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Azo-kötött immunszabályozó vegyületek szintézise

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(54) **SYNTHESIS OF AZO BONDED IMMUNOREGULATORY COMPOUNDS**

SYNTHESE VON AZOGEBUNDENEN, DAS IMMUNSYSTEM REGULIERENDEN VERBINDUNGEN

SYNTHESE DE COMPOSES IMMUNOREGULATEURS A LIAISON AZO

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(56) References cited:
WO-A-02/18324 WO-A-02/18330
US-A- 2 344 244 US-A- 3 345 356
US-B1- 6 423 713

- **CHU T-T ET AL: "A PROOF OF THE UNSYMMETRICAL STRUCTURE OF THE AZOXY GROUP" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC. US, vol. 55, 1 July 1933 (1933-07-01), pages 2841-2850, XP001064160 ISSN: 0002-7863**

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Description

1. Field of the Invention

[0001] The present invention relates to immunoregulatory compounds, methods of producing same and methods of treating diseases therewith.

2. Background of the Invention

[0002] Many people suffer from inflammatory bowel disease (IBD). IBD is a generic term used to refer to two inflammatory diseases, ulcerative colitis and Crohn's disease, and various medications are being used to treat inflammatory bowel disease. For example, mesalamine, 5-aminosalicylic acid (5-ASA) is used to treat ulcerative colitis, but is associated with various side effects. It can be absorbed as it passes through the GI tract, which can adversely affect the amount of mesalamine that reaches the lower GI tract, particularly the colon and rectum. Sulfasalazine has also been used, but is metabolized in the body to form mesalamine (5-aminosalicylic acid (5-ASA)) and sulfapyridine. Accordingly, sulfasalazine is associated with several adverse side effects, including nausea, vomiting, abdominal discomfort, male infertility, and headache. These adverse side effects are usually attributed to the activity of sulfapyridine in the GI tract, as well as that absorbed into the system. Olsalazine has also been used to treat ulcerative colitis, but is both relatively expensive to make and associated with adverse side effects including diarrhea.

[0003] Efforts have been made to minimize the side effects associated with these compounds, including efforts by the present inventors to provide compounds that, when reaching the gut mucosa, break down into one or more active compounds useful for treating inflammatory bowel disorders. Examples of such compounds are described, for example, in U.S. Patent No. 6,583,128 to Ekwuribe et al.

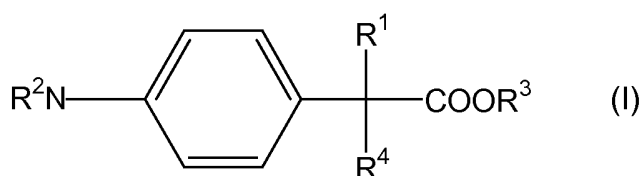
[0004] WO-A-02/18324 describes a synthesis process for compounds useful for the prophylaxis or treatment of diseases such as inflammatory conditions of the GI tract. The process requires a starting compound that is a carboxylic acid, that being (4-nitrophenyl) propionic acid, but the document offers only guidance for starting with an acid group and provides no discussion or guidance for using an aniline compound that includes alcohols or aldehydes as functional groups.

[0005] WO-A-02/18330 teaches aminophenyl-4-carboxylic acid amide compounds for the prophylaxis or treatment of various diseases including inflammatory bowel disease or liver diseases using aniline compounds with functional groups limited to an alcohol or aldehyde.

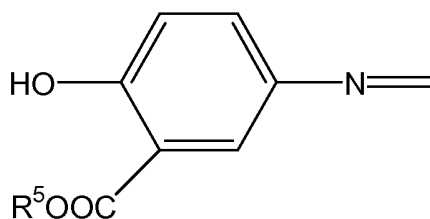
[0006] It would be beneficial to provide additional synthetic methods for preparing these compounds. The present invention provides such synthetic methods.

3. Summary of the Invention

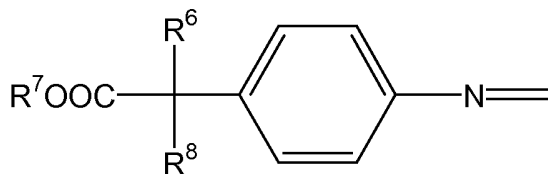
[0007] Synthetic methods for preparing compounds of the following formula are provided:



where R¹ and R³ are independently hydrogen or C₁ to C₄ alkyl, R⁴ is hydrogen and R² is:



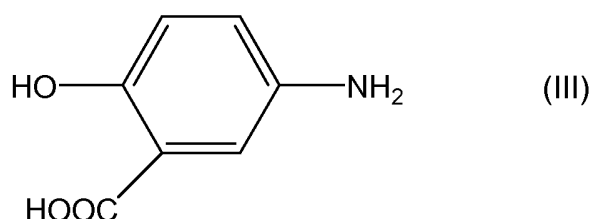
where R⁵ is selected from the group consisting of hydrogen and C₁ to C₄ alkyl, or



where R^6 , R^7 and R^8 are independently hydrogen or C_1 to C_4 alkyl, wherein at least R^6 is hydrogen, as well as the esters or pharmaceutically acceptable salts of such compounds.

[0008] The compounds prepared by these methods can be included in pharmaceutical compositions, and used in methods of treating inflammatory conditions.

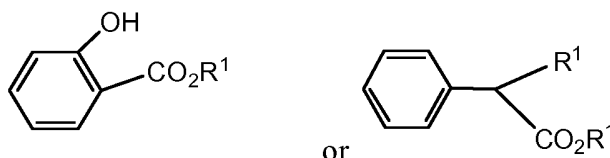
[0009] The active pharmaceutical ingredient may further comprise a compound of Formula III:



[0010] The first step of the synthesis typically starts with an aniline compound, which is converted to a diazonium salt. In one embodiment, the aniline compound to be converted to the diazonium salt includes a primary alcohol or aldehyde group, which can be oxidized to a carboxylic acid group following formation of the diazonium salt and coupling to a desired molecule.

[0011] In another embodiment, the aniline compound to be converted to the diazonium salt includes a nitrile or amide group, which can be hydrolyzed to the carboxylic acid following formation of the diazonium salt and coupling to a desired molecule.

[0012] The second step of the synthesis involves forming a diazonium salt, which can be performed using known chemistry. The resulting diazonium salt is then coupled with a compound of the formula:

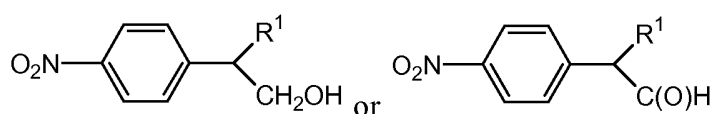


[0013] This coupling step typically provides predominantly a substitution at the 5-position of the salicylate, or a para substitution. In the embodiments where the aniline includes a primary alcohol or aldehyde group, the next step involves oxidizing the primary alcohol or aldehyde group to a carboxylic acid group. This can be accomplished using traditional oxidation chemistry, but optionally is performed using a catalytic amount of a chromium (VI) oxidant or other suitable oxidant in the presence of a stoichiometric amount of periodic acid.

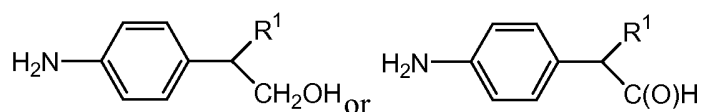
[0014] In the embodiments where the aniline includes a nitrile or amide group, the next step involves hydrolysis of the amide or nitrile to the carboxylic acid. The hydrolysis can be either acid or base catalyzed. However, nitrilases and/or amidases can also be used, which typically results in milder reaction conditions.

[0015] In either embodiment, following the oxidation of the primary alcohol or aldehyde to the carboxylic acid, or hydrolysis of the amide or nitrile to the carboxylic acid, a pharmaceutically acceptable carboxylate salt or suitable ester (i.e., where R^1 on the CO_2R^1 group is alkyl) can be formed using routine chemistry.

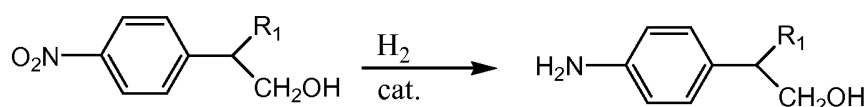
[0016] In an alternative embodiment of the first approach (where the aniline to be converted to the diazonium salt includes a primary alcohol or aldehyde group, the methods first involve converting a compound of the formula:



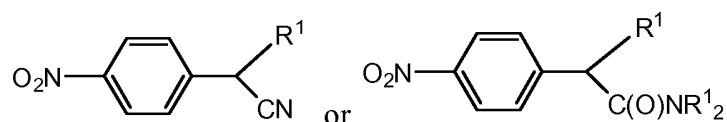
to a compound of formula:



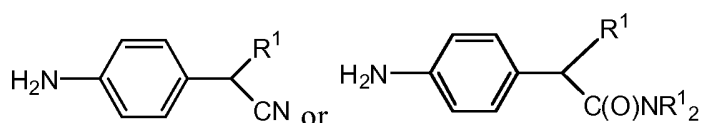
[0017] This conversion can be performed using standard reaction conditions well known to those of skill in the art, for example, as shown below with respect to the nitrobenzene including the primary alcohol group:



[0018] In an alternative embodiment of the second approach (where the aniline to be converted to the diazonium salt includes a nitrile or amide group), the methods first involve converting a compound of the formulas:

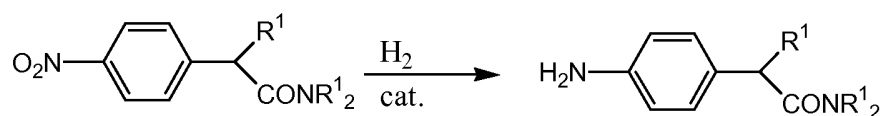
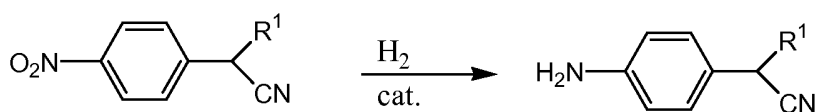


to a compound of the formulas:



[0019] The amide group can optionally include one or two alkyl, aryl, arylalkyl or alkylaryl groups in place of one or both of the hydrogen atoms, which groups are removed when the amide is hydrolyzed to the carboxylic acid. However, since such groups would not be present in the final molecule, it is often easier to simply use an unsubstituted amide group (i.e., CONH_2).

[0020] This conversion can be performed using standard reaction conditions well known to those of skill in the art, for example, as shown below:



4. Brief Description of the Drawings

[0021]

Figure 1 illustrates embodiments of the synthesis routes described herein.

Figure 2 illustrates additional embodiments of the synthesis routes described herein.

5. Detailed Description of the Invention

[0022] The invention will now be described with respect to preferred embodiments described herein. It should be appreciated however that these embodiments are for the purpose of illustrating the invention, and are not to be construed as limiting the scope of the invention as defined by the claims.

[0023] As shown below, various synthetic methods are provided for preparing the compounds described herein.

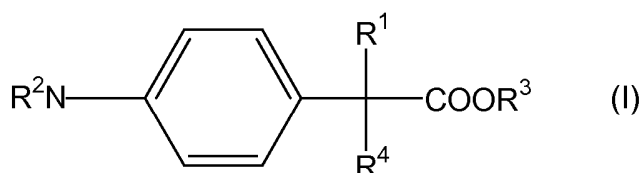
[0024] In a first embodiment (Scheme I in Figure 1), an aniline derivative including a primary alcohol or aldehyde group is used, where the primary alcohol or aldehyde group is ultimately oxidized to form a carboxylic acid. The carboxylic acid group can optionally be converted to a pharmaceutically acceptable carboxylate salt or ester.

[0025] In a second embodiment (Scheme II in Figure 2), an aniline derivative including a nitrile or amide group is used, where the nitrile or amide group is ultimately hydrolyzed to form a carboxylic acid. The first step in either embodiment involves forming a diazonium salt.

