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(71) Demandeur/Applicant:
ELAN PHARMACEUTICALS, INC., US

(72) Inventeurs/Inventors:
YEDNOCK, THEODORE A., US;
FREEDMAN, STEPHEN B., US;
LIEBERBURG, IVAN, US;
PLEISS, MICHAEL A., US;
KONRADI, ANDREI W., US;
SHOPP, GEORGE, US;
MESSERSMITH, ELIZABETH, US

(74) Agent: BARRIGAR INTELLECTUAL PROPERTY LAW

(54) Titre : METHODES ET COMPOSITIONS DE TRAITEMENT DE POLYARTHRITE RHUMATOIDE
(54) Title: METHODS AND COMPOSITIONS FOR TREATING RHEUMATOID ARTHRITIS

(57) Abrégé/Abstract:
This application relates to methods and compositions for treating rheumatoid arthritis by administering a combination therapy comprising methotrexate and an antibody to alpha 4 integrin or an immunologically active antigen binding fragment in therapeutically effective amounts. The application also relates generally to methods and compositions for treating rheumatoid arthritis by administering a combination therapy comprising methotrexate and small molecule alpha-4 integrin antagonist that inhibits the alpha-4 integrin ( 4 integrin) interaction with VCAM-1. The invention further relates to methods of preparing the compounds and methods of using the compounds and compositions.

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(71) Applicant (*for all designated States except US*): **ELAN PHARMACEUTICALS, INC.** [US/US]; 800 Gateway Boulevard, South San Francisco, California 94080 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **YEDNOCK, Theodore, A.** [US/US]; 184 Arroyo Road, PO Box 831, Forest Knolls, California 94933 (US). **FREEDMAN, Stephen, B.** [GB/US]; 388 Beale Street, Apt 1606, San Francisco, California 94105 (US). **LIEBERBURG, Ivan** [US/US]; 85 Hillcrest Road, Berkeley, California 94705 (US). **PLEISS, Michael, A.** [US/US]; 848 Stella Court, Sunnyvale, California 94087 (US). **KONRADI, Andrei, w.** [US/US]; 95 Cervantes #105, San Francisco, California 94123 (US). **SHOPP, George** [US/US]; 104 Claremont Avenue, South San Francisco, California 94080 (US). **MESSERSMITH, Elizabeth** [US/US]; 950 Sea View Drive, El Cerrito, California 94530 (US).

(74) Agents: **REA, Teresa, Stanek** et al.; BURNS, DOANE, SWECKER & MATHIS, LLP, PO BOX 1404, Alexandria, Virginia 22313-1404 (US).

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING RHEUMATOID ARTHRITIS

(57) Abstract: This application relates to methods and compositions for treating rheumatoid arthritis by administering a combination therapy comprising methotrexate and an antibody to alpha 4 integrin or an immunologically active antigen binding fragment in therapeutically effective amounts. The application also relates generally to methods and compositions for treating rheumatoid arthritis by administering a combination therapy comprising methotrexate and small molecule alpha-4 integrin antagonist that inhibits the alpha-4 integrin ( 4 integrin) interaction with VCAM-1. The invention further relates to methods of preparing the compounds and methods of using the compounds and compositions.

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# METHODS AND COMPOSITIONS FOR TREATING RHEUMATOID ARTHRITIS

## FIELD OF THE INVENTION

This application relates to methods and compositions for treating rheumatoid arthritis by administering a combination therapy comprising methotrexate and an antibody to alpha-4 integrin or an immunologically active antigen binding fragment in therapeutically effective amounts. The application also relates generally to methods and compositions for treating rheumatoid arthritis by administering a combination therapy comprising methotrexate and small molecule alpha-4 integrin antagonist that inhibits the alpha-4 integrin (α4 integrin) interaction with VCAM-1. The invention further relates to methods of preparing the compounds and methods of using the compounds and compositions.

## BACKGROUND OF THE INVENTION

### Inflammation

Inflammation is a response of vascularized tissues to infection or injury and is affected by adhesion of leukocytes to the endothelial cells of blood vessels and their infiltration into the surrounding tissues. In normal inflammation, infiltrating leukocytes release toxic mediators to kill invading organisms, phagocytize debris and dead cells, and play a role in tissue repair and the immune response. However, in pathologic inflammation, infiltrating leukocytes are over-responsive and can cause serious or fatal damage. *See, e.g.,* Hickey, *Psychoneuroimmunology II* (Academic Press 1990).

The integrins are a family of cell-surface glycoproteins involved in cell-adhesion, immune cell migration and activation. Alpha-4 (α4) integrin is expressed by all circulating leukocytes except neutrophils, and forms heterodimeric receptors in conjunction with either the beta1 (β1) or beta7 (β7) integrin subunits. Both alpha-4 beta-1 (α4β1) and alpha-4 beta-7 (α4β7) play a role in the migration of leukocytes across the vascular endothelium (Springer *et al.*, *Cell*, 1994 76: 301-14; Butcher *et al.*, *Science*, 1996, 272: 60-6) and contribute to cell activation and survival within the parenchyma (Damle *et al.*, *J. Immunol.*, 1993; 151: 2368-79; Koopman *et al.*, *J. Immunol.*, 1994, 152: 3760-7; Leussink *et al.*, *Acta Neuropathol.*, 2002, 103: 131-136). α4β1 is constitutively expressed on lymphocytes, monocytes, macrophages, mast cells, basophils and eosinophils.

α4β1 (also known as very late antigen-4, VLA-4), binds to vascular cell adhesion molecule-1 (VCAM-1) (Lobb *et al.*, *J. Clin. Invest.*, 1994, 94: 1722-8), which is expressed by the vascular endothelium at many sites of chronic inflammation (Bevilacqua *et al.*, 1993 *Annu. Rev. Immunol.*, 11: 767-804; Postigo *et al.*, 1993 *Res. Immunol.*,144: 723-35). α4β1 has other ligands, including fibronectin and other extracellular matrix (ECM) components.

Intercellular adhesion mediated by α4β1 and other cell surface receptors is associated with a number of inflammatory responses. At the site of an injury or other inflammatory stimulus, activated vascular endothelial cells express molecules that are adhesive for leukocytes. The mechanics of leukocyte adhesion to endothelial cells involves, in part, the recognition and binding of cell surface receptors on leukocytes to the corresponding cell surface molecules on endothelial cells. Once bound, the leukocytes migrate across the blood vessel wall to enter the injured site and release chemical mediators to combat infection.

**Rheumatoid arthritis**

Rheumatoid arthritis ("RA") is a chronic inflammatory disease that causes pain, swelling, stiffness, and loss of function, primarily the joints. RA is estimated to affect approximately 1 percent of the world's population. In the U.S. alone, an estimated 2.1 million people suffer from the disease. This relatively high frequency suggests a complex etiology and pathogenesis.

The disease process leading to RA begins in the synovium, the membrane that surrounds a joint creating a protective sac. In healthy individuals, the synovium produces synovial fluid that lubricates, nourishes and protects joint tissues. This clear fluid lubricates and nourishes the cartilage and bones inside the joint capsule. In individuals suffering from RA, the immune system, for unknown reasons, attacks the cells inside synovium. Leukocytes infiltrate from the circulation into the synovium causing continuous abnormal inflammation (*i.e.*, synovitis). Consequently, the synovium becomes inflamed, causing warmth, redness, swelling, and pain. The collagen in the cartilage is gradually destroyed, narrowing the joint space and eventually damaging bone. The inflammation causes erosive bone damage in the affected area. During this process, the cells of the synovium grow and divide abnormally, making the normally thin synovium thick and resulting in a joint that is swollen and puffy to the touch. *See, e.g.*, Paul, *Immunology* (3d ed., Raven Press, 1993).

It is believed that bone damage begins during the first year or two that a person has the disease. This is one reason why early diagnosis and treatment are important in the management of RA. As the disease progresses, abnormal synovial cells begin to invade and destroy the cartilage and bone within the joint. The surrounding muscles, ligaments, and tendons that support and stabilize the joint become weak and unable to work normally. RA also causes more generalized bone loss that may lead to osteoporosis, making bones fragile and more prone to fracture. All of these effects cause the pain, impairment and deformities associated with RA.

Although RA almost always develops in the wrists and knuckes, some patients experience the effects of the disease in places other than the joints. For instance, the knees and the ball of the foot are often affected as well. Often, many joints may be involved, and even the spine can be affected. In about 25% of people with RA, inflammation of small blood vessels can cause rheumatoid nodules, or lumps, under the skin. These are bumps under the skin that often form close to the joints. As the disease progresses, fluid may also accumulate, particularly in the ankles. Many patients with RA also develop anemia, or a decrease in the normal number of red blood cells. Other less prevalent effects include neck pain, dry eyes and dry mouth. On rare occasions, patients may also develop inflammation of the blood vessels, the lining of the lungs, or the sac enclosing the heart.

RA has several special features that differentiate it from other types of arthritis. For example, RA generally occurs in a symmetrical pattern – if one knee or hand is involved, the other one is also. The disease often affects the wrist joints and the finger joints closest to the hand. RA usually first affects the small joints of the hands and feet, but may also involve the wrists, elbows, ankles and knees. It can also affect other parts of the body besides the joints. In addition, patients with the disease may have fatigue, occasional fever, and a general sense of not feeling well (malaise).

Another distinct feature of RA is the variance between individuals. For some, it lasts only a few months or a year or two and subsides without causing any noticeable damage. Other people have mild or moderate disease, with periods of worsening symptoms (flares) and periods in which they feel better (remissions). In severe cases, the disease is chronically active most of the time, lasting for many years, and leading to serious joint damage and disability.

RA encompasses a number of disease subtypes, such as Felty's syndrome, seronegative RA, "classical" RA, progressive and/or relapsing RA, and RA with vasculitis. Some experts classify the disease into type 1 or type 2. Type 1, the less common form, lasts a few months at most and leaves no permanent disability. Type 2 is chronic and lasts for years, sometimes for life.

RA is believed to be one of several "autoimmune" diseases ("auto" means self), so-called because a person's immune system attacks his or her own body tissues. Although much has been learned about the process leading to RA, researchers have yet to uncover all of the factors that lead to this disease. One prevalent theory is that a combination of factors trigger RA, including an abnormal autoimmune response, genetic susceptibility, environmental, biologic factors, hormonal, and reproductive factors. Nonetheless, despite intensive research, the cause of RA remains obscure. *See* El-Gabalawy *et al.*, ARTHRITIS RES. 4(suppl 3):S297-S301 (2002).

RA occurs across all races and ethnic groups. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults may also develop juvenile RA. Like other forms of arthritis, RA exhibits a clear gender bias: approximatley two to three times as many women as men have the disease (Lawrence *et al.*, *Arthritis Rheum.*, 1998, 41:778-799). . However, a genetic predisposition has been identified and, in white populations, localized to a pentapeptide in the HLA-DR 1 locus of class II histocompatibility genes. Environmental factors may also play a role. Immunologic changes may be initiated by multiple factors.

Prominent immunologic abnormalities that may be important in pathogenesis include immune complexes found in joint fluid cells and in vasculitis. Plasma cells produce antibodies that contribute to these complexes. Lymphocytes that infiltrate the synovial tissue are primarily T helper cells, which can produce pro-inflammatory cytokines. Increased adhesion molecules contribute to inflammatory cell emigration and retention in the synovial tissue.

The onset is usually insidious, with progressive joint involvement, but may be abrupt, with simultaneous inflammation in multiple joints. Tenderness in nearly all inflamed joints and synovial thickening are common. Initial manifestations may occur in any joint.

Stiffness lasting less than 30 minutes on arising in the morning or after prolonged inactivity is common. Subcutaneous rheumatoid nodules are not usually an early

manifestation. Visceral nodules, vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, lymphadenopathy, Felty's syndrome, Sjögren's syndrome, and episcleritis are other manifestations. As many as 75% of patients improve symptomatically with conservative treatment during the first year of disease. However, less than 10% are eventually severely disabled despite full treatment. The disease greatly affects the lives of most RA patients. Complete bed rest is occasionally indicated for a short period during the most active, painful stage of severe disease. In less severe cases, regular rest should be prescribed.

Nonsteroidal anti-inflammatory drugs may provide important symptomatic relief and may be adequate as simple therapy for mild RA, but they do not appear to alter the long-term course of disease. Salicylates, such as aspirin, may be used for treatment.

Gold compounds usually are given in addition to salicylates or other NSAIDs if the latter do not sufficiently relieve pain or suppress active joint inflammation. In some patients, gold may produce clinical remission and decrease the formation of new bony erosions. Parenteral preparations include gold sodium thiomalate or gold thioglucose. Gold should be discontinued when any of the above manifestations appear. Minor toxic manifestations (*e.g.*, mild pruritus, minor rash) may be eliminated by temporarily withholding gold therapy, then resuming it cautiously about 2 wk after symptoms have subsided. However, if toxic symptoms progress, gold should be withheld and the patient given a corticosteroid. A topical corticosteroid or oral prednisone 15 to 20 mg/day in divided doses is given for mild gold dermatitis; larger doses may be needed for hematologic complications. A gold chelating drug, dimercaprol 2.5 mg/kg IM, may be given up to four to six times/day for the first 2 days and bid for 5 to 7 days after a severe gold reaction.

Hydroxychloroquine can also control symptoms of mild or moderately active RA. Toxic effects usually are mild and include dermatitis, myopathy, and generally reversible corneal opacity. However, irreversible retinal degeneration has been reported. Sulfasalazine may also be used for treatment of RA.

Oral penicillamine may have a benefit similar to gold and may be used in some cases if gold fails or produces toxicity in patients with active RA. Side effects requiring discontinuation are more common than with gold and include marrow suppression, proteinuria, nephrosis, other serious toxic effects (eg, myasthenia gravis, pemphigus, Goodpasture's syndrome, polymyositis, a lupuslike syndrome), rash, and a foul taste.

Steroids are the most effective short-term anti-inflammatory drugs. However, their clinical benefit for RA often diminishes with time. Steroids do not predictably prevent the progression of joint destruction. Furthermore, severe rebound follows the withdrawal of corticosteroids in active disease. Contraindications to steroid use include peptic ulcer, hypertension, untreated infections, diabetes mellitus, and glaucoma.

Immunosuppressive drugs are increasingly used in management of severe, active RA. However, major side effects can occur, including liver disease, pneumonitis, bone marrow suppression, and, after long-term use of azathioprine and malignancy.

Whatever may be the actual cause, there is no cure for RA, and although the disease is not fatal, disease complications and symptoms may persist throughout an individual's lifetime, and may even shorten survival by a few years. Affected joints may become deformed, and the performance of even ordinary tasks may be very difficult or impossible.

## SUMMARY OF THE INVENTION

Based on the above, new compositions and methods of preventing rheumatoid arthritis and treating the symptoms of rheumatoid arthritis are needed such that patients can have better quality of life.

The invention relates to combination therapies comprising methotrexate and an antibody to alpha-4 integrin or an immunologically active antigen binding fragment thereof or a small molecule alpha-4 integrin antagonist for use in a subject in need thereof. Preferably, the subject is a mammal. More preferably, the mammal is human.

The invention also relates to methods of treating rheumatoid arthritis in a subject in need thereof comprising administering in therapeutically effective amounts, a combination therapy comprising methotrexate and an antibody to alpha-4 integrin or an immunologically active antigen binding fragment thereof or a small molecule alpha-4 integrin antagonist. Preferably, the subject is a mammal. More preferably, the mammal is human.

The invention further relates to regimes for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and a therapeutically effective amount of a methotrexate and an antibody to alpha-4 integrin or an immunologically active antigen binding fragment thereof or a small molecule alpha-4 integrin antagonist. Preferably, the subject is a mammal. More preferably, the mammal is human.

In yet another embodiment, the invention relates to the use of the combination therapies as described herein in the preparation of a medicament for the treatment of rheumatoid arthritis.

These and other objects, advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the methods and formulations as more fully described below.

## BRIEF DESCRIPTIONS OF THE DRAWINGS

**FIG. 1.** Fig. 1 shows the effect of anti-alpha 4-integrin antibody *in vivo* prophylactically (upper panel), semi-therapeutic dosing (middle panel) and therapeutic dosing (lower panel).

**FIG. 2.** Fig. 2 shows the effect of anti-alpha4 antibodies (upper panel), anti-α4β7 (LPAM-1) antibodies (middle panel) and anti-VACM-1 antibodies *in vivo* using CIA models (lower panel).

**FIG. 3.** Fig. 3 shows the effects of anti-VLA-4, anti-VCAM-2 and anti-LPAM-1 antibodies *in vivo* in CIA models at semi-therapeutic dosing.

**FIG. 4.** Fig. 4 shows the effect of anti-VLA-4 antibody *in vivo* in CIA model at therapeutic dosing (upper panel). Effect of the compound of Formula P *in vivo* in CIA model at therapeutic dosing (lower panel).

**FIG. 5.** Fig. 5 shows the valuation of compounds in AIA Animal Model.

**FIG. 6.** Fig. 6 shows comparative effects of anti-alpha 4 antibodies and the compounds of Formulae W and Y in rat CIA model.

**FIG. 7.** Fig. 7 shows prophylactic treatment with anti-alpha 4 antibodies (PS/2) in the CIA Animal Model.

**FIG. 8.** Fig. 8 shows the therapeutic treatment with anti-alpha 4 antibody (GG5/3) in the AIA Animal Model.

**FIG. 9.** Fig. 9 shows the therapeutic treatment with anti-alpha 4 antibody (GG5/3) in the AIA Animal Model.

**FIG. 10.** Fig. 10 shows the results of dosage regimen for therapeutic treatment with small molecule alpha-4 antagonists in the AIA Animal Model.

**FIG. 11.** Fig. 11 shows the potency and specificity of compounds in the AIA Animal Model.

## DETAILED DESCRIPTION OF THE INVENTION

In accordance with this detailed description, the following abbreviations and definitions apply. It must be noted that as used herein, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an antibody" includes a plurality of such antibodies and reference to "the dosage" includes reference to one or more dosages and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention. Also contemplated are any values that fall within the cited ranges.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

## DEFINITIONS

By "protein" is meant to include but is not limited to immunoglobulins, enzymes, receptor, and fragments thereof. Although discussion of the formulation is provided in

reference to an antibody or immunoglobulin, other proteins are contemplated as interchangeable in the formulations disclosed.

By "immunoglobulin" is meant to include, but is not limited to, an antibody and antibody fragment (such as scFv, Fab, Fc, $F(ab')_2$), and other genetically engineered portions of antibodies. Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM. Several of these may be further divided into subclasses (isotypes), *e.g.*, IgG-1, IgG-2, IgG-3, and IgG-4; IgA-1 and IgA-2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called alpha ($\alpha$), delta ($\Delta$), epsilon ($\varepsilon$), gamma ($\gamma$), and mu ($\mu$), respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Preferably, the immunoglobulin recognizes and binds to alpha-4 integrin.

The term "antibody" is used in the broadest sense and includes monoclonal antibodies (including agonist and antagonist antibodies), antibody compositions with polyepitopic specificity, and antibody fragments (*e.g.*, Fab, $F(ab')_2$, scFv and Fv), so long as they exhibit the desired biological activity. "Antibody" is meant to include polyclonal antibodies, monoclonal antibodies, humanized antibodies, human antibodies, Primatized® antibodies and other antibodies produced via genetic engineering.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, 1975 *Nature* 256: 495 or by the many

improvements thereon derived in the intervening period. Some of these are discussed for instance in, Harlow *et al.*, USING ANTIBODIES: A LABORATORY MANUAL - PORTABLE PROTOCOL NO. 1 (Cold Spring Harbor Press, NY 1998); Harlow *et al.*, ANTIBODIES: A LABORATORY MANUAL (Cold Spring Harbor Press, NY 1988); and Shepherd *et al.*, MONOCLONAL ANTIBODIES: A PRACTICAL APPROACH (Oxford University Press, 2000).

The term "monoclonal antibodies" also includes "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. For example, the ability to bind to alpha-4 integrin. The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described for example in Clackson *et al.*, 1991 *Nature* 352: 624-628 and Marks *et al.*, 1991 *J. Mol. Biol.*, 222: 581-597.

"Humanized" forms of non-human (*e.g.*, murine, rabbit, bovine, equine, porcine, and the like) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies), which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibody may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise

at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

The expression "linear antibodies" are also included by the general term "antibody" and are a pair of tandem Fd segments ($V_H$-$C_H1$-$V_H$ -$C_H1$), which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

A "variant antibody" (also included by the generic term "antibody") is a molecule which differs in amino acid sequence from a "parent" antibody's amino acid sequence by virtue of addition, deletion and/or substitution of one or more amino acid residue(s) in the parent antibody sequence. In the preferred embodiment, the variant comprises one or more amino acid substitution(s) in one or more hypervariable region(s) of the parent antibody. For example, the variant may comprise at least one substitution, *e.g.*, from about one to about ten, and preferably from about two to about five, in one or more hypervariable regions of the parent antibody. Ordinarily, the variant will have an amino acid sequence having at least 75% amino acid sequence identity with the parent antibody heavy or light chain variable domain sequences, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the parent antibody residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. None of the N-terminal, C-terminal, or internal extensions, deletions, or insertions into the antibody sequence should be construed as affecting sequence identity or homology.

To analyze such properties, one should compare a Fab form of the variant to a Fab form of the parent antibody or a full length form of the variant to a full length form of the parent antibody, for example, because it has been found that the format of the antibody impacts its activity in the biological activity assays disclosed herein. The variant antibody of particular interest is one which displays at least about 10 fold, preferably at least about 20 fold, and most preferably at least about 50 fold, enhancement in biological activity when compared to the parent antibody. The "parent" antibody is one which is encoded by an amino acid sequence used for the preparation of the variant. Preferably, the parent antibody has a human framework region and has human antibody constant region(s). For example, the parent antibody may be a humanized or a human antibody.

An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

"Antibody fragments" comprise a portion of an intact antibody, generally the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

"Single-chain Fv" or "sFv" antibody fragments comprise the $V_H$ and $V_L$ domains of antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the $V_H$ and $V_H$ domains which enables the sFv to form the desired structure for antigen binding.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain ($V_H$) connected to a light chain variable domain ($V_L$) in the same polypeptide chain ($V_H$ -$V_L$). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites.

