_3$或苯基;

m 为 0－5;

p 为 1－5;

A 为 CH 或 N;

R^1和 R^2在彼此相邻时可以是甲二氧基。

在本发明方法的一较佳实施方式中，在式 I 化合物中，

R^a为氢;

n 为 2;

R^3和 R^4为氢。

在本发明方法的一较佳实施方式中，在式 I 化合物中，

R^a为氢;

R^3和 R^4为氢;

n 为 2－5。

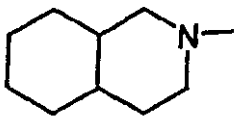
在本发明方法的一较佳实施方式中，在式 I 化合物中，

R^a为氢;

n 为 2;

R^3和 R^4为氢;

R^1、R^2和 R^7独立地表示氯、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O 苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、

吡咯基、-CH=CH-苯基、  、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N(苯基)_2$。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

n为3、4或5；

R^3和R^4为氢；

R^1、R^2和R^7独立地表示氟或氢。

在本发明方法的一较佳实施方式中，在式I化合物中，

R^a为氢；

n为2；

R^3和R^4为氢；

R^5和R^6独立地表示氢、$-CO_2H$、$-NO_2$、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$、卤素、-NH-C_1-C_6烷基、$-N(C_1$-C_6烷基$)_2$、$-NH_2$或吡咯基。

在本发明方法的一较佳实施方式中，在式I化合物中，

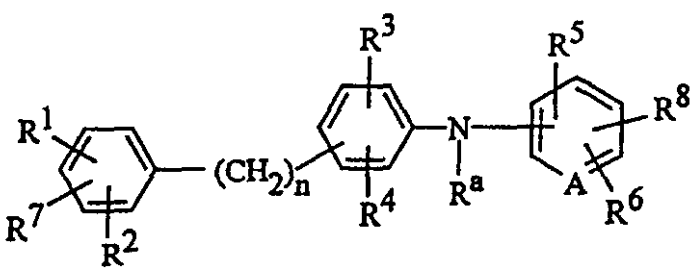
R^a为氢；

n为2；

R^3和R^4为氢；

R^5为$-CO_2H$。

在本发明的抑制淀粉样蛋白聚集成淀粉样沉积物的方法中，最好将淀粉样蛋白聚集抑制量的具有以下定义的式I化合物或其药用盐给药于需要抑制淀粉样蛋白聚集患者：



I

式中，

R^a为氢；

n为1-5；

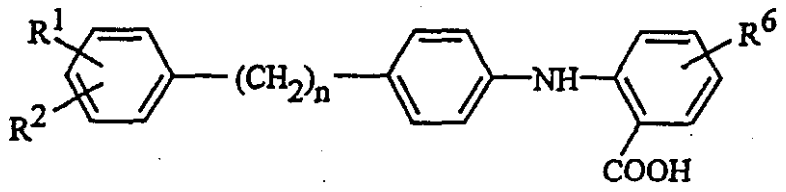
R^3和R^4为氢；

R^1、R^2和R^7独立地表示氯、$-N(CH_2CH_3)_2$、-OH、CH_3-、氟、$-CF_3$、苯基、氢、$-OCH_2$苯基、$-O(CH_2)_3N(CH_3)_2$、-O-苯基、$-O(CH_2)_7CH_3$、$-CH(CH_2OCH_2CH_3)_2$、吡咯基、-CH=CH-苯基、$-N[(CH_2)_3CH_3]_2$、取代的苯基、$-OCH_2$-取代的苯基、吡唑基或$-N(苯基)_2$；

R^5和R^6独立地表示氢、$-CO_2H$、$-NO_2$-、$-OCH_3$、咪唑基、-CN、氟、$-CH_3$、$-CF_3$或吡咯基；

R^8表示COOH或四唑基。

在本发明的化合物中，最佳的是具有式II的化合物及其药用盐：



II

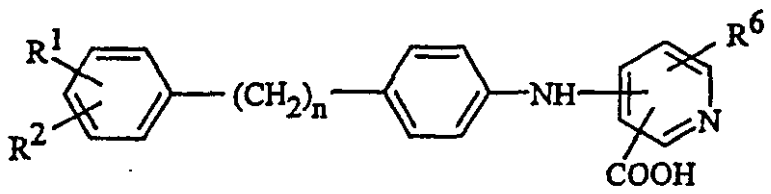
式中，

R^1为卤素；

R^2为氢或卤素；

n和R^6的定义与式I中的相同。

另一些较佳的是具有式III的化合物及其药用盐：



III

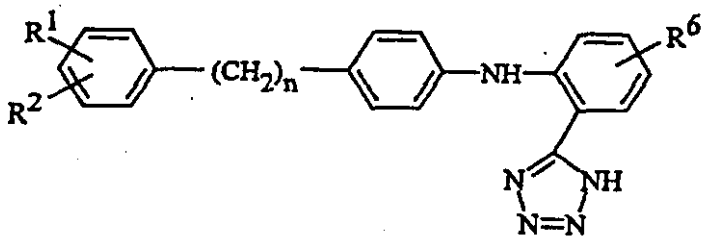
式中，

R^1为卤素；

R^2为氢或卤素；

n和R^6的定义与式I中的相同。

再一些较佳的是具有式 IV 的化合物及其药用盐：



IV

式中，

R^1 为卤素；

R^2 为氢或卤素；

n 和 R^6 的定义与式 I 中的相同。

在本发明方法的一较佳实施方式中，提供下述式 I 的新化合物：

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔4－(3,4－二氯苯基)乙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－{4－〔2－(3,4－二羟基苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(3,4,5－三羟基苯基)乙基〕苯氨基}苯甲酸；

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}苯甲酸；

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}苯甲酸；

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－3,5－二硝基苯甲酸；

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－〔4－(3,4－二氯苄基)苯氨基〕苯甲酸；

2－{4－〔2－(3,4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯氨基}苯甲酸；

2－〔4－(2－联苯－4－基乙基)苯氨基〕－5－硝基苯甲酸；

5-硝基-2-(4-苯乙基苯氨基)苯甲酸;

2-(4-苯乙基苯氨基)苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-5-甲氧基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}对苯二甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-5-甲基苯甲酸;

4-{4-[2-(3,4-二氯苯基)乙基]苯氨基}间苯二甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-5-甲磺酰基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-5-咪唑-1-基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-6-硝基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-4-硝基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-3-硝基苯甲酸;

5-氯基-2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-4,6-二氟苯甲酸;

6-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-2,3-二氟苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-6-氟苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-3-氟苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-3-甲基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-4-氟苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-3,5-二氟苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-3-三氟甲基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-6-三氟甲基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-5-三氟甲基苯甲酸;

2-{4-[2-(3,4-二氯苯基)乙基]苯氨基}-5-吡咯-1-基苯甲酸;

2-{4-[2-(4-苄氧基苯基)乙基]苯氨基}苯甲酸;

2-(4-{2-[4-(3-二甲基氨基丙氧基)苯基]乙基}苯氨基)苯甲酸;

2-{4-[2-(4-二乙基氨基苯基)乙基]苯氨基}苯甲酸;

2-{4-[2-(4-苯氧基苯基)乙基]苯氨基}苯甲酸;

2-{4-[2-(4-辛氧基苯基)乙基]苯氨基}苯甲酸;

2-(4-{2-[4-(2-乙氧基-1-乙氧基甲基乙基)苯基]乙基}苯氨基)苯甲酸;

2-{4-[2-(4-吡咯-1-基苯基)乙基]苯氨基}苯甲酸;

2-{4-[2-(4-苯乙烯基苯基)乙基]苯氨基}苯甲酸;

2－{4－〔2－（4－二丁基氨基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（4'－乙基联苯－4－基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（4－辛基苯基）乙基〕苯氨基}苯甲酸；

2－（4－{2－〔3－（3,5－二氯苯氧基）苯基〕乙基}苯氨基）苯甲酸；

2－（4－{2－〔4－（2－氯－6－氟－苄氧基）苯基〕乙基}苯氨基）苯甲酸；

2－{4－〔2－（4－吡唑－1－基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（4－二苯基氨基苯基）乙基〕苯氨基}苯甲酸；

2－（4－{2－〔4－（3,4－二氯苄氧基）苯基〕乙基}苯氨基）苯甲酸；

2－{4－〔2－（3,4－二氯苯基）丙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－（3,4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸；

2－〔〔4－〔2－（4－氯－3－三氟甲基苯基）乙基〕苯基〕氨基苯甲酸；或

2－〔4－（3,4－二氯苯基）苯基〕氨基苯甲酸。

本发明还提供下列化合物：

2－{4－〔4－（3,4－二氯苯基）乙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－{4－〔2－（3,4－二羟基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（4－二丁基氨基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（3,4,5－三羟基苯基）乙基〕苯氨基}苯甲酸；

2－{4－〔2－（3,4－二氯苯基）丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－{4－〔2－〔－（3,4－二氯苯基）丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸；

2－{4－〔4－（3,4－二氯苯基）丁基〕苯氨基}苯甲酸；

2－{4－〔4－（3,4－二氯苯基）丁基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔4－（3,4－二氯苯基）丁基〕苯氨基}－3,5－二硝基苯甲酸；

2－{4－〔5－（3,4－二氯苯基）戊基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔5－（3,4－二氯苯基）戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸；

2－〔4－（3,4－二氯苄基）苯氨基〕苯甲酸；

2－{4－〔2－（3,4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－（3,4－二氯苯基）乙基〕苯氨基}－5－硝基苯甲酸；

2－{4－〔2－（4－氯－3－三氟甲基苯基）乙基〕苯氨基}苯甲酸；

2－〔4－（2－联苯－4－基乙基）苯氨基〕－5－硝基苯甲酸；

5－硝基－2－（4－苯乙基苯氨基）苯甲酸；

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－氨基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)〕苯氨基}－5－硝基苯甲酸;

2－(4－苯乙基苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲氧基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}对苯二甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲基苯甲酸;

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}间苯二甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－甲磺酰基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－咪唑－1－基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－硝基苯甲酸;

5－氯基－2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4,6－二氟苯甲酸;

6－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－2,3－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－4－氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3,5－二氟苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－3－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－6－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－吡咯－1－基苯甲酸;

2－{4－〔2－(4－苄氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3－二甲基氨基丙氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯氧基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛氧基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(2－乙氧基－1－乙氧基甲基乙基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡咯－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－苯乙烯基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二丁基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4'－乙基联苯－4－基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－辛基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔3－(3,5－二氯苯氧基)苯基〕乙基}苯氨基)苯甲酸;

2－(4－{2－〔4－(2－氯－6－氟－苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(4－吡唑－1－基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二苯基氨基苯基)乙基〕苯氨基}苯甲酸;

2－(4－{2－〔4－(3,4－二氯苄氧基)苯基〕乙基}苯氨基)苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－氨基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－三氟甲基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)丙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸;

2－{4－〔2－(4－氯－3－三氟甲基苯基)乙基〕苯基}氨基苯甲酸;

2－{4－〔3－(4－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－硝基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－硝基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－二丙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(4－二乙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐一水和物;

2－{4－〔3－(3－二丙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二甲基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－乙氨基苯基)丙基〕苯氨基}苯甲酸;

2－(N－{4－〔3－(4－二乙基氨基苯基)丙基〕苯基}－N－乙氨基)苯甲酸;

2－{4－〔2－(3－二苄基氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－二甲基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔2－(4－乙酰氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－乙酰氨基苯基)乙基〕苯氨基}苯甲酸;

2－{4－〔2－(3－二丙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(3－二丁基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔3－(4－乙酰氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－乙酰氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二乙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔2－(3－哌啶－1－基苯基)乙基〕苯氨基}苯甲酸一盐酸盐;

2－{4－〔3－(4－二丙基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－二丁基氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－二丁基氨基苯基)丙基〕苯氨基}苯甲酸;

2－(4－{3－〔4－(1H－吡咯－1－基)苯基〕丙基}苯氨基)苯甲酸;

2－{4－〔3－(4－哌啶－1－基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－二乙基氨基甲酰基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－羧基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－二乙基氨基甲基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－丙氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－丙氨基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(4－吡咯烷－1－基苯基)丙基〕苯氨基}苯甲酸;

2－{4－〔3－(3－哌啶－1－基苯基)丙基〕苯氨基}苯甲酸;

{5－〔(1－丁基－1,2,3,4－四氢－6－喹啉基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸;

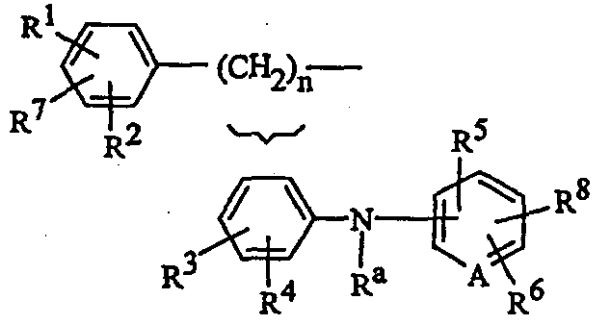
{5－〔(1－丁基－2,3－二氢－1H－吲哚－5－基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸;

3－{5－〔(1－丁基－1,2,3,4－四氢喹啉－6－基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}丙酸;

4－{5－〔(1－丁基－1,2,3,4－四氢喹啉－6－基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}丁酸;

2－〔4－(3,4－二氯苯基)苯基〕氨基苯甲酸。

本发明还提供上述式I中末端苯基烷基连接在中心的苯环的2或3位的化合物，即，式Ia化合物



Ia

典型的 2-和 3-取代的化合物是:

2-{3-〔2-(3,4-二氯苯基)乙基〕苯氨基}苯甲酸;

2-{2-〔2-(3,4-二氯苯基)乙基〕苯氨基}苯甲酸;

2-{3-〔3-(4-二乙基氨基苯基)丙基〕苯氨基}苯甲酸;

2-{3-〔3-(4-二正丙基氨基苯基)丙基〕苯氨基}苯甲酸;

2-{3-〔3-(4-正丙基氨基苯基)丙基〕苯氨基}苯甲酸;

2-{3-〔3-(4-〔2-二乙基氨基乙氨基〕苯基)丙基〕苯氨基}苯甲酸;

2-{2-〔3-(4-〔羟基羰基甲氨基〕苯基)丙基〕苯氨基}苯甲酸;

2-{2-〔2-(3-〔2-二乙基氨基乙氨基〕苯基)乙基〕苯氨基}苯甲酸;

2-{3-〔3-(4-吗啉代苯基)丙基〕苯氨基}苯甲酸;

2-{3-〔3-(4-哌嗪基苯基)丙基〕苯氨基}苯甲酸;

2-{3-〔2-(4-氯苯基)乙基〕苯氨基}苯甲酸;

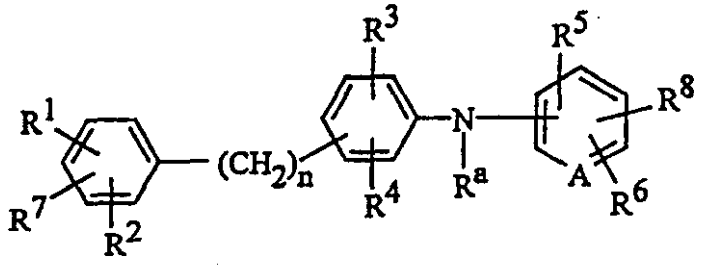
2-{3-〔3-(3,4-二氯苯基)丙基〕苯氨基}苯甲酸;

2-{4-〔4-(4-{4-甲基哌嗪基}苯基)丁基〕苯氨基}苯甲酸。

本发明还提供上述新化合物与药用稀释剂、载体或赋形剂混合的药剂。

本发明还提供将淀粉样沉积物成象的方法,该方法包括:

a. 将可检测量的式 I 的标记化合物或其药用盐导入患者:



I

式中,

R^a 为氢、C_1-C_6烷基或-CO-C_1-C_6烷基;

n 为 0-5;

R^1、R^2、R^3、R^4、R^5、R^6和 R^7独立地表示氢、卤素、-OH、$-NH_2$、NR^bR^c、

-COOH、-CO_2C_1-C_6烷基、-NO_2、-OC_1-C_{12}烷基、-C_1-C_8烷基、-CF_3、-CN、-OCH_2苯基、-OCH_2-取代的苯基、-$(CH_2)_m$-苯基、-O-苯基、-O-取代的苯基、-CH=CH-苯基、-$O(CH_2)_pNR^bR^c$、-CO-NR^bR^c、-NHCO-R^b、-$NH(CH_2)_pNR^bR^c$、-N(C_1-C_6烷基)$(CH_2)_pNR^bR^c$、-$CH(CH_2OC_1$-C_6烷基$)_2$;

R^8为 COOH、四唑基、-SO_2R^d或-$CONHSO_2R^d$;

R^b和R^c独立地表示氢、-C_1-C_6烷基、-$(CH_2)_m$-苯基或R^b和R^c与它们所连接的氮原子一起形成选自哌啶基、吡咯基、咪唑基、哌嗪基、4-C_1-C_6烷基哌嗪基、吗啉基、硫代吗啉基、十氢异喹啉或吡唑基的环;

R^d为氢、-C_1-C_6烷基、-CF_3或苯基;

m 为 0-5;

p 为 1-5;

A 为 CH 或 N;

R^1和R^2在彼此相邻时可以是甲二氧基;

b. 让标记化合物以足够的时间与淀粉样沉积物结合;

c. 检测与淀粉样沉积物结合的标记化合物.

在本发明方法的一较佳实施方式中，患者患有或被怀疑患有阿尔茨海默病。

在本发明方法的一较佳实施方式中，所述标记化合物是放射性标记的化合物。

在本发明方法的一较佳实施方式中，所述标记化合物用 MRI 检测。

本发明还提供下列较佳化合物及其药剂:

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}苯甲酸;

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-硝基苯甲酸;

2-{4-〔3-(3,4-二氯苯基)丙基〕苯氨基}苯甲酸 ;

2-〔〔4-〔2-(4-氯-3-三氟甲基苯基)乙基〕苯基〕氨基苯甲酸;

2-{4-〔3-(4-二乙基氨基苯基)丙基〕苯氨基}苯甲酸.

本发明还提供上述化合物的药用酸加成盐、酰胺和前药.

发明的详细描述

"烷基"一词是指 1-12 个碳原子的直链或支链烃。烷基的代表性例子有甲基、乙基、丙基、异丙基、异丁基、丁基、叔丁基、仲丁基、戊基、己基、辛基、癸基和 1,1-二甲基辛基。

较佳的烷基有 C_1-C_8 烷基，尤其是 C_1-C_6 烷基。

"烷氧基"一词是指与氧原子连接的烷基。烷氧基的代表性例子包括甲氧基、乙氧基、叔丁氧基、丙氧基和异丁氧基。较佳的烷氧基有 C_1-C_{12} 烷氧基，尤其是 C_1-C_6 烷氧基。

"卤素"一词包括氯、氟、溴和碘。

"取代的"一词分子中的一个或多个氢被另一种原子或原子团置换。例如，取代基包括卤素（尤其是氟）、-OH、-CF_3、-NO_2、-NH_2、-NH(C_1-C_6 烷基)、-N(C_1-C_6 烷基)$_2$、C_1-C_6 烷基、-OC_1-C_6 烷基、-CN、-CO_2H 和-CO_2-C_1-C_6 烷基。

"取代的苯基"一词是指其 1-4 个氢原子独立地被取代基（最好是上面所述的取代基）置换的苯环。典型的"取代的苯基"包括 4-氟苯基、3,4-二溴苯基、3-氟-4-甲基苯基、3,4-二氯苯基、3,4-亚甲二氧基苯基和 4-二甲基氨基苯基。

符号"-"表示共价键。

R^1、R^3 和 R^5 表示的取代基例如包括氨基（NR^bR^c）和酰氨基（-$NHCOR^b$）。R^b 和 R^c 可以是氢、烷基、苯基烷基和取代基苯基烷基，典型的 NR^bR^c 基团包括甲氨基、二乙基氨基、异丁基-丙氨基、苄氨基和 3,4-二甲氧基苄氨基。酰氨基的例子包括甲酰氨基、乙酰氨基、2-苯基乙酰氨基和 2-（3-硝基苯基）乙酰氨基。R^1、R^3 和 R^5 也可以是 N-甲基氨基甲氧基和 2-（N-苄氨基）乙氧基等氨基烷氧基（-O(CH_2)$_p$$NR^bR^c$）和氨基烷基氨基（-NH($CH_2$)$_p$$NR^bR^c$），如 3-（二甲基氨基）丙氨基和 2-（N-乙基-N-苄氨基）乙氨基。另外，R^1、R^3 和 R^5 等取代基可以是环状结构，例如，当 NR^bR^c 是该取代基的一部分时，R^b 和 R^c 与它们所连接的氮原子一起形成选自咪唑、吡咯、哌啶、哌嗪、4-C_1-C_6 烷基哌嗪、吗啉、硫代吗啉、吡唑和十氢异喹啉的环；

R^1、R^2、R^5、R^6 和 R^7 等取代基也可以是-CH=CH-苯基（即，苯乙烯基）、苯氧基、O-取代的苯基（如 3-碘苯氧基、2,4,6-三羟基苯氧基、2-氟-3-硝基苯氧基）、O-苄基和 O-取代的苄基，如 2-三氟甲基苄氧基和 4-氨基苄氧基。