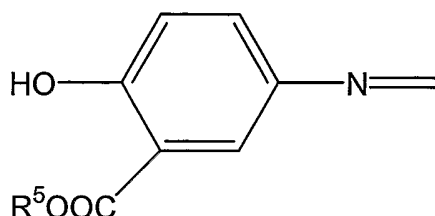
[0026] Each of these reaction conditions and the associated starting materials will be better understood with reference to the following detailed description.

5.1 The Compounds

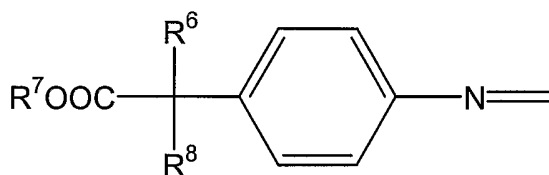
[0027] The compounds synthesized using the methods described herein include those having the following formula:



where R¹ and R³ are independently hydrogen or C₁ to C₄ alkyl and R⁴ is hydrogen. Preferably, R¹ and R³ are independently selected from the group consisting of H, CH₃, CH₂CH₃, and CH(CH₃)₂. More preferably, R¹ and R³ are H or CH₃. R² is:



or



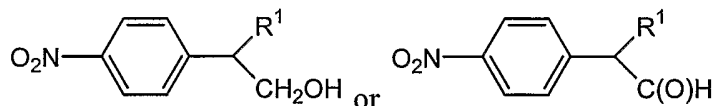
R⁵ is selected from the group consisting of hydrogen and C₁ to C₄ alkyl. Preferably, R⁵ is selected from the group consisting of H, CH₃, CH₂CH₃, and CH(CH₃)₂. More preferably, R⁵ is H or CH₃ and, most preferably, R⁵ is H. R⁶, R⁷ and R⁸ are independently hydrogen or C₁ to C₄ alkyl. Preferably, R⁶, R⁷ and R⁸ are independently selected from the group consisting of H, CH₃, CH₂CH₃, and CH(CH₃)₂. More preferably, R⁶, R⁷ and R⁸ are independently H or CH₃.

5.2 Synthetic Methods

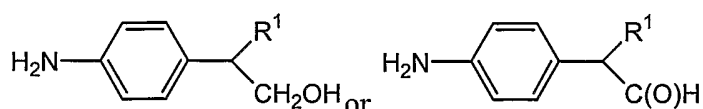
[0028] The individual reaction steps are discussed in more detail below.

5.2.1 Nitrobenzene Reduction to Aniline Starting Materials

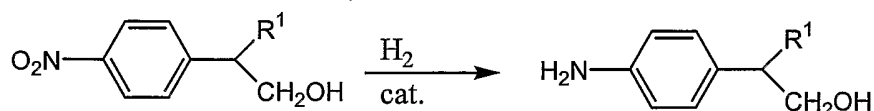
[0029] In an alternative embodiment of the embodiment shown in Scheme 1 (where the aniline to be converted to the diazonium salt includes a primary alcohol or aldehyde group), the methods first involve converting a compound of the formula:



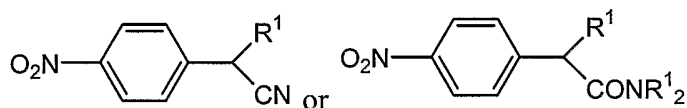
to a compound of formula:



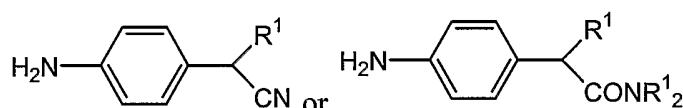
[0030] This conversion can be performed using standard reaction conditions well known to those of skill in the art, for example, as shown below:



[0031] In an alternative embodiment of the embodiment in Scheme II (where the aniline to be converted to the diazonium salt includes a nitrile or amide group), the methods first involve converting a compound of the formulas:

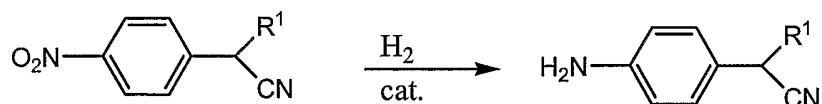


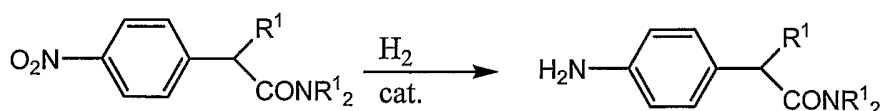
to a compound of the formulas:



where R^1 is as defined above. The amide group can include one or two alkyl, aryl, arylalkyl or alkylaryl groups (in addition to those defined by R^1) such as are well known in the art in place of one or both of the hydrogen atoms, which groups are removed when the amide is hydrolyzed to the carboxylic acid. However, since such groups would not be present in the final molecule, it is often easier to simply use an unsubstituted amide group (i.e., CONH_2).

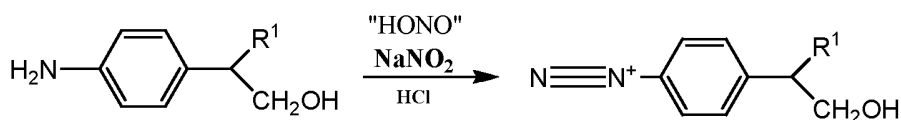
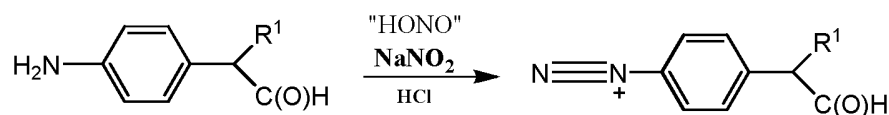
[0032] This conversion can be performed using standard reaction conditions well known to those of skill in the art, for example, as shown below:



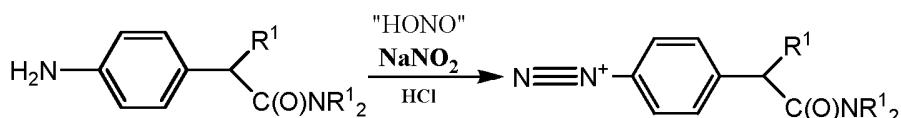
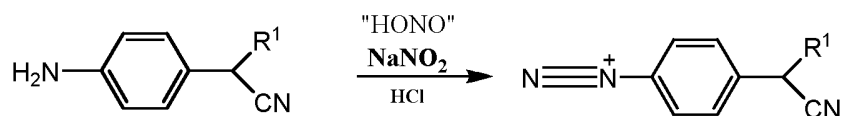


5.2.2 Conversion of Anilines to Diazonium Salts

[0033] The first step in Scheme I involves converting an aniline compound to a diazonium salt. The aniline compounds include a primary alcohol or aldehyde group, and the conversion involves the known reaction with NaNO_2 to convert anilines to diazonium salts. Such reaction conditions are well known to those of skill in the art, and the reactions are shown below.



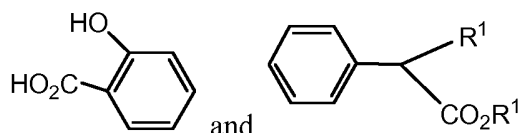
[0034] The first step in Scheme II also involves converting an aniline compound to a diazonium salt. The aniline compounds include a nitrile or amide group, and the conversion similarly involves the known reaction with NaNO_2 to convert anilines to diazonium salts. The reactions are shown below.



[0035] In the reactions shown above, R^1 is as defined elsewhere in this application. It is also contemplated that with respect to the amide groups, any substitution on the amide linkage that does not interfere with the subsequent chemistry is acceptable, since the amide is later hydrolyzed to the carboxylic acid and such groups will not appear, in any case, in the final molecule. Such groups include, for example, C_{1-10} straight, branched or cyclic alkyl groups, aryl groups such as those including one or more benzene or naphthalene rings, alkyl groups substituted with aryl groups (alkylaryl groups), aryl groups substituted with one to five alkyl groups (arylkalkyl groups) and the like.

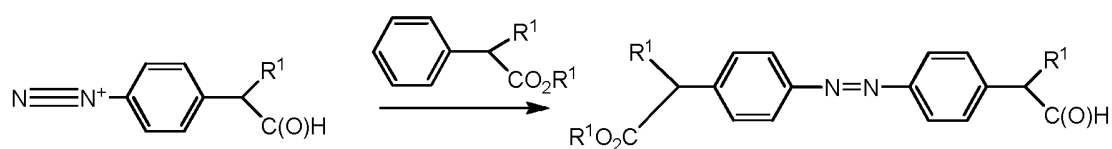
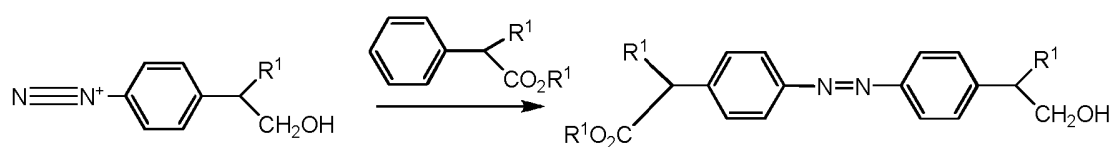
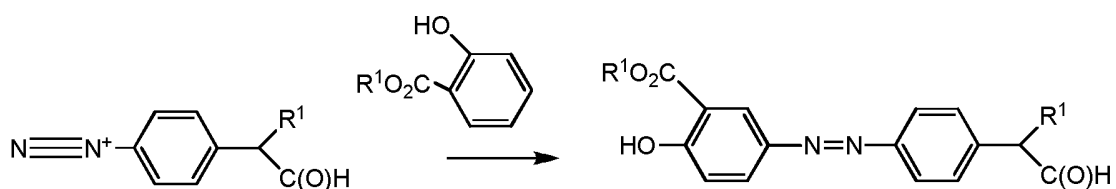
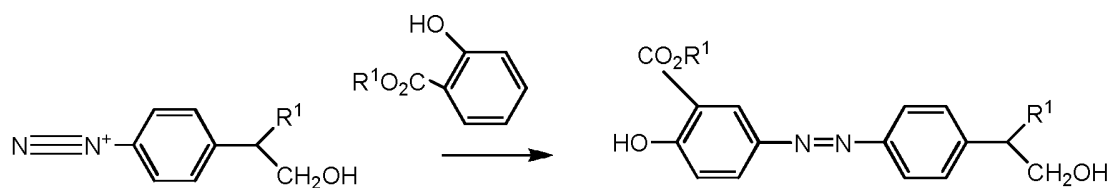
5.2.3 Electrophilic Aromatic Substitution Using Diazonium Salts

[0036] Electrophilic aromatic substitution reactions using diazonium salts are well known. The following two aromatic compounds are substituted with the previously described diazonium salts:

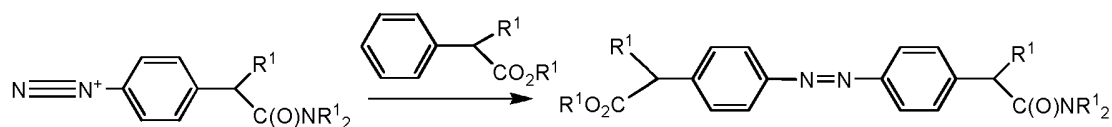
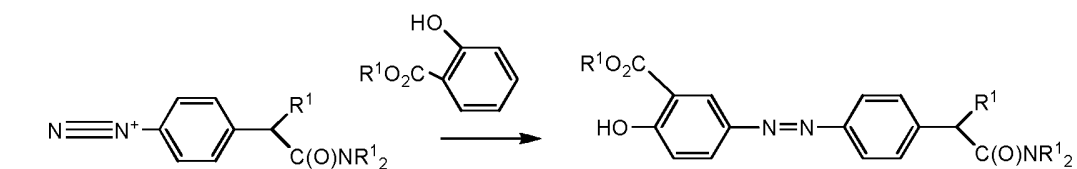
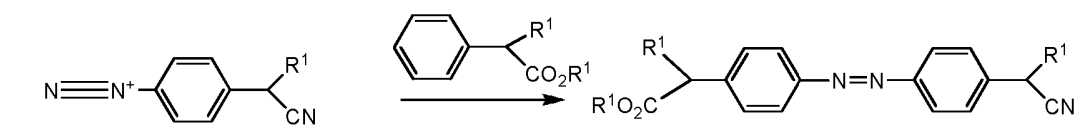
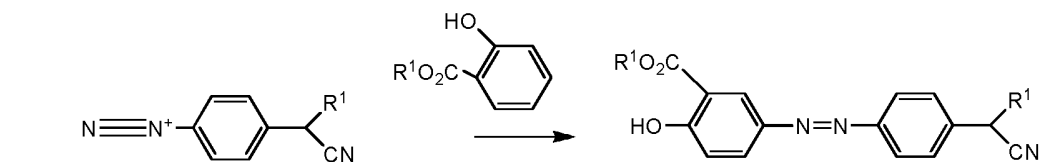


[0037] With respect to the first compound, substitution primarily takes place at a position para to the phenol group and meta to the carboxylic acid group. With respect to the second compound, substitution primarily takes place at a position para to the substituted (with R^1) acetic acid group.