The route of antibody administration is in accord with welll known methods, and may include injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, or intralesional routes, or by sustained release systems. The antibody can be administered continuously by infusion or by bolus injection. Therapeutic antibody compositions generally are placed into a container having a sterile access port, for

example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

A "stable" formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in PEPTIDE AND PROTEIN DRUG DELIVERY, 247-301 (Vincent Lee ed., New York, N.Y., 1991) and Jones, 1993 *Adv. Drug Delivery Rev.* 10: 29-90, for examples. Stability can be measured at a selected temperature for a selected time period as exemplified by the provided examples.

A protein, such as an antibody or fragment thereof, "retains its physical stability" in a pharmaceutical formulation if it shows no signs of aggregation, precipitation and/or denaturation upon visual examination of color and/or clarity, or as measured by UV light scattering or by size exclusion chromatography.

A protein "retains its chemical stability" in a pharmaceutical formulation, if the chemical stability at a given time is such that the protein is considered to still retain its biological activity. Chemical stability can be assessed by detecting and quantifying chemically altered forms of the protein. Chemical alteration may involve size modification (*e.g.*, clipping), which can be evaluated using size exclusion chromatography, SDS-PAGE and/or matrix-assisted laser desorption ionization/time-of-flight mass spectrometry (MALDI/TOF MS), for examples. Other types of chemical alteration include charge alteration (*e.g.*, occurring as a result of deamidation), which can be evaluated by ion-exchange chromatography, for example.

An antibody "retains its biological activity" in a pharmaceutical formulation, if the biological activity of the antibody at a given time is within about 10% (within the errors of the assay) of the biological activity exhibited at the time the pharmaceutical formulation was prepared as determined in an antigen binding assay, for example.

By "isotonic" is meant that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm. Isotonicity can be measured using a vapor pressure or ice-freezing type osmometer, for example.

As used herein, "buffer" refers to a buffered solution that resists changes in pH by the action of its acid-base conjugate components. The buffer of this invention has a pH in the range from about 3.0 to about 7.5; preferably from about pH 4.0 to about 7.0; more preferably

from about pH 5.0 to about 6.5; and most preferably has a pH of about 6.0±0.5. A pH of any point in between the above ranges is also contemplated.

A "preservative" is a compound which can be included in the formulation to essentially reduce bacterial action therein, thus facilitating the production of a multi-use formulation, for example. Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl and benzyl alcohol, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol.

By "patient" or "subject" is meant to include any mammal. A "mammal", for purposes of treatment, refers to any animal classified as a mammal, including but not limited to humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, and the like. Preferably, the mammal is human.

By "Antegren™" is meant to include the antibody also known as AN100226 (antibody code number) or natalizumab (USAN name). Antegren™ is a recombinant, humanized anti-alpha-4 integrin antibody. Preferably the disease or condition being treated in the mammal is one which is modulated when a therapeutically effective dose of Antegren™ is administered.

The terms "small molecule alpha-4-integrin antagonists" (*i.e.*, anti-alpha-4 agents and small molecule compounds) as used herein refer to any agent that binds specifically to an integrin comprising an alpha-4 subunit and inhibits activity of the integrin. Preferably such molecules bind to alpha-4 in a manner that prevents its interaction with VCAM1 and thereby VCAM-1 signaling. This also includes agents that specifically bind to alpha-4 integrin as well as agents that bind to an integrin dimer that comprises the alpha-4 integrin, *e.g.,* alpha-4 beta-1 (*i.e.*, α4β1 integrin) or alpha-4 beta-7 (*i.e.*, α4β7 integrin). Preferably, the agent is one that binds to alpha-4 in a manner, which inhibits VLA4 (alpha-4) from interacting with its cognate ligand, *i.e.*, beta-7 or beta-1. More preferably, the anti-alpha-4 agent inhibits VLA4 from interacting with VCAM-1.

The term "agent" is meant to include synthetic molecules (*e.g.,* antibodies, small molecules, peptides, or other synthetically produced molecules or compounds, as well as recombinantly produced gene products) as well as naturally occurring compounds (*e.g.,*

polypeptides, antibodies, antibody fragments and the like). Preferably the agent is an antagonist of alpha-4 beta-1 integrin interaction with its cognate ligand. Thus, the agent preferably binds to either VCAM-1 or to alpha-4 beta-1 integrin in a manner so as to inhibit or prevent VCAM-1 interaction with alpha-4 beta-1 integrin. The agent also inhibits VLA-4 recruitment of immune cells inhibiting an inflammatory response, which is responsible for the disease or condition being treated in the subject.

The term "efficacy" as used herein in the context of a chronic dosage regime refers to the effectiveness of a particular treatment regime. Efficacy can be measured based on change the course of the disease in response to an agent of the present invention.

The term "success" as used herein in the context of a chronic treatment regime refers to the effectiveness of a particular treatment regime. This includes a balance of efficacy, toxicity (*e.g.,* side effects and patient tolerance of a formulation or dosage unit), patient compliance, and the like. For a chronic administration regime to be considered "successful" it must balance different aspects of patient care and efficacy to produce the most favorable patient outcome.

The terms "specifically binds" or "binds specifically" as used herein refer to the situation in which one member of a specific binding pair will not show any significant binding to molecules other than its specific binding partner (*e.g.,* an affinity of about 1000 times or more for its binding partner). In the present invention, the small compounds, such as *N*-[*N*-(3-pyridinesulfonyl)-L-3,3-dimethyl-4-thiaprolyl]-*O*-[1-methylpiperzain-4-ylcarbonyl]-L-tyrosine isopropyl ester, will not show significant binding to any polypeptide other than an alpha-4 integrin or a receptor comprising an alpha-4 integrin. For example, the small compounds used in the methods of the invention that bind to an alpha-4 integrin with a binding affinity of greater than 0.3 nM are said to bind specifically to an alpha-4 integrin.

The term "substantially similar" as used herein is intended to mean any polypeptide that has an alteration in the sequence such that a functionally equivalent amino acid is substituted for one or more amino acids in the polypeptide, thus producing a change that has no or relatively little effect on the binding properties of the polypeptide. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity or similar size.

The terms "elicits an immune response" and "elicits a host immune response" as used herein refer to the production of an immune response to a receptor comprising an alpha-4

integrin in a subject upon introduction of an agent of the invention to the subject. An immune response in the subject can be characterized by a serum reactivity with an alpha-4 integrin receptor that is at least twice that of an untreated subject, more preferably three times the reactivity of an untreated subject, and even more preferably at least four times the reactivity of an untreated subject, with serum immunoreactivity measured using a serum dilution of approximately 1:100.

The terms "treating", "treatment", and the like are used herein to refer to obtaining a desired pharmacological and physiological effect. The effect may be prophylactic in terms of preventing or partially preventing a disease, symptom or condition thereof and/or may be therapeutic in terms of a partial or complete cure of a disease, condition, symptom or adverse effect attributed to the disease. The term "treatment", as used herein, covers any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it, *i.e.*, causing the clinical symptoms of the disease not to develop in a subject that may be predisposed to the disease but does not yet experience or display symptoms of the disease; (b) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms; or (c) relieving the disease, *i.e.*, causing regression of the disease and/or its symptoms or conditions. The invention is directed towards treating a patient's suffering from disease related to pathological inflammation. The present invention is involved in preventing, inhibiting, or relieving adverse effects attributed to pathological inflammation over long periods of time and/or are such caused by the physiological responses to inappropriate inflammation present in a biological system over long periods of time.

As used herein, "acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O), heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenoxy" refers to the group "alkenyl-O-".

"Substituted alkenoxy" refers to the group "substituted alkenyl-O-".

"Alkenyl" refers to alkenyl group preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

"Lower alkenyl" refers to an alkenyl group preferably having from 2 to 6 carbon atoms and having at least 1 site and preferably only 1 site of alkenyl unsaturation (*i.e.*, >C=C<). This term is exemplified by groups such as allyl, ethenyl, propenyl, butenyl, and the like.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, acyl,

acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, cycloalkyloxy, substituted cycloalkyloxy, heteroaryloxy, substituted heteroaryloxy, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted

heteroaryl, -$SO_2$-heterocyclic, -$SO_2$-substituted heterocyclic and -$SO_2$NRR where R is hydrogen or alkyl.

Preferably, the substituents are independently selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, halogen, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heterocyclic, substituted heterocyclic, hydroxyl, nitro, and oxycarbonylamino.

"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Alkyl" refers to linear or branched alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl and the like.

"Lower alkyl" refers to monovalent alkyl groups having from 1 to 5 carbon atoms including straight and branched chain alkyl groups. This term is exemplified by groups such as methyl, ethyl, *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl and the like. "Lower alkyl" may be optionally substituted with a halogen, such as chloro, fluoro, bromo and the like.

"Substituted alkyl" refers to an alkyl group, of from 1 to 10 carbon atoms, having from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxylaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, carboxyl, carboxylalkyl, carboxyl-

substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, cycloalkyloxy, substituted cycloalkyloxy, heteroaryloxy, substituted heteroaryloxy, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic and $-SO_2$NRR where R is hydrogen or alkyl.

Preferably, the substituents are independently selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,

carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, halogen, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heterocyclic, substituted heterocyclic, hydroxyl, nitro, and oxycarbonylamino.

"Alkylene" refers to linear and branched divalent alkyl groups having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-$CH_2$-), 1,6-heptylene, 1,8-octylene, ethylene (-$CH_2CH_2$-), the propylene isomers (*e.g.*, -$CH_2CH_2CH_2$- and -$CH(CH_3)CH_2$-) and the like.

"Lower alkylene" refers to divalent alkylene groups of from 1 to 4 carbon atoms including straight and branched chain alkylene groups. This term is exemplified by groups such as methylene, ethylene, *n*-propylene, *iso*-propylene (-$CH_2CH(CH_3)$- and -$CH(CH_3)CH_2$-) and the like.

"Substituted alkylene" refers to alkylene groups having from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -$OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -$OSO_2$-NRR where R is hydrogen or alkyl, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-

substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with -SO$_2$-alkyl, -SO$_2$-substituted alkyl, -SO$_2$-alkenyl, -SO$_2$-substituted alkenyl, -SO$_2$-cycloalkyl, -SO$_2$-substituted cycloalkyl, -SO$_2$-aryl, -SO$_2$-substituted aryl, -SO$_2$-heteroaryl, -SO$_2$-substituted heteroaryl, -SO$_2$-heterocyclic, -SO$_2$-substituted heterocyclic and -SO$_2$NRR where R is hydrogen or alkyl.

"Alkynyl" refers to alkynyl group preferably having from 2 to 10 carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

"Lower alkynyl" refers to an alkynyl group preferably having from 2 to 6 carbon atoms and having at least 1 site and preferably only 1 site of alkynyl unsaturation (*i.e.*, -C≡C-). This term is exemplified by groups such as acetyl (-C≡CH), propargyl (-CH$_2$-C≡CH), 3-butynyl (-CH$_2$CH$_2$C≡CH$_3$) and the like.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen,

hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -$OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -$OSO_2$-NRR where R is hydrogen or alkyl, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, -$NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -$SO_2$-alkyl, -$SO_2$-substituted alkyl, -$SO_2$-alkenyl, -$SO_2$-substituted alkenyl, -$SO_2$-cycloalkyl, -$SO_2$-substituted cycloalkyl, -$SO_2$-aryl, -$SO_2$-substituted aryl, -$SO_2$-heteroaryl, -$SO_2$-substituted heteroaryl, -$SO_2$-heterocyclic, -$SO_2$-substituted heterocyclic and -$SO_2$NRR where R is hydrogen or alkyl.

"Amidino" refers to the group $H_2NC(=NH)$- and the term "alkylamidino" refers to compounds having 1 to 3 alkyl groups (*e.g.*, alkylHNC(=NH)-).

"Amino" refers to the group -$NH_2$.

"Substituted amino" refers to the group -NRR, where each R group is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, -$SO_2$-alkyl, -$SO_2$-substituted alkyl, -$SO_2$-alkenyl, -$SO_2$-substituted alkenyl, -$SO_2$-cycloalkyl, -$SO_2$-substituted cycloalkyl, -$SO_2$-aryl, -$SO_2$-substituted aryl, -$SO_2$-heteroaryl, -$SO_2$-substituted heteroaryl, -$SO_2$-heterocyclic, -$SO_2$-substituted heterocyclic, provided that both R groups are not hydrogen; or the R groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

"Aminoacyl" refers to the groups -NRC(O)alkyl, -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl, -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the groups -NRC(O)NRR, -NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl, -NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl, -NRC(O)NR-substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted aryl, -NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl, -NRC(O)NR-heteroaryl, and -NRC(O)NR-substituted heteroaryl, -NRC(O)NR-heterocyclic, and -NRC(O)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl,

aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl, -NRC(O)O-substituted alkyl, -NRC(O)O-alkenyl, -NRC(O)O-substituted alkenyl, -NRC(O)O-alkynyl, -NRC(O)O-substituted alkynyl, -NRC(O)O-cycloalkyl, -NRC(O)O-substituted cycloalkyl, -NRC(O)O-aryl, -NRC(O)O-substituted aryl, -NRC(O)O-heteroaryl, -NRC(O)O-substituted heteroaryl, -NRC(O)O-heterocyclic, and -NRC(O)O-substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyl" refers to the groups -$NRSO_2$alkyl, -$NRSO_2$substituted alkyl, -$NRSO_2$cycloalkyl, -$NRSO_2$substituted cycloalkyl, -$NRSO_2$alkenyl, -$NRSO_2$substituted alkenyl, -$NRSO_2$alkynyl, -$NRSO_2$substituted alkynyl, -$NRSO_2$aryl, -$NRSO_2$substituted aryl, -$NRSO_2$heteroaryl, -$NRSO_2$substituted heteroaryl, -$NRSO_2$heterocyclic, and -$NRSO_2$substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonylamino" refers to the groups -$NRSO_2$NRR, -$NRSO_2$NR-alkyl, -$NRSO_2$NR-substituted alkyl, -$NRSO_2$NR-alkenyl, -$NRSO_2$NR-substituted alkenyl, -$NRSO_2$NR-alkynyl, -$NRSO_2$NR-substituted alkynyl, -$NRSO_2$NR-aryl, -$NRSO_2$NR-substituted aryl, -$NRSO_2$NR-cycloalkyl, -$NRSO_2$NR-substituted cycloalkyl, -$NRSO_2$NR-heteroaryl, and -$NRSO_2$NR-substituted heteroaryl, -$NRSO_2$NR-heterocyclic, and -$NRSO_2$NR-substituted heterocyclic, where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl,

aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyloxy" refers to the groups -$NRSO_2O$-alkyl, -$NRSO_2O$-substituted alkyl, -$NRSO_2O$-alkenyl, -$NRSO_2O$-substituted alkenyl, -$NRSO_2O$-alkynyl, -$NRSO_2O$-substituted alkynyl, -$NRSO_2O$-cycloalkyl, -$NRSO_2O$-substituted cycloalkyl, -$NRSO_2O$-aryl, -$NRSO_2O$-substituted aryl, -$NRSO_2O$-heteroaryl, -$NRSO_2O$-substituted heteroaryl, -$NRSO_2O$-heterocyclic, and -$NRSO_2O$-substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonylamino" refers to the groups -NRC(S)NRR, -NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl, -NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl, -NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-heterocyclic, and -NRC(S)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic (*e.g.*, 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7yl, and the like) provided that the point of attachment is through an aromatic ring atom. Preferred aryls include phenyl, naphthyl and 5,6,7,8-tetrahydronaphth-2-yl.

"Substituted aryl" refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic

and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -$SO_2$NRR where R is hydrogen or alkyl.

Preferred substituents are selected from the group consisting of hydroxy, acyl, acylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, amino, substituted amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and oxycarbonylamino.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.

"Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted

heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -$S(O)_2$-alkyl, -$S(O)_2$-substituted alkyl, -$S(O)_2$-cycloalkyl, -$S(O)_2$-substituted cycloalkyl, -$S(O)_2$-alkenyl, -$S(O)_2$-substituted alkenyl, -$S(O)_2$-aryl, -$S(O)_2$-substituted aryl, -$S(O)_2$-heteroaryl, -$S(O)_2$-substituted heteroaryl, -$S(O)_2$-heterocyclic, -$S(O)_2$-substituted heterocyclic, -$OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -$OSO_2$-NRR where R is hydrogen or alkyl, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, -$NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -$SO_2$NRR where R is hydrogen or alkyl.

"Aralkoxy" refers to aryl-alkylene-O- groups.

"Substituted aralkoxy" refers to substituted aryl-alkylene-O- groups.

"Carboxyl" refers to the group -COOH and pharmaceutically acceptable salts thereof.

"Carboxyl esters" refers -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-alkenyl, -C(O)O-substituted alkenyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-cycloalkyl, -

C(O)O-substituted cycloalkyl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -C(O)O-heterocyclic, and -C(O)O-substituted heterocyclic.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 3 to 8 carbon atoms having single or multiple unsaturation but which are not aromatic.

"Cycloalkoxy" refers to -O-cycloalkyl groups.

"Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

"Cycloalkyl", with regard to the compounds of Formulae I and II and the PEG derivatives, refers to cyclic alkyl groups of from 3 to 12 carbon atoms having a single or multiple condensed rings including, by way of example, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like. Preferably "cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring.

"Cycloalkyl", with regards to the compounds of Formulae III-IX, refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like. Excluded from this definition are multi-ring alkyl groups such as adamantanyl, etc.

"Lower cycloalkyl" refers to cyclic alkyl groups of from 3 to 6 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refers to a cycloalkyl or cycloalkenyl group, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents independently selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl,

carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic and $-SO_2NRR$ where R is hydrogen or alkyl.

Preferred substituents are selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, halogen, heteroaryl, substituted heteroaryl, heteroaryloxy,

substituted heteroaryloxy, heterocyclic, substituted heterocyclic, hydroxyl, nitro, and oxycarbonylamino.

"Guanidino" refers to the groups -NRC(=NR)NRR, -NRC(=NR)NR-alkyl, -NRC(=NR)NR-substituted alkyl, -NRC(=NR)NR-alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl, -NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl, -NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl, -NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl, -NRC(=NR)NR-heterocyclic, and -NRC(=NR)NR-substituted heterocyclic where each R is independently hydrogen and alkyl as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO$_2$-alkyl, -NRC(=NR)NRSO$_2$-substituted alkyl, -NRC(=NR)NRSO$_2$-alkenyl, -NRC(=NR)NRSO$_2$-substituted alkenyl, -NRC(=NR)NRSO$_2$-alkynyl, -NRC(=NR)NRSO$_2$-substituted alkynyl, -NRC(=NR)NRSO$_2$-aryl, -NRC(=NR)NRSO$_2$-substituted aryl, -NRC(=NR)NRSO$_2$-cycloalkyl, -NRC(=NR)NRSO$_2$-substituted cycloalkyl, -NRC(=NR)NRSO$_2$-heteroaryl, and -NRC(=NR)NRSO$_2$-substituted heteroaryl, -NRC(=NR)NRSO$_2$-heterocyclic, and -NRC(=NR)NRSO$_2$-substituted heterocyclic where each R is independently hydrogen and alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is fluoro, chloro or bromo.

"Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring or oxides thereof. Such heteroaryl groups can have a single ring (*e.g.*, pyridyl or furyl) or multiple condensed rings (*e.g.*, indolizinyl or benzothienyl) wherein one or more

of the condensed rings may or may not be aromatic provided that the point of attachment is through an aromatic ring atom. Additionally, the heteroatoms of the heteroaryl group may be oxidized, *i.e.*, to form pyridine N-oxides or 1,1-dioxo-1,2,5-thiadiazoles and the like. Additionally, the carbon atoms of the ring may be substituted with an oxo (=O). Preferred heteroaryls include pyridyl, pyrrolyl, indolyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1-oxo-1,2,5-thiadiazolyl and 1,1-dioxo-1,2,5-thiadiazolyl. The term "heteroaryl having two nitrogen atoms in the heteroaryl ring" refers to a heteroaryl group having two, and only two, nitrogen atoms in the heteroaryl ring and optionally containing 1 or 2 other heteroatoms in the heteroaryl ring, such as oxygen or sulfur.

"Substituted heteroaryl" refers to heteroaryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, -

$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -$SO_2NRR$ where R is hydrogen or alkyl.

Preferably the substituents are selected from the group consisting of those defined above as preferred for substituted aryl.

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

"Heteroaralkoxy" refers to the group heteroaryl-alkylene-O-.

"Substituted heteroaralkoxy" refers to the group substituted heteroaryl-alkylene-O-.

"Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino,

aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, -C(O)O-aryl, -C(O)O-substituted aryl, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic and $-SO_2NRR$ where R is hydrogen or alkyl.

Preferably, the substituents are selected from the group consisting of the preferred substitutents defined for substituted cycloalkyl.

Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, morpholinyl, thiomorpholino, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

"Heterocyclyloxy" refers to the group -O-heterocyclic and "substituted heterocyclyloxy" refers to the group -O-substituted heterocyclic.

"Lower alkylenecycloalkyl" refers to the group consisting of a lower alkylene-lower cycloalkyl, as defined herein. Such groups are exemplified by methylenecyclopropyl (-$CH_2$-cyclopropyl), ethylenecyclopropyl and the like.

"*N*,*N*-Dimethylcarbamyloxy" refers to the group -OC(O)N($CH_3$)$_2$.

"Oxo" refers to (=O).

"Oxyalkylene" refers to -$OCH_2CHR^d$- where $R^d$ is alkyl.