在本文中，"药用盐、酯、酰胺和前药"一词是指本发明化合物的羧酸盐、

氨基酸加成盐、酯、酰胺和前药，它们在合理的医学判断的范围内，适用于与患者组织接触而不会有过度的毒性、刺激、过敏性反应等，与合理的利益/风险比相称，并可有效地用于拟定的用途和本发明化合物的两性离子（如果可能的话）。“盐”一词是指本发明化合物的相对无毒的无机和有机酸加成盐。这些盐可在化合物的最终分离和纯化过程中原地制备或分别通过将纯化的化合物以其游离碱的形式与合适的有机或无机酸反应并将由此形成的盐分离而制备。代表性的盐包括氢溴酸盐、盐酸盐、硫酸盐、硫酸氢盐、硝酸盐、乙酸盐、草酸盐、戊酸盐、油酸盐、棕榈酸盐、硬脂酸盐、月桂酸盐、硼酸盐、苯甲酸盐、乳酸盐、磷酸盐、甲苯磺酸盐、柠檬酸盐、马来酸盐、富马酸盐、琥珀酸盐、酒石酸盐、萘酸盐、甲磺酸盐、葡萄糖酸盐、乳糖酸盐和月桂基磺酸盐等。这些可包括基于碱金属和碱土金属（如钠、锂、钾、钙、镁等）的阳离子以及无毒的铵、季铵和胺阳离子，包括但不限于铵、四甲基铵、四乙基铵、甲胺、二甲胺、三甲胺、三乙胺、乙胺等。（例如，可参见 S.M.Berge 等，药用盐(Pharmaceutical Salts)，*J. Pharm. Sci.*, 66:1-19 (1977)，该文纳入于此作为参考。）

本发明化合物的可药用的无毒的酯包括 C_1-C_6 烷基酯，其中，烷基为直链或支链。可药用酯还包括 C_5-C_7 环烷基酯和芳烷基酯，例如但不限于苄基。以 C_1-C_4 烷基酯为佳。本发明化合物的酯可用常法制备，例如，将式 I 的羧酸与乙醇或苄醇等醇反应。

本发明化合物的可药用的无毒的酰胺包括由氨、伯 C_1-C_6 烷基胺和仲 C_1-C_6 二烷基胺衍生的胺，其中，烷基为直链或支链。当为仲胺时，所述胺也可以是含有一个氮原子的 5 或 6 元杂环。以由氨、C_1-C_3 烷基伯酰胺和 C_1-C_2 二烷基仲酰胺衍生的胺为佳。本发明化合物的酰胺可用常法制备。

“前药”一词是指这样的化合物：它们例如通过血中水解而在体内迅速转化成上述结构式的本发明化合物。T.Higuchi 和.Stella, 作为新的给药系统的前药（Pro-drugs as Novel Delivery Systems），*C.S.Symposium Series* 第 14 卷和 Edward B.Roche 编，药物设计中的生物可逆的载体（Bioreversible Carriers in Drug Design），*American Pharmaceutical Association and Pergamon Press*, 1987 对此作了充分的讨论。这二篇文献纳入于此作为参考。

此外，本发明的化合物可以不是与药用溶剂（如水、乙醇等）形成溶剂合物的形式，也可以是形成溶剂合物的形式。对于本发明的目的而言，溶剂合物形式一般被认为与非溶剂合物形式等效。

本发明的化合物可由于化合物中的非对称中心的存在而呈不同的立体异构

体形式。化合物的所有立体异构体形式及其混合物（包括外消旋混合物）被认作构成本发明的一部分。

在本发明的成象方法的第一步骤中，将式I的标记化合物以可检测量导入患者组织中。化合物通常是药学组合物的一部分，通过本领域的技术人员公知的方法施药于组织或患者。

在本发明的方法中，化合物的施药方法可以是口服、直肠给药、肠胃外给药（静脉内给药、肌内给药或皮下给药）、脑池内给药、阴道内给药、腹腔内给药、膀胱内给药、局部给药（粉剂、软膏或滴剂）或颊用或鼻用喷剂。

适合肠胃外注射的组合物可包含生理学上可接受的无菌水性或非水性溶液、分散液、悬浮液或乳液和用于兑成注射用溶液或分散液的无菌粉末。合适的水性和非水性载体、稀释剂、溶剂或赋形剂包括水、乙醇、多元醇（丙二醇、聚乙二醇、丙三醇等）和它们的合适的混合物，植物油（如橄榄油），注射用有机酯（如油酸乙酯）。可通过例如使用包衣剂（如卵磷脂）、维持所需粒径（在分散液的情况下）和使用表面活性剂来维持合适的流动性。

这些组合物也可含辅剂，如防腐剂、湿润剂、乳化剂和分散剂。可用各种抗菌剂和抗真菌剂（例如，对羟基苯甲酸酯、氯丁醇、苯酚、山梨酸等）防止微生物的作用。也可加入等渗剂，例如，糖、氯化钠等。使用延长吸收剂（如单硬脂酸铝和明胶）可使注射用药学组合物的吸收延长。

口服用固体剂型包括胶囊、片剂、丸剂、粉剂和颗粒剂。在这些固体剂型中，活性化合物与下列物质混合：至少一种惰性常用赋形剂（或载体），如柠檬酸钠或磷酸二钙，或（a）填料或膨胀剂（例如，淀粉、乳糖、蔗糖、葡萄糖、甘露醇和硅酸）；（b）粘合剂，例如，羧甲基纤维素、海藻酸盐、明胶、聚乙烯基吡咯烷酮、蔗糖和阿拉伯胶；（c）增湿剂，如丙三醇；（d）崩解剂，例如，琼脂、碳酸钙、土豆或木薯淀粉、海藻酸、某些复合硅酸盐和碳酸钠；（e）溶液缓凝剂，例如，石蜡；（f）吸收促进剂，例如，季铵化合物；（g）湿润剂，例如，十六醇和单硬脂酸甘油酯；（h）吸收剂，例如，高岭土和膨润土；（i）润滑剂，例如，滑石粉、硬脂酸钙、硬脂酸镁、固态聚乙二醇、月桂基硫酸钠或它们的混合物。当为胶囊、片剂和丸剂时，剂型也可包含缓冲剂。

在使用乳糖和高分子量的聚乙二醇等赋形剂的软充填的和硬充填的明胶胶囊中，也可使用相似类型的固体成分作为填料。

固体剂型（如片剂、糖衣丸、胶囊、丸剂和颗粒剂）可用包衣剂和包壳剂（如肠衣和本领域公知的其它物质）制备。它们可含有乳浊剂，也可以是在小肠的

某一部分以延缓的形式释放活性化合物的组合物。可使用的包埋成分的例子有高分子物质和蜡。如果合适的话，活性化合物也可以是与一种或多种上述赋形剂一起装入微胶囊的形式。

口服用液体剂型包括药用乳液、溶液、悬浮液、糖浆、酏剂。除了活性化合物之外，液体剂型可含有本领域常用的惰性稀释剂（如水和其它溶剂）、增溶剂和乳化剂，例如，乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苄醇、苯甲酸苄酯、丙二醇、1,3-丁二醇、二甲基甲酰胺、油（尤其是棉籽油、花生油、玉米胚油、橄榄油、蓖麻油和麻油）、丙三醇、四氢糠醇、聚乙二醇、山梨糖醇的脂肪酸酯或这些物质的混合物等。

除了这些惰性稀释剂之外，上述组合物还可包含辅剂，如湿润剂、乳化剂、悬浮剂、甜味剂、调味剂和芳香剂。

除了活性化合物之外，悬浮液可含有悬浮剂，例如，乙氧基化异硬脂醇、聚氧乙烯山梨糖醇和山梨糖醇酐酯、微晶纤维素、偏氢氧化铝、膨润土、琼脂、黄蓍胶和这些物质的混合物等。

直肠给药用组合物最好是栓剂，可通过将本发明的化合物与合适的非刺激性赋形剂或载体（如可可脂、聚乙二醇或栓剂用蜡）混合而制得，栓剂在常温下为固体，但在体温下为液体，这样，它会在直肠或阴道腔中熔化，释放出活性化合物。

本发明化合物的局部施药剂型包括软膏、粉剂、喷雾剂和吸入剂。活性化合物在无菌条件下与生理学上可接受的载体和任何所需的防腐剂、缓冲剂或抛射剂混合。眼用制剂、眼膏、粉剂和溶液也被认为是在本发明的范围内。

在本发明的一较佳实施方式中，将标记化合物以可检测量导入患者中，在足以使化合物与淀粉样沉积物结合的时间过去之后，非损伤性地检测患者体内的标记化合物。在本发明的另一较佳实施方式中，将式I的标记化合物导入患者中，让化合物以足够时间与淀粉样沉积物结合，然后，采取患者的组织检样，体外检测组织中的标记化合物。在本发明的第三种实施方式中，采取患者的组织检样，将式I的标记化合物导入组织检样中。在足以使化合物与淀粉样沉积物结合的时间之后，检测化合物。

将标记化合物给药于患者可采用全身或局部给药途径。例如，标记化合物可以以传输于患者全身的方式给药。也可将标记化合物施药于特定器官或感兴趣的组织。例如，宜将脑中的淀粉样沉积物定位和定量，以诊断或追踪患者阿尔茨海默病的进展。

"组织"一词是指患者身体的一部分。组织的例子包括脑、心、肝、血管和动脉。可检测量是用所选检测方法检测出来而所需的标记化合物的量。导入患者中以供检测的标记化合物的量可容易地由本领域的技术人员确定。例如，将给予患者的标记化合物的量增加至该化合物可用所选检测方法检测出来。在化合物中导入标记以检测化合物。

"患者"一词是指人和其它动物。本领域的技术人员还精通于确定足以使化合物与淀粉样沉积物结合的时间。所需时间可容易地通过将可检测量的式I标记化合物导入患者然后在施药后的不同时间检测标记化合物而加以确定。

"结合"一词是指标记化合物与淀粉样沉积物之间的化学相互作用。结合的例子包括共价键、离子键、亲水性-亲水性相互作用、疏水性-疏水性相互作用和络合。

本领域的技术人员熟悉各种检测标记化合物的方法。例如，磁共振成象法(MRI)、正电子发射段层摄影法(PET)或单光子发射计算段层摄影法(SPECT)可用来检测放射性标记的化合物。导入化合物的标记将取决于所需的检测方法。例如，若选择PET作为检测方法，则化合物必须具有正电子发射原子，如^{11}C或^{18}F。

式I化合物中的合适标记的另一个例子是可用磁共振成象法(MRI)(该方法有时也称核磁共振法(NMR))检测的原子，如^{13}C、^{15}N或^{19}F等。此外，式I标记化合物也可用使用顺磁对比剂的MRI检测。

另一个检测方法的例子是电子顺磁共振法(EPR)。在该情况下，可使用本领域公知的EPR探头，如硝基氧。

淀粉样沉积物的成象也可定量进行，这样，可确定淀粉样沉积物的量。

本发明还提供通过施药于需要抑制淀粉样蛋白聚集的患者以淀粉样蛋白抑制量的式I化合物来抑制淀粉样蛋白聚集成淀粉样沉积物的方法。本领域的技术人员只需增加施药于患者的式I化合物量至淀粉样沉积物的生长减少或停止，就可容易地确定淀粉样蛋白抑制量。生长率可用成象法或通过采取患者的组织检样并观察其中的淀粉样沉积物而加以评估。

需要抑制淀粉样蛋白聚集的患者是患有淀粉样蛋白聚集的疾病或病症的患者。这些疾病和病症的例子包括布氏杆菌病、Muckle-Wells氏综合征、自发性淀粉样变性、淀粉样多神经病、淀粉样心肌病、全身性老年性淀粉样变性、具有淀粉样变性的遗传性小脑出血、阿尔茨海默病、唐氏先天愚征、绵羊瘙痒病、痉挛性假硬化症、苦鲁病、Gerstmann-Straussler-Scheinker氏综合征、甲状腺

髓样癌，透析患者中的单独心房淀粉样蛋白、β_2-微球蛋白淀粉样蛋白，包涵体肌炎、肌肉消耗性疾病中的β_2-淀粉样沉积物和胰岛糖尿病II型胰岛瘤。

本发明还提供化合物中的一个或多个原子已被放射性同位素置换的式I化合物（标记化合物）。放射性同位素可以是任何同位素。但优选^{3}H、^{123}I、^{125}I、^{131}I、^{11}C和^{18}F。本领域的技术人员熟悉将放射性同位素导入化合物的方法。例如，容易制得其中的一个碳原子为^{11}C或^{14}C的式I化合物。

本发明的化合物可以每日约0.1-1000mg的剂量施药于患者.对于体重约为70kg的普通成人，约0.01-100mg/kg体重/日的剂量就足够了。但所用具体剂量可进行变化。例如，剂量可取决于许多因素，包括患者的要求、需治疗的病症的严重性、所用化合物的药理活性。对于特定患者的最佳剂量的确定是本领域的技术人员公知的。

下面的实施例是用来举例说明本发明的具体实施方式，而绝非是用来限定包括权利要求书在内的申请文件的范围。

实施例

合成

式I化合物可用流程图6-9所示的几个途径制备。流程图1-5显示可用来得到所需起始胺（IV）、（VIII）、（XV）和（XXI）的合成途径。

在流程图1中，合适取代的醛（I）和硝基苯乙酸（II）在150℃于哌啶中加热时产生烯烃（III）。标准的氢化条件（如阮内镍）给出所需胺（IV）。

流程图2描述了含有三个亚甲基系链的胺（VIII）的合成。醛（I）与硝基酮（V）在氢氧化钠的存在下的缩合给出所需的α,β-不饱和酮，而该酮在标准氢化条件下(阮内镍)给出(VII)，然后在Wolff-Kishner条件下给出所需胺(VIII)。

流程图3与流程图2非常类似，所不同的是，醛（I）与取代的苯胺（IX）缩合。

流程图4示出标准的Wittig条件，在该条件中，起始物质（XII）和（XIII）分别通过醛醇缩合和内鎓盐化学而得到。醛（XII）与溴正膦（XIII）在碱（如丁基锂）的存在下反应，给出二烯（XIV）。（XIV）的标准还原条件（例如，阮内镍）给出所需胺（XV）。

流程图5示出含有5-亚甲基系链的胺（XXI）的合成。溴正膦（XVII）〔由相应的取代的溴化物（XVI）形成〕与硝基醛（XIX）〔由相应的醇（XVIII）的Swern氧化而得到〕在碱（如LHDMS）存在下的Wittig反应产生烯烃（XX）。

用标准条件（阮内镍）还原（XX），给出胺（XXI）。

流程图 6 示出一条得到式 I 化合物的途径。通过 Buchwald 偶合（方法 A）和其后的皂化或通过使用 Ullman 反应（方法 B），可从（IV）、（VIII）和（XV）等胺中分离出式 I 化合物。含羟基的式 I 化合物（如实施例 4 和 6）需要在合成的最后步骤中用试剂（如三溴化硼）将羟基保护基去甲基化。

当存在反应性官能团（如氨基和羧酸）时也要使用保护基，以避免不希望的副反应。通常将羧基转化成酯（如，叔丁基、苄基），一般将氨基酰化（如乙酰基或三甲基硅基）。这些和其它的此类保护基是有机化学家周知的，在 Greene 和 Wuts 编著，有机合成中的保护基（Protective Groups in Organic Synthesis），纽约 John Wiley and Sons 出版（1991 年第 2 版）中有详尽的描述。所有引文纳入于此作为参考。

流程图 7 示出通过（IV）、（VIII）和（XXI）等胺与氟-硝基中间体（XXIV）在碱（如 LHMDS 或三乙胺）的存在下反应产生酯（XXV）来合成式 I 化合物。然后可用标准条件（如氢氧化钠）将该酯皂化。

在流程图 8 中，可将胺（XV）与可容易得到的氟取代的羧酸〔如（XXVI）或（XXVII）〕在各种碱（如 DBU 或三乙胺）的存在下偶合，生成式 I 化合物。

流程图 9 描述了胺（VIII）与容易得到的甲酯（XXVIII）在碱（如咪唑）的存在下偶合，生成酯（XXIX）。然后可将该酯用常法皂化，生成式 I 化合物。

流程图 10 示出含氟中间体（XXIV）的合成，它通过将容易得到的甲酯（XXX）硝化成（XXVIII）而得到。用氟化钾处理（XXVIII），生成（XXIV）。

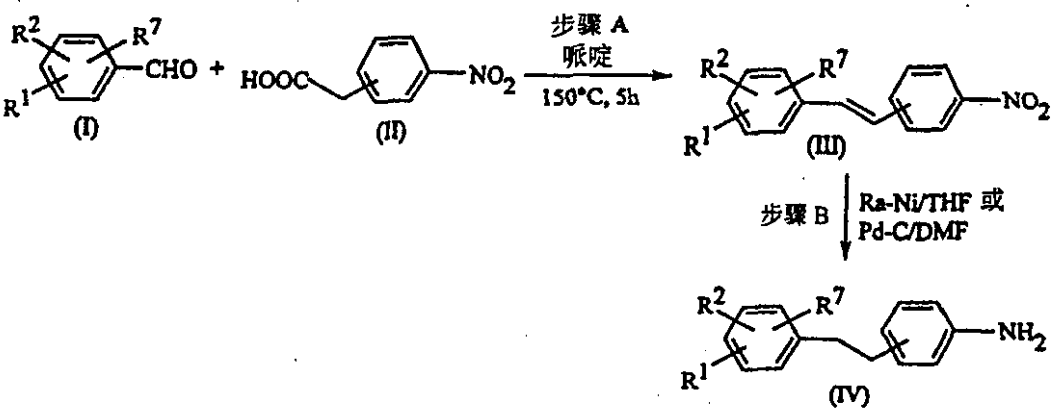
在流程图 11 中，示出与实施例 18 相关的化合物的合成。邻位取代的苯甲酸（XXVI）的钾盐与取代的苯胺（XXVII）在碳酸钾和乙酸铜的存在下反应，产生各种碘取代的氨基苯甲酸（XXVIII）。（XXVIII）与取代的硼酸和氟化钯的反应产生所需的取代的氨基苯甲酸（XXX）。

当然，应认识到，本发明的若干式 I 化合物可用标准的有机反应（如氧化、还原、烷基化、缩合、消去和类似的公知合成方法）由式 I 定义的其它化合物制得。例如，可容易地将 R^a 表示氢的式 I 化合物烷基化，形成 R^a 表示 C_1-C_6 烷基的化合物。R^1 表示 NH_2 的化合物可容易地通过与酰基卤或酸酐反应而酰化，形成 R^1 表示-$NHCOR^b$ 的化合物。类似地，可容易地将 R^1 表示 NO_2 的化合物还原，形成 R^1 表示 NH_2 的化合物。苯甲酸（其中，R^8 表示 COOH）可用常规方法容易地转化成酯、酰胺、盐和其它前药。例如，可将苯甲酸与草酰氯反应，形成酰基氯，然后，可容易地将该酰基氯与磺酰胺（如甲磺酰胺）反应，