[0038] The following reactions take place in connection with Scheme I.



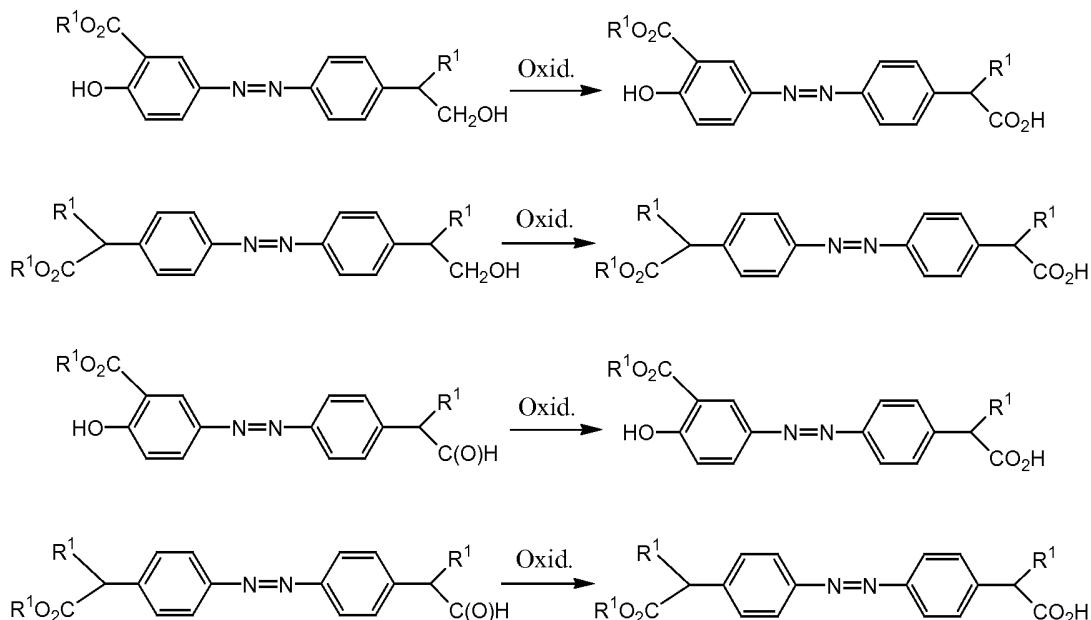
[0039] The following reactions take place with respect to Scheme II:



5.2.4 Oxidation of Primary Alcohol and Aldehyde Groups

[0040] With respect to Scheme I, the primary alcohol or aldehyde groups in the intermediate resulting from the diazonium coupling reaction are then oxidized to carboxylic acid groups.

[0041] The reactions are shown below:



[0042] In some embodiments, particularly those embodiments where there is a phenol group present, the oxidation chemistry may oxidize the phenol to a quinone-type compound. In such embodiments, the phenol can be protected with conventional protecting group chemistry (e.g., as a silyl ether, a THP ether, a benzyloxy, an ester, and the like), and deprotected after the oxidation step. Examples of suitable protecting groups for phenol groups which are amenable to various oxidation conditions are well known to those of skill in the art (see Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 2nd Ed.; Wiley: New York, 1991).

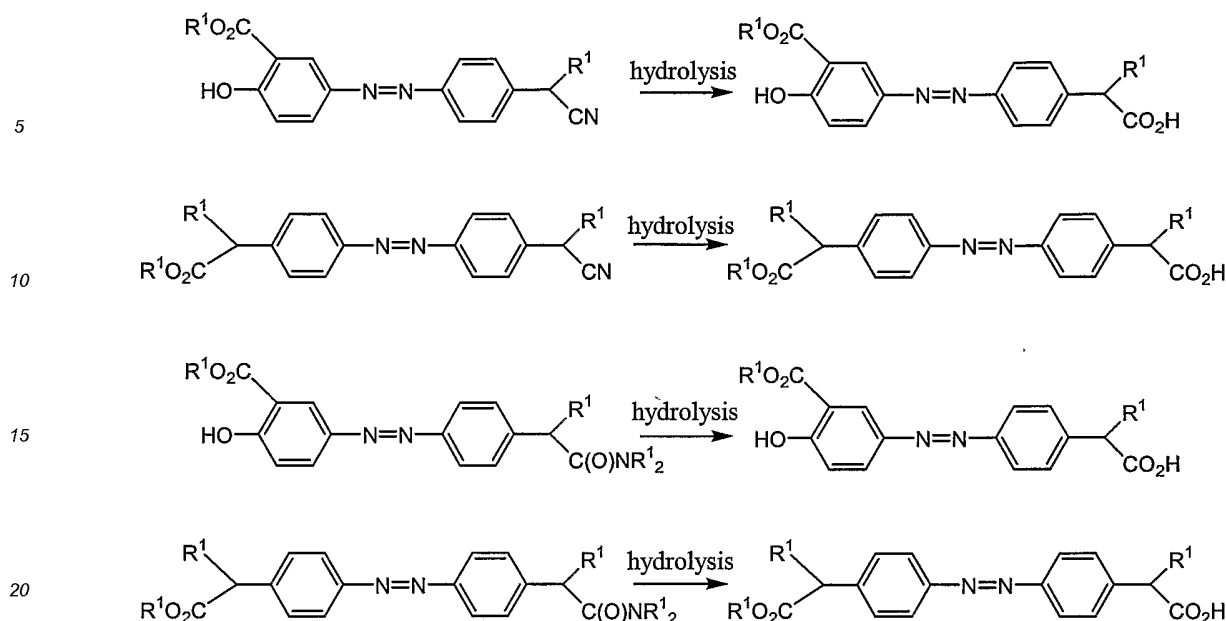
[0043] U.S. Patent No. 6,150,554 to Li et al teaches the oxidation of primary alcohols to carboxylic acids using catalytic CrO₃ and periodic acid (referred to in the literature as both HIO₄ and H₅IO₆) as the stoichiometric oxidant. This chromium catalyzed oxidation method avoids the chromium disposal issues associated with running a typical Jones oxidation reaction with stoichiometric CrO₃, reduces the epimerization of any α -chiral centers, and is a one step procedure. The reaction is mild, rapid, high yielding and only requires 1-2 mol% of CrO₃.

[0044] The oxidation of primary alcohols to carboxylic acids is well known in the art of organic synthesis. Typical reagents include chromium (VI) oxidizing agents (including, but not limited to, sodium and potassium dichromate, chromic acid, and the like), and manganese (VII) oxidizing agents such as potassium permanganate. The oxidation of aldehydes to carboxylic acids is also well known. While the same strong oxidizing agents used to oxidize primary alcohols can be used, much milder oxidizing agents can also be used. For example, ozone (or oxygen) and ultraviolet light and/or a suitable catalyst can often be used. Representative reaction conditions are described, for example, in U.S. Patent No. 6,680,395 to Springer.

[0045] Industrially, it is often preferred to use the mildest and/or least expensive oxidation conditions that result in the desired products. Accordingly, it can be preferred to use oxygen or ozone as an oxidizing agent where appropriate, or to use catalytic chromium (VI) salts along with a co-oxidizing agent such as periodic acid to regenerate the catalytic chromium (VI) salts where appropriate.

5.2.5 Hydrolysis of Nitrile and Amide Groups

[0046] The embodiment in scheme II does not require the use of primary alcohols in the starting material, so that oxidation from a primary alcohol to a carboxylic acid group can be avoided. This embodiment involves the use of an aniline that includes a nitrile (-CN) or amide (-C(O)NR¹₂) group in place of the primary alcohol group. The nitrile or amide groups can be hydrolyzed to a carboxylic acid group after the diazonium salt is coupled to a desired aromatic ring. The reactions are shown below.



[0047] Reaction conditions for converting a nitrile to a carboxylic acid group are well known to those of skill in the art, and are described, for example, in March, J. *Advanced Organic Chemistry*; 3rd ed., John Wiley: New York, (1985) and House, *Modern Synthetic Reactions*, 2d. ed., W.A. Benjamin, Inc., Menlo Park, CA, (1972). The conditions involve either using an acid or a base to catalyze the hydrolysis. A tautomer of an amide is believed to be an intermediate in the hydrolysis of a nitrile group to a carboxylic acid. For this reason, an amide group can be used in place of the nitrile for purposes of carrying out the synthetic method.

[0048] Biocatalytic hydrolysis of nitriles to carboxylic acids can be carried out under mild conditions, without affecting other functional groups. The nitrile group thus functions as a "masked" acid group. Nitrilase enzymes (for example, those from *Arabidopsis thaliana*, *Alcaligenes faecalis*, *Pseudomonas fluorescens*, *Rhodococcus rhodochrous*, and *Rhodococcus sp.*) are available commercially from companies such as Sigma-Adrich. The chemistry is described, for example, in Effenger and Osswald, "Catalyst for the (E)-selective hydrolysis of (E,Z)- α,β -unsaturated nitriles to carboxylic acids," *Tetrahedron: Asymmetry*, 12,:2581 (2001); Effenger and Osswald, "Selective hydrolysis of aliphatic dinitriles to mono-carboxylic acids, *Synthesis*, 1866 (2001); and Effenger and Osswald, "Enantioselective hydrolysis of (1)-arylacetonitriles, *Tetrahedron: Asymmetry*, 12:279 (2001), the contents of which are hereby incorporated by reference. Because the biocatalytic hydrolysis can involve milder conditions than either the acid or basic hydrolysis of nitriles, this method can be preferred, particularly for industrial synthesis of the compounds described herein.

[0049] A large number of amidases (enzymes that cleave amide groups) are also known and can be used to hydrolyze the amides to carboxylic acids. One potential advantage of using the amidases is that they tend to be selective for one enantiomer over another. In some embodiments, the compounds are formed as racemic mixtures or mixtures of diastereomers, and the amidases allow (via enzymatic resolution) the individual enantiomers or diastereomers to be separated. Of course, conventional methods, such as selective crystallization, chiral chromatography and the like, as are well known to those of skill in the art, can also be used to isolate enantiomerically enriched compounds.

[0050] The resulting carboxylic acid-containing compounds can often be easily separated from the amide-containing compounds by simply forming the carboxylate salts, which can be removed in a water extraction and then isolated by acidification of the carboxylate group to reform the carboxylic acid group. The amide groups not hydrolyzed by the enzyme (or, for that matter, via conventional acidic or basic hydrolysis) can be isolated from extraction with an organic solvent, and subjected to alternate hydrolysis conditions.