"Oxycarbonylamino" refers to the groups -$OC(O)NH_2$, -OC(O)NRR, -OC(O)NR-alkyl, -OC(O)NR-substituted alkyl, -OC(O)NR-alkenyl, -OC(O)NR-substituted alkenyl, -OC(O)NR-alkynyl, -OC(O)NR-substituted alkynyl, -OC(O)NR-cycloalkyl, -OC(O)NR-substituted cycloalkyl, -OC(O)NR-aryl, -OC(O)NR-substituted aryl, -OC(O)NR-heteroaryl, -OC(O)NR-substituted heteroaryl, - OC(O)NR-heterocyclic, and -OC(O)NR-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted

cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxysulfonyl" refers to the groups alkyl-$SO_2O$-, substituted alkyl-$SO_2O$-, alkenyl-$SO_2O$-, substituted alkenyl-$SO_2O$-, alkynyl-$SO_2O$-, substituted alkynyl-$SO_2O$-, aryl-$SO_2O$-, substituted aryl-$SO_2O$-, cycloalkyl-$SO_2O$-, substituted cycloalkyl-$SO_2O$-, heteroaryl-$SO_2O$-, substituted heteroaryl-$SO_2O$-, heterocyclic-$SO_2O$-, and substituted heterocyclic-$SO_2O$- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxysulfonylamino" refers to the groups -$OSO_2NH_2$, -$OSO_2NRR$, -$OSO_2NR$-alkyl, -$OSO_2NR$-substituted alkyl, -$OSO_2NR$-alkenyl, -$OSO_2NR$-substituted alkenyl, -$OSO_2NR$-alkynyl, -$OSO_2NR$-substituted alkynyl, -$OSO_2NR$-cycloalkyl, -$OSO_2NR$-substituted cycloalkyl, -$OSO_2NR$-aryl, -$OSO_2NR$-substituted aryl, -$OSO_2NR$-heteroaryl, -$OSO_2NR$-substituted heteroaryl, -$OSO_2NR$-heterocyclic, and -$OSO_2NR$-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxythiocarbonylamino" refers to the groups -$OC(S)NH_2$, -$OC(S)NRR$, -$OC(S)NR$-alkyl, -$OC(S)NR$-substituted alkyl, -$OC(S)NR$-alkenyl, -$OC(S)NR$-substituted alkenyl, -$OC(S)NR$-alkynyl, -$OC(S)NR$-substituted alkynyl, -$OC(S)NR$-cycloalkyl, -$OC(S)NR$-substituted cycloalkyl, -$OC(S)NR$-aryl, -$OC(S)NR$-substituted aryl, -$OC(S)NR$-heteroaryl, -$OC(S)NR$-substituted heteroaryl, -$OC(S)NR$-heterocyclic, and -$OC(S)NR$-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thioalkyl" refers to the groups -S-alkyl.

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

"Thioamidino" refers to the group RSC(=NH)- where R is hydrogen or alkyl.

"Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers to the group -S-substituted aryl.

"Thiocarbonylamino" refers to the group -C(S)NRR where each R is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiocycloalkyl" refers to the groups -S-cycloalkyl.

"Substituted thiocycloalkyl" refers to the group -S-substituted cycloalkyl.

"Thioheteroaryl" refers to the group -S-heteroaryl and "substituted thioheteroaryl" refers to the group -S-substituted heteroaryl.

"Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

"Thiol" refers to the group -SH.

"Optionally substituted" means that the recited group may be unsubstituted or the recited group may be substituted.

"Pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition or formulation that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. A pharmaceutically acceptable carrier or excipient as used in the specification and claims includes both one or more than one of such carriers.

"Pharmaceutically-acceptable cation" refers to the cation of a pharmaceutically-acceptable salt.

"Pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the compounds of this invention and which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts refer to pharmaceutically acceptable salts of the compounds, which salts are are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines,

disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

A "therapeutically effective amount" means the amount of a compound or antibody that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

As used herein, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

| | | |
|---|---|---|
| AC | = | acid ceramidase |
| CAN | = | acetonitrile |
| AcOH | = | acetic acid |
| ACTH | = | adrenocorticotropic hormone |
| ADEM | = | acute disseminated encephalomyelitis |
| ANA | = | Anti-nuclear antibodies |
| aq or aq. | = | aqueous |
| AUC | = | Area under the curve |
| BBB | = | blood brain barrier |
| bd | = | broad doublet |
| bm | = | broad multiplet |
| Bn | = | benzyl |
| Boc | = | *tert*-butoxycarbonyl |
| $Boc_2O$ | = | di-*tert*-butyl dicarbonate |
| BOP | = | benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate |
| bs | = | broad singlet |
| BSA | = | bovine serum albumin |
| C | = | constant region of an immunoglobulin |
| Cbz | = | carbobenzyloxy |
| cDNA | = | complementary deoxyribnucleic acid |
| CDR | = | complementarity determining region |
| CDR1 | = | complementarity determining region 1 |
| CDR2 | = | complementarity determining region 2 |
| CDR3 | = | complementarity determining region 3 |
| CFA | = | complete Freund's adjuvant |
| $CHCl_3$ | = | chloroform |
| $CH_2Cl_2$ | = | dichloromethane |
| CIDP | = | chronic immune demyelinating polyneuropathy |
| CNS | = | central nervous system |
| $(COCl)_2$ | = | oxalyl chloride |
| COX-2 | = | cyclooxygenase-2 |
| CRP | = | C-Reactive Protein |
| CS | = | Cockayne's syndrome |
| CSF | = | colony stimulating factor |
| d | = | doublet |
| DBU | = | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | = | 1,3-dicyclohexylcarbodiimide |
| dd | = | doublet of doublets |
| DMAP | = | 4-*N*,*N*-dimethylaminopyridine |
| DME | = | ethylene glycol dimethyl ether |

| | | |
|---|---|---|
| DMF | = | *N,N*-dimethylformamide |
| DMSO | = | dimethylsulfoxide |
| DNA | = | deoxyribonucleic acid |
| dt | = | doublet of triplets |
| EAE | = | experimental autoimmune encephalomyelitis |
| EBNA2 | = | Epstein-Barr virus nuclear antigen 2 |
| ECM | = | extracellular matrix |
| EDC | = | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| EDTA | = | Ethylenediamine tetraacetic acid |
| ELAMS | = | endothelial adhesion molecules |
| EM | = | electron microscopy |
| $Et_3N$ | = | triethylamine |
| $Et_2O$ | = | diethyl ether |
| EtOAc | = | ethyl acetate |
| EtOH | = | ethanol |
| eq or eq. | = | equivalent |
| FACS | = | Fluorescence activated Cell Sorter |
| FITC | = | Fluorescein isothiocyanate |
| Fmoc | = | *N*-(9-fluorenylmethoxycarbonyl) |
| FmocONSu | = | *N*-(9-fluorenylmethoxycarbonyl)-succinimide |
| FR | = | framework region |
| FR1 | = | framework region 1 |
| FR2 | = | framework region 2 |
| FR3 | = | framework region 3 |
| g | = | grams |
| GA | = | glatiramer acetate |
| GM-CSF | = | granulocyte monocyte colony stimulating factor |
| h or hr | = | hour |
| H | = | heavy chain of an immunoglobulin |
| HAMA | = | human anti-mouse antibody |
| HB or Hb | = | hemoglobin |
| HBr | = | hydrobromic acid |
| HBSS | = | Hank's Balanced Saline Solution |
| HCl | = | hydrochloric acid |
| Hct | = | hematocrit, or measurement of packed red blood cells obtained by centrifugation in a volume of a blood sample |
| H-E | = | hematoxylin-eosin |
| HEPES | = | 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid |
| hex A | = | hexoaminidase A |
| HIC | = | Hydrophobic interaction chromatography |
| HIG | = | human immunoglobulin |
| $H_2O$ | = | water |
| HOBT | = | 1-hydroxybenzotriazole hydrate |
| HUVEC | = | human umbilical vascular endothelial cells |
| IgG Fc | = | a binding domain of the immunoglobulin |

| | | |
|---|---|---|
| i.p. | = | intraperitoneal |
| ICAM-1 | = | intercellular adhesion molecule 1 |
| Ig | = | immunoglobulin |
| IgG | = | immunoglobulin G |
| IgM | = | immunoglobulin M |
| IL | = | interleukin |
| IL-1 | = | interleukin-1 |
| IL-2 | = | interleukin-2 |
| IL-8 | = | interleukin-8 |
| IBD | = | inflammatory bowel disease |
| IBDQ | = | inflammatory bowel disease questionairre |
| ITT | = | Intention-to-treat (including all subjects randomized, regardless of whether dosed) |
| $K_2CO_3$ | = | potassium carbonate |
| kg | = | kilogram |
| L | = | liter |
| LCMS | = | Liquid chromatography Mass Spectroscopy |
| LFA-1 | = | lymphocyte function-related antigen 1- (also known as $\beta_2$ integrin, CD11a/CD18 and $\alpha_L\beta_2$) |
| m | = | multiplet (when used with NMR data) |
| M | = | Molar |
| MAbs | = | monoclonal antibodies |
| Mac-1 | = | $\alpha_M\beta_2$ integrin (also known as CD11b/CD18) |
| MAdCAM-1 | = | mucosal addressin cell adhesion molecule |
| MALDI/TOF MS | = | MALDI/TOF MS matrix-assisted laser desorption ionization/time-of-flight mass spectrometry |
| MBP | = | myelin basic protein |
| MCH | = | Mean Corpusular Hemoglobin; Hb/RBC |
| MCHC | = | mean corpuscular hemoglobin count expressed as a percentage; Hb/Hct. |
| MCP-1 | = | monocyte chemotactic protein 1 |
| MCV | = | mean corpuscular volume; the avg. volume of erythrocytes, conventionally expressed in cubic micrometers per red cell. |
| MeOH | = | methanol |
| MES | = | 2-(*N*-morpholino)ethanesulfonic acid |
| mg | = | milligram |
| $MgSO_4$ | = | magnesium sulfate |
| min. | = | minute |
| MIP-1α | = | macrophage inflammatory protein 1 alpha |
| MIP-1β | = | macrophage inflammatory protein 1 beta |
| mL | = | milliliter |
| MLD | = | metachromatic leukodystrophy |
| mm | = | millimeter |

| | | |
|---|---|---|
| mM | = | millimolar |
| MOG | = | myelin-oligodendrocyte glycoprotein |
| mol | = | moles |
| mmol | = | millimol |
| mp | = | melting point |
| mpk | = | milligrams per killogram |
| MS | = | multiple sclerosis |
| N | = | normal |
| NaCl | = | sodium chloride |
| $Na_2CO_3$ | = | sodium carbonate |
| $NaHCO_3$ | = | sodium bicarbonate |
| NaOEt | = | sodium ethoxide |
| NaOH | = | sodium hydroxide |
| ng | = | nanograms |
| $NH_4Cl$ | = | ammonium chloride |
| NMM | = | *N*-methylmorpholine |
| NSAID | = | nonsteroidal anti-inflammatory |
| OtBu | = | *tert*-butoxy |
| PBS++ | = | Phosphate buffered saline |
| PCR | = | polymerase chain reaction |
| PEG | = | polyethylene glycol |
| Phe | = | L-phenylalanine |
| PKU | = | phenylketonuria |
| PLP | = | proteolipid protein |
| POEMS | = | polyneuropathy organomegaly endocrinopathy, M-protein and skin changes |
| PMSF | = | phenylmethylsulfonylfluoride |
| Pro | = | L-proline |
| PRP | = | prion related protein |
| psi | = | pounds per square inch |
| $PtO_2$ | = | platinum oxide |
| q | = | quartet |
| quint. | = | quintet |
| q.s. or Q.S. | = | bring to volume |
| RA | = | rheumatoid arthritis |
| RANTES | = | regulated upon activation, normal T-cell expressed and secreted chemokine (also known as small inducible cytokine A5) |
| RBC | = | red blood cell count |
| Rfs or $R_f$ | = | retention factor |
| RNA | = | ribonucleic acid |
| rpm | = | rotations per minute |
| rt or RT | = | room temperature |
| RT-PCR | = | reverse transcription polymerase chain reaction |
| s | = | singlet |
| SAE | = | Serious adverse event |
| SAMIs | = | selective adhesion molecule inhibitors |
| sat or sat. | = | saturated |

| | | |
|---|---|---|
| scFv | = | single chain Fv fragment |
| SCR | = | solochrome-R-cyanlin |
| SDS | = | sodium dodecyl sulfate |
| SDS-PAGE | = | sodium dodecyl sulfate polyacrylamide gel electrophoresis |
| t | = | triplet |
| t-BuOH | = | *tert*-butanol |
| TFA | = | trifluoroacetic acid |
| TGF-β | = | tumor growth factor beta |
| THF | = | tetrahydrofuran |
| TLC or tlc | = | thin layer chromatography |
| TNF | = | tumor necrosis factor |
| TNF-α | = | tumor necrosis factor alpha |
| TNF-β | = | tumor necrosis factor beta |
| Ts | = | tosyl |
| TsCl | = | tosyl chloride |
| TsOH | = | tosylate |
| TYR | = | tyrosine |
| μg | = | microgram |
| μL | = | microliter |
| μM | = | micromolar |
| μm | = | microns |
| UV | = | ultraviolet |
| VCAM-1 | = | vascular cell adhesion molecule 1 |
| $V_H$ | = | heavy chain of the variable domain |
| $V_L$ | = | light chain of the variable domain |
| VLA-4 | = | very late antigen 4 (also known as alpha-4 beta-1, $\alpha_4\beta_1$) |
| $V_t$ | = | Total volume |
| WBC | = | White Blood Cells |
| w/w | = | weight to weight |
| w/v | = | weight to volume |
| v/v | = | volume to volume |
| φ | = | phenyl |

## GENERAL ASPECTS OF THE INVENTION

The present invention is based on the surprising result that combination therapies of methotrexate and antibodies to alpha-4 integrin, such as Antegren™, as well as combination therapies of methotrexate and small molecule alpha-4 antagonists effectively suppress the deleterious effects of RA.

### Methotrexate

Methotrexate (Amethopterin®, Mexate®, Folex® and Rheumatrex®) interferes with the production and maintenance of DNA. It is not understood exactly how methotrexate works in rheumatoid arthritis, but reduces inflammation and slow worsening of the disease. Methotrexate is considered a disease-modifying antirheumatic drug (DMARD). It is effective in the early stages of rheumatoid arthritis to prevent disease progression, especially in combination with other medications.

Methotrexate is effective in relieving joint inflammation, slowing disease progression, and preventing disability by delaying joint destruction. Patients with rheumatoid arthritis may be more likely to continue treatment with methotrexate than with other DMARDs because of favorable results and tolerable side effects. Physicians often recommend that methotrexate be used with one or more combination therapy.

Combination therapy may allow for lower doses of an individual drug to be used, which may reduce the risk of adverse effects that can occur with higher doses. Methotrexate combined with hydroxychloroquine and sulfasalazine may be more effective that methotrexate alone.

Whatever may be the actual cause, there is no cure for RA, and although the disease is not fatal, disease complications and symptoms may persist throughout an individual's lifetime, and may even shorten survival by a few years. Affected joints may become deformed, and the performance of even ordinary tasks may be very difficult or impossible.

Notwithstanding what has been previously reported in the literature, new compounds, compositions and methods for using these compounds and compositions to inhibit rheumatoid arthritis are needed.

In a general sense, the method of the invention does not involve any particular mode of administration, since the mode of administration is dependent upon the form of the active agent and the formulation developed to administer the active agent. Modes of administration include, but are not limited to, oral, parenteral (*e.g.*, subcutaneous, subdural, intravenous, intramuscular, intrathecal, intraperitoneal, intracerebral, intraarterial, or intralesional routes of administration), topical, localized (*e.g.*, surgical application or surgical suppository), rectal, and pulmonary (*e.g.*, aerosols, inhalation, or powder). The route of administration would be based on the composition being administered (*e.g.*, immunoglobulin being administered intravenously versus small compound being administered orally), tissue targeting (*e.g.*,

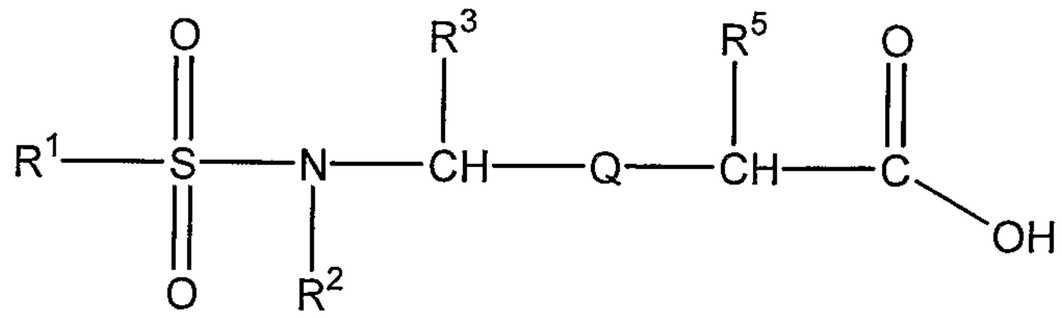
intrathecal administration to target the site of a spinal cord injury), and the like, as would be known to the artisan of ordinary skill.

Additionally, the anti-alpha-4 agents (*e.g.*, anti-alpha-4-antibodies, small compound alpha-4-integrin antagonists, and the like) can be combined with other compounds or compostions used to treat, ameliorate or palliate symptoms associated with rheumatoid arthritis. Furthermore, the compounds disclosed herein can be administered alone or in combination with other agents, such as alpha-4 integrin inhibitors, including anti-alpha-4 integrin antibodies and immunologically active fragments thereof (*e.g.*, natalizumab). When administered in combination, the small compound alpha-4-integrin antagonists may be administered in the same formulation as these other compounds or compositions, or in a separate formulation. When administered in combination, the anti-alpha-4-antibodies are generally administered in a separate formulation than the small compound alpha-4-integrin antagonists, other compounds, and compositions. When administered in combinations, the anti-alpha-4 agents may be administered prior to, following, or concurrently with the other compounds and compositions used to treat, ameliorate, or palliate symptoms. The invention relates to introducing relatively constant amounts of an active agent to a patient's circulatory system over a period of months or years. This chronic introduction of an agent that selectively binds to alpha-4 integrin or a dimer comprising alpha-4 integrin (*e.g.*, alpha-4 beta-1) results in suppression of pathological inflammation being maintained at a constant level over a period of time. By maintaining therapeutic levels of an active agent for a period of time, pathological inflammation can be chronically suppressed in the patient.

Compounds of Formulae I and II

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formulae I, IA, IB, IC, and II.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula I below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



I

wherein

$R^1$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^2$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $R^1$ and $R^2$ together with the nitrogen atom bound to $R^2$ and the $SO_2$ group bound to $R^1$ can form a heterocyclic or a substituted heterocyclic group;

$R^3$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when $R^2$ does not form a heterocyclic group with $R^1$, $R^2$ and $R^3$ together with the nitrogen atom bound to $R^2$ and the carbon atom bound to $R^3$ can form a heterocyclic or a substituted heterocyclic group;

$R^5$ is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z- $R^{8''}$ wherein $R^8$ and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where $R^8$ and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, $R^{8''}$ is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$;

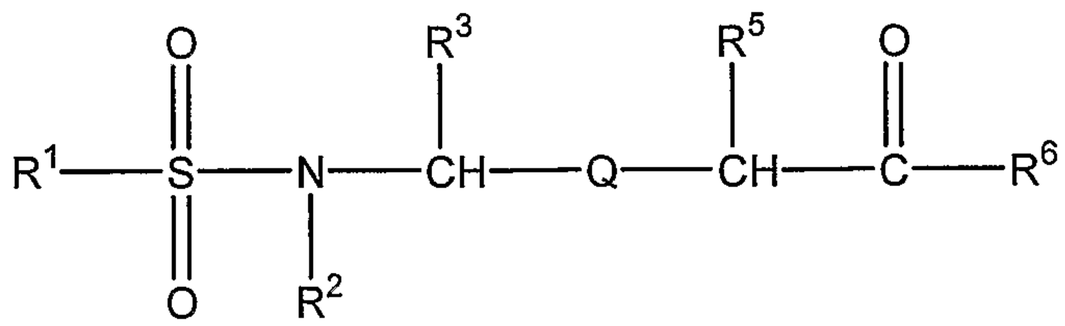
Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

*x* is an integer of from 1 to 4;

Q is $-C(X)NR^7-$ wherein $R^7$ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

In another embodiment, the compounds can be provided as prodrugs which convert (*e.g.*, hydrolyze, metabolize, etc.) *in vivo* to a compound of Formula I above. In a preferred example of such an embodiment, the carboxylic acid group of the compound of Formula I is modified into a group which, *in vivo*, will convert to a carboxylic acid group (including salts thereof). In a particularly preferred embodiment, such prodrugs are represented by compounds of Formula IA:



IA

wherein:

$R^1$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^2$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $R^1$ and $R^2$ together with the nitrogen atom bound to $R^2$ and the $SO_2$ group bound to $R^1$ can form a heterocyclic or a substituted heterocyclic group;

$R^3$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when $R^2$ does not form a heterocyclic group with $R^1$, $R^2$ and $R^3$ together with the nitrogen atom bound to $R^2$ and the carbon atom bound to $R^3$ can form a heterocyclic or a substituted heterocyclic group;

$R^5$ is - $(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z- $R^{8''}$ wherein $R^8$ and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where $R^8$ and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, $R^{8''}$ is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -$SO_2$-;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

*x* is an integer of from 1 to 4;

$R^6$ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where $R^9$ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and $R^{10}$ is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where $R^{11}$ is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein $R^7$ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof

with the following provisos

(A) when $R^1$ and $R^2$ together with the $SO_2$ group pendent to $R^1$ and the nitrogen pendent to $R^2$ form a saccharin-2-yl group, $R^3$ is $-CH_3$, $R^5$ is *p*-$[(CH_3)_2NC(O)O-]$benzyl and Q is -C(O)NH- then $R^6$ is not $-OC(CH_3)_3$;

(B) when $R^1$ is *p*-methylphenyl, $R^2$ and $R^3$ together with the nitrogen atom pendent to $R^2$ and the carbon atom pendent to $R^3$ form a pyrrodinyl ring derived from D-proline; $R^5$ is *p*-[(4-methylpiperazin-1-yl)NC(O)O-]benzyl derived from D-phenylalanine and Q is -C(O)NH- then $R^6$ is not
$-OC(CH_3)_3$;

(C) when $R^1$ is pyrimidin-2-yl, $R^2$ and $R^3$ together with the nitrogen atom bound to $R^2$ and the carbon atom bound to $R^3$ form a pyrrolidinyl ring, $R^5$ is *p*-$[(CH_3)_2NC(O)O-]$benzyl and Q is -C(O)NH- then $R^6$ is not
$-OC(CH_3)_3$; and

(D) when $R^1$ is *p*-methylphenyl, $R^2$ and $R^3$ together with the nitrogen atom pendent to $R^2$ and the carbon atom pendent to $R^3$ form a (2S)-piperazin-2-carbonyl ring; $R^5$ is *p*-$[(CH_3)_2NC(O)O-]$benzyl and Q is -C(O)NH- then $R^6$ is not $-OC(CH_3)_3$.

Further description of the compounds of the above Formulae I and IA and procedures and reaction conditions for preparing these compounds are described in U.S.S.N. 09/126,958 (filed July 31, 1998 and issued as U.S. Patent No. 6,489,300), herein incorporated by reference in its entirety.