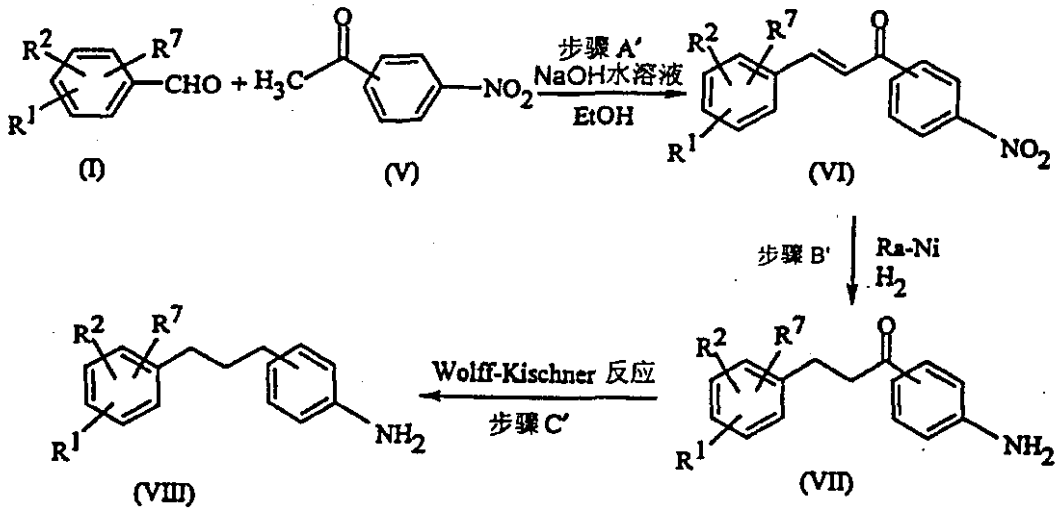
产生相应的 R^8 表示-$CONHSO_2CH_3$ 的本发明的化合物。

胺的形成

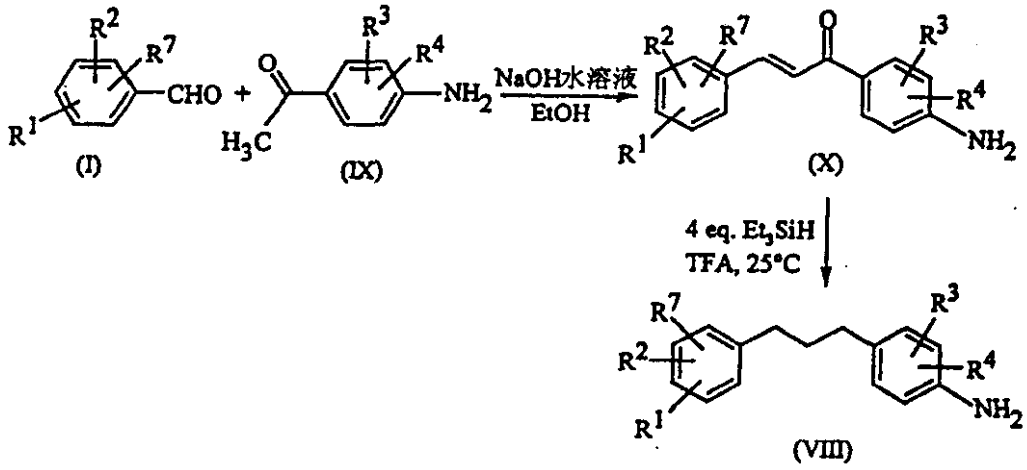
流程图 1



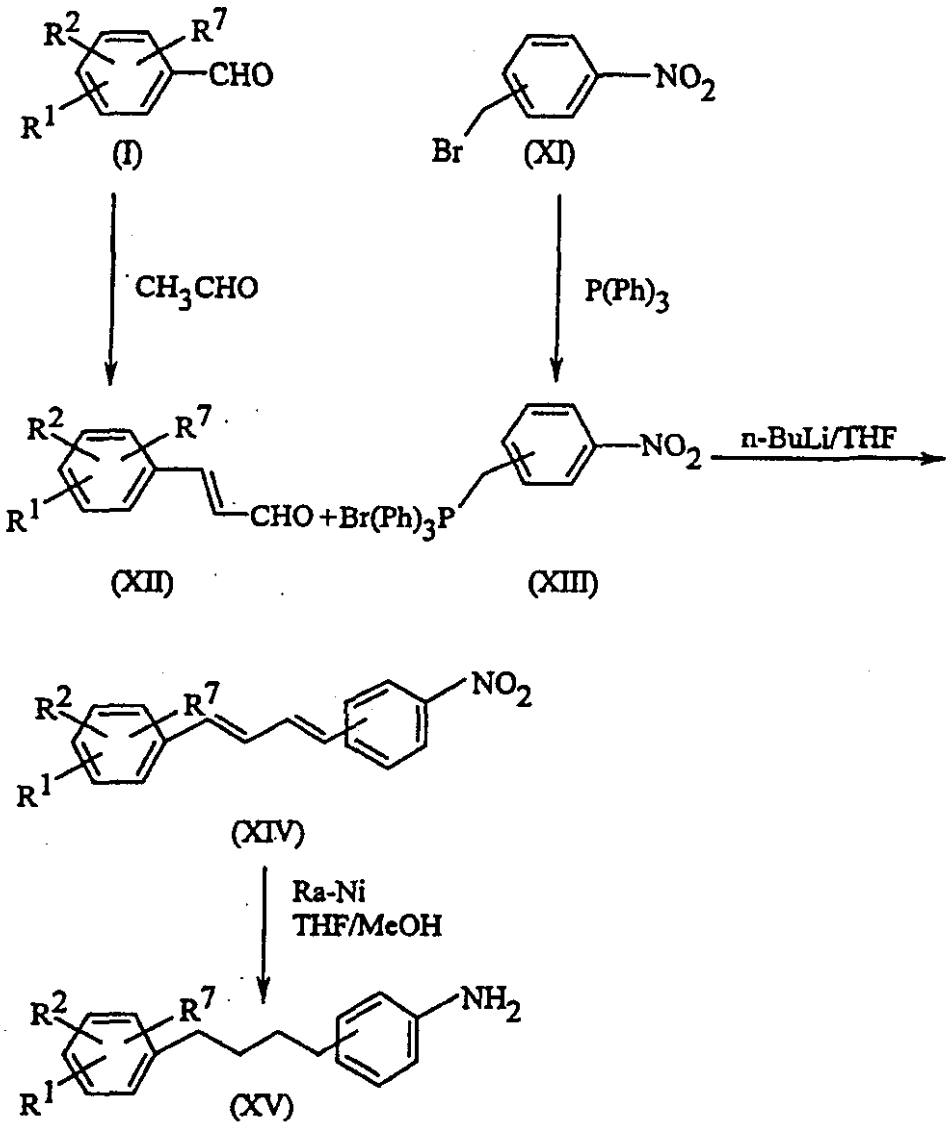
流程图 2



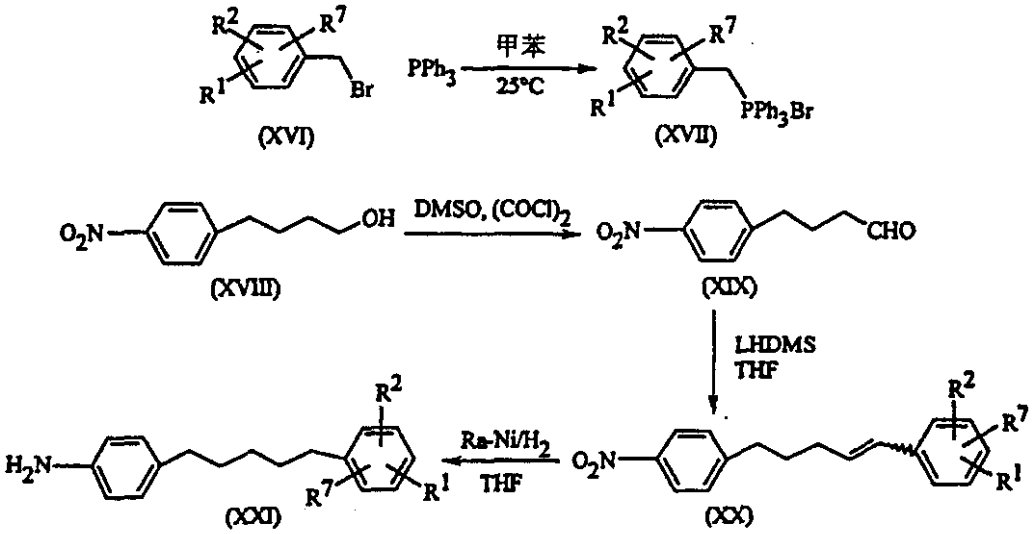
流程图 3


NaOH水溶液
EtOH
4 eq. Et3SiH
TFA, 25°C
(I)
(IX)
(X)
(VIII)

流程图 4

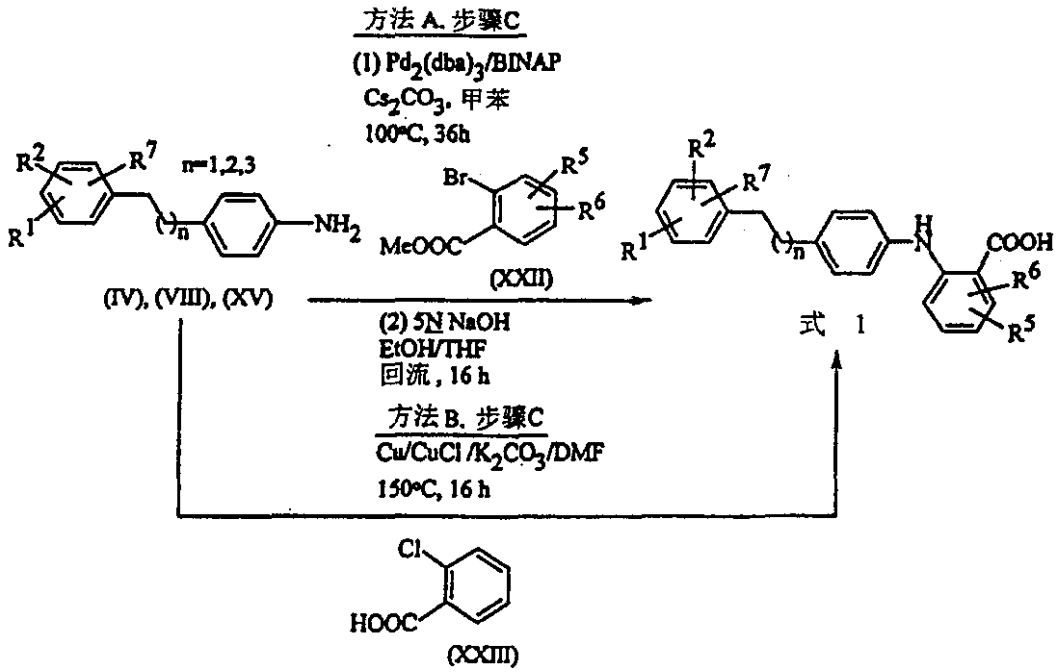

(I)
(XI)
CH3CHO
P(Ph)3
n-BuLi/THF
(XII)
(XIII)
(XIV)
Ra-Ni
THF/MeOH
(XV)

流程图 5

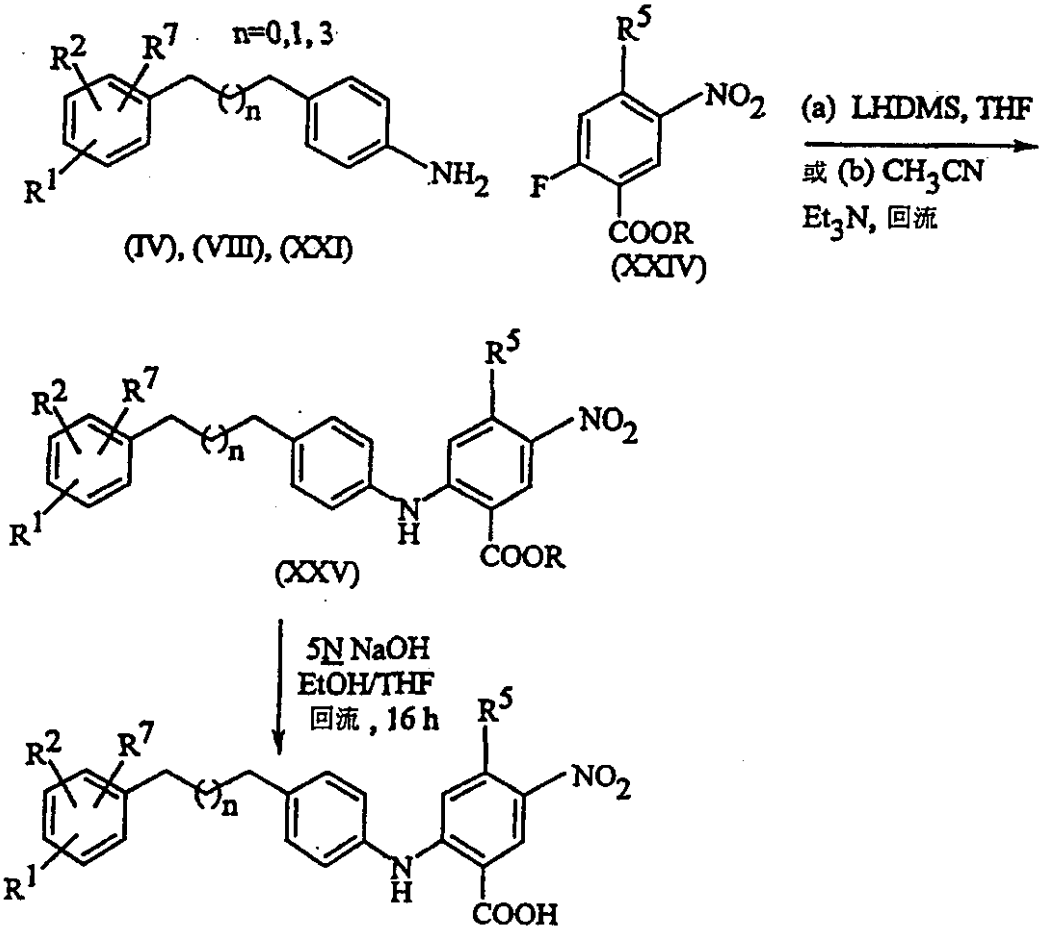


偶合途径

流程图 6



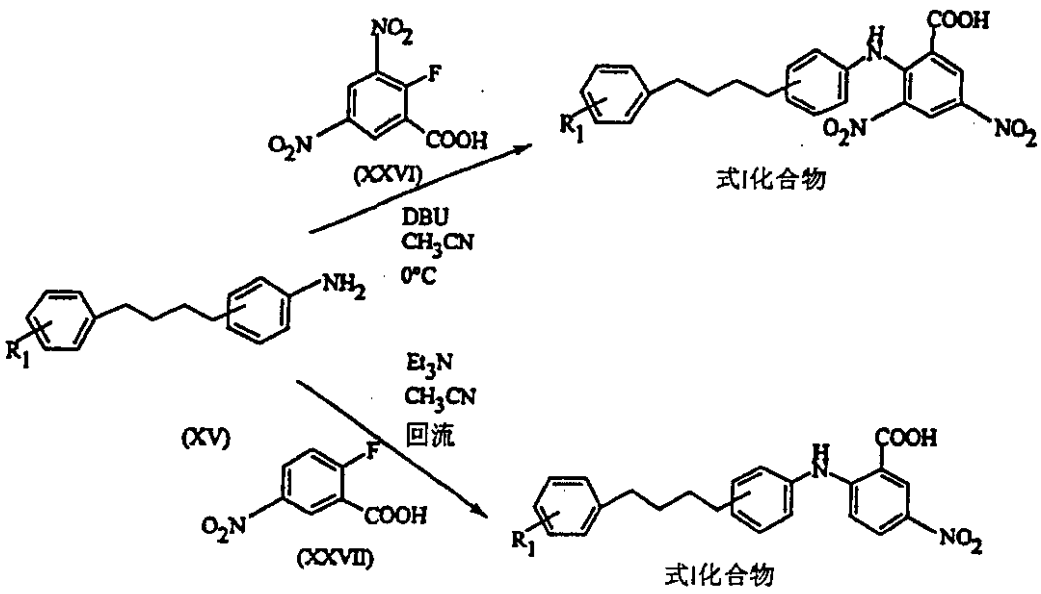
流程图 7



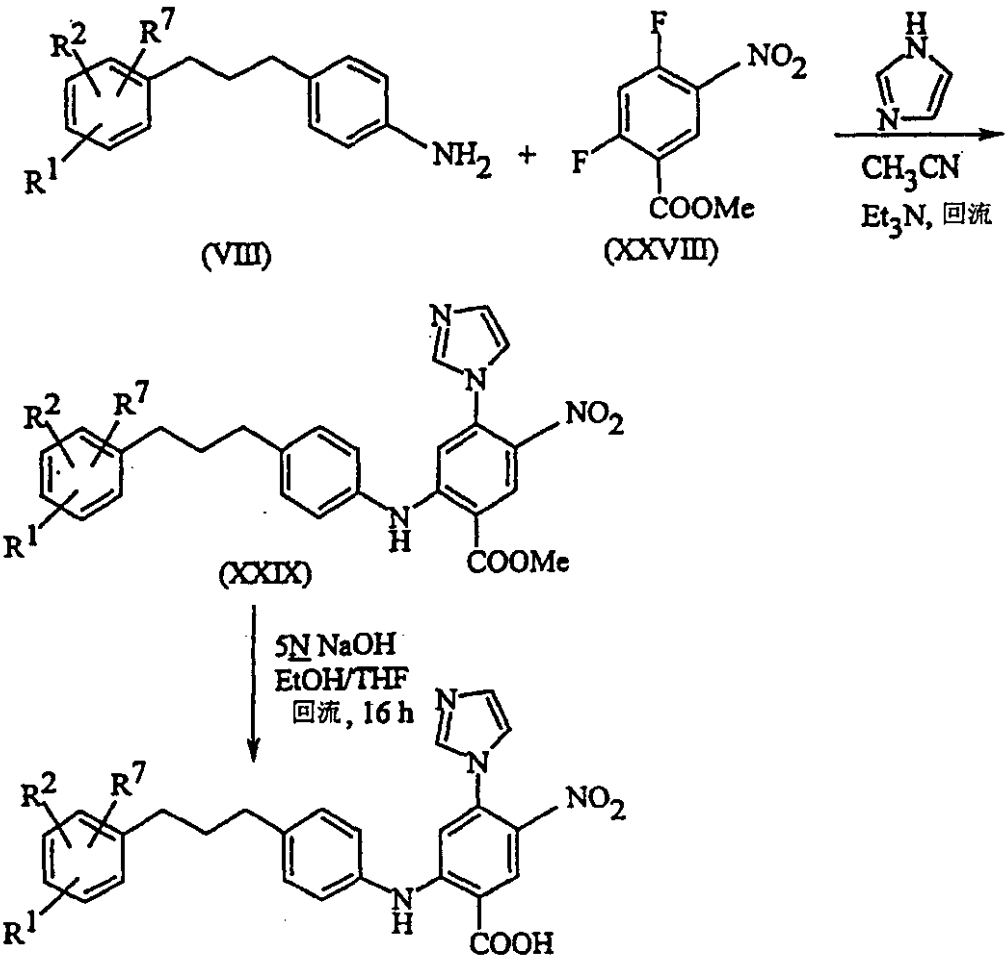
式 I 化合物

R 是形成酯的基团，如烷基或苄基。

流程图 8



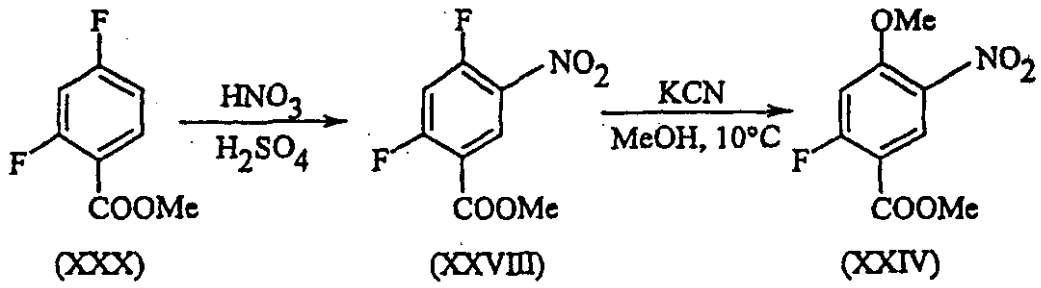
流程图 9



式 I 化合物

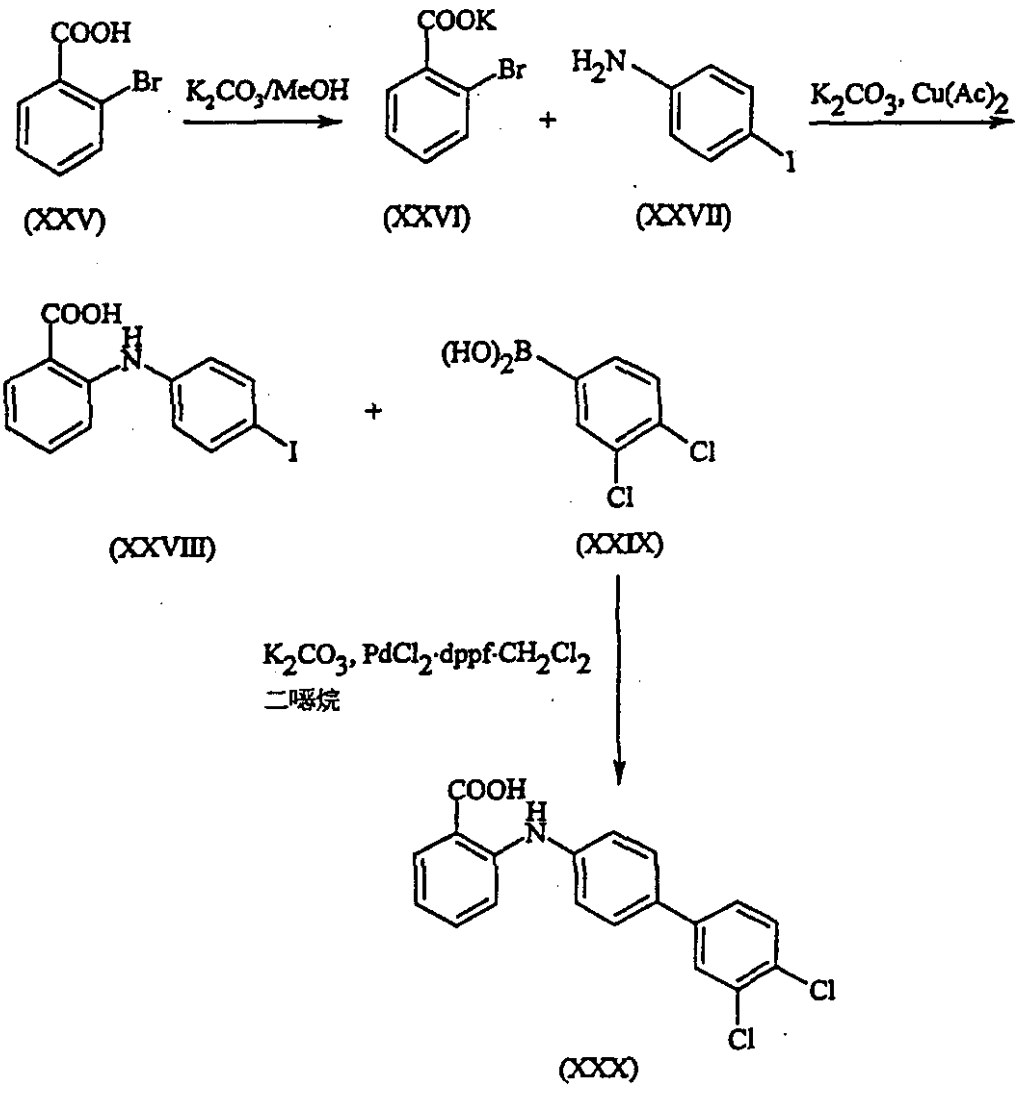
含氟中间体的形成

流程图 10



5

流程图 11



实施例 1

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸的制备

步骤 A(流程图 1)：1,2－二氯－4－〔2－(4－硝基苯基)乙烯基〕苯的制备

将对硝基苯乙酸(51.23g，0.28mol)和 3,4－二氯苯甲醛(49.50g，0.28mol)在哌啶(50mL)中的混合液在氮气氛中于 150－160℃加热 5 小时．将反应混合液冷却后，在滚热的甲醇(50mL)中研磨沉积物，然后在－5℃冷却 12 小时．滤去结晶沉积物，用冷甲醇漂洗，室温下在真空箱中干燥过夜，得到所需产物 22.71g(0.077mol，27％)，为橙色固体，mp. 190－191℃．

MS：294.9(M^+)．

步骤 B(流程图 1)：4－〔2－(3,4－二氯苯基)乙基〕苯胺的制备

将 1,2－二氯－4－〔2－(4－硝基苯基)乙烯基〕苯(98.0g，0.33mol)在四氢呋喃(1.6 L)中的样品在氢气氛中于阮内镍(R^a－Ni)(20g)的存在下在 25－40℃(ΔP＝13.5 psi)还原过滤反应混合物，将滤液真空浓缩，得到所需产物 85.0g(0.32mol，95.8％)，为橙色固体，mp. 68－70℃．

MS：266.1(M^+)．

步骤 C(流程图 6)：2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸的制备

方法 A

将 4－〔2－(3,4－二氯苯基)乙基〕苯胺(28.37g，106.59mmol)、2－溴苯甲酸甲酯(19.10g，88.82mmol)、碳酸铯(40.52g，124.35mmol)、三(二亚苄基丙酮)二钯(0)(2.44g，2.67mmol)和(S)－(2,2'－双(二对甲苯基膦基－1,1'－联萘(98％，(S)－甲苯基－BINAP)(2.71g，4.00mmol)(配位体/Pd＝1.5)在无水甲苯(300mL)中的混合物在氮气氛中于 100℃加热 34 小时．冷却至室温后，用乙醚稀释反应混合物，并用硅藻土过滤，然后用乙醚彻底漂洗．将滤液蒸干，得到褐色残余物(68g)．将所得残余物溶解在乙醇(50mL)和 THF(100mL)中，然后加入 5N 氢氧化钠水溶液(200mL)，将混合物回流 16 小时．真空下除去溶剂．将残余物用浓盐酸酸化至 pH 3．滤取产生的沉淀物，在滚热的甲醇－H_2O(4:1)中研磨，并在真空下于室温干燥 16 小时，得到实施例 1 的化合物(31.95g，0.083mol，77.6％)，为橙色固体，mp. 175.0－177.0℃．

元素分析：$C_{21}H_{17}NO_2Cl_2$

计算值：C, 65.30； H, 4.44； N, 3.63.