[0051] Optionally, the carboxylic acid groups can be converted to pharmaceutically acceptable carboxylate salts or esters, using known reaction conditions.

5.3 Pharmaceutical Formulations

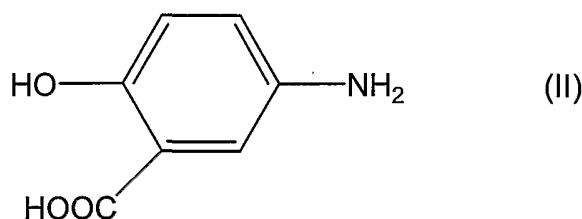
[0052] The compounds prepared according to the methods described herein can be included in pharmaceutical formulations, both for veterinary and for human medical use. The compounds can be administered per se as well as in the form of pharmaceutically acceptable esters, salts, and other physiologically functional derivatives thereof.

[0053] The formulations include those suitable for parenteral as well as non-parenteral administration, and specific

administration modalities include, but are not limited to, oral, rectal, buccal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, intrathecal, intra-articular, intraarterial, sub-arachnoid, bronchial, lymphatic, vaginal, and intra-uterine administration. Formulations suitable for oral and parenteral administration are preferred, with formulations suitable for oral administration most preferred.

[0054] In addition to the aforementioned ingredients, the formulations of this invention can further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

[0055] The active pharmaceutical ingredient can further include one or more other medicaments including, but not limited to, anti-inflammatory agents such as mesalamine, sulfasalazine, balsalazide, and olsalazine; immunomodulators such as azathioprine, 6-mercaptopurine, cyclosporine and methotrexate; steroidal compounds such as corticosteroids; and antibiotics such as metronidazole and ciprofloxacin. The active pharmaceutical ingredient preferably further comprises mesalamine, the compound of Formula II:

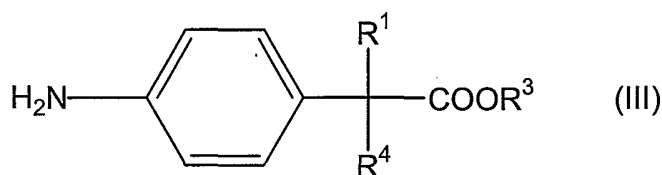


[0056] In therapeutic usage, the compounds can be used to treat an animal subject having or latently susceptible to an intestinal condition(s) or disease state(s) and in need of treatment therefor, by administering an effective amount of the compound to the animal. The animal can be a human or non-human animal (e.g., bird, dog, cat, cow, horse), preferably a mammal, and most preferably a human.

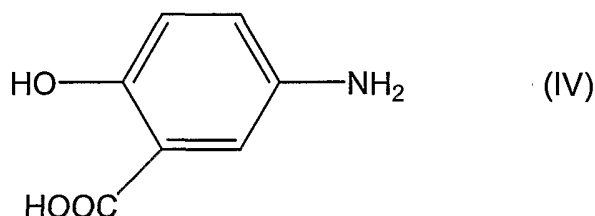
[0057] The compounds can be used to treat and/or prevent various diseases, particularly inflammatory conditions of the GI tract including, but not limited to, inflammatory conditions of the mouth such as mucositis, infectious diseases (e.g., viral, bacterial, and fungal diseases), and Crohn's disease; inflammatory conditions of the esophagus such as esophagitis, conditions resulting from chemical injury (e.g., lye ingestion), gastroesophageal reflux disease, bile acid reflux, Barrett's esophagus, Crohn's disease, and esophageal stricture; inflammatory conditions of the stomach such as gastritis (e.g., *Helicobacter pylori*, acid-peptic disease and atrophic gastritis), peptic ulcer disease, precancerous lesions of the stomach, non-ulcer dyspepsia, and Crohn's disease; inflammatory conditions of the intestine such as inflammatory bowel disease, celiac disease, Crohn's disease, bacterial overgrowth, peptic ulcer disease, and fissures of the intestine; inflammatory conditions of the colon such as Crohn's disease, ulcerative colitis, infectious colitis (e.g., pseudomembranous colitis such as *Clostridium difficile* colitis, salmonella enteritis, shigella infections, yersiniosis, cryptosporidiosis, microsporidial infections, and viral infections), radiation-induced colitis, colitis in the immunocompromised host (e.g., typhlitis), precancerous conditions of the colon (e.g., dysplasia, inflammatory conditions of the bowel, and colonic polyps), proctitis, inflammation associated with hemorrhoids, proctalgia fugax, and rectal fissures; liver gallbladder and/or biliary tract conditions such as cholangitis, sclerosing cholangitis, primary biliary cirrhosis, and cholecystitis; and intestinal abscess. The compounds can also be used to diagnose constituents, conditions, or disease states in biological systems or specimens, as well as for diagnostic purposes in non-physiological systems. Furthermore, the compounds can be used to treat or prevent condition(s) or disease state(s) in plant systems. By way of example, the compounds or individual active components of the conjugate can have insecticidal, herbicidal, fungicidal, and/or pesticidal efficacy amenable to usage in various plant systems.

[0058] Depending on the specific condition or disease state, the active pharmaceutical ingredient can be administered at any suitable therapeutically effective and safe dosage, as can readily be determined within the skill of the art and without undue experimentation. For example, the active pharmaceutical ingredient of the present invention can be administered at a dosage between about 0.1 and 200 mg/kg, preferably between about 1 and 90 mg/kg, and more preferably between about 10 and 80 mg/kg.

[0059] In some embodiments, the compounds can break down in the intestinal tract to form the metabolic product of Formula III:

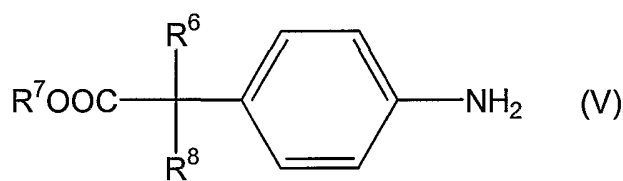


where R¹, R³ and R⁴ are as described above with reference to Formula I, and the metabolic product of Formula IV:



[0060] The metabolic product of Formula III can possess anti-inflammatory activity and/or immunoregulatory activity. The metabolic product of Formula IV can possess anti-inflammatory activity, and more particularly can inhibit prostaglandin synthetase I & II.

[0061] In other embodiments, the compounds can break down in the intestinal tract to form the metabolic product of Formula III and the metabolic product of Formula V:



where R⁶, R⁷ and R⁸ are as described above with reference to Formula I. The metabolic product of Formula V can possess anti-inflammatory activity and/or immunoregulatory activity. Accordingly, the compounds can provide immunoregulatory activity. The compounds can also inhibit prostaglandin synthetase I and II. The compounds can be used to treat various diseases, particularly ulcerative colitis, Crohn's disease and the like.

[0062] The present invention will now be described with reference to the following examples. It should be appreciated that these examples are for the purposes of illustrating aspects of the present invention, and do not limit the scope of the invention as defined by the claims.

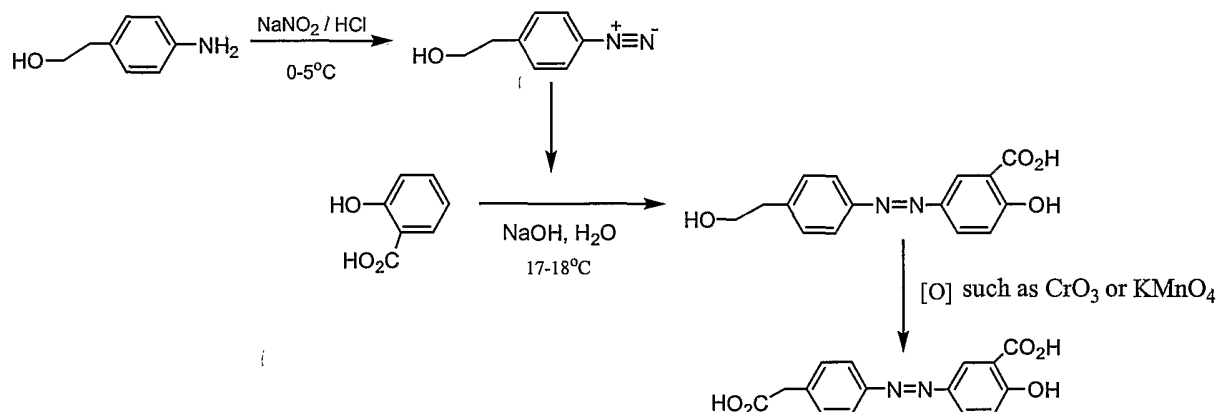
40 6. EXAMPLES

6.1 Example 1: Diazo Coupling of 4-Aminophenethyl alcohol with Salicylic Acid, followed by oxidation of the alcohol to the corresponding carboxylic acid:

45 [0063]

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6.1.1 Diazo Coupling of 4-Aminophenethyl alcohol with Salicylic Acid:

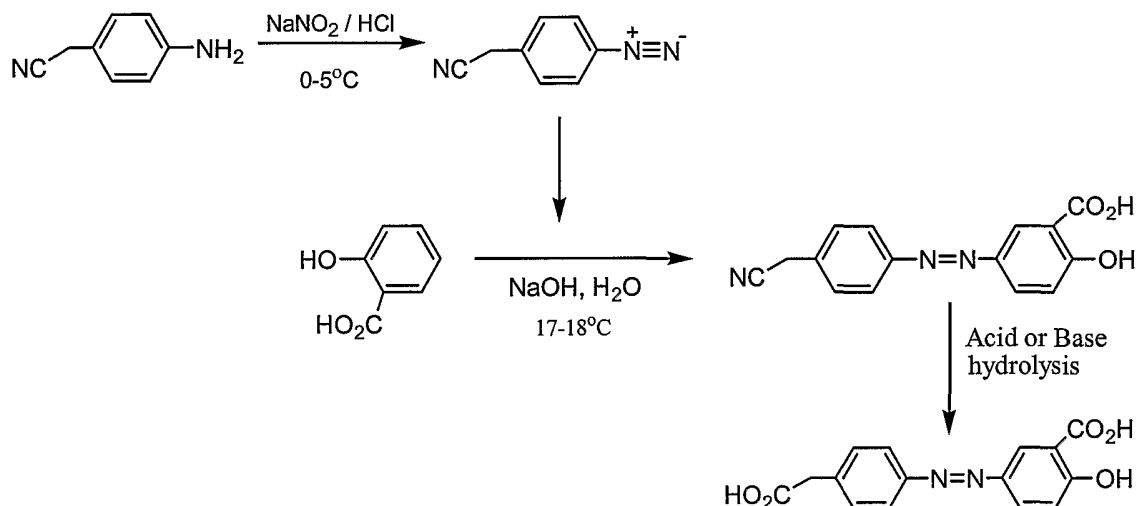
[0064] 4-Aminophenethyl alcohol (24.8mmol) is suspended in water (75mL) and concentrated hydrochloric acid (8mL) is added. The solution is cooled to 0°C in an ice bath with rapid stirring. Sodium nitrite (26.1mmol) in water (20mL) is added dropwise to the 4-aminophenethyl alcohol solution with rapid stirring. It may be important to keep the temperature between $0-5^\circ\text{C}$ at all times, especially during the NaNO_2 addition. The reaction is stirred for an additional period of time, for example, about 20 minutes. In the meantime, salicylic acid, sodium salt (74.4mmol) is dissolved in an aqueous NaOH solution (113mmol NaOH in 100mL H_2O). The solution is vigorously stirred at 17°C and at pH 13.3. The diazonium salt solution is added **dropwise** to the salicylic acid solution. It can be important to keep the temperature of the salicylic acid solution between $17-18^\circ\text{C}$ and the pH between 13.2-13.3 at all times, especially during the diazonium salt addition. The temperature can be regulated by adding ice and the pH regulated by adding NaOH , for example, 8M NaOH . After the addition is complete, the solution is allowed to warm room temperature and stirred for an additional period of time, for example, about 30 minutes. The reaction mixture is then suction filtered to remove any undissolved particulates or unwanted side products. The filtrate is acidified with aqueous HCl (10mL conc. HCl in 20mL H_2O) which produces a dark red precipitate. The precipitate is collected by suction filtration and washed several times with cold H_2O , until the filtrate is clear. The collected solid can be air dried overnight.