Preferably, in the compounds of Formulae I and IA above, $R^1$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl. More preferably $R^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl.

Preferably $R^1$, in the compounds of Formulae I and IA above is selected from the group consisting of phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-*t*-butoxyphenyl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, 2-carboxyphenyl, 2-(methoxycarbonyl)phenyl, 4-($H_2NC(O)$-)phenyl, 4-($H_2NC(S)$-)phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, 4-($CH_3C(O)NH$-) phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-($CH_3SC(=NH)$-)phenyl, 4-chloro-3-($H_2NS(O)_2$-)phenyl, 1-naphthyl, 2-naphthyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, morpholin-4-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methylimidazol-4-yl, 1-N-methylpyrazol-3-yl, 1-N-methylpyrazol-4-yl, 1-N-butylpyrazol-4-yl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, 1-N-methyl-5-methyl-3-chloropyrazol-4-yl, 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

Preferably, $R^2$, in the compounds of Formulae I and IA above is selected from the group consisting of methyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-φ.

In one preferred embodiment, $R^2$ and $R^3$, in the compounds of Formulae I and IA above together with the nitrogen atom bound to the $R^2$ substituent and the carbon bound to

the $R^3$ substituent form a heterocyclic group or a substituted heterocyclic group of 4 to 6 ring atoms having 1 to 2 heteroatoms in the ring selected from the group consisting of nitrogen, oxygen and sulfur which ring is optionally substituted with 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxy, oxo (=O), amino, phenyl, thiophenyl, thiobenzyl, (thiomorpholin-4-yl)C(O)O-, $CH_3S(O)_2$- and $CH_3S(O)_2O$-, or can be fused to another ring such as a phenyl or cycloalkyl ring to provide for a fused ring heterocycle of from 10 to 14 ring atoms having 1 to 2 heteroatoms in the ring selected from the group consisting of nitrogen, oxygen and sulfur. Such heterocyclic rings include azetidinyl (*e.g.*, L-azetidinyl), thiazolidinyl (*e.g.*, L-thiazolidinyl), piperidinyl (*e.g.*, L-piperidinyl), piperazinyl (*e.g.*, L-piperazinyl), dihydroindolyl (*e.g.*, L-2,3-dihydroindol-2-yl), tetrahydroquinolinyl (*e.g.*, L-1,2,3,4-tetrahydroquinolin-2-yl), thiomorpholinyl (*e.g.*, L-thiomorpholin-3-yl), pyrrolidinyl (*e.g.*, L-pyrrolidinyl), substituted pyrrolidinyl such as 4-hydroxypyrrolidinyl (*e.g.*, 4-α-(or β-)hydroxy-L-pyrrolidinyl), 4-oxopyrrolidinyl (*e.g.*, 4-oxo-L-pyrolidinyl), 4-fluoropyrrolidinyl (*e.g.*, 4-α-(or β-)fluoro-L-pyrrolidinyl), 4,4-difluoropyrrolidinyl (*e.g.*, 4,4-difluoro-L-pyrrolidinyl), 4-(thiomorpholin-4-ylC(O)O-)pyrrolidinyl (*e.g.*, 4-α-(or β-)-(thiomorpholin-4-ylC(O)O-)-L-pyrrolidinyl, 4-($CH_3S(O)_2O$-)pyrrolidinyl (*e.g.*, 4-α-(or β-)($CH_3S(O)_2O$-)-L-pyrrolidinyl, 3-phenylpyrrolidinyl (*e.g.*, 3-α-(or β-)phenyl-L-pyrrolidinyl), 3-thiophenylpyrrolidinyl (*e.g.*, 3-α-(or β-)-thiophenyl-L-pyrrolidinyl), 4-aminopyrrolidinyl (*e.g.*, 4-α-(or β-)amino-L-pyrrolidinyl), 3-methoxypyrrolidinyl (*e.g.*, 3-α-(or β-)methoxy-L-pyrrolidinyl), 4,4-dimethylpyrrolidinyl, substituted piperazinyl such as 4-N-Cbz-piperazinyl and 4-($CH_3S(O)_2$-)piperazinyl, substituted thiazolidinyl such as 5,5-dimethylthiazolindin-4-yl, 1,1-dioxo-thiazolidinyl (*e.g.*, L-1,1-dioxo-thiazolidin-2-yl), substituted 1,1-dioxo-thiazolidinyl such as L-1,1-dioxo-5,5-dimethylthiazolidin-2-yl, 1,1-dioxothiomorpholinyl (*e.g.*, L-1,1-dioxo-thiomorpholin-3-yl) and the like.

Q, in the compounds of Formulae I and IA above, is preferably -C(O)NH- or -C(S)NH-.

In the compounds of Formulae I and IA above, Ar is preferably aryl or substituted aryl and, even more preferably, is phenyl or substituted phenyl. Preferably, *x* is 1.

In the compounds of Formulae I and IA above, $R^5$ is preferably selected from all possible isomers arising by substitution with the following groups:

3-[$(CH_3)_2NC(O)O$-]benzyl,

4-[$(CH_3)_2NC(O)O$-]benzyl,

4-[(piperidin-1′-yl)C(O)O-]benzyl,

4-[(piperidin-4′-yl)C(O)O-]benzyl,

4-[(1′-methylpiperidin-4′-yl)C(O)O-]benzyl,

4-[(4′-hydroxypiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-formyloxypiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-ethoxycarbonylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-carboxylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(3′-hydroxymethylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-hydroxymethylpiperidin-1′-yl)C(O)O-]benzyl,

4-[(4′-phenyl-1′-Boc-piperidin-4′-yl)-C(O)O-]benzyl,

4-[(4′-piperidon-1′-yl ethylene ketal)C(O)O-]benzyl,

4-[(piperazin-4′-yl)-C(O)O-]benzyl,

4-[(1′-Boc-piperazin-4′-yl)-C(O)O-]benzyl,

4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-methylhomopiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(2-hydroxyethyl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-phenylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(4-trifluoromethylpyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyrimidin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-acetylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(pyridin-4-ylC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylNHC(O)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-(phenylNHC(S)-)piperazin-1′-yl)C(O)O-]benzyl,

4-[(4′-methanesulfonylpiperazin-1′-yl-C(O)O-)benzyl,

4-[(4′-trifluoromethanesulfonylpiperazin-1′-yl-C(O)O-)benzyl,

4-[(morpholin-4′-yl)C(O)O-]benzyl,

3-nitro-4-[(morpholin-4′-yl)-C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl)C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl sulfone)-C(O)O-]benzyl

(alternative nomenclature 4-[(1,1-dioxothiomorpholin-4-yl)-C(O)O-]benzyl),

4-[(pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-methylpyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(methoxycarbonyl)pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(hydroxymethyl)pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(2′-(N,N-dimethylamino)ethyl)($CH_3$)NC(O)O-]benzyl,

4-[(2′-(N-methyl-N-toluene-4-sulfonylamino)ethyl)($CH_3$)N-C(O)O-]benzyl,

4-[(2′-(morpholin-4′-yl)ethyl)($CH_3$)NC(O)O-]benzyl,

4-[(2′-(hydroxy)ethyl)($CH_3$)NC(O)O-]benzyl,

4-[bis(2′-(hydroxy)ethyl)NC(O)O-]benzyl,

4-[(2′-(formyloxy)ethyl)($CH_3$)NC(O)O-]benzyl,

4-[($CH_3OC(O)CH_2$)HNC(O)O-]benzyl,

4-[2′-(phenylNHC(O)O-)ethyl-]HNC(O)O-]benzyl,

3-chloro-4-[($CH_3$)$_2$NC(O)O-]benzyl,

3-chloro-4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

3-chloro-4-[(4′-(pyridin-2-yl)piperazin-1′-yl)C(O)O-]benzyl,

3-chloro-4-[(thiomorpholin-4′-yl)C(O)O-]benzyl, and

3-fluoro-4-[($CH_3$)$_2$NC(O)O-]benzyl.

In the compounds of Formula IA, $R^6$ is preferably 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, cyclopropylmethoxy, neopentoxy, 2-α-isopropyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, 2-methoxyphenoxy, 2-(morpholin-4-yl)ethoxy, -O($CH_2CH_2O$)$_2CH_3$, 2-(phenoxy)ethoxy, -$OCH_2C(CH_3)_2NHBoc$, -$NH_2$, benzyloxy, -$NHCH_2COOH$, -$NHCH_2CH_2COOH$, -NH-adamantyl, -$NHSO_2$-*p*-$CH_3$-φ, -$NHCH_2CH_2COOCH_2CH_3$, -NHOY′ where Y′ is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, -$OCH_2$-$OC(O)C(CH_3)_3$, -O($CH_2$)$_z$NHC(O)W where *z* is 1 or 2 and W is selected from

the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -$NR''C(O)$-$R'$ where $R'$ is aryl, heteroaryl or heterocyclic and $R''$ is hydrogen or -$CH_2C(O)OCH_2CH_3$.

Even more preferably, $R^6$ in the compounds of Formula IA is selected from the group consisting of methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, cyclopropylmethoxy, neopentoxy, 2-α-isopropyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, 2-methoxyphenoxy, 2-(morpholin-4-yl)ethoxy, -$O(CH_2CH_2O)_2CH_3$, 2-(phenoxy)ethoxy, -$OCH_2C(CH_3)_2NHBoc$, and benzyloxy.

Preferred compounds within the scope of Formulae I and IA above include by way of example:

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *n*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine cyclopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *n*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine cyclopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine ethyl ester

*N*-(α-toluenesulfonyl)-L-prolyl-L-4-(*N*-methylisonipecotoyloxy)phenylalanine ethyl ester

*N*-(α-toluenesulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-3-(*N*,*N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butylcarbonyloxy-4-phenylpiperidin-4-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylaminosulfonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylaminosulfonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(α-toluenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(piperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(α-toluenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *N*-adamantyl amide

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanylglycine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylaminosulfonyloxy)phenylalanine methyl ester

*N*-(toluene-4-sulfonyl)-L-(piperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-benzyloxycarbonylpiperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(isonipecotoyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

2-(saccharin-2-yl)propionoyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-D-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylaminosulfonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyrrolidin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine neopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine neopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine ethyl ester

2-(saccharin-2-yl)propionoyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

2-(saccharin-2-yl)propionoyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyrimidine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylaminosulfonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-acetylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)-3-nitrophenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*N*-methyl-2-(*tert*-butyl)glycinyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-*tert*-butyloxycarbonyl-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidin-2-one

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyrimidine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-carboxy-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidin-2-one

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-acetamidobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-*tert*-butylbenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(2-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-acetamidobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(3,3-dimethyl)prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(3,3-dimethyl)prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *iso*-propyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-acetylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-phenylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

2-(saccharin-2-yl)propionyl-L-4-(4′-methylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine (N′-*tert*-butoxycarbonyl-2-amino-2-methylpropyl) ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-acetylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-hydroxypiperidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-(morpholin-4′-yl)ethyl)carbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-hydroxyethyl)-N-methylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-4-(4′-(2-hydroxyethyl)piperazin-1-ylcarbonyloxy)-L-phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-formyloxyethyl)-N-methylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-hydroxyethyl)-N-methylcarbamyloxy)phenylalanine isopropyl ester

N-(toulene-4-sulfonyl)-L-prolyl-L-4-(N-(methoxycarbonylmethyl)carbamyloxy)phenylalanine *tert*-butyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(4-N,N-dimethylcarbamyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methoxypiperidin-1-ylcarbonyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methoxypiperidin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-*trans*-4-hydroxyprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(3-fluorobenzenesulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(morpholino-sulfonyl)-L-prolyl-L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(morpholino-sulfonyl)-L-prolyl-L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl-thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-*tert*-butylbenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-(3,3-dimethyl)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-methoxybenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-methoxybenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-oxo-thiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1-oxo-thiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-prolyl-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-prolyl-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-2-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-2-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,5-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,5-dichlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-chlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dimethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3-chlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3-chloro-4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thioprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(8-quinolinesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(8-quinolinesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(8-quinolinesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isoproplyl ester

*N*-(8-quinolinesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-(ethoxycarbonyl)piperidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3-sulfonamido-4-chloro-benzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-oxothiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenefulfonyl)-L-(1-oxothiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine cyclopropylmethyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine cyclopropylmethyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-methoxyphenyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *n*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *n*-propyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropionyloxymethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-(4'-(2'-aminoethyl)morpholino)carbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[4-(carboxy)piperidin-1-ylcarbonyloxy]phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N,N*-bis-(2-hydroxyethyl)carbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[3-(hydroxymethyl)piperidin-1-ylcarbonyloxy]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-trifluoromethanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-(*N*-phenylurea)benzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-methyl-N-(2-dimethylaminoethyl)carbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiapropyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethycarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-methylpiperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2'-pyridyl)-piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2'-pyridyl)-piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylcarbamylpiperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylcarbamylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-*n*-butylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyridin-4-ylcarbonyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*trans*-4-hydroxyprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[3-(hydroxymethyl)piperidin-1-ylcarbonyloxy]phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4,4-difluoro)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(4,4-difluoro)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-benzoylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methyl-1H-imidazole-4-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-4-(thiomorpholin-4-ylcarbonyloxy)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-4-hydroxyprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-benzoylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine methyl ester

*N*-(3-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[*N*-methyl-*N*-(2-(*N'*-methyl-*N'*-toluenesulfonyl-amino)ethyl)carbamyloxy]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[*N*-(2-(*N'*-phenylaminocarbonyloxy)ethyl)carbamyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-4-(*trans*-hydroxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-4-(*trans*-hydroxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

piperazine-1,4-dicarboxylic acid bis-{4-[(2S)-2-*tert*-butoxycarbonyl-2-((4R)-5,5-dimethyl-3-(toluene-4-sulfonyl)thiazolidine-4-carboxamido)ethyl]phenyl} ester

piperazine-1,4-dicarboxylic acid bis-{4-[(2S)-2-carboxy-2-((4R)-5,5-dimethyl-3-(toluene-4-sulfonyl)thiazolidine-4-carboxamido)ethyl]phenyl} ester

*N*-(toluene-4-sulfonyl)-L-(pyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(2-hydroxymethylpyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(2-hydroxymethylpyrrolidin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxycarbonylpyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

piperazine-1,4-dicarboxylic acid bis-{4-[(2S)-2-isopropoxycarbonyl-2-((2R)-1-(toluene-4-sulfonyl)pyrrolidine-2-carboxamido)ethyl]phenyl} ester

*N*-(toluene-4-sulfonyl)-L-(4-hydroxy)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-(2-methoxyethoxy)ethyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyrimidyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-fluoro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-methanesulfonylpyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-[2-(1,1-dioxo-2,3-dihydro-3,3-dimethyl-1,2-benzisothiazol-2-yl)acetyl]-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-[2-(*N*-2,10-camphorsultamyl)acetyl]-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-[2-(*N*-2,10-camphorsultamyl)acetyl]-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-[2-(*N*-2,10-camphorsultamyl)acetyl]-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4-hydroxy)prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyrimidyl)piperazin-1-ylcarbonyloxy)]phenylalanine

piperazine-1,4-dicarboxylic acid bis-{4-[(2S)-2-*tert*-butoxycarbonyl-2-((2R)-1-(toluene-4-sulfonyl)pyrrolidine-2-carboxamido)ethyl]phenyl} ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-oxo)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4-oxo)prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(*N*-phenylthiocarbonyl)piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-methylhomopiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

piperazine-1,4-dicarboxylic acid bis-{4-[(2S)-2-carboxyl-2-((2R)-1-(toluene-4-sulfonyl)pyrrolidine-2-carboxamido)ethyl]phenyl} ester

*N*-(toluene-4-sulfonyl)-L-4-(methanesulfonyloxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-aminocarbonylbenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-aminocarbonylbenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine ethyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-methylhomopiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1-methanesulfonylpyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-4-(methanesulfonyloxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(methanesulfonyl)-*N*-benzylglycinyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(4-hydroxy)prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-phenoxyethyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(3-chloro-1,5-dimethylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(5-trifluoromethyl-2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another ester selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester, *tert*-butyl ester and neopentyl ester.

More preferred compounds within the scope of Formulae I and IA and IB (below) include by way of example:

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *n*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine cyclopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *n*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine cyclopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine ethyl ester

*N*-(α-toluenesulfonyl)-L-prolyl-L-4-(*N*-methylisonipecotoyloxy)phenylalanine ethyl ester

*N*-(α-toluenesulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-3-(*N*,*N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butylcarbonyloxy-4-phenylpiperidin-4-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(α-toluenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(piperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(α-toluenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(piperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-benzyloxycarbonylpiperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(isonipecotoyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-D-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyrrolidin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine neopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine neopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyrimidine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-acetylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)-3-nitrophenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*N*-methyl-2-(*tert*-butyl)glycinyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-*tert*-butyloxycarbonyl-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidin-2-one

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyrimidine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-carboxy-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidin-2-one

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-acetamidobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-*tert*-butylbenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(2-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-acetamidobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(3,3-dimethyl)prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(3,3-dimethyl)prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *iso*-propyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-acetylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-phenylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine (N′-*tert*-butoxycarbonyl-2-amino-2-methylpropyl) ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-acetylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-hydroxypiperidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-(morpholin-4′-yl)ethyl)carbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-hydroxyethyl)-N-methylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-4-(4′-(2-hydroxyethyl)piperazin-1-ylcarbonyloxy)-L-phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-formyloxyethyl)-N-methylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-hydroxyethyl)-N-methylcarbamyloxy)phenylalanine isopropyl ester

N-(toulene-4-sulfonyl)-L-prolyl-L-4-(N-(methoxycarbonylmethyl)carbamyloxy)phenylalanine *tert*-butyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(4-N,N-dimethylcarbamyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methoxypiperidin-1-ylcarbonyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methoxypiperidin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-*trans*-4-hydroxyprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(3-fluorobenzenesulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(morpholino-sulfonyl)-L-prolyl-L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(morpholino-sulfonyl)-L-prolyl-L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl-thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-*tert*-butylbenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-(3,3-dimethyl)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-methoxybenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-methoxybenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-oxo-thiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1-oxo-thiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-prolyl-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-prolyl-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-2-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-2-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,5-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,5-dichlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-chlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dimethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3-chlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3-chloro-4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thioprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(8-quinolinesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(8-quinolinesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(8-quinolinesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isoproplyl ester

*N*-(8-quinolinesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-(ethoxycarbonyl)piperidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3-sulfonamido-4-chloro-benzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-oxothiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenefulfonyl)-L-(1-oxothiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine cyclopropylmethyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine cyclopropylmethyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-methoxyphenyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *n*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *n*-propyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropionyloxymethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-(4'-(2'-aminoethyl)morpholino)carbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[4-(carboxy)piperidin-1-ylcarbonyloxy]phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N,N*-bis-(2-hydroxyethyl)carbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[3-(hydroxymethyl)piperidin-1-ylcarbonyloxy]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-trifluoromethanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-(*N*-phenylurea)benzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-methyl-N-(2-dimethylaminoethyl)carbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiapropyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethycarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-methylpiperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2'-pyridyl)-piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2'-pyridyl)-piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylcarbamylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylcarbamylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-*n*-butylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyridin-4-ylcarbonyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*trans*-4-hydroxyprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[3-(hydroxymethyl)piperidin-1-ylcarbonyloxy]phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4,4-difluoro)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(4,4-difluoro)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-benzoylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methyl-1H-imidazole-4-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-4-(thiomorpholin-4-ylcarbonyloxy)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-4-hydroxyprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-benzoylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine methyl ester

*N*-(3-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[*N*-methyl-*N*-(2-(*N*'-methyl-*N*'-toluenesulfonyl-amino)ethyl)carbamyloxy]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[*N*-(2-(*N*'-phenylaminocarbonyloxy)ethyl)carbamyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-4-(*trans*-hydroxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-4-(*trans*-hydroxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(pyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(2-hydroxymethylpyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(2-hydroxymethylpyrrolidin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxycarbonylpyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-hydroxy)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-(2-methoxyethoxy)ethyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyrimidyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-fluoro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-methanesulfonylpyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4-hydroxy)prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyrimidyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-oxo)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4-oxo)prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(*N*-phenylthiocarbonyl)piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-methylhomopiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-4-(methanesulfonyloxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-aminocarbonylbenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-aminocarbonylbenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine ethyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-methylhomopiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1-methanesulfonylpyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-4-(methanesulfonyloxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(4-hydroxy)prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-phenoxyethyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

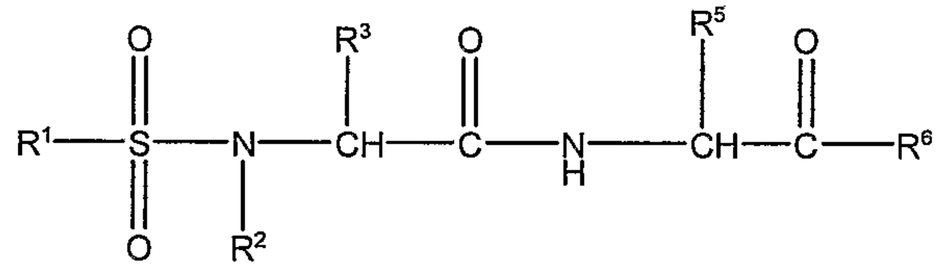
*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(3-chloro-1,5-dimethylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(5-trifluoromethyl-2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

and pharmaceutically acceptable salts thereof.