实测值：C, 65.40； H, 4.54； N, 3.50.

方法 B

将 2－氯苯甲酸(5.4g，0.034mol)、4－〔2－(3, 4－二氯苯基)乙基〕苯胺(10.0g，0.037mol)、无水碳酸钾（16.9g，0.12mol）、铜粉（4.94g，0.077mol）和氯化铜（I）（0.37g，0.0037mol）在无水二甲基甲酰胺（85mL）中的混合物在 150℃加热回流 24 小时．将反应混合物倾入热水（150mL）中，在加热板上加热至 90℃．加入木炭，将该混合物在 90℃搅拌 5 分钟．用滤纸将上述温热的褐色混合物过滤．然后用浓盐酸（pH 1）将冷却的滤液酸化，滤取沉淀物，在滚热的甲醇－H_2O(1: 2)中研磨，于室温真空干燥 16 小时，得到实施例 1 的化合物(2.3g，0.006mol，17.5％），为橙色固体，mp. 165.0－173.0℃．

元素分析：$C_{21}H_{17}NO_2Cl_2$

计算值：C, 65.30； H, 4.44； N, 3.63.

实测值：C, 65.68； H, 4.58； N, 3.60.

实施例 2

2－｛4－〔2－（3, 4－二氯苯基）乙基〕苯氨基｝－5－硝基苯甲酸的制备

步骤 C（流程图 6）：2－｛4－〔2－（3, 4－二氯苯基）乙基〕苯氨基｝－5－硝基苯甲酸甲酯的制备

将 4－〔2－（3, 4－二氯苯基）乙基〕苯胺（600mg，2.25mmol）、2－溴－5－硝基苯甲酸甲酯（489mg，1.88mmol）、碳酸铯（857mg，2.62mmol）、三（二亚苄基丙酮）二钯（0）（51mg，0.056mmol）和（S）－(2, 2'－双（二对甲苯基膦基－1, 1'－联萘（98％，（S）－甲苯基－BINAP）（58mg，0.085mmol）（配位体/Pd＝1.5）在无水甲苯（16mL）中的混合物在氮气氛中于 100℃加热 12 小时．冷却后，用乙醚稀释反应混合物，用硅藻土过滤，并用乙醚彻底漂洗．将滤液蒸干，得到褐色残余物．用快速色谱法（硅胶，5％乙酸乙酯/己烷）纯化，得到所需产物 540mg（1.21mmol，64％），mp. 107－108℃．

元素分析：$C_{22}H_{18}N_2Cl_2O_4$

计算值：C, 59.34； H, 4.07； N, 6.29.

实测值：C, 59.03； H, 4.04； N, 5.99.

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}－5－硝基苯甲酸的制备

将2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}5－硝基苯甲酸甲酯(340mg，0.76mmol)和1N氢氧化钠水溶液(4.0mL)在乙醇(4.0mL)和THF(4.0mL)中的溶液加热回流16小时．真空下除去溶剂．将残余物用水稀释，并用浓盐酸酸化至pH 1．然后将混合物用二氯甲烷提取，干燥(Na_2SO_4)，过滤，真空浓缩，得到所需产物329mg(0.76mmol，100％)，为黄色固体，mp. 214－217℃．

元素分析：$C_{21}H_{16}N_2Cl_2O_4$

计算值：C, 58.49； H, 3.74； N, 6.50.

实测值：C, 58.24； H, 3.81； N, 6.28.

实施例3

2－{4－〔4－(3,4－二氯苯基)乙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸的制备

往4－〔2－(3,4－二氯苯基)乙基〕苯胺(0.836g，3.14mmol)在THF(20mL)中的冷(－78℃)溶液中滴加LHDMS(6.28mL，1 M THF溶液，6.28mmol)．让反应混合物在－78℃搅拌10分钟．滴加2－氟－4－甲氧基－5－硝基苯甲酸甲酯(0.72g，3.14mmol)在THF(30mL)中的溶液，将所得溶液在－78℃搅拌30分钟．让反应混合物逐渐温热至室温，在氮气氛中搅拌2小时．将反应混合物用乙酸乙酯稀释，并用5N盐酸酸化(pH 3)．将有机层用硫酸钠干燥，过滤，真空浓缩，得到褐色残余物．往该残余物在乙醇(20mL)和THF(40mL)中的溶液加入5N NaOH(50mL)，将所得混合物回流过夜．真空下除去溶剂，用浓盐酸将残余物酸化(pH 3)．滤取沉淀物，在滚热的甲醇－H_2O(1:1)中研磨，真空箱中干燥16小时，得到实施例3的化合物(0.70g，1.51mmol，48％)，为橙色固体，mp. 208－209℃．

元素分析：$C_{22}H_{18}N_2O_5Cl_2$

计算值：C, 57.28； H, 3.93； N, 6.07.

实测值：C, 57.43； H, 3.69； N, 5.86.

实施例4

2－{4－〔2－(3,4－二羟基苯基)乙基〕苯氨基}苯甲酸的制备

步骤A(流程图1)：1,2－二甲氧基－4－〔2－(4－硝基苯基)乙烯基〕苯的制

备

按实施例 1 的步骤 A 中所述方法，由在吡啶（5mL）中的对硝基苯乙酸（25.0g，0.14mol）及 3,4-二甲氧基苯甲醛（21.0g，0.14mol）制得标题化合物 13.4g（0.047mol，34%），为黄色固体，mp: 133-134℃。

元素分析: $C_{16}H_{15}NO_4$

计算值: C, 67.36; H, 5.30; N, 4.91.

实测值: C, 66.81; H, 5.27; N, 4.84.

步骤 B（流程图 1）: 4-〔2-(3,4-二甲氧基苯基）乙基〕苯胺的制备

在氢气氛中于 25℃将 1,2-二甲氧基-4-〔2-(4-硝基苯基）乙烯基）苯（12.1g，0.042mol）在 10% Pd-C（2.0g）的存在下于二甲基甲酰胺（120mL）中还原。将反应混合物真空浓缩，得到固体。将该固体用甲醇（400mL）重结晶，得到所需产物 6.8g（0.026mol，63%），为白色结晶，mp. 115-116℃。

元素分析: $C_{16}H_{19}NO_2$

计算值: C, 74.68; H, 7.44; N, 5.44.

实测值: C, 74.60; H, 7.39; N, 5.35.

步骤 C（流程图 6）: 2-{4-〔2-(3,4-二甲氧基苯基）乙基〕苯氨基}苯甲酸的制备

按实施例 1 的步骤 C 的方法 B 中所述操作，由在无水 DMF（75mL）中的 4-〔2-(3,4-二甲氧基苯基）乙基〕苯胺（9.25g，0.036mol）、2-氯苯甲酸（5.2g，0.036mol）、无水碳酸钾（15.0g，0.11mol）、铜粉（0.45g，0.007mol）和催化量的氯化铜（I）制得标题化合物。用甲醇/H_2O 结晶后，得到所需产物 4.5g（0.012mol，33%）。mp: 137-139℃。

元素分析: $C_{23}H_{23}NO_4$

计算值: C, 73.19; H, 6.14; N, 3.71.

实测值: C, 73.47; H, 6.03; N, 3.78.

步骤 D: 2-{4-〔2-(3,4-二羟基苯基）乙基〕苯氨基}苯甲酸的制备

室温下，在氮气氛中往 2-{4-〔2-(3,4-二甲氧基苯基）乙基〕苯氨基}苯甲酸（0.28g，0.74mmol）在 CH_2Cl_2（20mL）中的溶液中加入 BBr3（3.5mL，1M CH_2Cl_2 溶液，3.5mmol）。让反应混合物在室温搅拌 2 小时，然后倾入冰水

（50mL）中．用乙酸乙酯提取该混合物，将有机层用水洗涤2次，用硫酸钠干燥，过滤，真空浓缩，得到所需产物0.24g（0.69mmol，93％）．mp. 215-217℃．

元素分析：$C_{21}H_{19}NO_4$

计算值：C, 72.19； H, 5.48； N, 4.00.

实测值：C, 71.80； H, 5.46； N, 3.99.

实施例5

2-{4-〔2-（4-二丁基氨基苯基）乙基〕苯氨基}苯甲酸的制备

步骤A（流程图1）：1,1-二丁基氨基-4-〔2-（4-硝基苯基）乙烯基）苯的制备

按实施例1的步骤A中所述方法，由在哌啶（5mL）中的对硝基苯乙酸（9.92g，0.055mol）和4-二丁基氨基苯甲醛（14.32g，0.055mol）制得标题化合物4.12g（0.012mol，16％），为红色固体．

MS：352.2.（M^+）； 353.2.（MH^+）.

步骤B（流程图1）：4-〔2-（4,4-二丁基氨基苯基）乙基〕苯胺的制备

按实施例1的步骤B中所述方法，由在甲醇（100mL）中的1,1-二丁基氨基-4-〔2-（4-硝基苯基）乙烯基）苯（4.10g，11.63mmol）和Ra-Ni（2.0g）在氢气氛中于21-32℃（ΔP=3.6 psi）制得标题化合物3.49g（10.76mmol，92.6％），为无水油状物．

MS：325.3（MH^+）.

步骤C（流程图6）：2-{4-〔2-（4-二丁基氨基苯基）乙基〕苯氨基}苯甲酸的制备

按实施例1的步骤C的方法B中所述的操作，由在无水DMF（30mL）中的2-氯苯甲酸（1.46g，9.36mmol）、4-〔2-（4,4-二丁基氨基苯基）乙基〕苯胺（3.31 g, 10.20mmol）、无水碳酸钾（4.27g，30.88mmol）、铜粉（1.25g，19.65mmol）和氯化铜（I）制得标题化合物0.39g（0.87mmol，8.6％）．mp. 115-117℃．

元素分析：$C_{29}H_{36}N_2O_2$

计算值：C, 78.34； H, 8.16； N, 6.30.

实测值：C, 78.15； H, 8.07； N, 6.10.

实施例 6

2－{4－〔2－(3, 4, 5－三羟基苯基）乙基〕苯氨基}苯甲酸的制备

步骤 A（流程图 1）：1, 2, 3－三甲氧基－5－〔2－(4－硝基苯基）乙烯基）苯的制备

按实施例 1 的步骤 A 中所述方法，由对硝基苯乙酸（18.6g，0.10mol）、3, 4, 5－三甲氧基苯甲醛（19.6g，0.10mol）和哌啶（5mL）制得呈固体的标题化合物 13.0g（0.041mol，41％）．mp：192－195℃．

步骤 B（流程图 1）：4－〔2－(3, 4, 5－三甲氧基苯基）乙基〕苯胺的制备

按实施例 1 的步骤 B 中所述方法，由在 THF（50mL）中的 1, 2, 3－三甲氧基－5－〔2－(4－硝基苯基）乙烯基）苯（9.5g，0.03mol）和 Ra-Ni（1.0g）在 21－26℃（ΔP＝9.6 psi）于氢气氛中制得标题化合物 6.6g（0.023mol，74％），为茶色粉末．mp. 91－93℃．

步骤 C（流程图 6）：2－{4－〔2－(3, 4, 5－三甲氧基苯基）乙基〕苯氨基}苯甲酸甲酯的制备

按实施例 1 的步骤 C 中所述方法，由在无水甲苯（100mL）中的 4－〔2－(3, 4, 5－三甲氧基苯基）乙基〕苯胺（0.75g，2.61mmol）、2－溴苯甲酸甲酯（0.47g，2.17mmol）、碳酸铯（0.99g，3.04mmol）、三（二亚苄基丙酮）二钯（0）（0.06g，0.065mmol）和（S）－(2,2'－双（二对甲苯基膦基－1, 1'－联萘（98％（S）－甲苯基－BINAP）（0.066g，0.098mmol）（配位体/Pd＝1.5）制得标题化合物 0.69g（1.63mmol，76％），为黄色油状物．

元素分析：$C_{25}H_{27}NO_5$

计算值：C, 71.24； H, 6.46； N, 3. 32.

实测值：C, 71.53； H, 6.24； N, 3.14.

2－{4－〔2－(3, 4, 5－三甲氧基苯基）乙基〕苯氨基}苯甲酸的制备

往 2－{4－〔2－3, 4, 5－三甲氧基苯基）乙基〕苯氨基}苯甲酸甲酯（0.62g，1.47mmol）在 THF-乙醇（2: 1，6mL）中的溶液中加入 1N 氢氧化钠溶液（4mL），将反应混合物加热回流 5 小时．然后将反应混合物真空浓缩，除去有机溶剂．

用浓盐酸将残余物酸化（pH 3）．滤取沉淀物，在滚热的甲醇-H_2O（4:1）中研磨，室温下真空干燥16小时，得到标题化合物0.59g（1.45mmol，98.5%），为白色固体．mp. 146.0-147.0℃．

元素分析：$C_{24}H_{25}NO_5$

计算值：C, 70.75； H, 6.18； N, 3.44.

实测值：C, 70.54； H, 6.43； N, 3.15.

步骤D: 2-{4-〔2-（3,4,5-三羟基苯基）乙基〕苯氧基}苯甲酸的制备

按实施例4的步骤D中所述方法，由在CH_2Cl_2（40mL）中的2-{4-〔2-（3,4,5-三甲氧基苯基）乙基〕苯氧基}苯甲酸(0.50g，1.23mmol)和BBr3(10mL，1M CH_2Cl_2溶液，10.0mmol）制得标题化合物0.25g（0.68mmol，65%），为绿色固体．mp：160.0-162.0℃．

元素分析：$C_{21}H_{19}NO_5 \cdot 1.44H_2O$

计算值：C, 64.46； H, 5.64； N, 3.58.

实测值：C, 64.07； H, 5.27； N, 3.39.

实施例7

2-{4-〔2-〔-（3,4-二氯苯基）丙基〕苯氧基}-4-甲氧基-5-硝基苯甲酸的制备

步骤A'（流程图2）：3-（3,4-二氯苯基）-1-（4-硝基苯基）丙烯酮的制备

将氢氧化钠（7.3g，0.18mol）溶解在水（80mL）和95% 乙醇（80mL）中，用冰水浴冷却至10℃．一次加入3,4-二氯苯甲醛（31.8g，0.18mol）．加入完毕后，将混合物温热至15℃．在该温度下加入1-（4-硝基苯基）乙酮（30.0g，0.18mol） 并剧烈搅拌．搅拌5分钟后，用95% 乙醇（300mL）稀释．将所得茶色混合物在室温搅拌30分钟，然后将烧瓶中的内容物在下面的冰水浴冷却下搅拌2小时．滤去淡褐色固体，水洗，空气干燥．将固体溶解在热THF（1.5L）中，用木炭处理．滤去所得混合物，将滤液用95% 乙醇（500mL）稀释．将该溶液过滤，烘干（40℃），得到呈淡褐色固体的标题化合物38.56g(0.12mol，66%）．mp. 220-223℃．

元素分析：$C_{15}H_9Cl_2NO_3$

计算值：C, 55.93； H, 2.82； Cl, 22.01； N, 4.35.

实测值：C, 55.79； H, 2.93； Cl, 22.16； N, 4.32.

步骤 B'（流程图 2）：1－（4－氨基苯基）－3－（3,4－二氯苯基）丙－1－酮的制备

在氢气氛中于 20－32℃（ΔP＝33.4 psi）将 3－（3,4－二氯苯基）－1－（4－硝基苯基）丙烯酮（34.56g，0.11mol）在 Ra-Ni（3.0g）的存在下于 THF（250mL）中还原。将反应混合液真空浓缩，用甲醇（100mL）重结晶，得到所需产物 23.5g（0.080mol，75％），为淡黄色固体。mp. 127－129℃。

元素分析：$C_{15}H_{13}Cl_2NO$

计算值：C, 61.24； H, 4.45； N, 4.76； Cl, 24.10.

实测值：C, 60.91； H, 4.60； N, 4.70； Cl, 23.98.

步骤 C'（流程图 2）：4－〔3－（3,4－二氯苯基）丙基〕苯胺的制备

将 1－（4－氨基苯基）－3－（3,4－二氯苯基）丙－1－酮（20.0g，0.068mol）、NH_2NH_2-H_2O（16mL）和 KOH（85％，5.6g）在乙二醇（160mL）中的混合液在氮气氛中加热回流 16 小时。冷却至室温后，将反应混合物倾入冰水中，用二氯甲烷（2 L）提取。将各层分离，将有机层用硫酸钠干燥，并真空浓缩，得到油状物。将该油状物通过快速色谱法（硅胶，二氯甲烷）纯化，得到油状的所需产物 14.00g（0.05mol，73％）。

元素分析：$C_{15}H_{15}Cl_2N$

计算值：C, 64.30； H, 5.40； N, 4.99； Cl, 25. 31.

实测值：C, 64.21； H, 5.59； N, 5.24； Cl, 24.87.

2,4－二氟－5－硝基苯甲酸甲酯的制备

徐徐搅拌下，将发烟硝酸 90％（8.5mL, 0.19mol）加入到在 1 L 烧杯中的浓硫酸 98％（125mL）中。室温下搅拌 10 分钟后，滴加 2,4－二氟苯甲酸甲酯（21.9g，0.127mol）。滴加完毕后，将反应混合物在室温下徐徐搅拌 40 分钟。然后将反应混合物倾入冰水中，搅拌 10 分钟。用乙酸乙酯提取混合物。将各层分离，将有机层用 1N 氯化钠、饱和碳酸氢钠、水和盐水依次洗涤，并用硫酸钠干燥，过滤，真空浓缩，得到黄色残余物。将该残余物用 10％乙酸乙酯/己烷洗涤，过滤，干燥，得到浅黄色固体 29.0g（0.133mol，82％）。mp. 78－80℃。

元素分析：$C_8H_5F_2NO_4$

计算值：C, 44.25； H, 2.32； N, 6.45.

实测值：C, 44.18； H, 2.39； N, 6.14.

2－氟－4－甲氧基－5－硝基苯甲酸甲酯的制备

将钠金属（1.27g，0.055mol）和甲醇（250mL）在0℃搅拌10分钟。将该溶液加入到2－氟－5－硝基苯甲酸甲酯（10.0g，0.046mol）在甲醇（250mL）中的溶液中，并将混合物在0－5℃搅拌20分钟。然后让反应混合物温热至室温，搅拌2小时。接着，将混合物过滤，得到米色沉淀物。用氯仿（70mL）重结晶，得到标题化合物1.825g（0.008mol，17％），为米色晶状固体。

元素分析：$C_9H_8FNO_5$

计算值：C, 47.17； H, 3.52； N, 6.11.

实测值：C, 47.09； H, 3.47； N, 6.00.

2－{4－〔3－（3, 4－二氯苯基）丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸甲酯的制备

将4－〔3－（3, 4－二氯苯基）丙基〕苯胺（0.94g，3.3mmol）、2－氟－4－甲氧基－5－硝基苯甲酸甲酯（0.75g，3.3mmol）和三乙胺（0.46mL）在乙腈（30mL）中的混合物加热回流120小时。将反应混合物冷却至室温，用二氯甲烷稀释，并用饱和碳酸氢钠洗涤。将有机层用硫酸钠干燥，浓缩，得到固体。将该固体用甲醇重结晶，得到所需产物0.67g（1.37mmol，42％）。

元素分析：$C_{24}H_{22}N_2Cl_2O_5 \cdot 0.42H_2O$

计算值：C, 58.01； H, 4.63； N, 5.64；

实测值：C, 57. 61； H, 4.51； N, 5.94.

2－{4－〔3－（3, 4－二氯苯基）丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸的制备

往2－{4－〔3－（3, 4－二氯苯基）丙基〕苯氨基}－4－甲氧基－5－硝基苯甲酸甲酯（0.30g，0.061mol）在THF（5mL）中的溶液中加入1N氢氧化钠水溶液（2.5mL），将混合物在室温搅拌36小时。除去溶剂，将残余物用浓盐酸酸化至pH 3。滤取沉淀物，真空干燥16小时。用甲醇重结晶，得到呈橙色固体的标题化合物0.21g（0.043mol，70％）。mp. 200－201℃。

元素分析：$C_{23}H_{20}N_2O_5Cl_2 \cdot 0.2H_2O$

计算值：C, 57.68； H, 4.29； N, 5.85； Cl, 14.81.

实测值：C, 57.71； H, 4.34； N, 5.58； Cl, 14.56.