6.1.2 Oxidation of the resulting alcohol to the corresponding carboxylic acid:

[0065] A mixture of alcohol formed above (0.7mol) and a solution of sodium carbonate is placed in 150mL of water. A solution of potassium permanganate (0.9mol) in water is added, with vigorous stirring, for 3-4 hours at a temperature of $4-5^\circ\text{C}$. The reaction mixture is allowed to warm to room temperature and the precipitated manganese dioxide is removed by suction filtration. The solution is concentrated under reduced pressure, a layer of ether is added, and the aqueous solution is acidified with dilute H_2SO_4 . The organic and aqueous phases are separated and the aqueous phase extracted 2-3 times with ether. The ether extracts are combined, dried over MgSO_4 , and the solvent removed under reduced pressure. The resulting solid can optionally be recrystallized.

6.2 Example 2: Diazo Coupling of 4-Aminobenzyl cyanide with Salicylic Acid, followed by hydrolysis of the nitrile to the corresponding carboxylic acid:

[0066]



6.2.1 Diazo Coupling of 4-Aminobenzyl cyanide with Salicylic Acid:

[0067] 4-Aminobenzyl cyanide (24.8mmol) is suspended in water (75mL) and concentrated hydrochloric acid (8mL) is added. The solution is cooled to 0°C in an ice bath with rapid stirring. Sodium nitrite (26.1mmol) in water (20mL) is added dropwise to the 4-aminophenylacetic acid solution with rapid stirring. It is preferred to keep the temperature between $0-5^\circ\text{C}$ at all times, especially during the NaNO_2 addition. The reaction is stirred for an additional 20 minutes. In the meantime, salicylic acid, sodium salt (74.4mmol) is dissolved in an aqueous NaOH solution (113mmol NaOH in 100mL H_2O). The solution is vigorously stirred at 17°C and at pH 13.3. The diazonium salt solution is added dropwise to the salicylic acid solution. It can be extremely important to keep the temperature of the salicylic acid solution between $17-18^\circ\text{C}$ and the pH between 13.2-13.3 at all times, especially during the diazonium salt addition. The temperature is regulated by adding ice and the pH regulated by adding NaOH , for example, 8M NaOH . After the addition is complete, the solution is allowed to warm room temperature and stirred for an additional period of time, such as about 30 minutes. The reaction mixture can be suction filtered to remove any undissolved particulates or unwanted side products, and the filtrate can be acidified with aqueous HCl (10mL conc. HCl in 20mL H_2O) to produce a dark red precipitate. The precipitate can be collected by suction filtration and washed several times with cold H_2O , until the filtrate is clear. The collected solid can be air dried overnight.

6.2.2 Hydrolysis of the nitrile to the corresponding carboxylic acid

a) Basic Conditions:

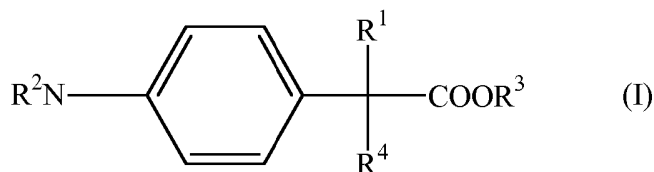
[0068] The nitrile formed above (1.2mol) and a solution of NaOH (2.3mol) can be placed in H_2O (260mL) in a round-bottom flask and heat to reflux using a condenser for approximately 5-10 h. Water (100mL) can be added through the condenser, then slowly with external cooling, 50% N_2SO_4 can be added. The upper layer containing the desired carboxylic acid can be separated and extracted with CH_2Cl_2 . The organic extracts can be combined, dried over MgSO_4 , and the solvent removed under reduced pressure. The resulting solid can optionally be recrystallized.

b) Acidic Conditions:

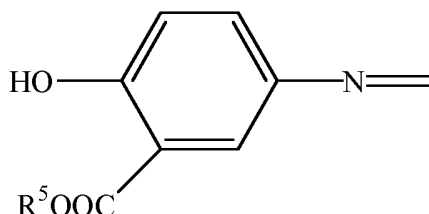
[0069] The nitrile formed above (0.85mol) and a solution of 50:50 H_2SO_4 :glacial acetic acid can be placed in H_2O (100mL) in a round-bottom flask and heated to reflux using a condenser for approximately 1 hour. The reaction mixture can be allowed to cool to room temperature and poured into 2-3 volumes of water with stirring. The desired crude product should precipitate. The resulting solid can be collected by suction filtration and washed with water until the filtrate is neutral. The resulting solid can optionally be recrystallized.

Claims

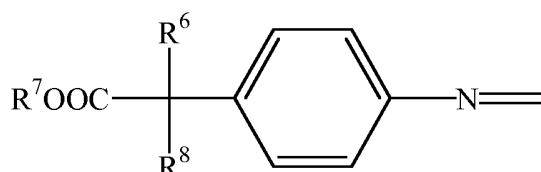
1. A method for preparing a compound of the formula:



where R^1 and R^3 are selected from the group consisting of H and C_1 - C_4 alkyl; R^4 is hydrogen; and R^2 is:

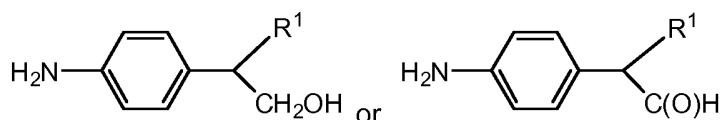


or



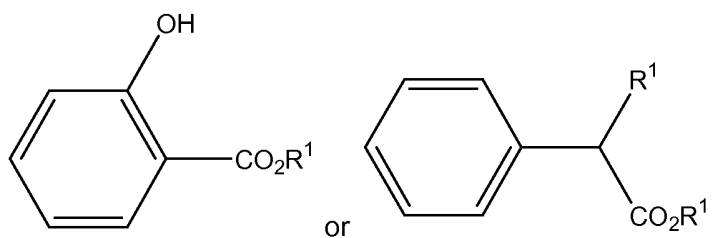
where R^5 , R^6 , R^7 and R^8 are independently hydrogen or C_1 to C_4 alkyl, wherein at least R^6 is hydrogen; or the esters or pharmaceutically acceptable salts thereof, comprising:

(a) converting a compound of one of the following formulas:



to a diazonium salt;

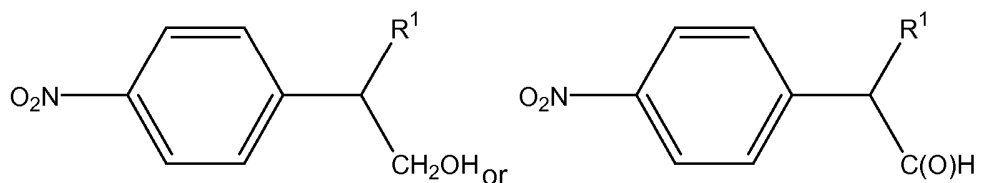
(b) reacting the diazonium salt with a compound of one of the following formulas:



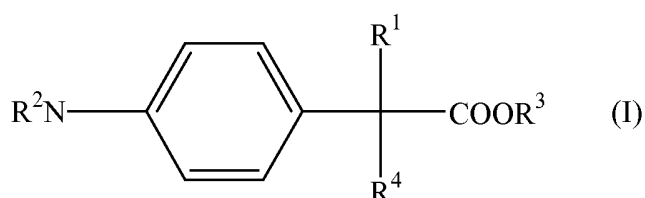
(c) oxidizing the primary alcohol or aldehyde group to a carboxylic acid group,
and

(d) optionally forming an ester or pharmaceutically acceptable salt of one or more of the carboxylic acid groups.

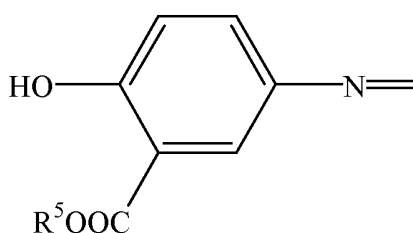
2. The method of Claim 1, wherein the aniline starting material is formed by reducing a nitrobenzene of one of the following formulas:



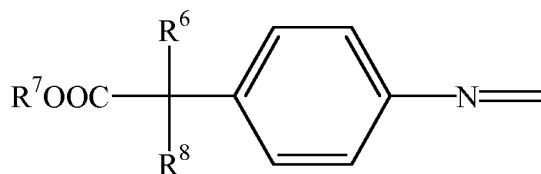
3. The method of Claim 1, wherein the oxidation of the primary alcohol or aldehyde group is performed using a chromium (VI) oxidizing agent.
4. The method of Claim 3, wherein the chromium (VI) oxidizing agent is present in catalytic amounts, and a co-oxidant is used to regenerate the chromium (VI) oxidizing agent.
5. The method of Claim 1, wherein the compound exists as a mixture of diastereomers, further comprising isolating an individual enantiomer from the mixture of diastereomers.
6. A method for preparing a compound of the formula:



where R¹ and R³ are selected from the group consisting of H and C₁-C₄ alkyl; R⁴ is hydrogen; and R² is:

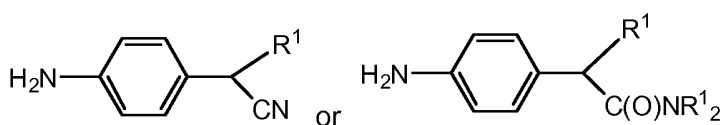


or



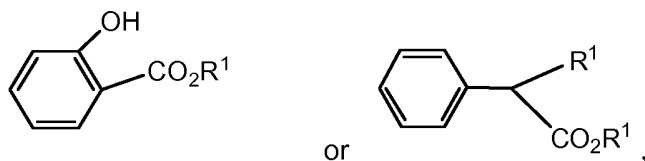
where R⁵, R⁶, R⁷ and R⁸ are independently hydrogen or C₁ to C₄ alkyl and wherein R⁶ is hydrogen; or the esters or pharmaceutically acceptable salts thereof, comprising:

(a) converting a compound of one of the following formulas:



to a diazonium salt;

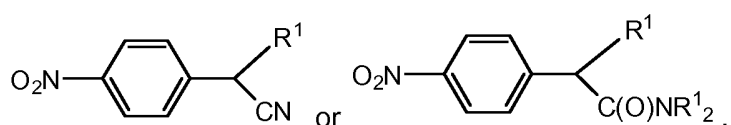
(b) reacting the diazonium salt with a compound of one of the following formulas:



(c) hydrolyzing the nitrile or amide group to form a carboxylic acid group, and

(d) optionally forming an ester or pharmaceutically acceptable salt of one or more of the carboxylic acid groups.

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7. The method of Claim 6, wherein the aniline starting material is formed by reducing a nitrobenzene of one of the following formulas:



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8. The method of claim 6 or 7, wherein the nitrile or amide is hydrolyzed to the carboxylic acid using acid catalysis.

9. The method of claim 6 or 7, wherein the nitrile or amide is hydrolyzed to the carboxylic acid using basic catalysis.

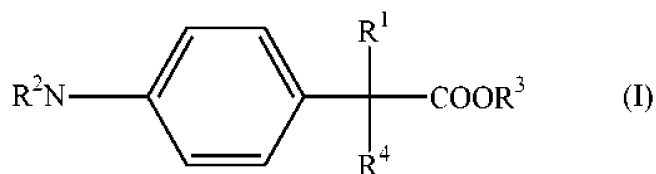
10. The method of claim 6 or 7, wherein the nitrile or amide is hydrolyzed to the carboxylic acid using enzymatic catalysis.