Preferred compounds of Formulae I and IA above include those set forth in Table 1 below:

Table 1



| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -O-*n*-butyl |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -O-cyclopentyl |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -O-*n*-butyl |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -O-cyclopentyl |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(piperidin-4-yl)C(O)O-]benzyl- | -$OCH_2CH_3$ |
| φ-$CH_2$- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1-methylpiperidin-4-yl)C(O)O-]benzyl- | -$OCH_2CH_3$ |
| φ-$CH_2$- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *m*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2CH_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1-Boc-4-phenylpiperidin-4-yl)-C(O)O-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-C($CH_3$)$_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $CH_3$- | H | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OCH($CH_3$)$_2$ |
| *p*-$CH_3$-φ- | $CH_3$- | H | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OC($CH_3$)$_3$ |
| *p*-$CH_3$-φ- | $CH_3$- | H | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OH |
| 1-methylimidazol-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OC($CH_3$)$_3$ |
| *p*-$NH_2$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OC($CH_3$)$_3$ |
| *p*-$CH_3$-φ- | $CH_3$- | H | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -OC($CH_3$)$_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -OC($CH_3$)$_3$ |
| φ-$CH_2$- | $R^2/R^3$ = cyclic -$CH_2$-S-C($CH_3$)$_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-NH-$CH_2$- (L-piperazinyl) | | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OH |
| φ-$CH_2$- | $R^2/R^3$ = cyclic -$CH_2$-S-C($CH_3$)$_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[($CH_3$)$_2$NC(O)O-]benzyl- | -OC($CH_3$)$_3$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-NH-$CH_2$- (L-piperazinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-(Cbz)$NHCH_2$- [L-4-N-(Cbz)-piperazinyl] | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $CH_3$- | H | *p*-[(piperidin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -OH |
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | -$CH_3$ | H | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$C(CH_3)_2$- (L-1,1-dioxo-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$C(CH_3)_2$- (L-1,1-dioxo-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 3-pyridyl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (**D**-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | -$CH_3$ | -$CH_3$ | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-nitro-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | -$CH_3$ | H | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | -$CH_3$ | -$CH_3$ | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl sulfone)-C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -OH |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(piperidin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(pyrrolidin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | $-OCH_2C(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | $-OCH_2C(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1-Boc-piperazin-4-yl)C(O)O-]benzyl- | $-OCH_2CH_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | $-OCH_2CH_3$ |
| *p*-$CH_3$-φ | $-CH_3$ | H | *p*-[(thiomorpholin-4-yl sulfone)-C(O)O-]benzyl- | $-OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $-CH_3$ | H | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $-CH_3$ | $-CH_3$ | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | $-OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic $-CH_2-CH_2-S-CH_2-$ (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | $-OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $-CH_3$ | H | *p*-[(thiomorpholin-4-yl sulfone)-C(O)O-]benzyl- | -OH |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | -$CH_3$ | -$CH_3$ | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| pyridin-3-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-nitro-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-N≡C-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$F_3C$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-S-$CH_2$- (L-thiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol) |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(piperazin-4-yl)C(O)O-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1-Boc-piperazin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(piperazin-4-yl)C(O)O-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-acetylpiperazin-1-yl)C(O)O-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methanesulfonylpiperazin-1-yl)-C(O)O-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 3-nitro-4-[(morpholin-4-yl)-C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1-Boc-piperazin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ | -$CH_3$ | -$C(CH_3)_3$ | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(1,1-dioxothiomorpholin-4-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(1,1-dioxothiomorpholin-4-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1,1-dioxothiomorpholin-4-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -OH |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$F_3CO$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$C(CH_3)_2$- (L-1,1-dioxo-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$C(CH_3)_2$- (L-1,1-dioxo-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(morpholin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$C(CH_3)_2$- (L-1,1-dioxo-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| pyrimidin-2-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[(4-methylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 2,5-dichlorothien-3-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3C(O)NH$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$C(CH_3)_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| pyridin-2-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *o*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *m*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 2,4-difluoro-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3C(O)NH$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$C(F)_3O$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-N≡C-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| morpholin-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$C(CH_3)_2$- (L-4,4-dimethyl pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$C(CH_3)_2$- (L-4,4-dimethyl pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| 1-methylimidazol-4-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3C(O)NH$-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$(CH_3)_3C$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| pyridin-3-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-N≡C-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-C(O)O-]benzyl- | -$OCH_2CH_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-acetylpiperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methanesulfonylpiperazin-1-yl)-C(O)O-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-φ-piperazin-1-yl)C(O)(O)-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(piperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-NH-$CH_2$- (L-piperazinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$F_3CO$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$C(CH_3)_2$- (4,4-dimethyl pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$C(CH_3)_2$- (4,4-dimethyl pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3C(O)NH$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *o*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| morpholin-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *m*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 2,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| morpholin-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *o*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 2,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| pyridin-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *m*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| pyridin-2-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylpyrazol-4-yl | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methanesulfonylpiperazin-1-yl)- C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-φ-piperazin-1-yl)C(O)(O)-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -O-$CH_2C(CH_3)_2$-$NHC(O)OC(CH_3)_3$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -O-$CH_2CH_2$- (morpholin-4 yl) |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-acetylpiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-hydroxypiperidin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$(CH_3)_3C$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| 2,5-dichlorothien-3-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -OH |
| *p*-$CH_3O$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-$C(CH_3)_2$- (4,4-dimethyl pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-methylpiperazin-1-yl)C(O)O-]-benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[$(CH_3)_2$NC(O)O-]-benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(thiomorpholin-4-yl)C(O)O-]-benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(morpholin-4-yl)-$CH_2CH_2$NHC(O)O-]benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[$(CH_3)_2NC(O)O$-]-benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -OH |
| pyridin-2-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-(O)-$CH_2$- (L-1-oxothiomorpholin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 4-Cl-3-($NH_2$-$SO_2$-)-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(thiomorpholin-4-yl)C(O)O-]-benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[$(CH_3)_2NC(O)O$-]-benzyl- | -$OCH(CH_3)_2$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$HOCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(2-(hydroxymethyl)pyrrolidin-1-yl)-C(O)O-]-benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(2-(hydroxymethyl)pyrrolidin-1-yl)-C(O)O-]-benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(2-($CH_3OC(O)$-)pyrrolidin-1-yl)-C(O)O-]-benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(HC(O)O-)piperidin-1-yl)-C(O)O-]- benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(hydroxypiperidin-1-yl)-C(O)O-]- benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(thiomorpholin-4-yl)C(O)O-]-benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-($CH_3CH_2OC(O)$-)piperidin-1-yl)C(O)O-]-benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-($HOCH_2CH_2$-)piperazin-1-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$HC(O)OCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$HOCH_2CH_2N(CH_3)C(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$CH_3OC(O)CH_2NHC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| quinolin-8-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3O$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-(O)-$CH_2$- (L-1-oxothiomorpholin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$H_2N$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| quinolin-8-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-(O)-$CH_2$- (L-1-oxothiomorpholin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 1-*n*-butylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylpyrazol-3-yl | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 2-($CF_3C(O)$-)-1,2,3,4-tetrahydro-isoquinolin-7-yl | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(φNHC(O)-)-piperazin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methoxypiperidin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-4-ylC(O))piperazin-1-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-CH(OH)$CH_2$- (L-4-hydroxopyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *m*-F-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-methoxypiperidin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(φNHC(O)-)piperazin-1-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-(φNHC(O)NH)φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-methylpiperidin-1-yl)-C(O)O-]-benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[$(CH_3)_2$NC(O)O-]-benzyl- | -$OCH(CH_3)_2$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-($CH_3SO_2$-)piperazin-1-yl)-C(O)O]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(morpholin-4-yl)$CH_2CH_2NHC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(HO(O)-)piperidin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(HOCH_2CH_2)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$O_2N$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-($HOCH_2$-)piperidin-1-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 3-chloro-4-[$(CH_3)_2NC(O)O$)-]-benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylpyrazol-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *m*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *o*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 3,5-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 2,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$NH_2$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-N≡C-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH(OH)CH_2$- (L-4-hydroxypyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2C(O)CH_2$- (L-4-oxypyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| pyridin-2-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-Cl-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *m*-Cl-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *o*-Cl-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 3,4-dichloro-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 3,5-dichloro-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2CH_3$ |
| pyridin-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| quinolin-8-yl | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *m*-Cl-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| pyridin-2-yl | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 3,4-dichloro-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 2,5-dichlorothien-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *m*-$CH_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *o*-$CH_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 3,4-dimethoxy-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 2,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 3,4-dichloro-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *m*-Cl-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 2,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S(O)-$CH_2$- (L-1-oxothiomorpholin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[(4-methylpiperzin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH(OH)CH_2$- (L-4-hydroxypyrrolidinyl) | | *p*-[(thiomorpholin-4yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(3-($HOCH_2$-)piperidin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CF_2$-$CH_2$- (L-4,4-difluoro-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$O(CH_2CH_2O)_2CH_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH$(-O-C(O)thiomorpholin-4-yl-$CH_2$- (L-4-(thiomorpholin-4-yl)C(O)O-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CF_2$-$CH_2$- (L-4,4-difluoro-pyrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyrimidin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(φC(O)-)piperazin-1-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-fluoro-4-[$(CH_3)_2NC(O)O$-]-benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]-benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]-benzyl- | -$OC(CH_3)_3$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2N$-(-$SO_2CH_3$)-$CH_2$- (L-4-methanesulfonyl-piperazinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-Br-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-Br-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$NH_2C(=N)$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_3$ |
| *p*-N≡C-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH$(-O-C(O)thiomorpholin-4-yl)-$CH_2$- (L-4-(thiomorpholin-4-yl)C(O)O-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -OH |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)-C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-C$(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyrimidin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -OH |
| quinolin-8-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-C$(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -OH |
| pyridin-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-C$(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-C$(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *m*-F-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -OH |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S- (thiazolidin-2-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S- (thiazolidin-2-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-$NH_2$-C(=N)-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -$OCH_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2$-C(O)-$CH_2$- (L-4-oxopyrrolidinyl) | | *p*-[(4-methylpiperazin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S- (thiazolidin-2-yl) | | *p*-[(4-pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-$NO_2$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S- (thiazolidin-2-yl) | | *p*-[(4-pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-Br-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -OH |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(φC(O)-)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(φNHC(S)-)piperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S- (thiazolidin-2-yl) | | *p*-[(4-$CH_3$-homopiperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[*p*-$CH_3$-φ-$SO_2N(CH_3)CH_2CH_2N(CH_3)$-C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[φNHC(O)O-$CH_2CH_2$NHC(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| 3-Cl-4-F-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2$-$SO_2$-$CH_2$- (L-1,1-dioxothiomorpholin-3-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH(-OSO_2CH_3)$-$CH_2$- (L-4-methanesulfoxy-pyrrolidinyl) | | *p*-[$(CH_3)_2$NC(O)O-]benzyl- | -$OC(CH_3)_3$ |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$H_2NC(O)$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$H_2N$-C(=N)-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$H_2NC(O)$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-$H_2N$-C(=N)-φ | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -OH |
| *p*-$NO_2$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)-C(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]-benzyl- | $-OCH_2CH_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]-benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S- (thiazolidin-2-yl) | | *p*-[(4-$CH_3$-homopiperazin-1-yl)C(O)O-]-benzyl- | -OH |



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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH_2N(-SO_2-CH_3)CH_2$- (4-methanesulfonyl-piperazin-2-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CH_3$-φ- | $R^2/R^3$ = cyclic -$CH_2CH(-OSO_2-CH_3)CH_2$- (L-4-methanesulfoxy-pyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| pyridin-3-yl | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(thiomorpholin-4-yl)C(O)O-]benzyl- | -$OCH(CH_3)_2$ |
| 3,4-difluoro-φ- | $R^2/R^3$ = cyclic -$CH_2$-$CH_2$-S-$CH_2$- (L-thiomorpholin-3-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2CH(OH)CH_2$- (L-4-hydroxypyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |
| *p*-Br-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| *p*-$CF_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| *p*-$CF_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| *p*-$CF_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -$OC(CH_3)_3$ |
| *p*-F-φ- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2CH(OH)CH_2$- (L-4-hydroxypyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| *p*-$CF_3O$-φ- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 3-chloro-4-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 3-chloro-4-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH(CH_3)_2$ |

| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic $-CH_2-S-C(CH_3)_2-$ (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | -OH |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | $-OCH(CH_3)_2$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | $-OC(CH_3)_3$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic $-CH_2-S-C(CH_3)_2-$ (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]benzyl- | $-OC(CH_3)_3$ |
| 1-methylimidazol-4-yl- | $R^2/R^3$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O]benzyl- | $-OCH(CH_3)_2$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic $-CH_2-S-C(CH_3)_2-$ (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | $-OCH_2CH_2O\varphi$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$-(L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]-benzyl- | -OH |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$-(L-5,5-dimethylthiazolidin-4-yl) | | 3-chloro-4-[(4-(pyridin-2-yl)piperazin-1-yl)C(O)O-]-benzyl- | -$OCH_2CH_3$ |
| 1,5-dimethyl-3-chloropyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$-(L-5,5-dimethylthiazolidin-4-yl) | | *p*-[4-[5-$CF_3$-pyridin-2-yl)piperazin-1 yl)-C(O)O-]benzyl- | -OH |
| *p*-F-φ- | $R^2/R^3$ = cyclic -$CH_2CH(OH)CH_2$-(L-4-hydroxypyrrolidinyl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |
| pyridin-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$-(L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -OH |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$-(L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2C(CH_3)_3$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$-(L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2O$-C(O)C($C(CH_3)_3$ |



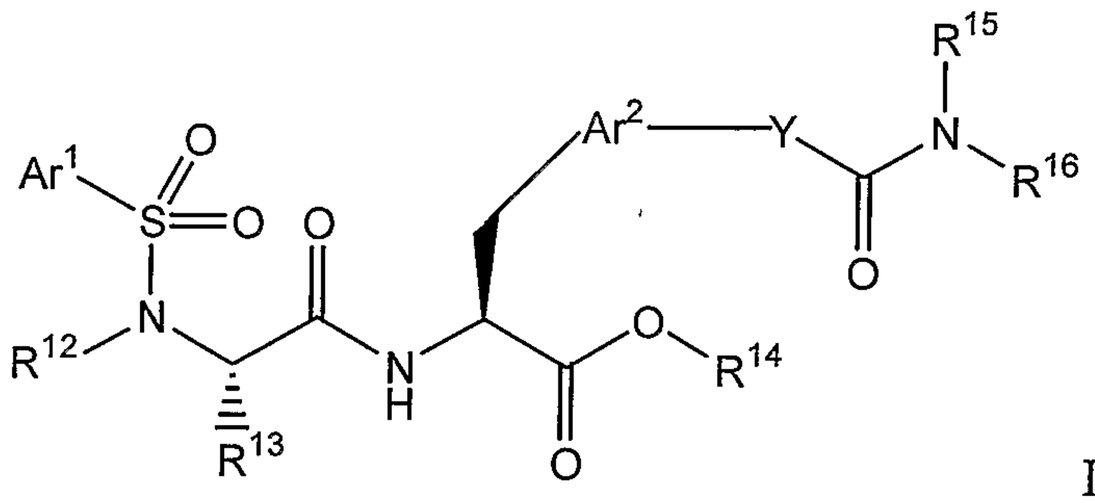
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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| pyridin-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2C(CH_3)_3$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | 2-$CH_3O$-φ-O- |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2$cyclopropyl |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2CH_2CH_3$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2CH_2CH_2CH_3$ |
| 1-methylpyrazol-4-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -O-$CH_3$ |
| pyridin-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OC(CH_3)_3$ |

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| $R^1$ | $R^2$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| pyridin-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2CH_3$ |
| pyridin-3-yl- | $R^2/R^3$ = cyclic -$CH_2$-S-$C(CH_3)_2$- (L-5,5-dimethylthiazolidin-4-yl) | | *p*-[$(CH_3)_2NC(O)O$-]benzyl- | -$OCH_2$cyclopropyl |

In a preferred embodiment of the compounds of Formulae I and IA, the compounds are defined by Formula IB below:



IB

wherein:

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

$Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R^{12}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl or $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic group;

$R^{13}$ is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic group;

$R^{14}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl;

$R^{15}$ is selected from the group consisting of alkyl, and substituted alkyl, or $R^{15}$ and $R^{16}$ together with the nitrogen atom to which they are bound form a heterocyclic or substituted heterocyclic group;

$R^{16}$ is selected from the group consisting of alkyl and substituted alkyl or $R^{15}$ and $R^{16}$ together with the nitrogen atom to which they are bound form a heterocyclic or substituted heterocyclic group; and

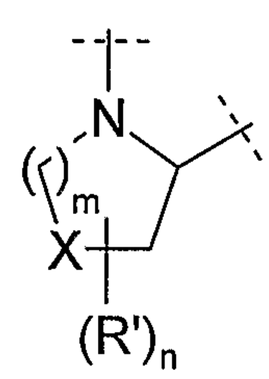
Y is selected from the group consisting of -O-, $-NR^{100}-$, and $-CH_2-$ wherein $R^{100}$ is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof.

Preferably, in the compounds of Formula IB above, $R^{12}$ is alkyl, substituted alkyl, or $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic group. Preferably, in the compounds of Formula IB above, $R^{14}$ is hydrogen or alkyl.

Preferably, in the compounds of Formula IB above, $Ar^1$ is selected from the group consisting of phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-*t*-butoxyphenyl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, 2-carboxyphenyl, 2-(methoxycarbonyl)phenyl, 4-($H_2NC(O)$-)phenyl, 4-($H_2NC(S)$-)phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, 4-($CH_3C(O)NH$-)phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$-]phenyl, 4-chloro-3-[$H_2NS(O)_2$-]phenyl, 1-naphthyl, 2-naphthyl, pyridin-2-yl, pyridin-3-yl, pyridine-4-yl, pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-*N*-methylimidazol-4-yl, 1-*N*-methylpyrazol-3-yl, 1-*N*-methylpyrazol-4-yl, 1-*N*-butylpyrazol-4-yl, 1-*N*-methyl-3-methyl-5-chloropyrazol-4-yl, 1-*N*-methyl-5-methyl-3-chloropyrazol-4-yl, 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

Preferably, in the compounds of Formula IB above, $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic of the formula:



wherein

X is selected from the group consisting of -S-, -SO-, -$SO_2$, and optionally substituted -$CH_2$-;

*m* is an integer of 0 to 12;

*n* is an integer of 0 to 2; and

R' is selected from the group consisting of alkyl, substituted alkyl, and amino.

Preferably, m is 1, X is -S- or -$CH_2$-, R' is alkyl or substituted alkyl.

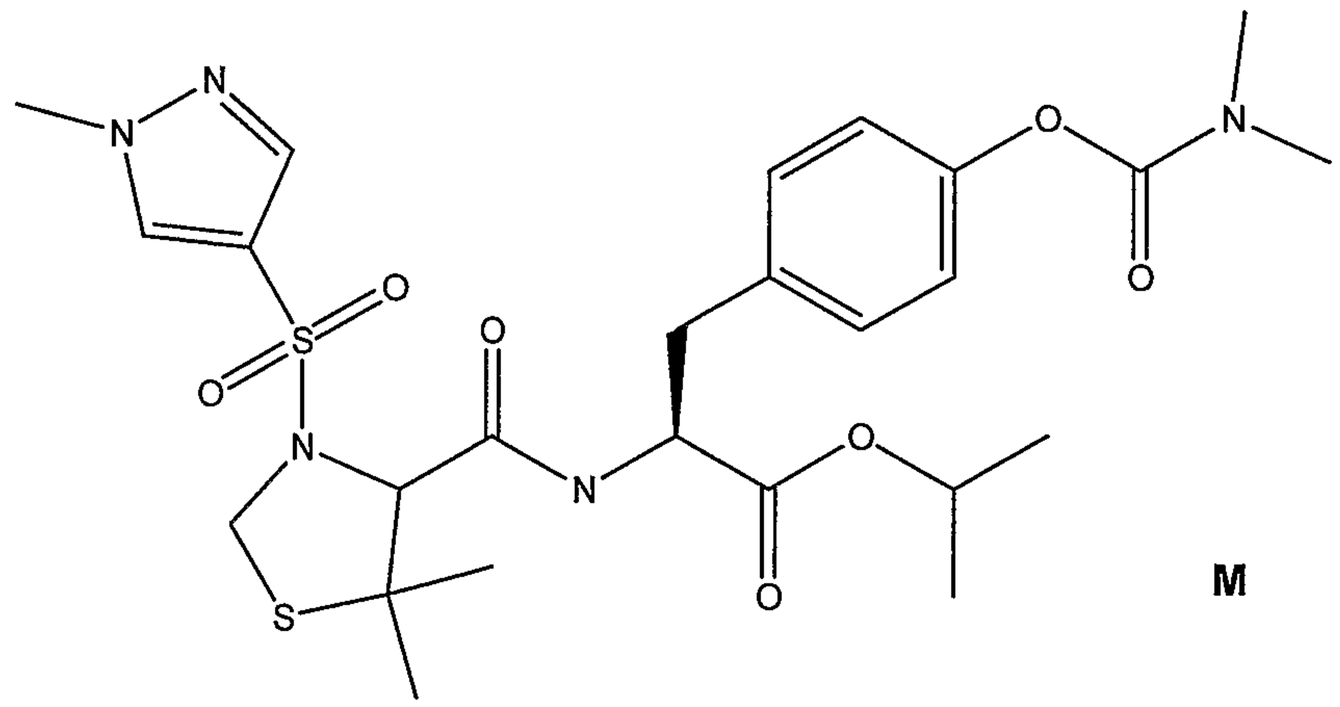
Even more preferably, $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic selected from the group consisting of azetidinyl, thiazolidinyl, piperidinyl, piperazinyl, thiomorpholinyl, pyrrolidinyl, 4-hydroxypyrrolidinyl, 4-oxopyrrolidinyl, 4-fluoropyrrolidinyl, 4,4-difluoropyrrolidinyl, 4-(thiomorpholin-4-ylC(O)O-)pyrrolidinyl, 4-[$CH_3S(O)_2O$-]pyrrolidinyl, 3-phenylpyrrolidinyl, 3-thiophenylpyrrolidinyl, 4-aminopyrrolidinyl, 3-methoxypyrrolidinyl, 4,4-dimethylpyrrolidinyl, 4-*N*-Cbz-piperazinyl, 4-[$CH_3S(O)_2$-]piperazinyl, thiazolidin-3-yl, 5,5-dimethyl-thiazolidin-3-yl, 5,5-dimethylthiazolindin-4-yl, 1,1-dioxo-thiazolidinyl, 1,1-dioxo-5,5-dimethylthiazolidin-2-yl and 1,1-dioxothiomorpholinyl.

Preferably, in the compounds of Formula IB, $Ar^2$ is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and 4-pyrid-2-onyl.