实施例 8

2－{4－〔2－〔－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸的制备

2－{4－〔2－〔－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸甲酯的制备

将 2,4－二氯－5－硝基苯甲酸甲酯(1.63g, 7.5mmol)、咪唑(0.56g, 8.25mmol)和三乙胺 (1.14mL, 8.25mmol)在乙腈 (50mL) 中的混合物在室温搅拌 16 小时。往该深橙色溶液中加入 4－〔3－(3,4－二氯苯基)丙基〕苯胺(2.10g, 7.5mmol)和三乙胺 (1.14mL, 8.25mmol)，将混合物加热回流过夜。使反应混合物冷却，真空浓缩，得到残余物。将该残余物用二氯甲烷稀释，并用饱和碳酸氢钾溶液洗涤。将有机层用硫酸钠干燥，过滤，真空浓缩，得到粗油。用快速色谱法(硅胶，10％乙酸乙酯/己烷)纯化，得到所需产物 1.0g (1.90mmol，25％)。

MS: 524.1 (M^+).

2－{4－〔2－〔－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸的制备

按实施例 8 中所述方法，由在 THF (30mL) 中的 2－{4－〔2－〔－(3,4－二氯苯基)丙基〕苯氨基}－4－咪唑－1－基－5－硝基苯甲酸甲酯 (1.0g, 1.9mmol)、1N NaOH (2.0mL)制得标题化合物 0.30g (0.6mmol，32％)，为橙色固体。

元素分析：$C_{25}H_{20}Cl_2N_4O_4 \cdot 0.2H_2O$

计算值：C, 58.31； H, 3.99； N, 10.88； Cl, 13.89.

实测值：C, 58.34； H, 4.07； N, 10.73； Cl, 13.41.

实施例 9

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酸的制备

2－{4－〔3－(3,4－二氯苯基)丙基〕苯氨基}苯甲酸甲酯的制备

按实施例 2 的步骤 C 中所述方法，由在无水甲苯 (15mL)中的 4－〔3－(3,4－二氯苯基)丙基〕苯胺 (600mg，2.14mmol)、2－溴苯甲酸甲酯 (380mg, 1.78mmol)、碳酸铯(812mg，2.49mmol)、三(二亚苄基丙酮)二钯(0)(49mg,

0.053mmol）和（S）-（2,2'-双（二对甲苯基膦基-1,1'-联萘（98%，（S）-甲苯基-BINAP）（54mg，0.080mmol）（配位体/Pd＝1.5）制得呈黄色油状的标题化合物 0.61g（1.47mmol，69%），为黄色油状物。

MS: 414（M^+），416（MH^+）.

元素分析：$C_{23}H_{21}Cl_2O_2N \cdot 0.4H_2O$

计算值：C, 65.25; H, 5.23; N, 3.30.

实测值：C, 65.76; H, 5.18; N, 3.10.

2-{4-〔3-（3,4-二氯苯基）丙基〕苯氨基}苯甲酸的制备

按实施例 2 中所述方法，由在乙醇（4mL）和 THF（4mL）中的 2-{4-〔3-（3,4-二氯苯基）丙基）苯氨基}苯甲酸甲酯（0.41g，0.99mmol）和 1N NaOH（4.0mL）制得标题化合物 0.32g（0.80mmol，81%），为黄色固体。mp. 120-126℃。

元素分析：$C_{22}H_{19}Cl_2O_2N \cdot 0.75H_2O$

计算值：C, 64.04; H, 5.00; N, 3.39.

实测值：C, 64.17; H, 4.69; N, 3.18.

实施例 10

2-{4-〔4-（3,4-二氯苯基）丁基〕苯氨基}苯甲酸的制备

(反)-3-（3,4-二氯苯基）-2-丙烯醛的制备

将 3,4-二氯苯甲醛（140.0g，0.8mol）和乙醛（300mL）冷却至 5℃。将氢氧化钾（5.1g，0.091mol）溶解在热甲醇（40mL）中，将所得溶液加入到上述冷却的混合物中，同时，将内温维持在 25-30℃。将混合物在冰水浴中搅拌 40 分钟，然后用乙酸酐（400mL）处理。加入完毕后，将混合物冷却至 100℃并搅拌 30 分钟，然后冷却至 30℃。往该混合物中加入 12N HCl/H_2O（102mL/1.2 L），将所得混合物加热回流 30 分钟，然后冷却至室温。将该多相混合物过滤，水洗，得到褐色固体。将所得粗产物溶解在乙酸乙酯中，水洗，用硫酸钠干燥，蒸干。用己烷/乙酸乙酯（9:1）重结晶，得到标题化合物 76.5g（0.38mol，48%）。mp: 91-93℃。

元素分析：$C_9H_6Cl_2O$

计算值：C, 53.77; H, 3.01; Cl, 35.27.

实测值：C, 53.75; H, 3.10; Cl, 35. 58.

(反),(反)-1,2-二氯-4-〔4-(4-硝基苯基)-1,3-丁二烯基〕苯的制备

将在氯仿(1.5 L)中的溴化4-硝基苄(200.0g,0.93mol)和三苯膦(244.0g,0.93mol)的混合物加热回流过夜。将反应混合物冷却至室温,真空浓缩,除去氯仿,然后悬浮在乙醚中,剧烈搅拌。过滤悬浮液,用乙醚洗涤所得米色固体,在80℃干燥16小时,得到溴化〔(4-硝基苯基)甲基〕三苯基正膦433.0g(0.91mol,98%)。将溴化〔(4-硝基苯基)甲基〕三苯基正膦(100.0g,0.23mol)在无水THF(500mL)中的溶液冷却至5℃。滴加正丁基锂(2.4m,96mL,0.23mol),将温度维持在5-10℃。然后移去冷却浴,让反应混合物温热至室温。4小时后,滴加(反)-3-(3,4-二氯苯基)-2-丙醛(36.2g,0.18mol)在THF(100mL)中的溶液,将所得混合物在室温搅拌16小时。将混合物过滤,,并将滤液真空浓缩,得到残余物。用快速色谱法(硅胶,20%乙酸乙酯/己烷)纯化,得到所需产物16.0g(0.05mol,28%)。mp.125-135℃。

元素分析:$C_{16}H_{11}Cl_2NO_2$

计算值:C,60.02; H,3.46; N,4.37; Cl,22.15.

实测值:C,59.77; H,3.47; N,4.40; Cl,22.39.

4-〔4-(3,4-二氯苯基)丁基〕苯胺的制备

按实施例1的步骤B中所述方法,在20-26℃(ΔP=19.3 psi)于氢气氛中,由在THF(75mL)和甲醇(75mL)中的(反),(反)-1,2-二氯-4-〔4-(4-硝基苯基)-1,3-丁二烯基〕苯(15.42g,0.048mol)、Ra-Ni(1g)制得呈固体的标题化合物10.97g(0.037mol,78%)。mp.50-52℃。

元素分析:$C_{16}H_{17}NCl_2$

计算值:C,65.32; H,5.82; N,4.76.

实测值:C,65.43; H,5.84; N,4.61.

2-{4-〔4-(3,4-二氯苯基)丁基〕苯氨基}苯甲酸的制备

按实施例1的步骤C的方法B中所述操作,由在无水DMF(5mL)中的4-〔4-(3,4-二氯苯基)丁基〕苯胺(0.50g,1.7mmol)、2-氯苯甲酸(0.24g,1.56mmol)、无水碳酸钾(0.71g,5.15mmol)、铜粉(0.21g,3.28mmol)和氯化铜(I)(0.015g,0.15mmol)制得标题化合物。mp.98-105℃。

实施例 11

2－(4－〔4－(3,4－二氯苯基)丁基〕苯氨基)－5－硝基苯甲酸的制备

将 2－氟－5－硝基苯甲酸 (1.85g，0.01mol)、4－〔4－(3,4－二氯苯基)丁基〕苯胺 (2.94g，0.01mol)和三乙胺 (2.80mL)在乙腈 (110mL)中的混合物加热回流 48 小时。将反应混合物冷却、真空浓缩，除去溶剂。并将所得残余物溶解在二氯甲烷中，用稀盐酸洗涤。将有机层用硫酸钠干燥，真空浓缩，得到粗固体。用快速色谱法(硅胶，二氯甲烷)纯化，得到所需产物 1.40g(0.003mol，30％)。

元素分析：$C_{23}H_{19}N_2O_4Cl_2$

计算值：C, 60.27； H, 4.18； N, 6.11； Cl, 14.47.

实测值：C, 60.16； H, 4.41； N, 6.09； Cl, 15.69.

实施例 12

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}3,5－二硝基苯甲酸的制备

往 4－〔4－(3,4－二氯苯基)丁基〕苯胺 (1.47g，5.0mmol)和 DBU (0.75mL，7.5mmol)在乙腈 (25mL)中的冷 (0℃)溶液中滴加 2－氟－2,5－二硝基苯甲酸 (1.15g，5.0mmol)在乙腈 (15mL)中的溶液。在 0℃搅拌 30 分钟后，用稀盐酸将反应混合物中和，用乙酸乙酯提取，用硫酸钠干燥，过滤，真空浓缩，得到粗残余物。用乙醇重结晶，得到标题化合物 2.06g (4.1mmol，82％)，为亮橙色固体。

元素分析：$C_{23}H_{19}Cl_2N_3O_6$

计算值：C, 54.77； H, 3.80； N, 8.33； Cl, 14.06.

实测值：C, 54.68； H, 4.00； N, 8.12； Cl, 13.81.

实施例 13

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－5－硝基苯甲酸的制备

溴化〔(3,4－二氯苯基)甲基〕三苯基正膦的制备

将 4－溴甲基－1,2－二氯苯 (2.40g，0.01mol)和三苯膦 (5.24g，0.02mol)在甲苯 (30mL)中的混合物在室温搅拌 16 小时。将固体过滤，用甲苯漂洗，并在室温烘干，得到所需产物 3.95g (0.0078mol，78％)，为白色粉末。

^{1}H-NMR〔二甲亚砜 (DMSO)： ppm〕: 7.89-7.61(m, 15H), 7.50(d, J = 8.3 Hz, 1H), 7.04(t, J = 2.3 Hz, 1H), 6.97(m, 1H), 5.20(d, J = 15.9 Hz, 2H).

4－（4－硝基苯基）丁醛的制备

往草酰氯（在二氯甲烷中的 2.0 M 溶液，14.1mL, 28.2mmol）在二氯甲烷（20mL）中的冷（－70℃）溶液中滴加二甲亚砜（4.40g，56.32mmol）。然后将所得反应混合物在氮气氛中于－70℃搅拌 30 分钟。滴加 4－（4－硝基苯基）丁－1－醇（5.00g，25.6mmol）在二氯甲烷（3mL）中的溶液，将反应混合物在－70℃搅拌 1 小时。加入三乙胺（16mL, 115mmol），然后让反应混合物逐渐温热至室温，并搅拌 30 分钟。接着用水将混合物的反应中止，用乙酸乙酯提取。将有机层用 0.1N 盐酸溶液、水和盐水洗涤，用硫酸钠干燥，过滤，真空浓缩，得到淡褐色油状物。将该油状物用快速色谱法（硅胶，50％乙酸乙酯/己烷）纯化，得到所需产物 3.20g（16.56mmol，65％）。

^{1}H-NMR（DMSO: ppm）：9.75（s, 1H）, 8.12（d, J = 8.3 Hz, 2H）, 7.30（d, J = 8.3 Hz, 2H）, 2.72（t, J = 7.7 Hz, 2H）, 2.47（t, J = 7.1 Hz, 2H）, 1.94（m, 2H）.

1, 2－二氟－4－〔5－（4－硝基苯基）－1－戊烯基〕苯的制备

将溴化〔（3, 4－二氟苯基）甲基〕三苯基正膦（3.95g，7.9mmol）在无水 THF（20mL）中的溶液冷却至 0℃。滴加 LHDMS（1.0 M/THF, 9mL, 9.0mol），将温度维持在 0℃。搅拌 30 分钟后，滴加 4－（4－硝基苯基）丁醛（1.45g, 7.5mmol）在 THF（5mL）中的溶液，让混合物在 2 小时内温热至室温。然后用水将混合物的反应中止，并用乙酸乙酯提取。将有机层用 0.1N 盐酸溶液、水和盐水洗涤，用硫酸钠干燥，过滤，真空浓缩，得到淡褐色油状物。将该油状物用快速色谱法（硅胶，10％乙酸乙酯/己烷）纯化，得到所需产物 2.5g（7.4mmol，99％）。

MS: 335（M^+）, 337（MH^+）.

4－〔5－（3, 4－二氟苯基）戊基〕苯胺的制备

按实施例 1，步骤 B 中所述方法，在 25－40℃（$\Delta P = 9.9$ psi）由在 THF（50mL）中的 1, 2－二氟－4－〔5－（4－硝基苯基）－1－戊烯基〕苯（2.5g, 7.4mmol）和 Ra-Ni（1g）制得标题化合物 1.06g（3.4mmol，46％）。

^{1}H-NMR（DMSO: ppm）：7.45(d, J = 8.3 Hz, 1H), 7.41(d, J = 2.2 Hz, 1H), 7.12(m, 1H), 6.74(d, J = 8.3 Hz, 2H), 6.40(d, J = 8.3 Hz, 2H), 4.73(s, 2H), 2.50(t, J = 7.7 Hz, 2H), 2.31(t, J = 7.6 Hz, 2H), 1.6-1.5(m, 4H), 1.5-1.4(m, 2H).

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－5－硝基苯甲酸的制备

往4－〔5－(3,4－二氯苯基)戊基〕苯胺(0.231g，0.75mmol)在THF(2mL)中的冷(－78℃)溶液中滴加LHDMS(2.25mL,1 M己烷溶液,2.25mmol)。将反应混合物在－78℃搅拌10分钟。滴加2－氟－5－硝基苯甲酸(0.139g，0.75mmol)在THF(2mL)中的溶液，并将该溶液在－78℃搅拌30分钟。氮气氛中逐渐温热至室温并搅拌2小时。用乙酸乙酯稀释反应混合物，并用1N HCl酸化(pH 3)。将有机层用硫酸钠干燥，过滤，真空浓缩，得到褐色残余物。将残余物用快速色谱法(硅胶，2%甲醇/二氯甲烷)纯化，然后用甲醇重结晶，得到所需产物265mg(0.56mmol，75%)。mp. 147－148℃。

元素分析：$C_{24}H_{22}Cl_2N_2O_4 \cdot 0.37H_2O$

计算值：C, 60.05； H, 4.77； N, 5.84.

实测值：C, 59.67； H, 4.64； N, 5.51.

实施例14

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸的制备

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基5－硝基苯甲酸甲酯的制备

按实施例13中所述方法，由在THF(5mL)中的4－〔5－(3,4－二氯苯基)戊基〕苯胺(231mg，0.75mmol)、LHDMS(6.28mL,1 M THF溶液,6.28mmol)和2－氟－4－甲氧基－5－硝基苯甲酸甲酯(172g，0.75mmol)制得标题化合物。将标题化合物用快速色谱法(硅胶，10%乙酸乙酯/己烷)纯化，得到所需产物145mg(0.28mmol，37%)。

MS：515.2(M^+)，517.2(MH^+)。

2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸的制备

按实施例2中所述方法，由在THF(1.2mL)中的2－{4－〔5－(3,4－二氯苯基)戊基〕苯氨基}－4－甲氧基－5－硝基苯甲酸甲酯(145mg，0.28mmol)和1N氢氧化钠水溶液(0.56mL)制得标题化合物。将标题化合物用快速色谱法(硅胶，10%甲醇/二氯甲烷)纯化，然后用甲醇重结晶，得到所需产物58mg(0.12mmol，41%)。mp. 192－193℃。

元素分析：$C_{25}H_{24}Cl2N_2O_5$

计算值：C, 59.65； H, 4.81； N, 5. 56.

实测值：C, 59.29； H, 4.58； N, 5.36.

实施例 15

2－{4－〔3－(3, 4－二氯苯基）丙基〕苯氨基}－5－硝基苯甲酸的制备

2－{4－〔3－(3, 4－二氯苯基）丙基〕苯氨基}－5－硝基苯甲酸甲酯的制备

按实施例 2 的步骤 C 中所述方法，由在无水甲苯（15mL）中的 4－〔3－(3, 4－二氯苯基）丙基〕苯胺（420mg，1.25mmol）、2－溴苯甲酸甲酯（310mg，1.25mmol）、碳酸铯（569mg，1.75mmol）、三（二亚苄基丙酮）二钯（0）（34mg，0.037mmol）和（S）－(2, 2'－双（二对甲苯基膦基－1, 1'－联萘（98％，（S）－甲苯基－BINAP）（38mg，0.056mmol）（配位体/Pd=1.5）制得标题化合物 0.51g（1.11mmol，74％），为橙色固体．mp. 117－118℃．

MS: 457.1 (M^+)； 459.1 (MH^+)

2－{4－〔3－(3, 4－二氯苯基）丙基〕苯氨基}－5－硝基苯甲酸的制备

按实施例 2 中所述的方法，由在乙醇（2mL）和 THF（4mL）中的 2－{4－〔3－(3, 4－二氯苯基）丙基〕苯氨基}－5－硝基苯甲酸甲酯（0.50g，1.09mmol）、2N NaOH（5.0mL）制得标题化合物 0.49g（1.10mmol，100％），为橙色固体．mp. 153－155℃．

MS: 443.2 (M^+), 445.2 (MH^+)

实施例 16

2－{4－〔2－(3, 4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸的制备

2－{4－〔2－(3, 4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸甲酯的制备

按实施例 2 的步骤 C 中所述的方法，由在无水甲苯（32mL）中的 4－〔2－(3, 4－二甲基苯基）乙基〕苯胺（1.0g，4.43mmol）、2－溴－5－硝基苯甲酸甲酯（0.96g，3.69mmol）、碳酸铯（1.68g，5.17mmol）、三（二亚苄基丙酮）二钯（0）（101mg，0.11mmol）和（S）－(2, 2'－双（二对甲苯基膦基－1, 1'－联萘（98％，（S）－甲苯基－BINAP）（113mg，0.17mmol）（配位体/Pd＝1.5）制得标题化合物 1.31g（3.24mmol，73％），为黄色固体．mp. 115－117℃．

MS: 405 (M^+)

元素分析：$C_{24}H_{24}O_4N_2 \cdot 0.25H_2O$

计算值：C, 71.27； H, 5.98； N, 6.93.

实测值：C, 70.48； H, 6.03； N, 6.85.

2－{4－〔2－(3, 4－二甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸的制备

按实施例 2 中所述方法，由在乙醇（50mL）和 THF（50mL）中的 2－{4－〔2－(3, 4－二甲基苯基)乙基〕苯氨基}－5－硝基苯甲酸甲酯(1.12g, 2.76mmol)和 1N NaOH（50mL）制得标题化合物 1.03g (2.63mmol，81％），为黄色固体。mp. 214－216℃。

元素分析：$C_{23}H_{22}O_4N_2 \cdot 0.25H_2O$

计算值：C, 69.99； H, 5.74； N, 7.18.

实测值：C, 69.90； H, 5.82； N, 6.81.

实施例 17

2－〔〔4－〔2－(4－氯－3－三氟甲基苯基）乙基〕苯基〕氨基苯甲酸的制备

步骤 A（流程图 1）：反－1－氯－2－三氟甲基－4－〔2－(4－硝基苯基）乙烯基）苯的制备

将对硝基苯乙酸（51.85g，0.29mol)和 4－氯－3－三氟甲基苯甲醛（47.85g，0.23mol)在哌啶（19.5g，0.23mol)中的混合物在氮气氛中于 150－160℃加热 1 小时。将反应混合物冷却至 80－100℃，加入回流中的异丙醇（150mL）。将混合物继续冷却至室温，然后冷却下放置 5 小时。滤取晶状沉淀物，用冷异丙醇漂洗，在真空箱中于室温干燥过夜，得到反－1－氯－2－三氟甲基－4－〔2－(4－硝基苯基）乙烯基）苯 22.53g (68.75mmol，30％），为橙色固体。mp. 173－174℃。

MS：327.0 (M^+)

步骤 B（流程图 1）：4－〔2－(4－氯－3－三氟甲基苯基）乙基〕苯胺的制备

按实施例 1 的步骤 B 中所述的方法，于 18－29℃（ΔP＝20.5 psi)在氢气氛中由在 THF（0.5 L）中的反－1－氯－2－三氟甲基－4－〔2－(4－硝基苯基）乙烯基）苯（22.53g，0.069mol)和 Ra-Ni（22g）制得呈白色固体的标题化合物 20.0g (66.73mmol，97％）。mp. 62－64℃。

MS：298.1 (M^+)

2-〔〔4-〔2-(4-氯-3-三氟甲基苯基)乙基〕苯基〕氨基苯甲酸的制备

往4-〔2-(4-氯-3-三氟甲基苯基)乙基〕苯胺(4.33g，14.45mmol)在THF(50mL)中的冷(-78℃)溶液中滴加LHMDS(43.35mL, 43.35mmol)(1M/THF)。将反应混合物在-78℃搅拌10分钟。滴加2-氟苯甲酸(2.02g，14.45mmol)在THF(50mL)中的溶液。将混合物在-78℃搅拌2小时，然后温热至室温，再搅拌3小时。将反应混合物真空浓缩(40℃)，除去有机溶剂。将残余物用3N盐酸溶液酸化至pH 3。滤取沉淀物，用10% HCl(40mL)漂洗，真空干燥过夜，得到呈灰白色固体的所需产物4.3g(10.24mmol，70%)。mp. 150-152℃。

元素分析：$C_{22}H_{17}O_2NClF_3 \cdot 0.59H_2O$

计算值：C, 61.39； H, 4.26； N, 3.25.

实测值：C, 61.01； H, 4.34； N, 3.30.