11. The method of claim 6 or 7, wherein the isolation step involves enzymatic resolution of one of the enantiomers during the hydrolysis of a nitrile or amide group.

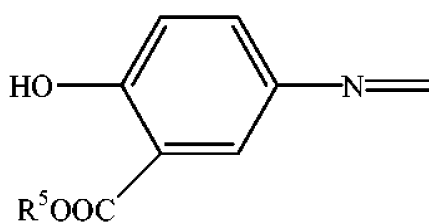
12. The method of any preceding Claim, wherein the compound that is formed is 5-(4-carboxymethyl-phenylazo)-2-hydroxy-benzoic acid, 5-[4-(1-carboxy-ethyl)-phenylazo]-2-hydroxy-benzoic acid or 4-(4-carboxymethyl-phenylazo)-phenylacetic acid.

Patentansprüche

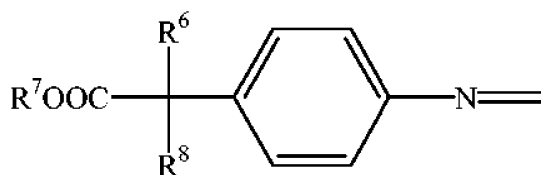
1. Verfahren zur Herstellung einer Verbindung mit der Formel:



wobei R¹ und R³ aus der Gruppe, bestehend aus H und C₁-C₄-Alkyl, ausgewählt werden; und wobei R⁴ Wasserstoff ist; und wobei R² Folgendes ist:

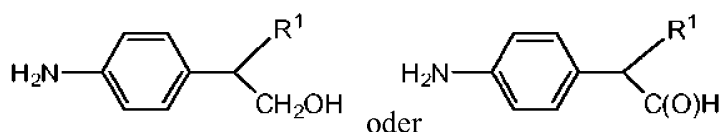


oder



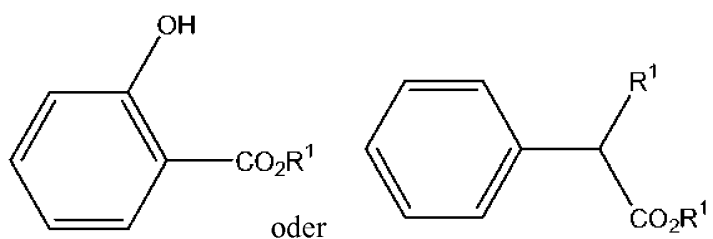
wobei R^5 , R^6 , R^7 und R^8 unabhängig Wasserstoff oder C_1 -bis C_4 -Alkyl sind, wobei mindestens R^6 Wasserstoff ist; oder die Ester oder pharmazeutisch zulässigen Salze von diesen, umfassend:

(a) Umwandeln einer Verbindung mit einer der folgenden Formeln:



in ein Diazoniumsalz;

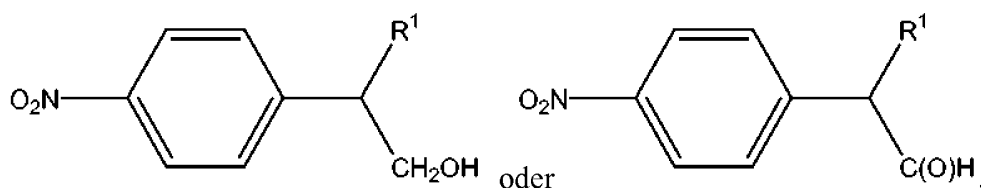
(b) Herbeiführen einer Reaktion des Diazoniumsalzes mit einer Verbindung mit einer der folgenden Formeln:



(c) Oxidieren des primären Alkohols oder der Aldehydgruppe zu einer Carboxylgruppe und

(d) optional Bilden eines Esters oder pharmazeutisch zulässigen Salzes aus einer oder mehreren der Carboxylgruppen.

2. Verfahren nach Anspruch 1, wobei der Anilinausgangsstoff gebildet wird durch Reduzieren eines Nitrobenzens mit einer der folgenden Formeln:

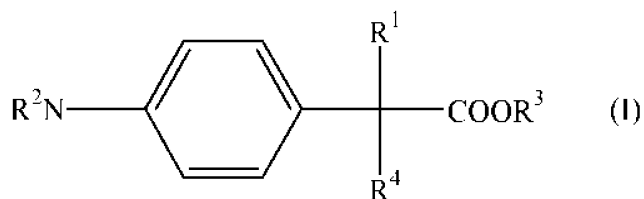


3. Verfahren nach Anspruch 1, wobei die Oxidation des primären Alkohols oder der Aldehydgruppe mit Hilfe eines Chrom(VI)-Oxidationsmittels durchgeführt wird.

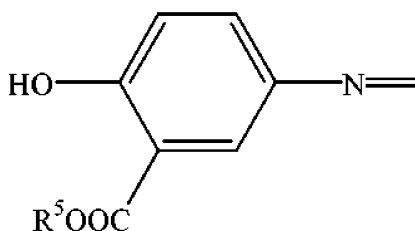
4. Verfahren nach Anspruch 3, wobei das Chrom(VI)-Oxidationsmittel in katalytischen Mengen vorliegt und ein Co-Oxidationsmittel verwendet wird, um das Chrom(VI)-Oxidationsmittel zu regenerieren.

5. Verfahren nach Anspruch 1, wobei die Verbindung als Gemisch von Diastereomeren vorliegt, weiter umfasst das Isolieren eines individuellen Enantiomers aus dem Gemisch von Diastereomeren.

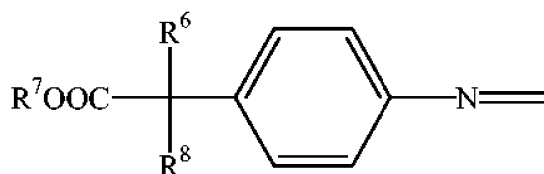
6. Verfahren zur Herstellung einer Verbindung mit der Formel:



wobei R^1 und R^3 aus der Gruppe, bestehend aus H und C_1 - C_4 -Alkyl, ausgewählt werden; und wobei R^4 Wasserstoff ist; und wobei R^2 Folgendes ist:

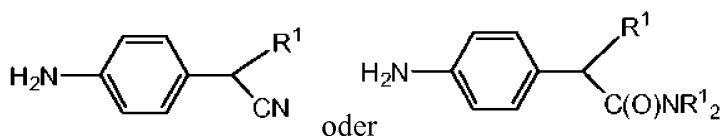


oder



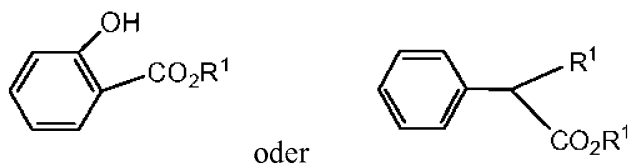
wobei R^5 , R^6 , R^7 und R^8 unabhängig Wasserstoff oder C_1 - bis C_4 -Alkyl sind und wobei R^6 Wasserstoff ist; oder die Ester oder pharmazeutisch zulässigen Salze von diesen, umfassend:

(a) Umwandeln einer Verbindung mit einer der folgenden Formeln:



in ein Diazoniumsalz;

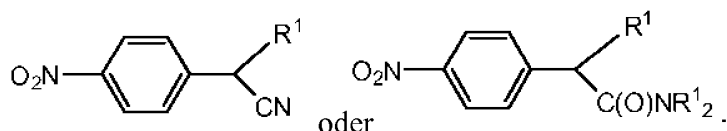
(b) Herbeiführen einer Reaktion des Diazoniumsalzes mit einer Verbindung mit einer der folgenden Formeln:



(c) Hydrolysieren der Nitril- oder Amidgruppe in eine Carboxylgruppe und

(d) optional Bilden eines Esters oder pharmazeutisch zulässigen Salzes aus einer oder mehreren Carboxylgruppen.

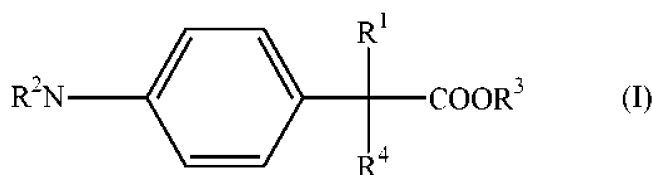
7. Verfahren nach Anspruch 6, wobei der Anilinausgangsstoff gebildet wird durch Reduzieren eines Nitrobenzens mit einer der folgenden Formeln:



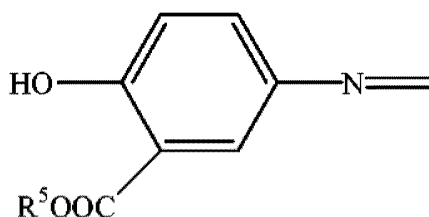
8. Verfahren nach Anspruch 6 oder 7, wobei das Nitril oder Amid mittels Säurekatalyse zur Carbonsäure hydrolysiert wird.
9. Verfahren nach Anspruch 6 oder 7, wobei das Nitril oder Amid mittels Basekatalyse zur Carbonsäure hydrolysiert wird.
10. Verfahren nach Anspruch 6 oder 7, wobei das Nitril oder Amid mittels Enzymkatalyse zur Carbonsäure hydrolysiert wird.
11. Verfahren nach Anspruch 6 oder 7, wobei der Isolierungsschritt die enzymatische Trennung eines der Enantiomere während der Hydrolyse einer Nitril- oder Amidgruppe umfasst.
12. Verfahren nach einem der vorstehenden Ansprüche, wobei die Verbindung, die gebildet wird, 5-(4-Carboxymethylphenylazo)-2-hydroxybenzoesäure, 5-[4-(1-Carboxyethyl)phenylazo]-2-hydroxybenzoesäure oder 4-(4-Carboxymethylphenylazo)phenyllessigsäure ist.

Revendications

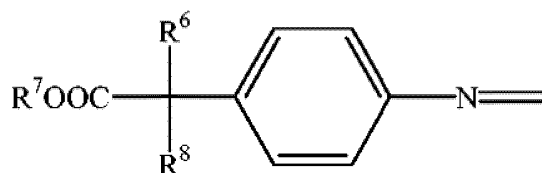
1. Procédé de préparation d'un composé de formule :



où R¹ et R³ sont choisis dans le groupe constitué par un atome H et un groupe alkyle en C₁ à C₄ ; R⁴ représente un atome d'hydrogène ; et R² représente :

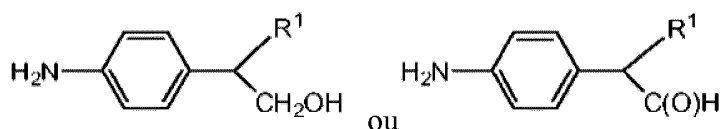


ou



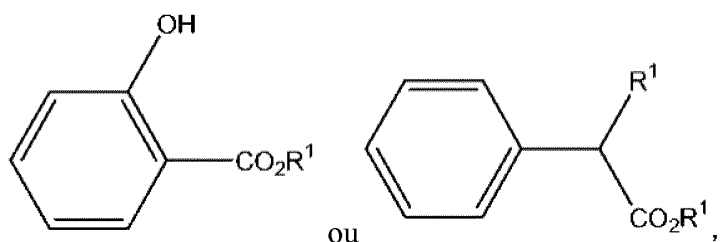
où R⁵, R⁶, R⁷ et R⁸ représentent indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, au moins ledit groupe R⁶ représentant un atome d'hydrogène ; ou les esters ou des sels pharmaceutiquement acceptables de ceux-ci, comprenant :

(a) la conversion d'un composé de l'une des formules suivantes :



en sel de diazonium ;

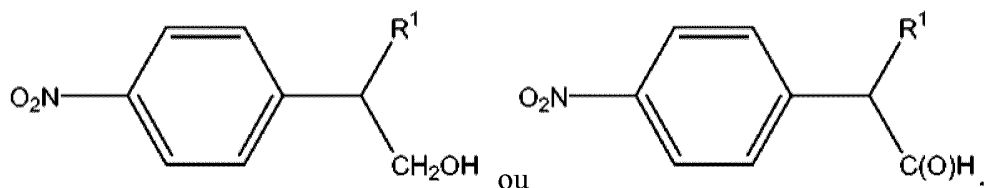
(b) la mise en réaction du sel de diazonium avec un composé de l'une des formules suivantes :



(c) l'oxydation du groupe alcool primaire ou aldéhyde en groupe acide carboxylique, et

(d) la formation éventuelle d'un ester ou d'un sel pharmaceutiquement acceptable de l'un ou plusieurs des groupes acide carboxylique.