Preferably, in Formula IB, Y is -O-, and when Y is -O-, the moiety -$OC(O)NR^{15}R^{16}$ is preferably selected from the group consisting of $(CH_3)_2NC(O)O$-, (piperidin-1-yl)C(O)O-, (4-hydroxypiperidin-1-yl)C(O)O-, (4-formyloxypiperidin-1-yl)C(O)O-, (4-ethoxycarbonylpiperidin-1-yl)C(O)O-, (4-carboxylpiperidin-1-yl)C(O)O-, (3-hydroxymethylpiperidin-1-yl)C(O)O-, (4-hydroxymethylpiperidin-1-yl)C(O)O-, (4-piperidon-1-yl ethylene ketal)C(O)O-, (piperazin-1-yl)-C(O)O-, (1-Boc-piperazin-4-yl)-C(O)O-, (4-methylpiperazin-1-yl)C(O)O-, (4-methylhomopiperazin-1-yl)C(O)O-, (4-(2-hydroxyethyl)piperazin-1-yl)C(O)O-, (4-phenylpiperazin-1-yl)C(O)O-, (4-(pyridin-2-yl)piperazin-1]-yl)C(O)O-, (4-(4-trifluoromethylpyridin-2-yl)piperazin-1-yl)C(O)O-, (4-

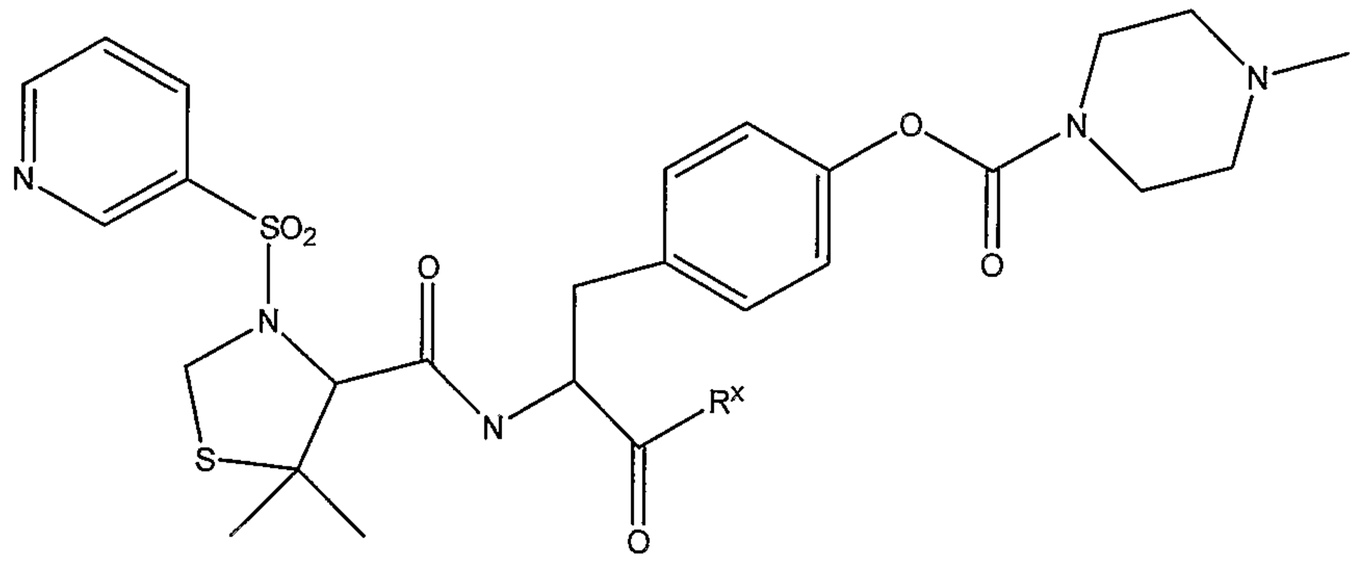
(pyrimidin-2-yl)piperazin-1-yl)C(O)O-, (4-acetylpiperazin-1-yl)C(O)O-, (4-(phenylC(O)-)piperazin-1-yl)C(O)O-, (4-(pyridin-4'-ylC(O)-)piperazin-1-yl)C(O)O, (4-(phenylNHC(O)-)piperazin-1-yl)C(O)O-, (4-(phenylNHC(S)-)piperazin-1-yl)C(O)O-, (4-methanesulfonylpiperazin-1-yl-C(O)O-, (4-trifluoromethanesulfonylpiperazin-1-yl-C(O)O-, (morpholin-4-yl)C(O)O-, (thiomorpholin-4-yl)C(O)O-, (thiomorpholin-4'-yl sulfone)-C(O)O-, (pyrrolidin-1-yl)C(O)O-, (2-methylpyrrolidin-1-yl)C(O)O-, (2-(methoxycarbonyl)pyrrolidin-1-yl)C(O)O-, (2-(hydroxymethyl)pyrrolidin-1-yl)C(O)O-, (2-(N,N-dimethylamino)ethyl)($CH_3$)NC(O)O-, (2-(N-methyl-N-toluene-4-sulfonylamino)ethyl)($CH_3$)N-C(O)O-, (2-(morpholin-4-yl)ethyl)($CH_3$)NC(O)O-, (2-(hydroxy)ethyl)($CH_3$)NC(O)O-, bis(2-(hydroxy)ethyl)NC(O)O-, (2-(formyloxy)ethyl)($CH_3$)NC(O)O-, ($CH_3OC(O)CH_2$)HNC(O)O-, and 2-[(phenylNHC(O)O-)ethyl-]HNC(O)O-.

Preferably, the compound is the compound of Formula M below:



M

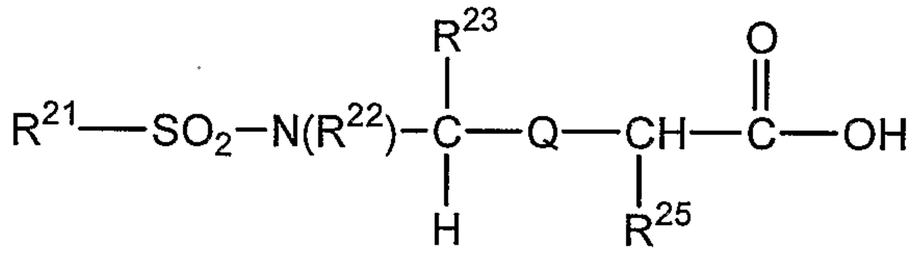
In a preferred embodiment, the compounds are defined by Formula IC below



IC

wherein $R^x$ is hydroxy or $C_{1-5}$ alkoxy and pharmaceutically acceptable salts thereof. Preferably, the compound is *N*-[*N*-(3-pyridinesulfonyl)-L-3,3-dimethyl-4-thiaprolyl]-*O*-[1-methylpiperazin-4-ylcarbonyl]-L-tyrosine isopropyl ester (the compound of Formula N).

In another aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula II below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



II

wherein:

$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^{22}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $R^{21}$ and $R^{22}$ together with the nitrogen atom bound to $R^{22}$ and the $SO_2$ group bound to $R^{21}$ can form a heterocyclic or a substituted heterocyclic group;

$R^{23}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where $R^{22}$ and $R^{23}$ together with the nitrogen atom bound to $R^{22}$ and the carbon atom bound to $R^{23}$ can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

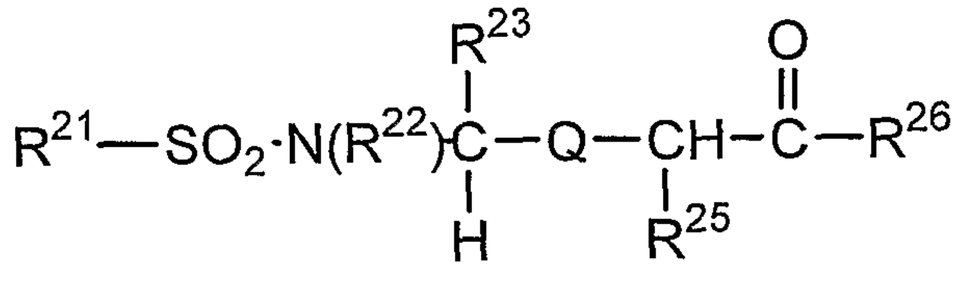
Q is $-C(X)NR^{7}-$ wherein $R^{7}$ is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur; and

$R^{25}$ is $-CH_2Ar^{22}-R^{25'}$ where $Ar^{22}$ is aryl or heteroaryl and $R^{25'}$ is selected from the group consisting of aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclic-O-, substituted heterocyclic-O-, heteroaralkoxy, and substituted heteroaralkoxy ;

and pharmaceutically acceptable salts thereof.

In another embodiment, the compounds of this invention can also be provided as prodrugs which convert (*e.g.*, hydrolyze, metabolize, etc.) *in vivo* to a compound of Formula II above. In a preferred example of such an embodiment, the carboxylic acid in the compound of Formula II is modified into a group which, *in vivo*, will convert to the carboxylic acid (including salts thereof). In a particularly preferred embodiment, such prodrugs are represented by compounds of Formula IIA:



IIA

where

$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^{22}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and $R^{21}$ and $R^{22}$ together with the nitrogen atom bound to $R^{22}$ and the $SO_2$ group bound to $R^{21}$ can form a heterocyclic or a substituted heterocyclic group;

$R^{23}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and $R^{22}$ and $R^{23}$ together with the nitrogen atom bound to $R^{22}$ and the carbon atom bound to $R^{23}$ can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

$R^{25}$ is $-CH_2Ar^{22}-R^{25'}$ where $Ar^{22}$ is aryl or heteroaryl and $R^{25'}$ is selected from the group consisting of aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy, , heterocyclic-O-, substituted heterocyclic-O-, heteroaralkoxy, and substituted heteroaralkoxy ;

$R^{26}$ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^{29}R^{30}$ where $R^{29}$ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and $R^{30}$ is selected from the group consisting of hydrogen and $-CH_2COOR^{31}$ where $R^{31}$ is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein $R^7$ is selected from the group consisting of hydrogen and alkyl; and

X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

Further description of the compounds of the above Formulae II and IIA and procedures and reaction conditions for preparing these compounds are described in U.S.S.N.s

09/127,346 (filed July 31, 1998), 09/688,820 (Continuation, filed October 17, 2000 and issued as U.S. Patent No. 6,583,139) and 10/382,988 (Continuation, filed March 7, 2003), all of which are herein incorporated by reference in their entirety.

Preferably, in the compounds of Formulae II and IIA above, $R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl. More preferably $R^{21}$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl.

Even more preferably, in the compounds of Formulae II and IIA above, $R^{21}$ is selected from the group consisting of 4-methylphenyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

Preferably, $R^{22}$, in the compounds of Formulae II and IIA above, is hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-φ.

In another preferred embodiment, $R^{22}$ and $R^{23}$, in the compounds of Formulae II and IIA above, and $R^{32}$ and $R^{33}$, in the compounds of Formula IIB, together with the nitrogen atom bound to $R^{22}$ or $R^{32}$ and the carbon atom bound to $R^{23}$ or $R^{33}$ form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl.

Q, in the compounds of Formulae II and IIA above, is preferably -C(O)NH- or -C(S)NH-.

In the compounds of Formulae II and IIA, $R^{25}$ is preferably selected from the group consisting of all possible isomers arising by substitution with the following groups: 4-(2-carboxyphenoxy)benzyl, 4-(benzyloxy)benzyl, 4-[(1-methylpiperidin-4-yl)-O-]benzyl, 4-(imidazolid-2-one-1-yl)benzyl, and 4-(3-formylimidazolid-2-one-1-yl)benzyl.

In the compounds of Formula IIA, $R^{26}$ is preferably 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2-α-*iso*-propyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, $-NH_2$, benzyloxy, $-NHCH_2COOH$, $-NHCH_2CH_2COOH$, -NH-adamantyl, $-NHCH_2CH_2COOCH_2CH_3$, $-NHSO_2$-*p*-$CH_3$-φ, $-NHOR^8$ where $R^8$ is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, $-OCH_2$-$OC(O)C(CH_3)_3$, $-O(CH_2)_zNHC(O)W$ where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, $-NR''C(O)-R'$ where R′ is aryl, heteroaryl or heterocyclic and R″ is hydrogen or $-CH_2C(O)OCH_2CH_3$.

Preferred compounds within the scope of Formulae II and IIA above include by way of example the following:

*N*-(Toluene-4-sulfonyl)-L-prolyl-4-(α-methylbenzyloxy)-L-phenylalanine

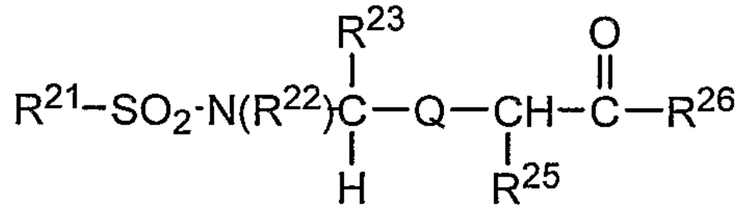
*N*-(Toluene-4-sulfonyl)-L-prolyl-4-(2-carboxyphenoxy)-L-phenylalanine

*N*-(Toluene-4-sulfonyl)-L-prolyl-O-(benzyl)-L-tyrosine

and pharmaceutically acceptable salts thereof.

Preferred compounds of Formulae II and IIA above include those set forth in Table 2 below.

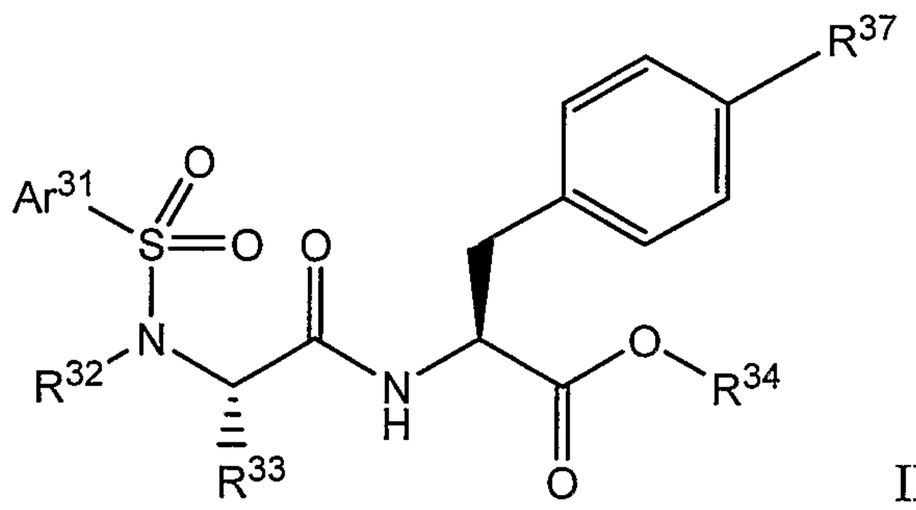
Table 2



| $R^{21}$ | $R^{22}$ | $R^{23}$ | $R^{25}$ | $R^{26}$ | Q = -C(O)NR$^7$- wherein $R^7$ is: |
|---|---|---|---|---|---|
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[O-(*o*-carboxyphenyl)]-benzyl- | -OH | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-benzyloxybenzyl- | -OH | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(1-methylpiperidin-4-yl)-O-]benzyl- | -$OCH_2CH_3$ | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(imidazolid-2-one-1-yl)benzyl- | -$OC(CH_3)_3$ | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[3-formylimidazolid-2-one-1-yl)benzyl- | -OH | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[(imidazolid-2-one-1-yl)benzyl- | -OH | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[1-H-2-oxo-3-methyl tetrahydro pyrimidin-1-yl]benzyl- | -Ot-Bu | H |

| $R^{21}$ | $R^{22}$ | $R^{23}$ | $R^{25}$ | $R^{26}$ | Q = -C(O)NR$^7$- wherein $R^7$ is: |
|---|---|---|---|---|---|
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[1-H-2-oxo-3-methyl tetrahydro pyrimidin-1-yl]benzyl- | -OH | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 4-[2-methoxy phenyl]-benzyl- | -Ot-Bu | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | 4-[2-methoxy phenyl]-benzyl- | -OH | H |
| p-$CH_3$-φ- | $R^{22}/R^{23}$ = cyclic 3 carbon atoms (L-pyrrolidinyl) | | *p*-[2,4,5-trioxo-3-(3-chlorophenyl)-tetrahydroimidazol-1-yl]-benzyl- | -OBz | H |

In a preferred embodiment of the compounds of Formulae II and IIA, the compounds are defined by Formula IIB below:



IIB

wherein:

$Ar^{31}$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

$R^{32}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group;

$R^{33}$ is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group;

$R^{34}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl; and

$R^{37}$ is aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy;

and pharmaceutically acceptable salts thereof.

Preferably, in the compounds of Formula IIB above, $R^{32}$ is alkyl, substituted alkyl, or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group and $R^{34}$ is hydrogen or alkyl.

Preferably, in the compounds of Formula IIB above, $R^{37}$ is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic. In a preferred

embodiment, $R^{37}$ is substituted aryl wherein the aryl is substituted with one to three substituents independently selected from the group consisting alkyl and alkoxy. In a preferred embodiment, $R^{37}$ is substituted heteroaryl wherein the heteroaryl is substituted with one to three substituents independently selected from the group consisting alkyl, alkoxy, and oxo. In another preferred embodiment $R^{37}$ is substituted aryl or heteroaryl wherein aryl or heteroaryl is 2,6-di-substituted. In yet another preferred embodiment $R^{37}$ is 2,6-di-substituted aryl wherein the substituents are independently selected from the group consisting of alkyl and alkoxy. In yet another preferred embodiment $R^{37}$ is 2,6-di-substituted heteroaryl wherein the substituents are independently selected from the group consisting of alkyl, oxo, and alkoxy. In another preferred embodiment, $R^{37}$ is selected from the group consisting of 2,6-dialkoxyaryl, 2,6-dialkoxyheteroaryl, 2-alkyl-6-alkoxyaryl, 2-alkyl-6-alkoxyheteroaryl, 2-oxo-6-alkoxyheteroaryl, 2-oxo-6-alkylheteroaryl, and optionally substituted imidazolidin-2,4-dion-3-yl.

Preferably in the compounds of Formula IIB above, $Ar^{31}$ is selected from the group consisting of 4-methylphenyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

When describing the compounds, compositions and methods of this invention, the following terms have the following meanings, unless otherwise indicated.

Compound Preparation for Compounds of Formulae I and II

The compounds of Formulae I and II can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, *i.e.*, as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

According to the following compound preparation, $R^1$, $R^2$, $R^3$, $R^5$, $R^6$, and $R^7$ are as defined herein for Formulae I, IA, II, and IIA. In addition, according to the following compound preparation, $R^1$ is equivalent to:

$Ar^1$ as herein defined for Formula IB,

$R^{21}$ as herein defined for Formulae II and IIA, and

$Ar^{21}$ as herein defined for Formula IIB;

$R^2$ is equivalent to:

$R^{12}$ as herein defined for Formula IB,

$R^{22}$ as herein defined for Formulae II and IIA, and

$R^{32}$ as herein defined for Formula IIB;

$R^3$ is equivalent to:

$R^{13}$ as herein defined for Formula IB,

$R^{23}$ as herein defined for Formulae II and IIA, and

$R^{33}$ as herein defined for Formula IIB;

$R^5$ is equivalent to:

$R^{25}$ as herein defined for Formulae II and IIA; and

$R^6$ is equivalent to:

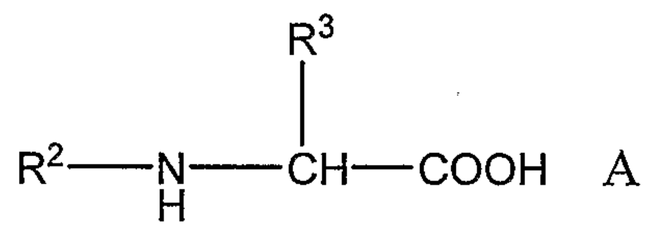
OH for Formulae I and II,

$OR^{14}$ as herein defined for Formula IB,

$R^{26}$ as herein defined for Formula IIA, and

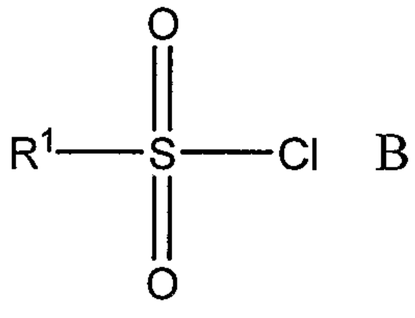
$OR^{34}$ as herein defined for Formula IIB.

In a preferred method of synthesis, the compounds of Formulae I, IA, II, and IIA, wherein Q is $-C(O)NR^7-$, and compounds of Formulae IB, IC, and IIB are prepared by first coupling an amino acid of Formula A:



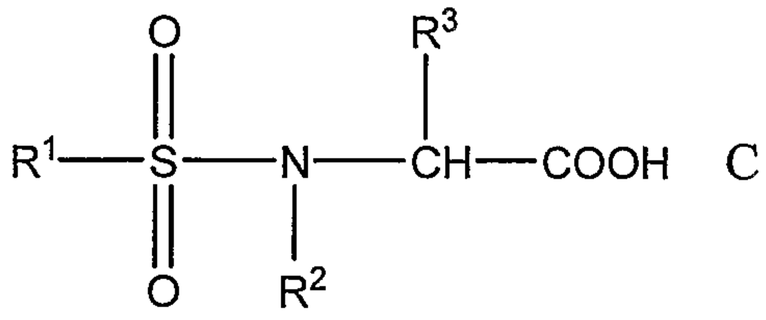
A

with a sulfonyl chloride of Formula B:



B

to provide an *N*-sulfonyl amino acid of Formula C:



C

This reaction is typically conducted by reacting the amino acid of Formula A with at least one equivalent, preferably about 1.1 to about 2 equivalents, of sulfonyl chloride B in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting *N*-sulfonyl amino acid C is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

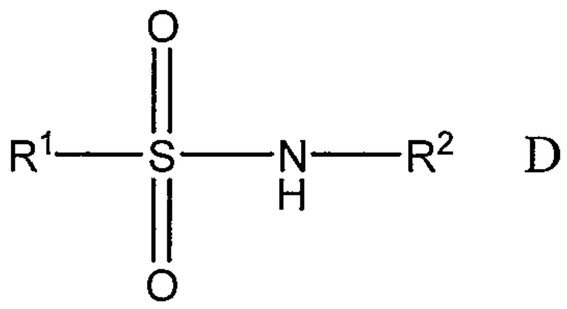
The amino acids of Formula A employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Examples of suitable amino acids for use in this reaction include, but are not limited to, L-proline, *trans*-4-hydroxyl-L-proline, *cis*-4-hydroxyl-L-proline, *trans*-3-phenyl-L-proline, *cis*-3-phenyl-L-proline, L-(2-methyl)proline, L-pipecolinic acid, L-azetidine-2-carboxylic acid, L-indoline-2-carboxylic acid, L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, L-thiazolidine-4-carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid, glycine, 2-*tert*-butylglycine, D,L-phenylglycine, L-alanine, α-methylalanine, *N*-methyl-L-phenylalanine, L-diphenylalanine, sarcosine, D,L-phenylsarcosine, L-aspartic acid β-*tert*-butyl ester, L-glutamic acid γ-*tert*-butyl ester, L-(*O*-benzyl)serine, 1-aminocyclopropanecarboxylic acid, 1-aminocyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid (cycloleucine) 1-aminocyclohexanecarboxylic acid, L-serine and the like. If desired, the corresponding carboxylic acid esters of the amino acids of Formula A, such as the methyl esters, ethyl esters and the like, can be employed in the above reaction with the sulfonyl chloride B. Subsequent hydrolysis of the ester group to the carboxylic acid using conventional reagents and conditions, *i.e.*, treatment with an alkali metal hydroxide in an inert diluent such as methanol/water, then provides the *N*-sulfonyl amino acid C.