实施例18

2-〔4-(3,4-二氯苯基)苯氨基〕苯甲酸的制备

邻溴苯甲酸钾盐的制备

往邻溴苯甲酸(201.03g，1.0mol)在甲醇(500mL)中的溶液加入碳酸钾(69g，1.0mol)。将混合物浓缩，得到所需产物(239.1g，1.0mol，100%)。

2-〔(4-碘苯基)氨基〕苯甲酸的制备

将邻溴苯甲酸钾盐(47.8g，0.2mol)、4-碘苯胺(43.8g，0.2mol)、碳酸钾(13.8g，0.1mol)和乙酸铜(2.87g，6%)在二甘醇二甲醚(100mL)中的混合物加热回流30分钟。将反应混合物用水(1.0L)稀释，过滤。用稀乙酸将滤液酸化。滤取生成的沉淀物，用水洗涤，并在50℃真空干燥16小时。用乙酸乙酯重结晶，得到呈固体的所需产物(29.7g，0.087mol，44%)。mp. 205-206℃。

元素分析：$C_{13}H_{10}NO_2I$

计算值：C, 45.05； H, 2.97； N, 4.13.

实测值：C, 45.05； H, 2.97； N, 3.92.

2-〔4-(3,4-二氯苯基)苯氨基〕苯甲酸的制备

将3,4-二氯苯基硼酸(880mg，2.3mmol)、2-〔(4-碘苯基)氨基〕苯甲

酸（339mg，1mmol）、$PdCl_2$·dppf·二氯甲烷〔与二氯甲烷配位的氯化 1,1'-双（二苯基膦基）二茂铁合钯（II）（1:1）〕（67mg，0.082mmol）、碳酸钾（829mg，6mmol）和 H_2O（2mL）在二噁烷（15mL）中的混合物加热回流 1 小时。将反应混合物用乙酸乙酯稀释，过滤。将滤液用 1N 盐酸处理，用水、盐水洗涤，用硫酸钠干燥，真空浓缩，得到黄色固体。将该黄色固体用快速色谱法（硅胶，10% 甲醇/二氯甲烷）纯化，得到所需产物 272mg（0.76mmol，76%）。mp.>220℃。

元素分析：$C_{19}H_{13}O_2NCl_2$

计算值：C, 63.23； H, 3.71； N, 3.88.

实测值：C, 62.95； H, 3.73； N, 3.63.

用上述一般性的方法，制得本发明的下述化合物：

实施例 19

2-{4-〔3-（4-二乙基氨基苯基）丙基〕苯氨基}苯甲酸

MS：403（M^+）.

元素分析：$C_{26}H_{30}N_2O_2 \cdot 0.40\ mol\ H_2O$

计算值：C, 69.31； H, 6.87； N, 6.12.

实测值：C, 69.29； H, 7.04； N, 6.35.

实施例 20

2-{4-〔3-（4-硝基苯基）丙基〕苯氨基}苯甲酸

mp. 150-153℃

MS：376（M^+）.

实施例 21

2-{4-〔3-（3-硝基苯基）丙基〕苯氨基}苯甲酸

mp. 164-167℃

MS：376（M^+）.

元素分析：$C_{22}H_{20}N_2O_4 \cdot 2.20\ mol\ H_2O$

计算值：C, 63.51； H, 5.91； N, 6.73.

实测值：C, 63.56； H, 5.45； N, 6.46.

实施例 22

2－{4－〔3－（4－氨基苯基）丙基〕苯氧基}苯甲酸

mp. 110－112℃

MS: 347 ($M+1^+$).

实施例 23

2－{4－〔3－（3－氨基苯基）丙基〕苯氧基}苯甲酸

mp. 109℃

MS: 333 ($M+1^+$).

实施例 24

2－{4－〔2－（4－氨基苯基）苯氧基}苯甲酸

mp. 198－201℃

MS: 333 ($M+1^+$).

元素分析: $C_{21}H_{20}N_2O_2 \cdot 0.1\ mol\ H_2O$

计算值: C, 75.47; H, 6.09; N, 8.38.

实测值: C, 75.32; H, 6.12; N, 8.27.

实施例 25

2－{4－〔2－（4－二丙基氨基苯基）乙基〕苯氧基}苯甲酸一盐酸盐

mp. 176－177 C

MS: 417 ($M+1^+$).

元素分析: $C_{27}H_{32}N_2O_2$

计算值: C, 71.59; H, 7.34; N, 6.18; Cl, 7.83.

实测值: C, 71. 31; H, 7.24; N, 6.19; Cl, 7.74.

实施例 26

2－{4－〔2－（4－二乙基氨基苯基）乙基〕苯氧基}苯甲酸一盐酸盐一水和物

MS: 389 ($M+1^+$).

元素分析: $C_{25}H_{28}N_2O_2 \cdot HCl \cdot H_2O$

计算值: C, 67.78; H, 7.05; N, 6. 32; Cl, 8.00.

实测值：C, 67.83； H, 7.01； N, 6.30； Cl, 7.75.

实施例 27

2－{4－〔3－（3－二丙基氨基苯基）丙基〕苯氨基}苯甲酸

MS：431（$M+1^+$）.

元素分析：$C_{28}H_{34}N_2O_2 \cdot 0.2H_2O$

计算值：C, 77.46； H, 7.99； N, 6.45.

实测值：C, 77.43； H, 7.86； N, 6.40.

实施例 28

2－{4－〔3－（3－二甲基氨基苯基）丙基〕苯氨基}苯甲酸

mp. 115－117℃

MS：374（M^+），375（$M+1^+$）.

元素分析：$C_{24}H_{26}N_2O_2 \cdot 0.1H_2O$

计算值：C, 76.61； H, 7.02； N, 7.44.

实测值：C, 76.57； H, 7.21； N, 7.47.

实施例 29

2－{4－〔3－（4－乙氨基苯基）丙基〕苯氨基}苯甲酸

mp. 133℃

MS：375（$M+1^+$）.

元素分析：$C_{24}H_{26}N_2O_2 \cdot 0.1H_2O$

计算值：C, 76.61； H, 7.02； N, 7.44.

实测值：C, 76.62； H, 7.06； N, 7.36.

实施例 30

2－（N－{4－〔3－（4－二乙基氨基苯基）丙基〕苯基}－N－乙基氨基）苯甲酸

MS：431（$M+1^+$）.

元素分析：$C_{28}H_{34}N_2O_2$

计算值：C, 78.10； H, 7.96； N, 6.51.

实测值：C, 78.02； H, 8.17； N, 6.50.

实施例 31

2－｛4－〔2－（3－二苄基氨基苯基）乙基〕苯氨基｝苯甲酸

mp. 95.5－97.5℃。

元素分析：$C_{35}H_{32}N_2O_2$

计算值：C, 82.00； H, 6.29； N, 5.46.

实测值：C, 81.81； H, 6.58； N, 5.44.

实施例 32

2－｛4－〔3－（3－二乙基氨基苯基）丙基〕苯氨基｝苯甲酸

MS：403（$M+1^+$）.

元素分析：$C_{26}H_{30}N_2O_2 \cdot 0.1H_2O$

计算值：C, 77.23； H, 7.53； N, 6.93.

实测值：C, 77.14； H, 7.82； N, 6.88.

实施例 33

2－｛4－〔2－（3－氨基苯基）乙基〕苯氨基｝苯甲酸

mp. 182－184℃。

MS：333（$M+1^+$）.

元素分析：$C_{21}H_{20}N_2O_2 \cdot 0.25H_2O$

计算值：C, 74.87； H, 6.13； N, 8.43.

实测值：C, 74.86； H, 6.16； N, 8.32.

实施例 34

2－｛4－〔3－（4－二甲基氨基苯基）丙基〕苯氨基｝苯甲酸

MS：375（$M+1^+$）.

元素分析：$C_{24}H_{26}N_2O_2 \cdot 0.1H_2O$

计算值：C, 76.61； H, 7.02； N, 7.44.

实测值：C, 76.52； H, 7.22； N, 7.49.

实施例 35

2－｛4－〔2－（4－乙酰基氨基苯基）乙基〕苯氨基｝苯甲酸

mp. 224℃。

MS: 375 ($M+1^+$).

实施例 36

2-{4-〔2-(3-乙酰基氨基苯基)乙基〕苯氨基}苯甲酸

mp. 213-215℃.

MS: 375 ($M+1^+$).

实施例 37

2-{4-〔2-(3-二丙基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐

mp. 189-193℃.

MS: 417 ($M+1^+$).

元素分析: $C_{27}H_{32}N_2O_2 \cdot HCl$

计算值: C, 71.58; H, 7.34; N, 6.18; Cl, 7.83.

实测值: C, 71.48; H, 7.35; N, 6.10; Cl, 7.66.

实施例 38

2-{4-〔2-(3-二丁基氨基苯基)乙基〕苯氨基}苯甲酸一盐酸盐

mp. 175-180℃.

MS: 445 (M^+).

元素分析: $C_{29}H_{36}N_2O_2 \cdot HCl$

计算值: C, 72.40; H, 7.75; N, 5.82; Cl, 7.37.

实测值: C, 72.61; H, 7.95; N, 5.78; Cl, 7.23.

实施例 39

2-{4-〔3-(4-乙酰基氨基苯基)丙基〕苯氨基}苯甲酸

mp. 176-178℃.

MS: 389 ($M+1^+$).

实施例 40

2-{4-〔3-(3-乙酰基氨基苯基)丙基〕苯氨基}苯甲酸

mp. 140-145℃.

MS: 389 ($M+1^+$).

实施例 41

2－{4－〔2－（3－二乙基氨基苯基）乙基〕苯氨基}苯甲酸一盐酸盐

mp. 166－171℃。

MS: 389 ($M+1^+$).

元素分析: $C_{25}H_{28}N_2O_2 \cdot HCl$

计算值: C, 70.66; H, 6.88; N, 6.59; Cl, 8.34.

实测值: C, 70.48; H, 6.89; N, 6.57; Cl, 18.39.

实施例 42

2－{4－〔2－（3－哌啶－1－基苯基）乙基〕苯氨基}苯甲酸一盐酸盐

mp. 187－193℃。

MS: 401 ($M+1^+$).

元素分析: $C_{26}H_{28}N_2O_2 \cdot HCl$

计算值: C, 71.46; H, 6.69; N, 6.41; Cl, 8.11.

实测值: C, 71.28; H, 6.73; N, 6. 35; Cl, 8.30.

实施例 43

2－{4－〔3－（4－二丙基氨基苯基）丙基〕苯氨基}苯甲酸

MS: 431 ($M+1^+$).

元素分析: $C_{29}H_{34}N_2O_2$

计算值: C, 78.10; H, 7.96; N, 6.51.

实测值: C, 77.91; H, 8.03; N, 6.43.

实施例 44

2－{4－〔3－（4－二丁基氨基苯基）丙基〕苯氨基}苯甲酸

MS: 459 ($M+1^+$).

元素分析: $C_{30}H_{38}N_2O_2$

计算值: C, 78.56; H, 8.35; N, 6.11.

实测值: C, 78.40; H, 8.50; N, 6.19.

实施例 45

2－{4－〔3－（3－二丁基氨基苯基）丙基〕苯氨基}苯甲酸

MS: 459 ($M+1^+$).

元素分析: $C_{30}H_{38}N_2O_2$

计算值: C, 78.56; H, 8.35; N, 6.11.

实测值: C, 78.40; H, 8.43; N, 6.11.

实施例 46

2-(4-{3-〔4-(1H-吡咯-1-基)苯基〕丙基}苯氨基)苯甲酸

mp. 131-136℃.

MS: 397 ($M+1^+$).

元素分析: $C_{26}H_{24}N_2O_2 \cdot 0.2H_2O$

计算值: C, 78.05; H, 6.15; N, 7.00.

实测值: C, 77.95; H, 6.17; N, 7.08.

实施例 47

2-{4-〔3-(4-哌啶-1-基苯基)丙基〕苯氨基}苯甲酸

MS: 415 ($M+1^+$).

元素分析: $C_{27}H_{30}N_2O_2 \cdot 0.2H_2O$

计算值: C, 77.55; H, 7.33; N, 6.70.

实测值: C, 77.37; H, 7.35; N, 6.63.

实施例 48

2-{4-〔3-(4-二乙基氨基甲酰基苯基)丙基〕苯氨基}苯甲酸

mp. 57-62℃.

MS: 431 ($M+1^+$).

元素分析: $C_{27}H_{30}N_2O_3 \cdot 0.3H_2O$

计算值: C, 74.39; H, 7.07; N, 6.43.

实测值: C, 74.23; H, 6.97; N, 6.27.

实施例 49

2-{4-〔3-(4-羧基苯基)丙基〕苯氨基}苯甲酸

mp. 236-239℃.

MS: 375 (M^+).

实施例 50

2－{4－〔3－（4－二乙基氨基甲基苯基）丙基〕苯氨基}苯甲酸

mp. 137℃.

MS: 417 ($M+1^+$).

实施例 51

2－{4－〔3－（4－丙氨基苯基）丙基〕苯氨基}苯甲酸

MS: 389 ($M+1^+$).

元素分析: $C_{25}H_{28}N_2O_2 \cdot 0.2H_2O$

计算值: C, 76.58; H, 7.30; N, 7.14.

实测值: C, 76.61; H, 7.29; N, 7.03.

实施例 52

2－{4－〔3－（3－丙氨基苯基）丙基〕苯氨基}苯甲酸

MS: 389 ($M+1^+$).

元素分析: $C_{25}H_{28}N_2O_2 \cdot 0.1H_2O$

计算值: C, 76.93; H, 7.28; N, 7.18.

实测值: C, 76.85; H, 7.44; N, 7.06.

实施例 53

2－{4－〔3－（4－吡咯烷－1－基苯基）丙基〕苯氨基}苯甲酸

mp. 171－177℃.

MS: 401 ($M+1^+$).

元素分析: $C_{26}H_{28}N_2O_2 \cdot 0.2H_2O$

计算值: C, 77.27; H, 7.08; N, 6.93.

实测值: C, 77.09; H, 6.97; N, 6.96.

实施例 54

2－{4－〔3－（3－哌啶－1－基苯基）丙基〕苯氨基}苯甲酸

mp. 59－61℃.

MS: 415 ($M+1^+$).

元素分析: $C_{27}H_{30}N_2O_2 \cdot 0.3H_2O$

计算值：C, 77.22； H, 7.34； N, 6.67.

实测值：C, 77.18； H, 7.25； N, 6.49.

实施例 55

{5－〔(1－丁基－1, 2, 3, 4－四氢－6－喹啉基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸

mp. 222－224℃.

MS: 391 ($M+1^+$).

实施例 56

{5－〔(1－丁基－2, 3－二氢－1H－吲哚－5－基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}乙酸

mp. > 250℃.

MS: 377 ($M+1^+$).

元素分析：$C_{18}H_{20}N_2O_3S2 \cdot 0.4H_2O$

计算值：C, 56.34； H, 5.46； N, 7. 30； S, 16.71.

实测值：C, 56.27； H, 5.18； N, 7.31； S, 16.74.

实施例 57

3－{5－〔(1－丁基－1, 2, 3, 4－四氢喹啉－6－基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}丙酸

mp. 214－215℃.

MS: 405 ($M+1^+$).

实施例 58

4－{5－〔(1－丁基－1, 2, 3, 4－四氢喹啉－6－基)亚甲基〕－4－氧代－2－硫代噻唑烷－3－基}丁酸

mp. 152－154℃.

MS: 417 ($M-1^+$), 418 (M^+), 419 ($M+1^+$).

元素分析：$C_{21}H_{26}N_2O_3S2 \cdot 0.2H_2O$

计算值：C, 59.74； H, 6.30； N, 6.64； S, 15.19.

实测值：C, 59.59； H, 6.16； N, 6.52； S, 15.38.

实施例 59

2－｛4－〔3－（3,4－二氯苯基）丙基〕苯氨基｝－5－甲基苯甲酸

mp. 98－99℃。

MS: 414 (M^+).

实施例 60

N－（2－｛4－〔3－（3,4－二氯苯基）丙基〕苯氨基｝苯甲酰基）甲磺酰胺由实施例 9 的产物与甲磺酰胺反应而制得。

mp. 53－61℃

元素分析: $C_{23}H_{22}Cl_2N_2O_3S \cdot 0.13H_2O$

计算值: C, 57.58; H, 4.68; N, 5.84.

实测值: C, 57.20; H, 4.66; N, 5.51.

实施例 61

2－｛4－〔2－（3,4－二甲基苯基）乙基〕苯氨基｝－5－硝基苯甲酸

mp. 214－216℃

元素分析: $C_{23}H_{22}N_2O_4 \cdot 0.25H_2O$

计算值: C, 69.99; H, 5.74; N, 7.18.

实测值: C, 69.90; H, 5.82; N, 6.81.

实施例 62

2－〔4－（2－联苯－4－基乙基）苯氨基〕－5－硝基苯甲酸

mp. 239－244℃

MS: 439 (MH^+).

实施例 63

2－｛4－〔2－（4－氯－3－三氟甲基苯基）乙基〕苯氨基｝－5－硝基苯甲酸

mp. 207－209℃

元素分析: $C_{22}H_{16}ClF_3N_2O_4$

计算值: C, 56.85; H, 3.47; N, 6.03.

实测值: C, 56.75; H, 3.71; N, 5.83.

实施例 64

5－氨基－2－｛4－〔2－(3,4－二氯苯基)乙基〕苯氨基｝苯甲酸通过实施例 2 的产物与氢气在阮内镍的存在下反应而制得。

mp. 137－142℃

元素分析：$C_{21}H_{18}Cl_2N_2O_2 \cdot 0.96mol\ THF$

计算值：C, 63.94; H, 4.72; N, 6.00.

实测值：C, 64.33; H, 4.91; N, 6.35.

实施例 65

5－硝基－2－(4－苯乙基苯氨基)苯甲酸

mp. 198－202℃

元素分析：$C_{21}H_{18}N_2O_4 \cdot 0.11H_2O$

计算值：C, 69.22; H, 5.04; N, 7.69.

实测值：C, 69.59; H, 5.27; N, 7.22.

实施例 66

2－｛4－〔2－(4－氟－3－三氟甲基苯基)乙基〕苯氨基｝苯甲酸

mp. 148－150℃

元素分析：$C_{22}H_{17}F_4NO_2$

计算值：C, 65.51; H, 4.25; N, 3.47.

实测值：C, 65.51; H, 4.13; N, 3.46.

实施例 67

2－｛4－〔2－(3,4－二氯苯基)乙基〕苯氨基｝－5－硝基苯甲酸

mp. 203－208℃

元素分析：$C_{21}H_{16}F_2N_2O_4$

计算值：C, 63.32; H, 4.05; N, 7.03.

实测值：C, 62.94; H, 4.37; N, 6.87.

实施例 68

｛4－〔2－(3,4－二氯苯基)乙基〕苯基｝－〔2－(1H－四唑－5－基)苯基〕胺按实施例 1 中所述方法，使用由市售的 2－氰苄腈和叠氮化钠在标准反应条

件下合成的四唑氟中间体而制得。mp.129 收缩，152－157℃。

元素分析：$C_{21}H_{17}Cl_2N_5 \cdot 0.15$ 乙酸乙酯$\cdot 0.15$ 己烷

计算值：C, 61.80； H, 4.64； N, 16.12.

实测值：C, 61.61； H, 4.28； N, 15.83.

实施例 69

2－{4－〔2－（4－氟－3－三氟甲基苯基）乙基〕苯氨基}－5－硝基苯甲酸

mp. 190－193℃

元素分析：$C_{22}H_{16}F_4N_2O_4$

计算值：C, 58.93； H, 3.60； N, 6.25.

实测值：C, 58.69； H, 3.42； N, 6.57.

实施例 70

2－（4－苯乙基苯氨基）苯甲酸

mp. 173－182℃

元素分析：$C_{21}H_{19}NO_2$

计算值：C, 79.47； H, 6.03； N, 4.41.

实测值：C, 79.42； H, 5.97； N, 4.47.

实测值：C, 79.59； H, 6.03； N, 4.50.

实施例 71

2－{4－〔2－（3, 4－二氯苯基）乙基〕苯氨基}－5－氟苯甲酸

mp. 180－182℃

元素分析：$C_{21}H_{16}Cl_2FNO_2 \cdot 0.06H_2O$

计算值：C, 62.23； H, 4.01； N, 3.46.

实测值：C, 61.83； H, 4.04； N, 3.29.

实施例 72

2－{4－〔2－（3, 4－二氯苯基）乙基〕苯氨基}烟酸

mp. 168－171℃

元素分析：$C_{20}H_{16}Cl_2N_2O_2$

计算值：C, 62.03； H, 4.16； N, 7.23.

*实测值：C, 62.11； H, 4.17； N, 7.07.

实施例 73

2－{4－〔2－（3－氯苯基）乙基〕苯氨基}－5－硝基苯甲酸

mp. 192.5－194.5℃

元素分析：$C_{21}H_{17}ClN_2O_4$

计算值：C, 63.56； H, 4.32； N, 7.06.

实测值：C, 63.83； H, 4.62； N, 6.79.

实施例 74

2－{4－〔2－（4－氯苯基）乙基〕苯氨基}－5－硝基苯甲酸

mp. 210－212℃

元素分析：$C_{21}H_{17}ClN_2O_4 \cdot 0.26H_2O$

计算值：C, 62.82； H, 4.40； N, 6.98.

实测值：C, 62.51； H, 4.34； N, 6.58.

实施例 75

2－{4－〔2－（3, 4－二氯苯基）乙基〕苯氨基}－5－甲基苯甲酸

mp. 153－160℃

元素分析：$C_{22}H_{19}Cl_2NO_2 \cdot 0.61H_2O$

计算值：C, 64.25； H, 4.96； N, 3.41.

实测值：C, 63.87； H, 4.64； N, 3.55.

实施例 76

2－{4－〔2－（2－氯苯基）乙基〕苯氨基}－5－硝基苯甲酸

mp. 236－238℃。

实施例 77

2－{4－〔2－（2, 4－二氯苯基）乙基〕苯氨基}－5－硝基苯甲酸

mp. 200.5－202.5℃

元素分析：$C_{21}H_{16}Cl_2N_2O_4$

计算值：C, 58.49； H, 3.74； N, 6.50.

实测值：C, 58.33； H, 3.67； N, 6.29.