- 25 2. Procédé selon la revendication 1, le matériau de départ d'aniline étant formé en réduisant un nitrobenzène de l'une des formules suivantes :

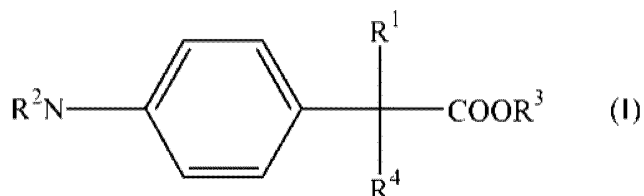


- 35 3. Procédé selon la revendication 1, ladite oxydation du groupe alcool primaire ou aldéhyde étant effectuée à l'aide d'un agent oxydant de chrome (VI).

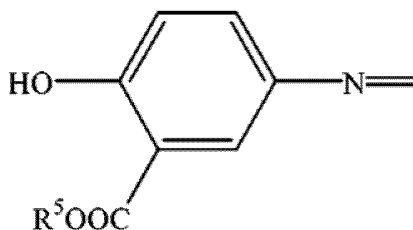
- 40 4. Procédé selon la revendication 3, ledit agent oxydant de chrome (VI) étant présent en quantités catalytiques, et un co-oxydant étant utilisé pour régénérer l'agent oxydant de chrome (VI).

5. Procédé selon la revendication 1, ledit composé existant sous la forme d'un mélange de diastéréoisomères, comprenant en outre l'isolement d'un énantiomère individuel à partir du mélange de diastéréoisomères.

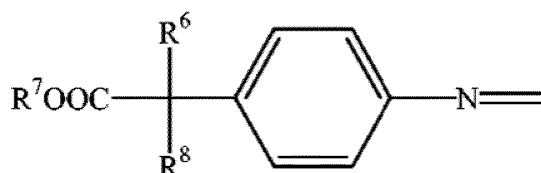
- 45 6. Procédé de préparation d'un composé de formule :



55 où R¹ et R³ sont choisis dans le groupe constitué par un atome H et un groupe alkyle en C₁ à C₄ ; R⁴ représente un atome d'hydrogène ; et R² représente :

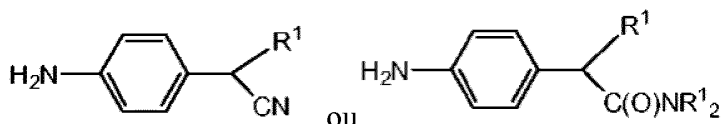


ou



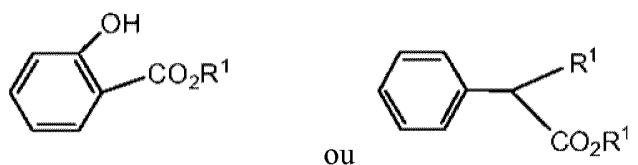
où R^5 , R^6 , R^7 et R^8 représentent indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 et R^6 représentant un atome d'hydrogène ; ou des esters ou des sels pharmaceutiquement acceptables de ceux-ci, comprenant :

(a) la conversion d'un composé de l'une des formules suivantes :



en sel de diazonium ;

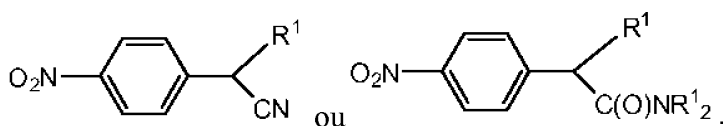
(b) la mise en réaction du sel de diazonium avec un composé de l'une des formules suivantes :



(c) l'hydrolyse du groupe nitrile ou amide pour former un groupe acide carboxylique, et

(d) la formation éventuelle d'un ester ou d'un sel pharmaceutiquement acceptable de l'un ou plusieurs des groupes acide carboxylique.

7. Procédé selon la revendication 6, le matériau de départ d'aniline étant formé en réduisant un nitrobenzène de l'une des formules suivantes :



8. Procédé selon la revendication 6 ou 7, ledit nitrile ou amide étant hydrolysé en acide carboxylique au moyen d'une catalyse acide.

9. Procédé selon la revendication 6 ou 7, ledit nitrile ou amide étant hydrolysé en acide carboxylique au moyen d'une catalyse basique.

5 10. Procédé selon la revendication 6 ou 7, ledit nitrile ou amide étant hydrolysé en acide carboxylique au moyen d'une catalyse enzymatique.

11. Procédé selon la revendication 6 ou 7, l'étape d'isolement impliquant la résolution enzymatique de l'un des énantiomères pendant l'hydrolyse d'un groupe nitrile ou amide.

10 12. Procédé selon l'une quelconque des revendications précédentes, ledit composé qui est formé étant l'acide 5-(4-carboxyméthyl-phénylazo)-2-hydroxy-benzoïque, l'acide 5-[4-(1-carboxy-éthyl)-phénylazo]-2-hydroxy-benzoïque ou l'acide 4-(4-carboxyméthyl-phénylazo)-phénylacétique.

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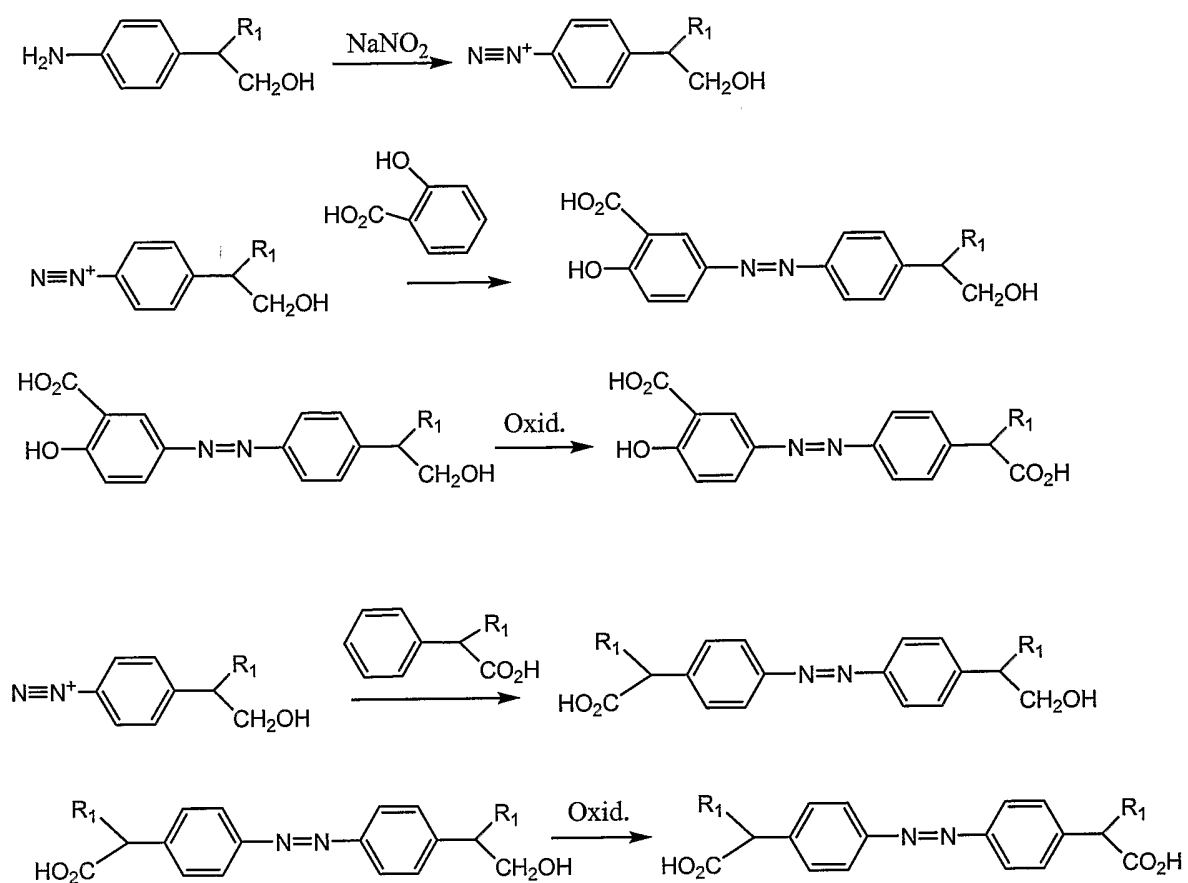
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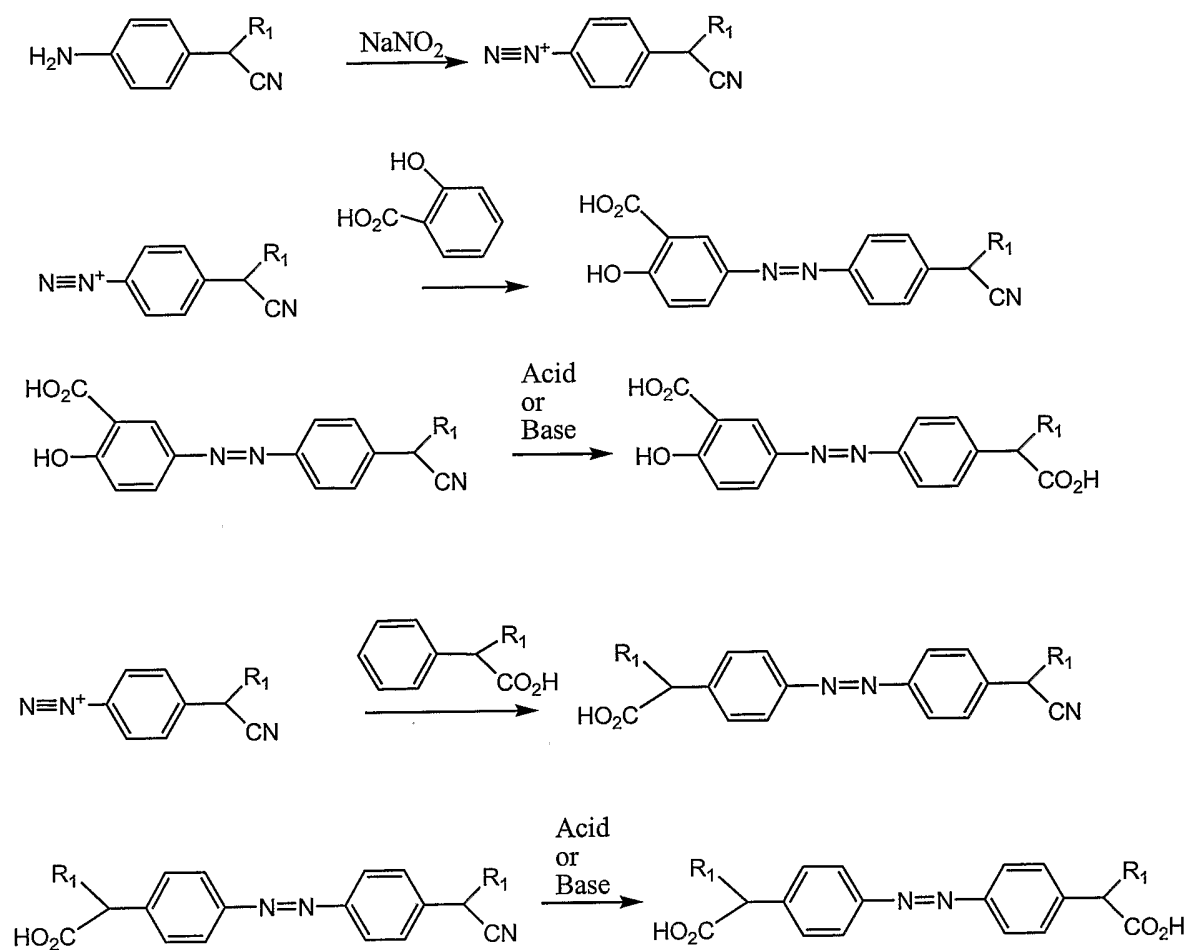
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Scheme I