Similarly, the sulfonyl chlorides of Formula B employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by

conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, *i.e.*, from compounds of the formula $R^1$-$SO_3H$, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the sulfonyl chlorides of Formula B can be prepared from the corresponding thiol compound, *i.e.*, from compounds of the formula $R^1$-SH, by treating the thiol with chlorine ($Cl_2$) and water under conventional reaction conditions.

Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, *p*-toluenesulfonyl chloride, α-toluenesulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-amidinobenzenesulfonyl chloride, 4-*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethylbenzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the *N*-sulfonyl amino acids of Formula C.

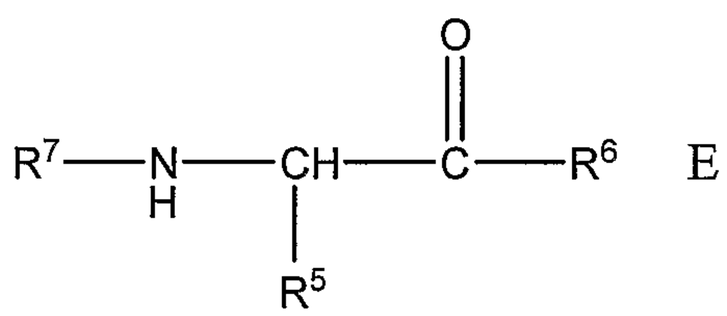
The intermediate *N*-sulfonyl amino acids of Formula C can also be prepared by reacting a sulfonamide of Formula D:



D

with a carboxylic acid derivative of the formula $L(R^3)CHCOOR^y$ where L is a leaving group, such as chloro, bromo, iodo, mesylate, tosylate and the like, and $R^y$ is hydrogen or an alkyl group. This reaction is typically conducted by contacting the sulfonamide D with at least one equivalent, preferably 1.1 to 2 equivalents, of the carboxylic acid derivative in the presence of a suitable base, such as triethylamine, in an inert diluent, such as DMF, at a temperature ranging from about 24°C to about 37°C for about 0.5 to about 4 hours. This reaction is further described in Zuckermann *et al.*, *J. Am. Chem. Soc.*, **1992**, *114*, 10646-10647. Preferred carboxylic acid derivatives for use in this reaction are α-chloro and α-bromocarboxylic acid esters such as *tert*-butyl bromoacetate and the like. When a carboxylic acid ester is employed in this reaction, the ester group is subsequently hydrolyzed using conventional procedures to afford an *N*-sulfonyl amino acid of Formula C.

The compounds of the present invention are then prepared by coupling the intermediate *N*-sulfonyl amino acid of Formula C with an amino acid derivative of Formula E:



E

This coupling reaction is typically conducted using well-known coupling reagents such as carbodiimides, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphonate) and the like. Suitable carbodiimides include, by way of example, dicyclohexylcarbodiimide (DCC), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (EDC) and the like. If desired, polymer supported forms of carbodiimide coupling reagents may also be used including, for example, those described in *Tetrahedron Letters*, **34**(48), 7685 (1993).

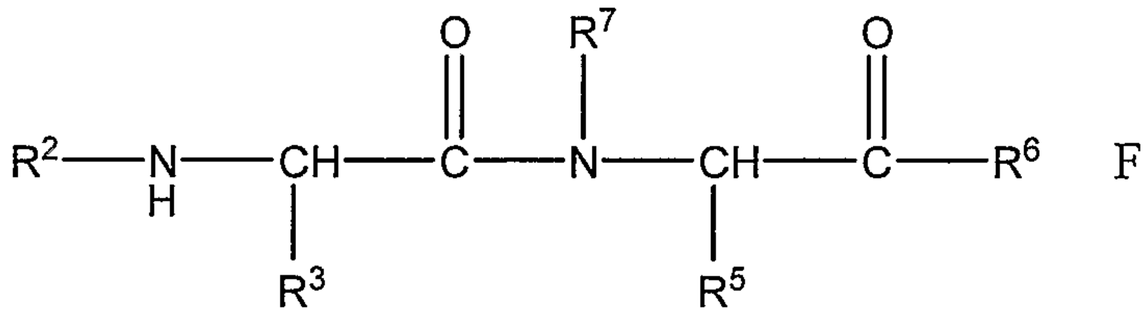
Additionally, well-known coupling promoters, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be used to facilitate the coupling reaction.

This coupling reaction is typically conducted by contacting the *N*-sulfonylamino acid C with about 1 to about 2 equivalents of the coupling reagent and at least one equivalent, preferably about 1 to about 1.2 equivalents, of amino acid derivative E in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N*,*N*-dimethylformamide and the like. Generally, this reaction is conducted at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours. Upon completion of the reaction, the compound of the present invention is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the *N*-sulfonyl amino acid C can be converted into an acid halide and the acid halide coupled with amino acid derivative E to provide compounds of the present invention. The acid halide of C can be prepared by contacting C with an inorganic acid halide, such as thionyl chloride, phosphorous trichloride, phosphorous tribromide or phosphorous penta-chloride, or preferably, with oxalyl chloride under conventional conditions. Generally, this reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either neat or in an inert solvent, such as dichloromethane or carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, such as DMF, may also be used in this reaction.

The acid halide of *N*-sulfonyl amino acid C is then contacted with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of amino acid derivative E in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like. Upon completion of the reaction, the compound of the present invention is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the compounds of the present invention can be prepared by first forming a diamino acid derivative of Formula F:



F

The diamino acid derivatives of Formula F can be readily prepared by coupling an amino acid of Formula A with an amino acid derivative of Formula E using conventional amino acid coupling techniques and reagents, such carbodiimides, BOP reagent and the like, as described above. Diamino acid F can then be sulfonated using a sulfonyl chloride of Formula B and using the synthetic procedures described above to provide a compound of the present invention.

The amino acid derivatives of Formula E employed in the above reactions are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. For example, amino acid derivatives of Formula E can be prepared by *C*-alkylating commercially available diethyl 2-acetamidomalonate (Aldrich, Milwaukee, Wisconsin, USA) with an alkyl or substituted alkyl halide. This reaction is typically conducted by treating the diethyl 2-acetamidomalonate with at least one equivalent of sodium ethoxide and at least one equivalent of an alkyl or substituted alkyl halide in refluxing ethanol for about 6 to about 12 hours. The resulting C-alkylated malonate is then deacetylated, hydrolyzed and decarboxylated by heating in aqueous hydrochloric acid at reflux for about 6 to about 12 hours to provide the amino acid, typically as the hydrochloride salt.

Examples of amino acid derivatives of Formula E suitable for use in the above reactions include, but are not limited to, L-tyrosine methyl ester, L-3,5-diiodotyrosine methyl ester, L-3-iodotyrosine methyl ester, β-(4-hydroxy-naphth-1-yl)-L-alanine methyl ester, β-(6-hydroxy-naphth-2-yl)-L-alanine methyl ester, and the like. If desired, of course, other esters or amides of the above-described compounds may also be employed.

For ease of synthesis, the compounds of the present invention are typically prepared as an ester, *i.e.*, where $R^6$ is an alkoxy or substituted alkoxy group and the like. If desired, the

ester group can be hydrolysed using conventional conditions and reagents to provide the corresponding carboxylic acid. Typically, this reaction is conducted by treating the ester with at least one equivalent of an alkali metal hydroxide, such as lithium, sodium or potassium hydroxide, in an inert diluent, such as methanol or mixtures of methanol and water, at a temperature ranging about 0°C to about 24°C for about 1 to about 10 hours. Alternatively, benzyl esters may be removed by hydrogenolysis using a palladium catalyst, such as palladium on carbon. The resulting carboxylic acids may be coupled, if desired, to amines such as β-alanine ethyl ester, hydroxyamines such as hydroxylamine and *N*-hydroxysuccinimide, alkoxyamines and substituted alkoxyamines such as *O*-methylhydroxylamine and *O*-benzylhydroxylamine, and the like, using conventional coupling reagents and conditions as described above.

As will be apparent to those skilled in the art, other functional groups present on any of the substituents of the compounds of the present invention can be readily modified or derivatized either before or after the above-described coupling reactions using well-known synthetic procedures. For example, a nitro group present on a substituent of a compound of the present invention or an intermediate thereof may be readily reduced by hydrogenation in the presence of a palladium catalyst, such as palladium on carbon, to provide the corresponding amino group. This reaction is typically conducted at a temperature of from about 20°C to about 50°C for about 6 to about 24 hours in an inert diluent, such as methanol. Compounds having a nitro group on, *e.g.*, the $R^3$ substituent, can be prepared, for example, by using a 4-nitrophenylalanine derivative and the like in the above-described coupling reactions.

Similarly, a pyridyl group can be hydrogenated in the presence of a platinum catalyst, such as platinum oxide, in an acidic diluent to provide the corresponding piperidinyl analogue. Generally, this reaction is conducted by treating the pyridine compound with hydrogen at a pressure ranging from about 20 psi to about 60 psi, preferably about 40 psi, in the presence of the catalyst at a temperature of about 20°C to about 50°C for about 2 to about 24 hours in an acidic diluent, such as a mixture of methanol and aqueous hydrochloric acid. Compounds having a pyridyl group can be readily prepared by using, for example, β-(2-pyridyl)-, β-(3-pyridyl)- or β-(4-pyridyl)-L-alanine derivatives in the above-described coupling reactions.

Additionally, when a substituent of a compound of the present invention or an intermediate thereof contains a primary or secondary amino group, such amino groups can be further derivatized either before or after the above coupling reactions to provide, by way of example, amides, sulfonamides, ureas, thioureas, carbamates, secondary or tertiary amines and the like. Compounds having a primary amino group on such a substituent may be prepared, for example, by reduction of the corresponding nitro compound as described above. Alternatively, such compounds can be prepared by using an amino acid derivative of Formula E derived from lysine, 4-aminophenylalanine and the like in the above-described coupling reactions.

By way of illustration, a compound of the present invention or an intermediate thereof having a substituent containing a primary or secondary amino group can be readily *N*-acylated using conventional acylating reagents and conditions to provide the corresponding amide. This acylation reaction is typically conducted by treating the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of a carboxylic acid in the presence of a coupling reagent such as a carbodiimide, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphonate) and the like, in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N*,*N*-dimethylformamide and the like, at a temperature ranging from about 0°C to about 37°C for about 4 to about 24 hours. Preferably, a promoter, such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, is used to facilitate the acylation reaction. Examples of carboxylic acids suitable for use in this reaction include, but are not limited to, *N*-*tert*-butyloxycarbonylglycine, *N*-*tert*-butyloxycarbonyl-L-phenylalanine, *N*-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester, benzoic acid, *N*-*tert*-butyloxycarbonylisonipecotic acid, *N*-methylisonipecotic acid, *N*-*tert*-butyloxycarbonylnipecotic acid, *N*-*tert*-butyloxycarbonyl-L-tetrahydroisoquinoline-3-carboxylic acid, *N*-(toluene-4-sulfonyl)-L-proline and the like.

Alternatively, a compound of the present invention or an intermediate thereof containing a primary or secondary amino group can be *N*-acylated using an acyl halide or a carboxylic acid anhydride to form the corresponding amide. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the acyl halide or carboxylic acid anhydride in an inert diluent, such as dichloromethane, at a temperature ranging from about of about -70°C to

about 40°C for about 1 to about 24 hours. If desired, an acylation catalyst such as 4-(*N*,*N*-dimethylamino)pyridine may be used to promote the acylation reaction. The acylation reaction is preferably conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like.

Examples of acyl halides and carboxylic acid anhydrides suitable for use in this reaction include, but are not limited to, 2-methylpropionyl chloride, trimethylacetyl chloride, phenylacetyl chloride, benzoyl chloride, 2-bromobenzoyl chloride, 2-methylbenzoyl chloride, 2-trifluoromethylbenzoyl chloride, isonicotinoyl chloride, nicotinoyl chloride, picolinoyl chloride, acetic anhydride, succinic anhydride and the like. Carbamyl chlorides, such as *N*,*N*-dimethylcarbamyl chloride, *N*,*N*-diethylcarbamyl chloride and the like, can also be used in this reaction to provide ureas. Similarly, dicarbonates, such as di-*tert*-butyl dicarbonate, may be employed to provide carbamates.

In a similar manner, a compound of the present invention or an intermediate thereof containing a primary or secondary amino group may be *N*-sulfonated to form a sulfonamide using a sulfonyl halide or a sulfonic acid anhydride. Sulfonyl halides and sulfonic acid anhydrides suitable for use in this reaction include, but are not limited to, methanesulfonyl chloride, chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride and the like. Similarly, sulfamoyl chlorides, such as dimethylsulfamoyl chloride, can be used to provide sulfamides (*e.g.*, >N-$SO_2$-N<).

Additionally, a primary and secondary amino group present on a substituent of a compound of the present invention or an intermediate thereof can be reacted with an isocyanate or a thioisocyanate to give a urea or thiourea, respectively. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the isocyanate or thioisocyanate in an inert diluent, such as toluene and the like, at a temperature ranging from about 24°C to about 37°C for about 12 to about 24 hours. The isocyanates and thioisocyanates used in this reaction are commercially available or can be prepared from commercially available compounds using well-known synthetic procedures. For example, isocyanates and thioisocyanates are readily prepared by reacting the appropriate amine with phosgene or thiophosgene. Examples of

isocyanates and thioisocyanates suitable for use in this reaction include, but are not limited to, ethyl isocyanate, *n*-propyl isocyanate, 4-cyanophenyl isocyanate, 3-methoxyphenyl isocyanate, 2-phenylethyl isocyanate, methyl thioisocyanate, ethyl thioisocyanate, 2-phenylethyl thioisocyanate, 3-phenylpropyl thioisocyanate, 3-(*N*,*N*-diethylamino)propyl thioisocyanate, phenyl thioisocyanate, benzyl thioisocyanate, 3-pyridyl thioisocyanate, fluorescein isothiocyanate (isomer L), and the like.

Furthermore, when a compound of the present invention or an intermediate thereof contains a primary or secondary amino group, the amino group can be reductively alkylated using aldehydes or ketones to form a secondary or tertiary amino group. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of an aldehyde or ketone and at least one equivalent based on the amino compound of a metal hydride reducing agent, such as sodium cyanoborohydride, in an inert diluent, such as methanol, tetrahydrofuran, mixtures thereof and the like, at a temperature ranging from about 0°C to about 50°C for about 1 to about 72 hours. Aldehydes and ketones suitable for use in this reaction include, by way of example, benzaldehyde, 4-chlorobenzaldehyde, valeraldehyde and the like.

In a similar manner, when a compound of the present invention or an intermediate thereof has a substituent containing a hydroxyl group, the hydroxyl group can be further modified or derivatized either before or after the above coupling reactions to provide, by way of example, ethers, carbamates and the like. Compounds of Formulae I and II having a hydroxyl group on the $R^5$ substituent, for example, can be prepared using an amino acid derivative of Formula E derived from tyrosine and the like in the above-described reactions.

By way of example, a compound of the present invention or an intermediate thereof having a substituent containing a hydroxyl group can be readily *O*-alkylated to form ethers. This *O*-alkylation reaction is typically conducted by contacting the hydroxy compound with a suitable alkali or alkaline earth metal base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, to form the alkali or alkaline earth metal salt of the hydroxyl group. This salt is generally not isolated, but is reacted *in situ* with at least one equivalent of an alkyl or substituted alkyl halide or sulfonate, such as an alkyl chloride, bromide, iodide, mesylate or tosylate, to afford the ether. Generally, this reaction is conducted at a temperature ranging from about 60°C to about 150°C for about 24 to about 72

hours. Preferably, a catalytic amount of sodium or potassium iodide is added to the reaction mixture when an alkyl chloride or bromide is employed in the reaction.

Examples of alkyl or substituted alkyl halides and sulfonates suitable for use in this reaction include, but are not limited to, *tert*-butyl bromoacetate, *N*-*tert*-butyl chloroacetamide, 1-bromoethylbenzene, ethyl α-bromophenylacetate, 2-(*N*-ethyl-*N*-phenylamino)ethyl chloride, 2-(*N*,*N*-ethylamino)ethyl chloride, 2-(*N*,*N*-diisopropylamino)ethyl chloride, 2-(*N*,*N*-dibenzylamino)ethyl chloride, 3-(*N*,*N*-ethylamino)propyl chloride, 3-(*N*-benzyl-*N*-methylamino)propyl chloride, *N*-(2-chloroethyl)morpholine, 2-(hexamethyleneimino)ethyl chloride, 3-(*N*-methylpiperazine)propyl chloride, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, 2-(4-hydroxy-4-phenylpiperidine)ethyl chloride, *N*-*tert*-butyloxycarbonyl-3-piperidinemethyl tosylate and the like.

Alternatively, a hydroxyl group present on a substituent of a compound of the present invention or an intermediate thereof can be *O*-alkylating using the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(*N*,*N*-dimethylamino)-1-propanol and the like, is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as *N*-*tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the *O*-alkylated product.

In a similar manner, a compound of the present invention or an intermediate thereof containing a aryl hydroxy group can be reacted with an aryl iodide to provide a diaryl ether. Generally, this reaction is conducted by forming the alkali metal salt of the hydroxyl group using a suitable base, such as sodium hydride, in an inert diluent such as xylenes at a temperature of about -25°C to about 10°C. The salt is then treated with about 1.1 to about 1.5 equivalents of cuprous bromide dimethyl sulfide complex at a temperature ranging from about 10°C to about 30°C for about 0.5 to about 2.0 hours, followed by about 1.1 to about 1.5 equivalents of an aryl iodide, such as sodium 2-iodobenzoate and the like. The reaction is then heated to about 70°C to about 150°C for about 2 to about 24 hours to provide the diaryl ether.

Additionally, a hydroxy-containing compound can also be readily derivatized to form a carbamate. In one method for preparing such carbamates, a hydroxy compound of the

present invention or an intermediate thereof is contacted with about 1.0 to about 1.2 equivalents of 4-nitrophenyl chloroformate in an inert diluent, such as dichloromethane, at a temperature ranging from about -25°C to about 0°C for about 0.5 to about 2.0 hours. Treatment of the resulting carbonate with an excess, preferably about 2 to about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5 to 2 hours, followed by about 1.0 to about 1.5 equivalents of a primary or secondary amine provides the carbamate. Examples of amines suitable for using in this reaction include, but are not limited to, piperazine, 1-methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine, pyrrolidine, piperidine and the like.

Alternatively, in another method for preparing carbamates, a hydroxy-containing compound is contacted with about 1.0 to about 1.5 equivalents of a carbamyl chloride in an inert diluent, such as dichloromethane, at a temperature ranging from about 25°C to about 70°C for about 2 to about 72 hours. Typically, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Additionally, at least one equivalent (based on the hydroxy compound) of 4-(*N*,*N*-dimethylamino)pyridine is preferably added to the reaction mixture to facilitate the reaction. Examples of carbamyl chlorides suitable for use in this reaction include, by way of example, dimethylcarbamyl chloride, diethylcarbamyl chloride and the like.

Likewise, when a compound of the present invention or an intermediate thereof contains a primary or secondary hydroxyl group, such hydroxyl groups can be readily converted into a leaving group and displaced to form, for example, amines, sulfides and fluorides. For example, derivatives of 4-hydroxy-L-proline can be converted into the corresponding 4-amino, 4-thio or 4-fluoro-L-proline derivatives via nucleophilic displacement of the derivatized hydroxyl group. Generally, when a chiral compound is employed in these reactions, the stereochemistry at the carbon atom attached to the derivatized hydroxyl group is typically inverted.

These reactions are typically conducted by first converting the hydroxyl group into a leaving group, such as a tosylate, by treatment of the hydroxy compound with at least one equivalent of a sulfonyl halide, such as *p*-toluenesulfonyl chloride and the like, in pyridine. This reaction is generally conducted at a temperature of from about 0°C to about 70°C for

about 1 to about 48 hours. The resulting tosylate can then be readily displaced with sodium azide, for example, by contacting the tosylate with at least one equivalent of sodium azide in an inert diluent, such as a mixture of *N*,*N*-dimethylformamide and water, at a temperature ranging from about 0°C to about 37°C for about 1 to about 12 hours to provide the corresponding azido compound. The azido group can then be reduced by, for example, hydrogenation using a palladium on carbon catalyst to provide the amino ($-NH_2$) compound.

Similarly, a tosylate group can be readily displaced by a thiol to form a sulfide. This reaction is typically conducted by contacting the tosylate with at least one equivalent of a thiol, such as thiophenol, in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in an inert diluent, such as *N*,*N*-dimethylformamide, at a temperature of from about 0°C to about 37°C for about 1 to about 12 hours to provide the sulfide. Additionally, treatment of a tosylate with morpholinosulfur trifluoride in an inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours affords the corresponding fluoro compound.