实施例 78

2－｛4－〔2－（3, 4－二氯苯基）乙基〕苯氨基｝－6－三氟甲基苯甲酸

mp. 130－132℃

元素分析：$C_{22}H_{16}Cl_2F_3NO_2$

计算值：C, 58.17； H, 3.55； N, 3.08.

实测值：C, 58.25； H, 3.65； N, 3.05.

实施例 79

2－｛4－〔2－（4－二丁基氨基苯基）乙基〕苯氨基｝－5－硝基苯甲酸

mp. > 260℃

实施例 80

2－｛4－〔2－（3, 4－二氯苯基）乙基〕苯氨基｝－5－二甲基氨基苯甲酸

mp. 75－80℃

实施例 81

2－｛4－〔2－（3, 5－二氯苯基）乙基〕苯氨基｝苯甲酸

mp. 191－194℃

元素分析：$C_2lH_{17}Cl_2N02$

计算值：C, 65.30； H, 4.44； N, 3.63.

实测值：C, 65.38； H, 4.29； N, 3.52.

实施例 82

2－（4－｛2－〔（4aS, 8aR）－4－（八氢异喹啉－2－基）苯基〕乙基｝苯氨基）苯甲酸按实施例 1，用十氢异喹啉醛而制得，而十氢异喹啉醛由反－十氢异喹啉和对氟苯甲醛在标准反应条件下得到。mp. 203－206℃。

元素分析：$C_{30}H_{34}N_2O_2 \cdot 0.12H_2O$

计算值：C, 78.89； H, 7.56； N, 6.13.

实测值：C, 78.49； H, 7.58； N, 5.90.

下列实施例的化合物通过前述方法而制得，或通过使用标准的组合合成方

法，将卤代苯甲酸酯与取代的苯胺反应，形成相应的二芳基胺，然后皂化成式I的苯甲酸而得到。下面的反应以0.15毫摩尔等级进行。将各卤代苯甲酸酯反应物（0.18 M）在甲苯中的溶液置于2英钱反应瓶中。将各苯胺反应物溶解在无水甲苯中，形成0.15 M溶液。用Distriman吸液管将1mL（0.15mmol，1当量）的各卤代苯甲酸酯溶液加入到合适的加入了1mL（0.18mmol，1.2当量）的苯胺反应物的瓶中。将0.025 M的$Pd_2(dba)_3$〔二钯-三（二亚苄基丙酮）〕和0.075 M的BINAP〔2,2'-双（二苯基膦基）-1,1'-联萘〕溶解在甲苯中，制得催化剂溶液，将0.25mL该催化剂溶液加入到各反应瓶中。将碱〔通常是碳酸铯（68mg，0.21mmol，1.40当量）〕加入到各反应瓶中，给瓶加盖，将其置于摇箱中，在100℃加热48小时。然后将反应混合物冷却，蒸去反应溶剂。将固体残余物悬浮在400μL乙酸乙酯中，滤去所有催化剂。将滤液浓缩蒸干，得到苯甲酸部分被酯化（例如，苄酯或甲酯）的式I化合物。将所得酯溶解在500μLTHF/乙醇（1：1，v/v）中，加入300μL的5 M氢氧化钠。将所得溶液在60℃振荡5小时，然后冷却，浓缩蒸干，得到所需式I化合物。用此方法得到的典型化合物如下。这些化合物的结构式一般通过质谱分析加以确定。

实施例83

2-（3',5'-二氯-3-甲基联苯-4-基氨基）苯甲酸

MS：371； MW：372.2495.

实施例84

2-（3',5'-二溴-3-甲基联苯-4-基氨基）苯甲酸

MS：459； MW：461.1515.

实施例85

2-（4-1,3-苯并间二氧杂环戊烯-5-基-2-甲基苯氨基）苯甲酸

MS：347； MW：347.3683.

实施例86

2-（2,2',4'-三氯联苯-4-基氨基）苯甲酸

MS：391； MW：392.6678.

实施例 87

2－〔2－氯－3', 4'－二氟联苯－4－基氨基〕苯甲酸

MS: 359; MW: 359.7578.

实施例 88

2－〔3'－溴－2－氟联苯－4－基氨基〕苯甲酸

MS: 401; MW: 402.6737.

实施例 89

2－｛4－〔2－(3, 4－二氟苯基)乙基〕苯氨基｝－5－硝基苯甲酸

实施例 90

2－｛4－〔2－(3, 4－二氟苯基)乙基〕苯氨基｝－3－硝基苯甲酸

实施例 91

3－｛4－〔2－(3, 4－二氟苯基)乙基〕苯氨基｝苯甲酸

实施例 92

5－｛4－〔2－(3, 4－二氟苯基)乙基〕苯氨基｝间苯二甲酸

实施例 93

2－｛4－〔2－(3, 4－二氟苯基)乙基〕苯氨基｝苯甲酸

实施例 94

2－｛4－〔2－(3, 4－二氟苯基)乙基〕苯氨基｝－4, 5－二甲氧基苯甲酸

实施例 95

2－｛4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基｝－3－硝基苯甲酸

实施例 96

3－｛4－〔2－(3－氯－4－甲基苯基)乙基〕苯氨基｝苯甲酸

实施例 97

5－{4－〔2－（3－氯－4－甲基苯基）乙基〕苯氨基}间苯二甲酸

实施例 98

2－{4－〔2－（3－氯－4－甲基苯基）乙基〕苯氨基}苯甲酸

实施例 99

4－（4－{2－〔（4aS, 8aR）－4－（八氢异喹啉－2－基）苯基〕乙基}苯氨基）苯甲酸

实施例 100

2－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}－5－甲氧基苯甲酸

实施例 101

2－{4－〔2－（3－甲氧基苯基）乙基〕苯氨基}苯甲酸

实施例 102

2－{4－〔2－（3－溴苯基）乙基〕苯氨基}苯甲酸

实施例 103

2－{4－〔2－（3－氟苯基）乙基〕苯氨基}苯甲酸

实施例 104

2－{4－〔2－（3, 4－二氯苯基）乙基〕苯氨基}－5－甲氧基苯甲酸

实施例 105

4－{4－〔2－（3, 4－二氯苯基）乙基〕苯氨基}烟酸

实施例 106

2－〔2－（4－氟－3－三氟甲基苯基）－2, 3－二氢－1H－异吲哚－5－基氨基〕苯甲酸

实施例 107

2－{4－〔2－（3－氟－4－甲基苯基）乙基〕苯氨基}苯甲酸

实施例 108

2－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}－5－硝基苯甲酸

实施例 109

4－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}苯甲酸

实施例 110

4－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}－3－甲氧基－6－硝基苯甲酸

实施例 111

4－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}－3－甲氧基苯甲酸

实施例 112

2－{4－〔2－（3－氟－4－甲基苯基）乙基〕苯氨基}－5－甲氧基苯甲酸

实施例 113

{4－〔2－（3－氟－4－甲基苯基）乙基〕苯基}－（2－甲氧基－5－硝基苯基）胺

实施例 114

2－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}－3－硝基苯甲酸

实施例 115

3－{4－〔3－（4－二乙基苯基）丙基〕苯氨基}苯甲酸

实施例 116

2－{4－〔2－（3,4－二甲氧基苯基）乙基〕苯氨基}苯甲酸

mp. 159－161℃

实施例 117

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸一钠

mp. 107－108℃

实施例 118

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸一钾

mp. > 200℃

实施例 119

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸钙盐(1:1)

mp. > 220℃

实施例 120

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸 2－羟基－1,1－二羟甲基乙铵

mp. 185－187℃

实施例 121

2－{4－〔4－(3,4－二氯苯基)丁基〕苯氨基}－5－甲氧基苯甲酸

mp. 155－158℃

实施例 122

2－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸

mp. 184－185℃

实施例 123

2－{3－〔2－(4－氯苯基)乙基〕苯氨基}苯甲酸

mp. 155－157℃

实施例 124

2－{3－〔2－(3,4－二甲基苯基)乙基〕苯氨基}苯甲酸

mp. 182－184℃

实施例 125

2－{4－〔2－(2,4－二甲氧基苯基)乙基〕苯氨基}苯甲酸

mp. 180－181℃

实施例 126

2－{4－〔2－(2－氯苯基)乙基〕苯氨基}苯甲酸

mp. 140－143℃

实施例 127

2－{4－〔2－(2－羟基苯基)乙基〕苯氨基}苯甲酸

mp. 218－219℃

实施例 128

2－{4－〔2－(3－氯苯基)乙基〕苯氨基}苯甲酸

mp. 152－154℃

实施例 129

2－〔4－(2－联苯－4－基乙基)苯氨基〕苯甲酸

mp. 200－202℃

实施例 130

2－{4－〔2－(2,4－二氯苯基)乙基〕苯氨基}苯甲酸

mp. 181－183℃

实施例 131

3－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基}苯甲酸

mp. 137－138℃

实施例 132

4－{4－〔2－(3,4－二氯苯基)乙基〕苯氨基)苯甲酸

mp. 214－215℃

实施例 133

2－｛4－〔2－（3,4,5－三甲氧基苯基）乙基〕苯氨基｝苯甲酸

mp. 146－147℃

实施例 134

2－｛4－〔2－（4－苯氧基苯基）乙基〕苯氨基｝苯甲酸

mp. 153－154℃

实施例 135

2－｛4－〔5－（3,4－二氯苯基）戊基〕苯氨基｝苯甲酸

mp. 106－108℃

实施例 136

2－｛4－〔2－（4－｛2－羟基羰基苯基氨基｝苯基）乙基〕苯氨基｝苯甲酸

MS: 451（$M^{\square 1}$）.

实施例 137

2－（3',5'－二氯联苯－4－基氨基）苯甲酸

mp. > 220℃

实施例 138

4－｛4－〔3－（3,4－二氯苯基）丙基〕苯氨基｝－2－甲氧基－5－硝基苯甲酸

mp. 74－78℃

实施例 139

2－｛4－〔3－（3,4－二氯苯基）丙基〕苯氨基｝－5－氟苯甲酸

mp. 122－123℃

实施例 140

5－氨基－2－｛4－〔5－（3,4－二氯苯基）戊基〕苯氨基｝苯甲酸

mp. 182－184℃

实施例 141

N－（2－｛4－〔3－（3,4－二氯苯基）丙基〕苯氧基｝苯甲酰基）－C,C,C－三氟甲磺酰胺

MS: 531 (M^-).

实施例 142

N－（2－｛4－〔3－（3,4－二氯苯基）丙基〕苯氧基｝苯甲酰基）苯磺酰胺

MS: 539.

实施例 143

2－｛4－〔2－（3,4－二氯苯基）乙基〕苯氧基｝－5－三氟甲基苯甲酸

mp. 190－192℃; MS: 453 (M^{-1}).

实施例 144

4－｛4－〔2－（3,4－二氯苯基）乙基〕苯氧基｝间苯二甲酸

mp. 264－266℃

实施例 145

2－｛4－〔2－（3,4－二氯苯基）乙基〕苯氧基｝－4－三氟甲基苯甲酸

mp. 134－136℃; MS: 454 (M^+).

实施例 146

2－｛4－〔2－（3,4－二氯苯基）乙基〕苯氧基｝－3－三氟甲基苯甲酸

MS: 454 (M^+).

实施例 147

2－（｛4－〔2－（3,4－二氯苯基）乙基〕苯基｝甲氧基）－5－二甲基氨基苯甲酸

mp. 128－131℃

实施例 148

2－（｛4－〔2－（3,4－二氯苯基）乙基〕苯基｝甲氧基）苯甲酸

MS: 400 (M^+).

实施例 149

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-二丙基氨基苯甲酸

MS: 485 (M^+).

实施例 150

5-二丁基氨基-2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}苯甲酸

MS: 513 (M^+).

实施例 151

2-{4-〔2-(3,4-二氯苯基)乙基〕苯氨基}-5-二乙基氨基苯甲酸

mp. 106-110℃

实施例 152

2,2'-〔1,2-乙二基二(4,1-亚苯基亚氨基)〕二-苯甲酸

实施例 153

4-〔3-〔4-(二乙基氨基)苯基〕丙基)-N-(2-甲氧基-5-硝基苯基)苯胺

实施例 154

2-{3-〔2-(4-氯苯基)乙基〕苯氨基}苯甲酸

实施例 155

2-{3-〔3-(3,4-二氯苯基)丙基〕苯氨基}苯甲酸

实施例 156

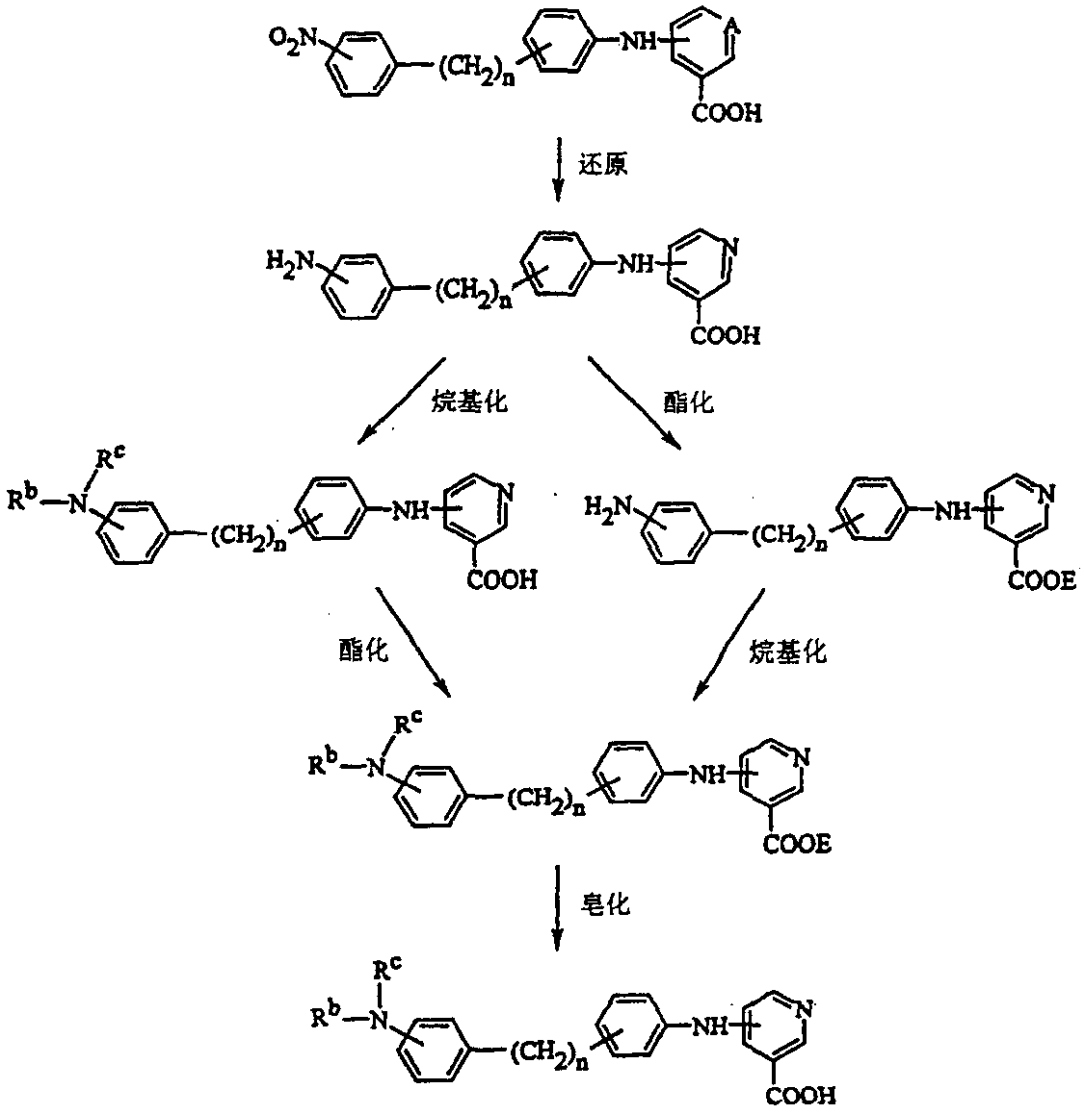
2-{3-〔3-(4-二乙基氨基苯基)丙基〕苯氨基}苯甲酸

实施例 157

2-{3-〔3-(4-二正丙基氨基苯基)丙基〕苯氨基}苯甲酸

下述实施例 158－163 举例说明本发明的化合物在合成本发明的其它化合物和衍生物中作为起始物质和中间体的应用。这些实施例举例说明了硝基还原成氨基、氨基的烷基化和羧酸基团的酯化。这些反应见述于下面的归纳化了的流程图 12 中。

流程图 12



其中，R^b和 R^c的定义同上，E 为形成酯的基团，例如 C_1-C_6烷基（如甲基、2,2,2－三氯乙基）、苄基、二苯基甲基等。

实施例 158

2－{4－〔3－（4－硝基苯基）丙基〕苯氨基}苯甲酸

室温下往 4－〔3－（4－硝基苯基）丙基〕 苯胺（4.08g，15.9mmol）和 2－溴苯甲酸（3.52g，17.5mmol）在异丙醇（100mL）中的浆液中加入乙酸铜（87mg，

0.478mmol）和乙酸钾（3.44g，35.0mmol）。将所得混合物加热回流 23 小时，然后冷却至室温。减压下除去溶剂后，将残余物用水（100mL）稀释，并用 1.0 M 氢氧化钠水溶液碱化至 pH 9.0。将水层用乙醚（20mL，二次）洗涤，并用 1.0 M 盐酸溶液酸化至 pH 3.0。用抽吸法将形成的沉淀物过滤，并在 60℃真空干燥，得到呈米黄色固体的标题化合物（5.75g，得率 96％）。mp. 150－153℃。

MS（Fab）：376（MH^+）。

实施例 159

2－{4－〔3－（4－氨基苯基）丙基〕苯氨基}苯甲酸

室温下在氩气氛中往 2－{4－〔3－（4－硝基苯基）丙基〕苯氨基}苯甲酸（实施例 158）（3.0g，7.97mmol）在 DMF（40mL）中的溶液中加入 10％Pd-C（300mg）。往烧瓶中导入氢气（1 atm），将混合物在室温搅拌 14 小时。用硅藻土将反应混合物过滤，除去 Pd-C，真空浓缩。将残余物用甲醇（约 50mL）稀释，真空浓缩。此操作重复 3 次，以完全除去 DMF。将残余物再用甲醇稀释，滤去不溶物。真空下除去滤液中的溶剂，得到油状物，将该油状物用乙腈（50mL）稀释，缓慢滴加水（100mL）。过滤形成的沉淀物，在 60℃真空干燥，得到呈白色固体的标题化合物（2.34g，得率 85％）。mp. 110－112℃。

MS(Fab)：347（MH^+）。

实施例 160

2－{4－〔3－（4－氨基苯基）丙基〕苯氨基}苯甲酸甲酯

室温下往 2－{4－〔3－（4－氨基苯基）丙基〕苯氨基}苯甲酸（实施例 159）（2.34g，6.75mmol）在甲醇（50mL）中的溶液中加入浓硫酸（1.0mL）。将混合物回流搅拌 3.0 日.在 5℃用三乙胺（10mL）中止反应， 减压下除去溶剂。将残余物用水（20mL）稀释，并用乙醚（20mL，4 次）提取。将合并的乙醚层用水（10mL）和盐水（10mL）洗涤，用无水硫酸钠干燥。减压下除去溶剂，通过柱层析纯化，得到呈黄色无定形质的粗标题化合物（2.59g）。使用该物质而未作进一步纯化。

实施例 161

2－{4－〔3－（4－二乙基氨基苯基）丙基〕苯氨基}苯甲酸甲酯和 2－{4－〔3－（4－乙氨基苯基）丙基〕苯氨基}苯甲酸甲酯

在5℃往 上述粗酯（2.59g，约6.75mmol）和乙醛（2.0mL, 35.1mmol）在乙腈（50mL）中的溶液中加入 $NaBH_3CN$（1.70g，27.0mmol），将悬浮液搅拌30分钟，同时，监测pH并加入1.0 M盐酸水溶液，使混合物保持适度酸性（pH 3.0-4.0）。让反应混合物用1.0小时温热至室温，然后用1.0 M氢氧化钠水溶液碱化至pH 9.0。减压下浓缩反应混合物，除去乙腈，将所得水溶液用1.0 M盐酸水溶液酸化至pH 3.0。将所得水溶液用氯仿（20mL, 3次）提取，将合并的提取液用盐水（5mL）洗涤。用无水硫酸钠干燥后，减压下除去溶剂，通过柱层析（硅胶60N，正己烷/氯仿/三乙胺 50: 98: 2）纯化。最先洗脱出来的是二烷基化物（1.07g，38%），为黄色无定形物。

MS（Fab）：417（MH^+）.

随后洗脱出来的是单烷基化物（0.79g，30%），为黄色无定形物。

MS（Fab）：389（MH^+）.

实施例162

2-{4-〔3-（4-二乙基氨基苯基）丙基〕苯氨基}苯甲酸

室温下往2-{4-〔3-（4-二乙基氨基苯基）丙基〕苯氨基}苯甲酸甲酯（1.68g，4.03mmol）在乙醇（50mL）中的乳液加入3 M氢氧化钾水溶液（4.0mL, 12.0mmol），然后将混合物加热回流40分钟。将反应混合物冷却至室温，用1.0 M盐酸水溶液中和至pH 9.0。减压下将混合物浓缩，除去乙醇，将所得水溶液用氯仿（50mL, 3次）提取。将合并的提取液用盐水（10mL）洗涤，用无水硫酸钠干燥。减压下除去溶剂，通过柱层析（硅胶60N，浓 NH_4OH/甲醇/氯仿 0.2: 2: 100至0.5: 5: 100）纯化，得到黄色油状物。将该油状物用丙酮稀释，将所得溶液在室温减压浓缩，得到呈无定形固体的标题化合物（1.62g，0.2水和物，99%）.

MS（Fab）：403（MH^+）.