Figure 1



Scheme II

Figure 2

REFERENCES CITED IN THE DESCRIPTION

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- WO 0218324 A [0004]
- WO 0218330 A [0005]
- US 6150554 A, Li [0043]
- US 6680395 B, Springer [0044]

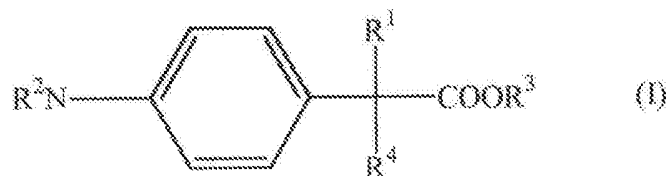
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- **GREENE, T. W. ; WUTS, P. G. M.** Protective Groups in Organic Synthesis. Wiley, 1991 [0042]
- **MARCH, J.** Advanced Organic Chemistry. John Wiley, 1985 [0047]
- **HOUSE.** Modern Synthetic Reactions. W.A. Benjamin, Inc, 1972 [0047]
- **EFFENGER ; OSSWALD.** Catalyst for the (E)-selective hydrolysis of (E,Z)- α,β -unsaturated nitriles to carboxylic acids. *Tetrahedron: Asymmetry*, 2001, vol. 12, 2581 [0048]
- Selective hydrolysis of aliphatic dinitriles to monocarboxylic acids. **EFFENGER ; OSSWALD.** Synthesis. 2001, 1866 [0048]
- **EFFENGER ; OSSWALD.** Enantioselective hydrolysis of (1)-arylacetonitriles. *Tetrahedron: Asymmetry*, 2001, vol. 12, 279 [0048]

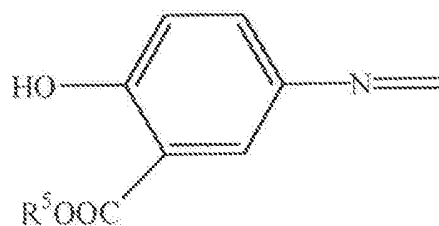
AZO-KÖTÉSŰ IMMUNSZABÁLYOZÓ VEGYÜLETEK SZINTÉZISE

Szabadalmi igénypontok

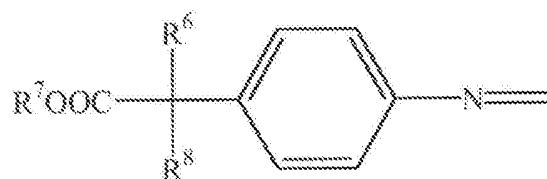
1. Eljárás egy vegyület előállítására, amely a következő általános képletű:



ahol R^1 és R^3 jelentése a következőkből álló csoportból van választva: H és C_1 - C_4 -alkil; R^4 jelentése hidrogén; és R^2 jelentése a következő:



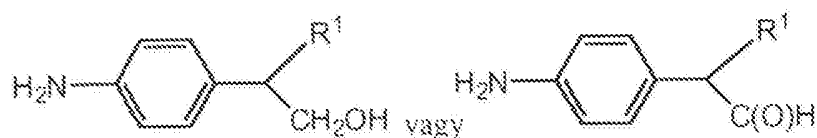
vagy



ahol R^5 , R^6 , R^7 és R^8 jelentése egymástól függetlenül hidrogén vagy C_1 - C_4 -alkil, ahol legalább R^6 jelentése hidrogén;

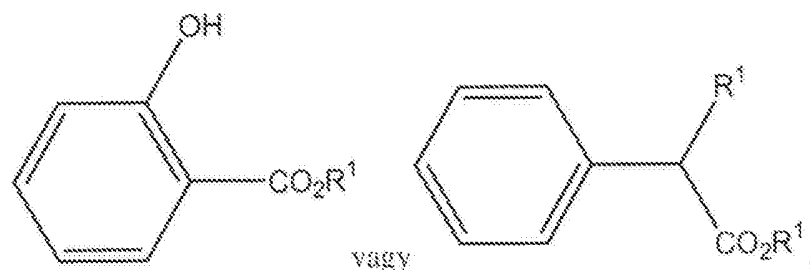
vagy annak észtereinek vagy gyógyszerészetileg elfogadható sóinak az előállítására, amely magában foglalja a következőket:

- (a) egy vegyület átalakítása, amely a következő általános képletek közül az egyikkel rendelkezik:



egy diazonium-sóvá;

- (b) a diazonium-só reagáltatása egy vegyülettel, amely a következő általános képletek közül az egyikkel rendelkezik:

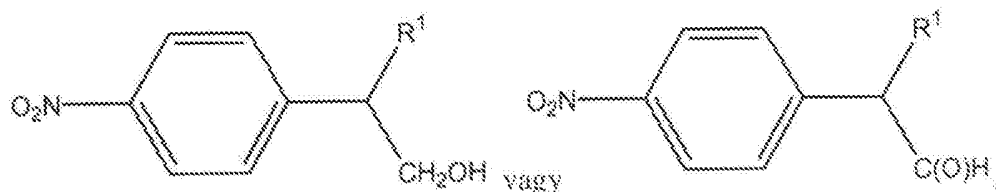


- (c) a primer alkohol vagy aldehid csoport oxidálása egy karbonsav csoporttá,

és

(d) opcionálisan egy észter vagy gyógyszerészetileg elfogadható só képzése a karbonsav csoportok közül egyből vagy többől.

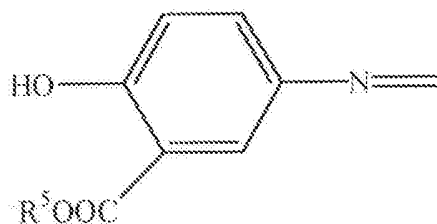
2. Eljárás az 1. igénypont szerint, ahol az amilin kiindulási anyag egy nitrobenzol redukálása révén van képezve, amely a következő általános képletek közül az egyikkel rendelkezik:



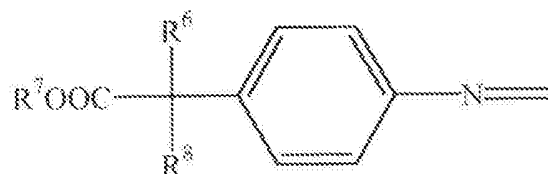
3. Eljárás az 1. igénypont szerint, ahol a primer alkohol vagy aldehid csoport oxidálása egy króm (VI) oxidálószer alkalmazásával van megvalósítva.
4. Eljárás a 3. igénypont szerint, ahol a króm (VI) oxidálószer katalitikus mennyiségben áll rendelkezésre és egy ko-oxidálószer van alkalmazva, hogy a króm (VI) oxidálószer legyen regenerálva.
5. Eljárás az 1. igénypont szerint, ahol a vegyület egy diasztereomerekből álló keverékként áll rendelkezésre, amely továbbá magában foglalja egy egyedi enantiomer izolálását a diasztereomerekből álló keverékből.
6. Eljárás egy vegyület előállítására, amely a következő általános képletű:



ahol R^1 és R^2 jelentése a következőkből álló csoportból van választva: H és C_1 - C_4 -alkil; R^4 jelentése hidrogén; és R^3 jelentése a következő:



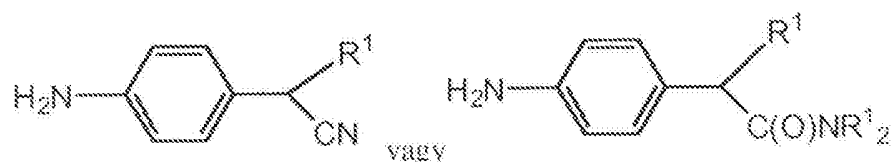
vagy



ahol R^5 , R^6 , R^7 és R^8 jelentése egymástól függetlenül hidrogén vagy C_1 - C_4 -alkil és ahol R^8 jelentése hidrogén;

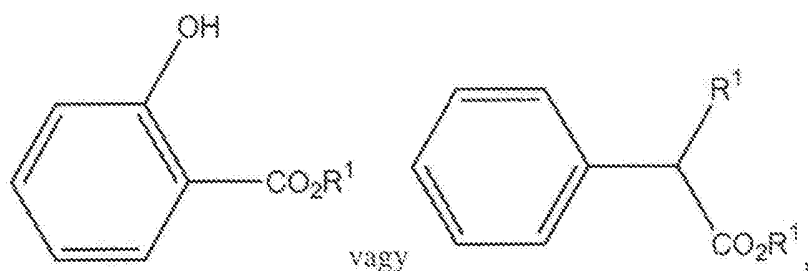
vagy annak észtereinek vagy gyógyszerészetileg elfogadható sóinak az előállítására, amely magában foglalja a következőket:

- (a) egy vegyület átalakítása, amely a következő általános képletek közül az egyikkel rendelkezik:



egy diazonium-sóvá;

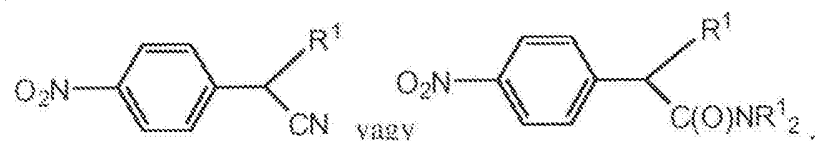
- (b) a diazonium-só reagáltatása egy vegyülettel, amely a következő általános képletek közül az egyikkel rendelkezik:



- (c) a nitril vagy amid csoport hidrolizálása, hogy egy karbonsav csoport legyen képezve, és

- (d) opcionálisan egy észter vagy gyógyszerészetileg elfogadható só képzése a karbonsav csoportok közül egyből vagy többől.

7. Eljárás a 6. igénypont szerint, ahol az anilín kiindulási anyag egy nitrobenzol redukálása révén van képezve, amely a következő általános képletek közül az egyikkel rendelkezik:



8. Eljárás a 6. vagy 7. igénypont szerint, ahol a nitril vagy amid a karbonsavvá savkatalízis alkalmazásával van hidrolizálva.
9. Eljárás a 6. vagy 7. igénypont szerint, ahol a nitril vagy amid a karbonsavvá báziskatalízis alkalmazásával van hidrolizálva.
10. Eljárás a 6. vagy 7. igénypont szerint, ahol a nitril vagy amid a karbonsavvá enzimatis katalízis alkalmazásával van hidrolizálva.
11. Eljárás a 6. vagy 7. igénypont szerint, ahol az izolálási lépés magában foglalja az enantiomerek közül az egyiknek az enzimatis rezolválását (angolul: „enzymatic resolution”) egy nitril vagy amid csoportnak a hidrolizálása közben.
12. Eljárás az előző igénypontok bármelyike szerint, ahol a vegyület, amely képezve van, a következő: 5-(4-karboxi-metil-fenil-azo)-2-hidroxi-benzoész, 5-[4-(1-karboxi-etil)-fenil-azo]-2-hidroxi-benzoész vagy 4-(4-karboxi-metil-fenil-azo)-fenil-ecetsav.