元素分析：$C_{26}H_{30}N_2O_2 \cdot 0.20H_2O$

计算值：C, 76.89； H, 7.54； N, 6.90.

实测值：C, 76.73； H, 7.67； N, 7.10.

实施例163

2-{4-〔3-（4-乙氨基苯基）丙基〕苯氨基}苯甲酸

按实施例162中所述方法，由2-{4-〔3-（4-乙氨基苯基）丙基〕苯氨基}

苯甲酸甲酯（得自实施例 161）、乙醇（10mL）和 3 M 氢氧化钾溶液（1.0mL）制得呈黄色固体的标题化合物 253mg （0.1 水和物，90％）。

MS（Fab）：375（MH^+）.

元素分析：$C_{24}H_{26}N_2O_2 \cdot 0.10H_2O$

计算值：C, 76.61； H, 7.02； N, 7.44.

实测值：C, 76.62； H, 7.06； N, 7.36.

生物学实施例

用已很好建立的指示在治疗阿尔茨海默病的临床有用性的若干体外和体内试验评估代表性的式 I 化合物。

淀粉样蛋白试验

BASSR（β－淀粉样蛋白自我接种(self-seeding)放射性测定）

材料：

原液：

测定用缓冲液：50mM 磷酸钠，pH 7.5，100mM 氯化钠，0.02％NaN_3，1 M 尿素（过滤，在 4℃贮存）

可溶性 Aβ（1－40）肽（加州 Torrance 市 Bachem 公司产品）：2.2mg/mL 去离子水溶液（以等分试样贮存在 -20℃，解冻后保持在冰上）在贮存 1 周后会自我接种。通常，应将溶液贮存至测定中未出现停滞期。

^{125}I 标记的 Aβ（1－40）：150K－350K cpm/μL100％ 乙腈-0.1％三氟乙酸（TFA）-1％β－巯基乙醇（以等分试样贮存在 -20℃）。

^{125}I 标记的 Aβ(1－40)可按 H.LeVine, III 在 *Neurobiol. Aginig*, 16, 755 (1995)(该文纳入于此作为参考）中所述方法制备，也可由伊利诺斯州 Arlington Heights 的 Amersham 公司购得。

最终测定条件：每次测定须用 30μM 可溶性 Aβ（1－40）/去离子水/测定用缓冲液 + 20K + 50Kcpm ^{125}I 标记的 Aβ（1－40）。将受试化合物溶解在 DMSO 中，

通常形成 5－50mM 原液，使测定时的 DMSO 最终浓度小于 1％v/v。

测定：用于 50 次测定的反应混合液（在冰上）包含每次测定所需的 0.1－0.2μL ^{125}I 标记的 A ^{125}I 标记的 Aβ（1－40）＋1μL 可溶性 Aβ（1－40）+13.5μL 测定用缓冲液。下面是足以满足 50 个测定孔所需的反应混合液的各成分的量：

5－10μL 干的 ^{125}I 标记的 Aβ（1－40）

675μL 测定用缓冲液

50μL 可溶性 Aβ（1－40）

测定方法

1） 通过将各成分混合并贮存在冰上而制得上述反应混合液

2） 将 14.5μL 反应混合液吸移至冰上的聚丙烯 U 形底 96 孔微量滴定板的 50 个孔的各孔中。（Costar 3794）。

3） 将 1.7μL 稀释过的受试化合物（包括溶剂对照）以 8 个一列加入到各孔中。从 1mM（最终浓度为 100μM）起的在测定用缓冲液-尿素中的连续 3 倍稀释液＝7 种稀释液＋零。因此，96 孔板各可容纳 11 个试样＋1 个刚果红对照（在 2 倍步骤中，0.039μM－最终的 5μM）。

4） 将滴定板用铝膜（Beckman538619）密封，在冰上培育 10 分钟。

5） 将温度升至 37℃，培育 3－5 小时（取决于肽的种类）。

6） 剥去铝膜，在各孔中加入 200μL 冰冷的含尿素的测定用缓冲液，用 96 孔板（Millipore MAGV N22，马萨诸塞州 Bedfird 市）中的孔径 0.2μm 的 GVWP 滤膜真空过滤，收集放射性标记的纤丝。用本领域技术人员公知的标准方法测定纤丝的放射性活性。

BASST（β－淀粉样蛋白自我接种，硫黄素 T）

一种测定自我接种的淀粉样蛋白纤丝生长的方法

方法：

材料：

原液：

测定用缓冲液：50mM 磷酸钠，pH 7.5，100mM 氯化钠，0.02％NaN_3，1 M 尿

素（过滤，在4℃贮存）

可溶性 Aβ（1-40）：2.2mg/mL 去离子水溶液（以等分试样贮存在-20℃，解冻后保持在冰上）在贮存1周后会自我接种。通常，应将溶液贮存至测定中未出现停滞期。

最终测定条件：30μM 可溶性 Aβ（1-40）/去离子水/测定用缓冲液。将受试化合物溶解在 DMSO 中，通常形成 5-50mM 原液，使测定时的 DMSO 最终浓度小于 1% v/v。

测定：用于 50 次测定的反应混合液（在冰上）包含每次测定所需的 1μL 可溶性 Aβ（1-40）+13.5μL 测定用缓冲液。下面是 50 个测定孔的各孔中滴入的的反应混合液的各成分的量：

50μL 可溶性 Aβ（1-40）

675μL 测定用缓冲液

测定方法

1） 通过将各成分混合并贮存在冰上而制得上述反应混合液

2） 将 14.5μL 反应混合液吸移至冰上的聚苯乙烯 U 形底 96 孔微量滴定板（Corning 25881-96）的 50 个孔的各孔中。

3） 将 1.7μL 稀释过的受试化合物（包括溶剂对照）以 8 个一列加入到各孔中。从 1mM（最终浓度为 100μM）起的在测定用缓冲液-尿素中的连续 3 倍稀释液 = 7 种稀释液 + 零。因此，96 孔板各可容纳 11 个试样 + 1 个刚果红对照（在 2 倍步骤中，0.039μM - 最终的 5μM）。

4） 将滴定板用铝膜密封，在冰上培育 10 分钟。

5） 将温度升至 37℃，培育 3-5 小时（取决于肽的种类）。

6） 剥去铝膜，在各孔中加入 250μL 在 50mM 甘氨酸-NaOH 中的 5μM 硫黄素 T（ThT）[T-3516，Sigma-Aldrich 公司产品]，pH 8.5。5 分钟内读取滴定板读数器上的荧光（ex = 440nm/20nm；em = 485nm/20nm）。

BAPA（β-淀粉样肽聚集）

此测定方法是测定化合物抑制β-淀粉样肽聚集的活性。

此测定方法的用途是提供一种用基于过滤的端点测定来测定β-淀粉样蛋白聚集的更高容量的方法。在该测定方法中，用六氟异丙醇（HFIP）将初始的淀粉样肽分解成单体状态，并使用 33μM 的浓度，该浓度足够地高，使得聚集会在几小时内于 pH 6.0 出现。

方法:

β-淀粉样肽聚集，pH 6.0（BAPA）

在 96 孔板（Costar 3794）中加入 25μL 50mM 磷酸钠缓冲液（pH 6.0）、10μL 在 20％HFIP 中的 0.5mg/mL Aβ（1-40）肽 + 0.1μL 测定用放射性碘记的 ^{125}I Aβ（1-40）[^{125}I Aβ（1-40）]和 1μL 受试化合物（起始浓度为 50mM，DMSO 浓度小于 1％）。然后在室温培育 2-4 小时。用 200μL 50mM 磷酸缓冲液（pH 6.0）停止反应，用 0.2μm 96 孔滤板（Millipore MAGU N22）过滤。用 100μL 同一磷酸缓冲液洗涤滤板。使滤器浸透 Meltilex（1450-441）后，用 Microbeta 计数器检测聚集，并作本底校正。

BATYM 测定

方法:

将所需的 Aβ（1-42）（加利福尼亚肽）的六氟异丙醇原液变干。将 Aβ（1-42）溶解在 DMSO 中，然后与磷酸盐缓冲的盐水（PBS）（pH 7.4）混合。将混合的 Aβ（1-42）溶液用 0.2μ Omnipore 膜注射滤器（马萨诸塞州 Bedfird 市 Millipore 公司产品）过滤。将在 DMSO 中的受试化合物（50 次浓缩物）加入到 96 孔板的各孔（0.5μL/孔）中。并在各孔中加入 24.5μL 的 Aβ（1-42）溶液。将板在 1,000g 离心 5 分钟，在 37℃培育 1 日（Aβ 1-42，最终浓度为 100μM）。

培育后，在各孔中加入 250μL 硫黄素 T 在甘氨酸-NaOH 缓冲液（pH 8.5，50mM）中的 30μM 溶液，用荧光板读数器测定荧光（ex = 440nm/20nm；em = 485nm/20nm）。用下式由荧光的减小计算出抑制活性:

抑制（％）= {（F（Aβ）-F（Aβ + 化合物））}/{（F（Aβ）-F（溶剂 + 化合物））} × 100

用下列方程式通过曲线拟合程序计算出 IC_{50}。由二个不同实验重复 3 次得到数据。

抑制（x）= 100 −100/ {1 + （x/IC_{50}）^{n}}

x = 受试化合物浓度（M）

IC_{50} = （M）

n = Hill 氏系数

代表性的式 I 化合物在上述测定中显示出 0.1μM 至 100μM 以上的抑制活性（IC_{50}）。

用上述方法测得的本发明的具体的代表性化合物的结果示于下面的表 1。

表 1. 式 I 化合物的β-淀粉样蛋白抑制活性

实施例 No.	BASSR (IC50 =μM)	BASST (IC50 =μM)	BATYM (IC50 =μM)	BAPA (IC50 =μM)
1	10 (P), >100 (P) (6x), >100 (Q), >100 (R), >100 (S), 52 (T) >100 (Z)	2, 4, 30, 10 (P) 3 (Q) >100 (R) 11 (S), 11 (T) 6 (Z)	50, 58.8 (P) 57.8 (Q)	60 (P), >100 (P)86 (Q), >60 (R), >60 (S), 11 (T)
2	2.2, 4.1, 4.1, 12, 4.5	1, 1.5 (P)	6.52 (P)	70 (P)
3	4.5, 5, 5 (所有 3 个 V 形) 15 (ppt), 5 (Q)	2 (P) 3 (Q)	11.7 (P)	>60 (P)
4	30, >100 (3x)	3, 4, 8	26.3, 30.7	67
5	70, >100	4.5	10	74
6	15, 21, 20, 40	4, 1, 3	21.5	>60
7	18, 13, 12, 20	2	8.83	39
8	15, 15, 18, 15	3, >100	7.17	
9	20 (ppt), 30, 52, 40 (P)	1, 2 (P)	20.1, 28.2 (P) 38.6 (R)	75 (P)
10	70, 50	4	75.7	67
11	18 (ppt), 20 (ppt), 20 (2x), >100 (P) >100, 21, 30 (Q)	1, 1, 3 (P) 1, 0.8 (Q)	5.62 (P) 6.78 (Q)	23 (P) 9 (Q)
12	20 (4x)	1, 1	3.93	>60
13	21, >100, 20 (ppt), 15 (ppt), >100	0.9	6.41	6
14	18 (ppt), 8, 6 (ppt), 7 (ppt)	1.0	10.9	>10 (V 形)
15	100 (3x)P 100, 16 (V 形) 12, 15, 11 (Q)	1 (P) 1.2 (Q)	8.52 (P) 7.26 (Q) 7.07 (Q)	>60 (P) 7 (Q)

表 1. 式 I 化合物的β-淀粉样蛋白抑制活性（续）

实施例 No.	BASSR (IC50 =μM)	BASST (IC50 =μM)	BATYM (IC50 =μM)	BAPA (IC50 =μM)
16	18, 7.5, 10 (P) 70, 32, 42 (Q)	3, 0, 3 (P) 1.1, 0.8, 0.6 (Q)	12 (P) 10.3 (Q)	13 (P)
17	>100 (ppt) (3x)	6.2	64.5	>60 (Q), 41 (R)
18	>100 (5x) (P)	30, >100 (P)	>100 (P)	9, >40, 53 (P), 12
19	3, 4, >100, 2.2	>100, 1, 1, 1.5	31.0, 34.0	>60, 43
20	4.2	6	68.6	22
21	3	4	62.7	26
22	3	9	>100	24
23	20	2	>100	17
24	>100	20	>100	91
25	>100	4	21.1	47
26	>100	1	>100	57
27	>100	3	19.8	74
28	>100	5	42.3	27
29	>100	4	38.1	30
30	30, 20	4, 2	75.3	38
31	>100	1	22.6	86
32	>100	1	29.2	96
33	>100	>100	>100	>10
34	45	3	45.0	48
35	>100	100	>100	154
36	>100	>100	>100	149
37	>100	0.8	30.2	25
38	20, 10 (V)	3	23.4	184
39	>100	20	>100	21
40	>100	3.0	>100	53
41	>100	5	49.7	42
42	>100	2	55.6	30
43	>100	0.3	24.2	63
44	>100	1	26.5	52
45	>100	1	21.5	32
46	>100	6	34.3	
47	>100	2	38.2	
48	25	10	>100	
49	>100	>100	>100	
50	>100	>100	>100	
51	85	0.8	39.1	

表 1. 式 I 化合物的β-淀粉样蛋白抑制活性（续）

实施例 No.	BASSR (IC50 =μM)	BASST (IC50 =μM)	BATYM (IC50 =μM)	BAPA (IC50 =μM)
52	75	0.5	36. 5	
53	>100	0.3	30.0	
54	>100	0.4	43.9	
55	12	2	5.1	101
56	>100	3	11.5	30
57	4.8	1.5	4.0	50
58	3. 5	1	5.1	60
59	>100	>100	>100	3
60	>100	3	40.7	8
61	18, 7.5, 10	3, 0.3	12	13
62	>100	1. 5	8.98	
63	15, 15, 18 (ppt)	1	9.43	45
64	>100	5	35	>100
65	60, 80	1.5	15.9	>100 (V 形)
66	>100 (ppt), >100 (ppt)	2.1	50.1	>100
67	41	4	13.3	>60
68	>100, >100	1	>100	110
69	2 (V 形), 3.5 (ppt)	0.8	11.7	58
70	20, 100	10	>100	65
71	>100	3		>60
72	40, 15, 12	2, 2.5	74.8	>60, >60
73	25, 35, 40	0.3	9.43	>60
74	6, 18, 19, 18	0.3, 0.5	8.36	>60
75	>100	2.2	46.2	>60
76	3	0.5	8.59	>60
77	18, 15	8, 0.3	9.49	>60
78	70	0.1	>100	8
79	3.1, 50, 38, 70, 70, 30, 40	1, 0.3, 0.3, 0.3	9.14	51
80	>100	4	24.8	>60
81	>100	15	48.4	73
82	>100, >100, >100	2, 0.3, 0.3		
83	>100	>100		9, 47, 29
84	>100	>100		5, 40, 21
85	>100	18		8, 77, 45

表 1. 式 I 化合物的β-淀粉样蛋白抑制活性（续）

实施例 No.	BASSR (IC50 =μM)	BASST (IC50 =μM)	BATYM (IC50 =μM)	BAPA (IC50 =μM)
86	40	18		>10, 89, 37
87	>100	50		>10, 15, 32
88	>100	10		>10, 37, 27
116	>100, >100	18, 30		96
117	>100	3	61.3	>100
118	>100, >100	6		>60
119	>100	3		>60
120	>100	3		>60
121	>100, >100	1		
122	>100	2	>100	>60
123	>100 (3 x), 14	3, 3	70.8	
	4, 18, >100, >100 (Q)	3.2, 4 (Q)	85.2 (Q)	>60 (Q)
124	>100	10	62.7	
125	82	10	>100	80
126	>100, >100	4, 5	84	63
	30, 100 (Q)	10, 4 (Q)	73.9 (Q)	>60 (Q)
127	>100 (ppt)	10	>100	67
128	>100 (ppt) (4 x) 11, >100 (3 x)	10, 41, 6	75	60
	15, 20, 10, 7.5 (Q)	7, 3, 3 (Q)	>60 (Q)	>60 (Q)
	15, >100 (3 x) Q			
129	1 (V 形) (2 x) >100 (ppt)	10, 3, 2, 2	>100	>102
130	>100 (3 x)	2, >100, 50	47.5	238
131	>100	10	93.5	>60
132	>100	10	>100	60
133	>100	>100	>100	>60
134	>100	2	36.5	>60
135	>100	1.2	31.2	>60
136	>100	3	>100	53
137	>100, >100	3		52
141	>100	7	56.7	>50
142	>100	2.1	26.9	55
143	>100 (4 x)	40, 30	>100	2, >60, >60
144	15, 25	40	>100	114

表 1. 式 I 化合物的β-淀粉样蛋白抑制活性（续）

实施例 No.	BASSR (IC50 =μM)	BASST (IC50 =μM)	BATYM (IC50 =μM)	BAPA (IC50 =μM)
145	10, 40, 30	4	56.8	9
146	>100	30	>100	>60
147	>100	10	93.4	>60
148	>100		>100	
149	>100	>100	>100	>60
150	>100	10	>100	76
151	>100, >100	5, >100	>100	108
154	>100	3, 30	70.8	
155	>100	3	44.6	
156			27.8	
157			25.9	

具体值之后的括号内的字母表示受试化合物的具体的合成批号。“P”、“Q”、“R”、“S”、“T”和“Z”、表示同一化合物的不同批号。例如，10（P）表示受试化合物是 P 批的。若未标明批号，则该化合物为 P 批的。

缩写“ppt”是指沉淀物，表示沉淀物在所示浓度形成。此外，“V 形”一词是指沉淀后观察到抑制。

数目和×（即，4×）之后的数值是指化合物测试 4 次，各次的结果相同。

本发明化合物在常用来评估治疗与淀粉样蛋白聚集相关的疾病（尤其是阿尔茨海默病和其它淀粉样变性）的试剂的体内测定中还显示出良好的活性。在一个测定中，通过皮下注射硝酸银、弗罗因德完全佐剂和静脉内注射淀粉样蛋白促进因子，将淀粉样蛋白导入小鼠脾脏内。在 11 日内，每日施用硝酸银。从第 1 日至第 11 日，将受试化合物每日给予小鼠。在第 12 日，杀死小鼠，取出脾脏，制备组织标本，用刚果红染色，显微镜下对脾脏中被双折射的刚果红染色的淀粉样蛋白占据的区域的百分比进行定量。在此测试中，相对于未处理的对照，评估出本发明化合物抑制脾脏淀粉样蛋白沉积的活性可达 70％。

在另一个体内测试中，用转基因小鼠评估本发明的化合物。小鼠该小鼠具有带感染性蛋白启动子的人β-淀粉样前体蛋白转基因，这在 Hsiao 等，“相关

记忆缺陷、Aβ评估和转基因小鼠的淀粉样斑(Correlative memory deficits, Aβ elevation, and amyloid pasques in transgenic mice)”, *Science* 1966; 274: 99-102 中有描述。这些转基因小鼠在约 9 月龄时逐步显现出β-淀粉样沉积。至 15 月龄，出现大量扩散、密集的老年斑，主要在新皮层、嗅球和海马。从 8 月龄（在就要出现淀粉样沉积之前）起给小鼠口服本发明化合物，继续数月（至约 14-18 月龄）。然后杀死小鼠，取脑。对脑中的淀粉样物的量作组织学和生化学定量。在此模型中，相对于未处理的对照物，评估出本发明化合物抑制皮层和海马中的淀粉样蛋白积聚的活性可达 49%。

上述数据表明，代表性的本发明化合物在用来测定蛋白聚集抑制活性的标准测定方法中显示出活性。本发明化合物显示出优异的特异性（例如，如在 BASST、BATYM 和 BAPA 测定中所示）。因此，本发明化合物对临床上抑制淀粉样蛋白聚集和对淀粉样沉积进行成象以供诊断用是非常有用的。本发明的化合物以药剂的形式使用，下面的实施例举例说明典型的组合物。

实施例 164

片剂

成分	量
实施例 1 的化合物	50mg
乳糖	80mg
玉米淀粉（混合用）	10mg
玉米淀粉（糊剂用）	8mg
硬脂酸镁（1%）	2mg
	150mg

将实施例 1 的化合物与乳糖和玉米淀粉（混合用）混合，均匀掺和，得到粉末。将玉米淀粉（糊剂用）悬浮在 6mL 水中，搅拌加热，形成糊剂。将该糊剂加入到上述混合的粉末中，将混合物制粒。让湿颗粒通过#8 硬筛，在 50℃干燥。将混合物用 1%硬脂酸镁润滑，压片。每日给予患者 1-4 片，以预防淀粉样蛋白聚集和治疗阿尔茨海默病。

实施例 165

非经肠的溶液

在 700mL 丙二醇和 200mL 水的注射用溶液中加入 20.0g 化合物 19（实施例 19）。搅拌所得混合物，用盐酸将 pH 调整至 5.5。使用注射用水将体积调整至 1000mL。将所得溶液灭菌，以 2.0mL（40mg 化合物 19）充入各 5.0mL 安瓿中，氮气氛中密封。将上述溶液注射于患甲状腺髓样癌并需要治疗的患者。

实施例 166

药膏制剂

将 10mg 2－｛4－〔3－（3,4－二氯苯基）丙基〕苯氨基｝苯甲酸与 1mL 丙二醇和 2mg 含树脂类交联剂的丙烯酸类聚合物粘合剂混合。将混合物涂敷在可渗透的背衬（30 cm^2）上，贴在患者的上背，对淀粉样多神经病作持续释放治疗。

上面对本发明化合物及其制造和使用方式和方法进行了充分、清楚和完整的描述，使与其相关的领域的技术人员能够制造和使用之。应该明白，上面描述的是本发明的优选实施方式，可在不偏离权利要求书中所述的本发明的实质和范围的条件下对本发明作各种变更。下面的权利要求书具体指出和清楚地要求保护说明书中所述的本发明的主题。