Furthermore, a compound of the present invention or an intermediate thereof having a substituent containing an iodoaryl group, for example, when $R^5$, of Formula I or II, is a (4-iodophenyl)methyl group, can be readily converted either before or after the above coupling reactions into a biaryl compound. Typically, this reaction is conducted by treating the iodoaryl compound with about 1.1 to about 2 equivalents of an arylzinc iodide, such as 2-(methoxycarbonyl)phenylzinc iodide, in the presence of a palladium catalyst, such as palladium tetra(triphenylphosphine), in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 24°C to about 30°C until the reaction is complete. This reaction is further described, for example, in Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

In some cases, the compounds of the present invention or intermediates thereof may contain substituents having one or more sulfur atoms. Such sulfur atoms will be present, for example, when the amino acid of Formula A employed in the above reactions is derived from L-thiazolidine-4-carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid and the like. When present, such sulfur atoms can be oxidized either before or after the above coupling reactions to provide a sulfoxide or sulfone compound using conventional reagents and reaction conditions. Suitable reagents for oxidizing a sulfide compound to a sulfoxide include, by way of example, hydrogen peroxide, 3-chloroperoxybenzoic acid (MCPBA), sodium periodate and the like. The oxidation

reaction is typically conducted by contacting the sulfide compound with about 0.95 to about 1.1 equivalents of the oxidizing reagent in an inert diluent, such as dichloromethane, at a temperature ranging from about -50°C to about 75°C for about 1 to about 24 hours. The resulting sulfoxide can then be further oxidized to the corresponding sulfone by contacting the sulfoxide with at least one additional equivalent of an oxidizing reagent, such as hydrogen peroxide, MCPBA, potassium permanganate and the like. Alternatively, the sulfone can be prepared directly by contacting the sulfide with at least two equivalents, and preferably an excess, of the oxidizing reagent. Such reactions are described further in March, "*Advanced Organic Chemistry*", 4th Ed., pp. 1202-1202, Wiley Publishers, (1992).

As described above, the compounds of the present invention having an $R^2$ substituent other an hydrogen can be prepared using an *N*-substituted amino acid of Formula A, such as sarcosine, *N*-methyl-L-phenylalanine and the like, in the above-described coupling reactions. Alternatively, such compounds can be prepared by *N*-alkylation of a sulfonamide of Formula I or C (where $R^2$ is hydrogen) using conventional synthetic procedures. Typically, this *N*-alkylation reaction is conducted by contacting the sulfonamide with at least one equivalent, preferably 1.1 to 2 equivalents, of an alkyl or substituted alkyl halide in the presence of a suitable base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, at a temperature ranging from about 25°C to about 70°C for about 2 to about 48 hours. Examples of alkyl or substituted alkyl halides suitable for use in this reaction include, but are not limited to, methyl iodide, and the like.

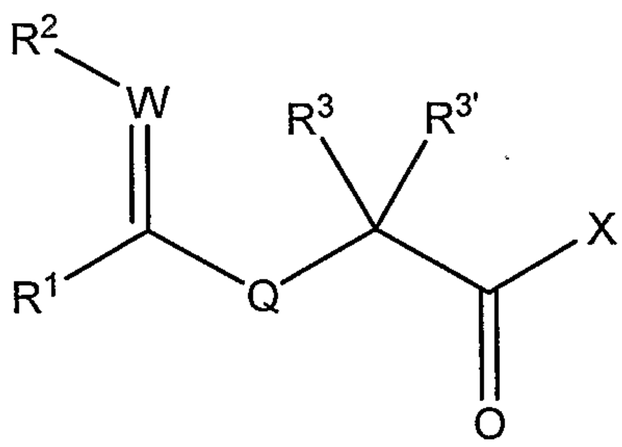
Additionally, the sulfonamides of Formula I or C wherein $R^2$ is hydrogen and $R^1$ is a 2-alkoxycarbonylaryl group can be intramolecularly cyclized to form 1,2-benzisothiazol-3-one derivatives or analogues thereof. This reaction is typically conducted by treating a sulfonamide, such as *N*-(2-methoxycarbonylphenylsulfonyl)glycine-L-phenylalanine benzyl ester, with about 1.0 to 1.5 equivalents of a suitable base, such as an alkali metal hydride, in a inert diluent, such as tetrahydrofuran, at a temperature ranging from about 0°C to about 30°C for about 2 to about 48 hours to afford the cyclized 1,2-benzisothiazol-3-one derivative.

Lastly, the compounds of Formula I or II where Q is $-C(S)NR^7-$ are prepared by using an amino thionoacid derivative in place of amino acid A in the above described synthetic procedures. Such amino thionoacid derivatives can be prepared by the procedures described in Shalaky *et al.*, *J. Org. Chem.*, 61:9045-9048 (1996) and Brain *et al.*, *J. Org. Chem.*, 62:3808-3809 (1997) and references cited therein.

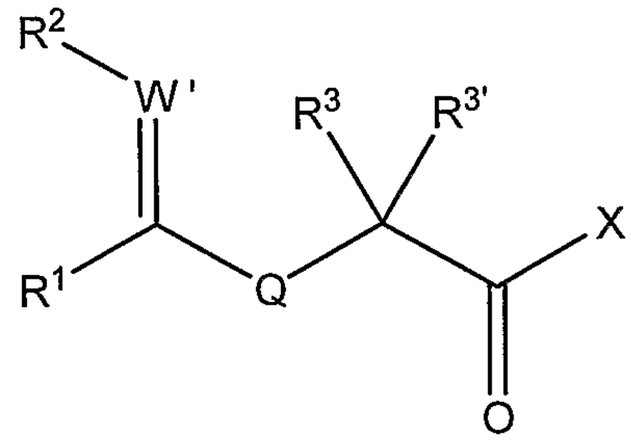
Compounds of Formulae III-IX

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formulae IIIa, IIIb, IVa, IVb, Va, Vb, Vc, Vd, Ve, VIa, VIb, VIIa, VIIb, VIIc, VIId, VIIe, VIIIa, VIIIb, IXa, IXb, IXc, IXd, and IXe.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula IIIa and/or IIIb below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



and



IIIa IIIb

wherein, in Formula IIIa, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form an aryl, cycloalkenyl, heteroaryl or heterocyclic group having at least five atoms in the aryl, cycloalkenyl, heteroaryl or heterocyclic group and optionally containing or additionally containing in the case of heteroaryl and heterocyclic groups 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heteroaryl or heterocyclic group is mono-cyclic;

in Formula IIIb, $R^1$ and $R^2$, together with the carbon atom and W' to which they are bound respectively, are joined to form a cycloalkyl, cycloalkenyl or heterocyclic group having at least five atoms in the cycloalkyl, cycloalkenyl or heterocyclic group and optionally containing or additionally containing in the case of the heterocyclic group 1 to 3

heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heterocyclic group is mono-cyclic;

and further wherein said aryl, cycloalkyl, cycloalkenyl, heteroaryl or heterocyclic group of Formula IIIa or IIIb is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-N[S(O)_2-R']_2$ and $-N[S(O)_2-NR']_2$ where each R′ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^3$ and $R^{3'}$ are independently selected from the group consisting of hydrogen, isopropyl, $-CH_2Z$ where Z is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl,

substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and

where $R^3$ and $R^{3'}$ are joined to form a substituent selected from the group consisting of =CHZ where Z is defined above provided that Z is not hydroxyl or thiol, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic and substituted heterocyclic;

Q is selected from the group consisting of -O-, -S-, -S(O)-, $-S(O)_2$, and $-NR^4$-;

$R^4$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic or, optionally, $R^4$ and $R^1$ or $R^4$ and $R^2$, together with the atoms to which they are bound, are joined to form a heteroaryl, a substituted heteroaryl, a heterocyclic or a substituted heterocyclic group;

W is selected from the group consisting of nitrogen and carbon; and

W' is selected from the group consisting of nitrogen, carbon, oxygen, sulfur, S(O), and $S(O)_2$;

X is selected from the group consisting of hydroxyl, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, cycloalkoxy, substituted cycloalkoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy and -NR″R″ where each R″ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

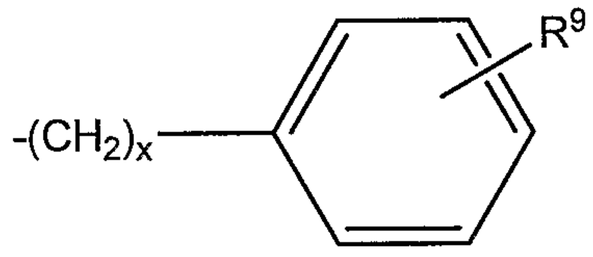
and enantiomers, diastereomers and pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula IIIa and/or IIIb has a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15μM or less.

Preferably, $R^3$ is $-(CH_2)_x$-Ar-$R^9$, where Ar is aryl, substituted aryl, heteroaryl and substituted heteroaryl; $R^9$ is selected from the group consisting of acyl, acylamino, acyloxy, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, oxythiocarbonylamino, thioamidino, thiocarbonylamino, aminosulfonylamino,

aminosulfonyloxy, aminosulfonyl, oxysulfonylamino and oxysulfonyl; and *x* is an integer from 0 to 4. $R^{3'}$ is preferably alkyl or hydrogen; more preferably, $R^{3'}$ is hydrogen.

More preferably, $R^3$ is a group of the formula:

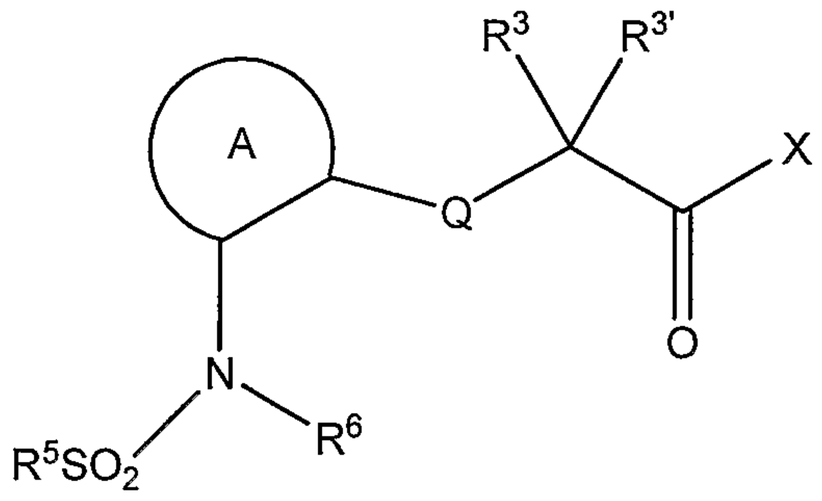



wherein $R^9$ and *x* are as defined herein. Preferably, $R^9$ is in the *para* position of the phenyl ring; and *x* is an integer of from 1 to 4, more preferably, *x* is 1.

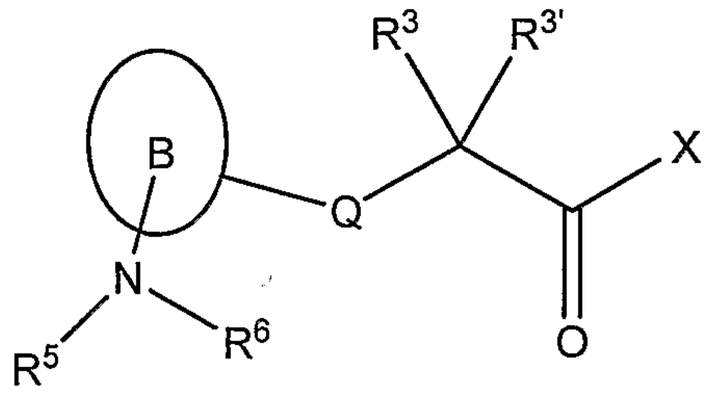
In a preferred embodiment, $R^9$ is selected from -O-Z-$NR^{11}R^{11'}$ and -O-Z-$R^{12}$ wherein $R^{11}$ and $R^{11'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, and where $R^{11}$ and $R^{11'}$ are joined to form a heterocycle or a substituted heterocycle, $R^{12}$ is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -$SO_2$-. More preferably, $R^9$ is -OC(O)$NR^{11}R^{11'}$, wherein $R^{11}$ and $R^{11'}$ are as defined herein.

Z is preferably -C(O)-. Preferably, Q is -$NR^4$-.

In a preferred embodiment, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula IVa and/or IVb below.



IVa



IVb

wherein $R^3$, $R^{3'}$ and X are as defined herein;

ring A and ring B independently form a heteroaryl or substituted heteroaryl group having two nitrogen atoms in the heteroaryl ring;

$R^5$ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^6$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-SO_2R^{10}$ where $R^{10}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

or optionally, one of, $R^4$ and ring A, $R^4$ and $R^5$, $R^4$ and $R^6$, or $R^5$ and $R^6$, together with the atoms to which they are bound, can be joined to form a heterocyclic or substituted heterocyclic ring;

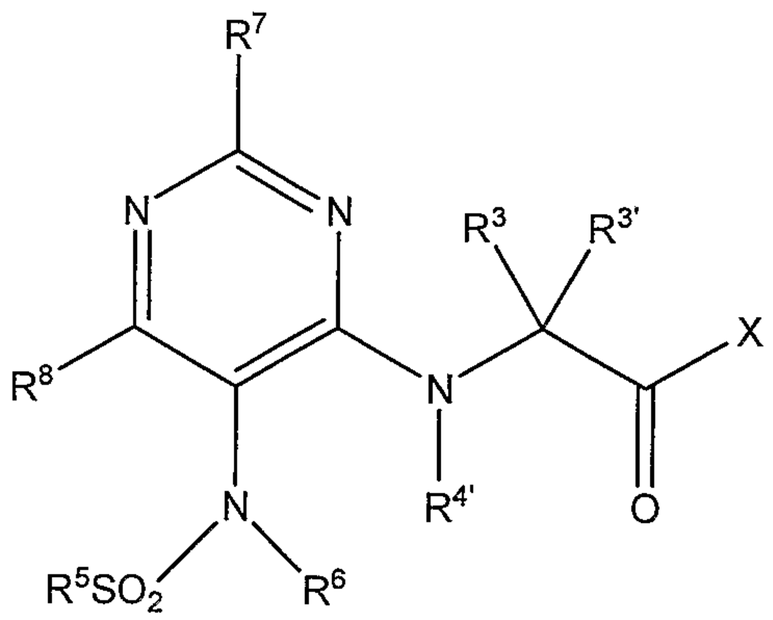
and enantiomers, diastereomers and pharmaceutically acceptable salts thereof; and provided that ring B does not form a 6-amino or substituted amino pyrimidin-4-yl group.

Preferably, ring A forms a pyridazine, pyrimidine or pyrazine ring; more preferably, a pyrimidine or pyrazine ring; wherein the pyridazine, pyrimidine or pyrazine ring is optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

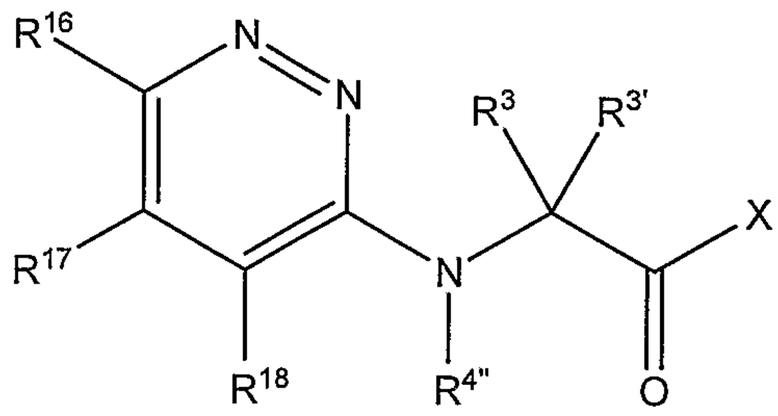
Preferably, ring B forms a pyridazine, pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or a 1,1-dioxo-1,2,5-thiadiazole ring; more preferably, a pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or a 1,1-dioxo-1,2,5-thiadiazole ring; wherein the pyridazine, pyrimidine or pyrazine ring is optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

Preferably the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula IVa.

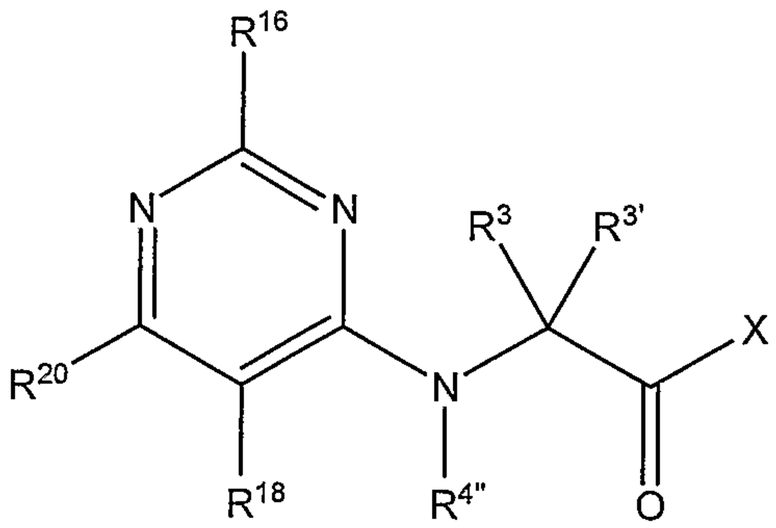
In another preferred embodiment, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula Va, Vb, Vc, Vd, or Ve:



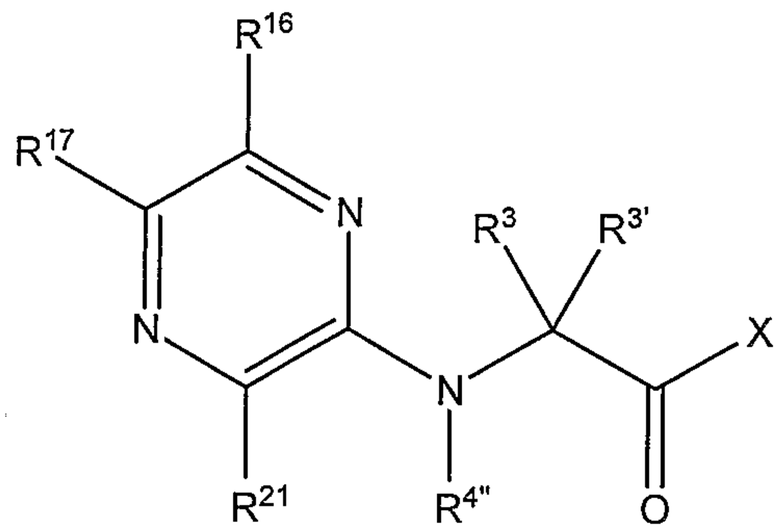
Va



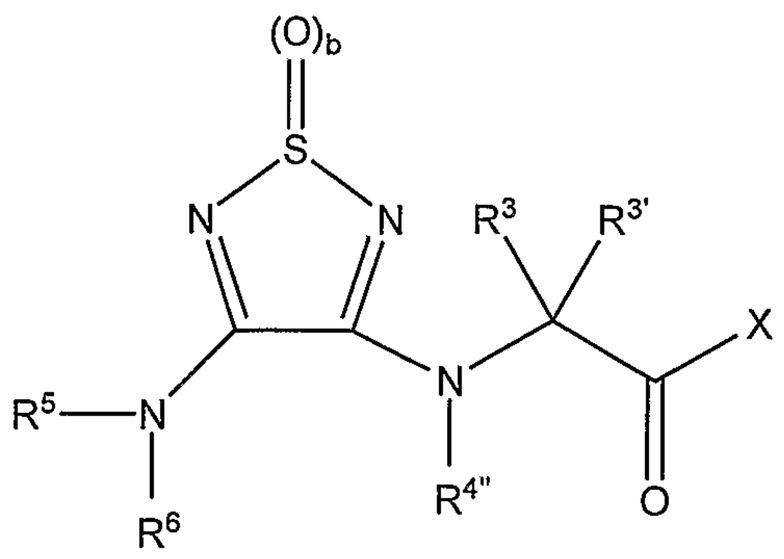
Vb



Vc



Vd



Ve

wherein $R^3$, $R^{3'}$ and X are as defined herein;

$R^{4'}$ is selected from the group consisting of hydrogen and alkyl or, optionally, one of, $R^{4'}$ and $R^5$, $R^{4'}$ and $R^6$, $R^5$ and $R^6$, $R^5$ and $R^8$, or $R^6$ and $R^8$, together with the atoms to which they are bound, are joined to form a heterocyclic, a substituted heterocyclic, a heteroaryl or substituted heteroaryl group optionally containing from 1 to 3 additional hetero ring atoms selected from the group consisting of oxygen, nitrogen and sulfur;

$R^{4''}$ is selected from the group consisting of hydrogen and alkyl;

$R^5$ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^6$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-SO_2R^{10}$ where $R^{10}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, amino, substituted amino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{16}$ and $R^{17}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

$R^{18}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{20}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

*b* is 1 or 2;

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof.

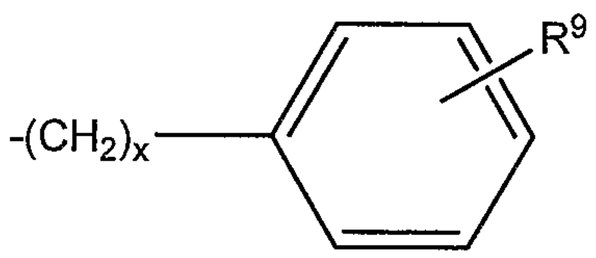
Preferably, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formula Va, Vc, or Vd.

Preferably, in the compounds of Formula Va, Vc, and Vd

$R^5$, $R^{18}$, and $R^{21}$ are independently selected from the group consisting of heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

$R^7$ and $R^{16}$ are independently amino or substituted amino;

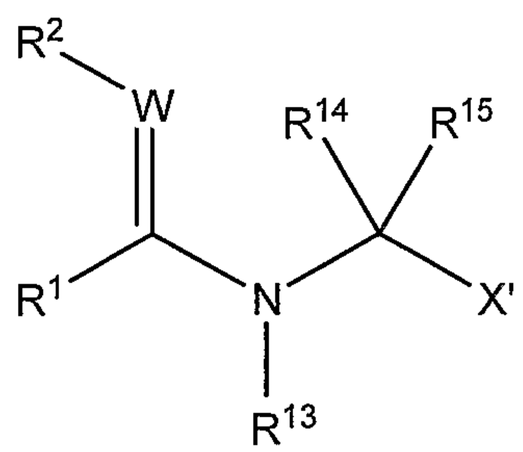
$R^3$ is a group of the formula:




wherein $R^9$ is selected from the group consisting acyl, acylamino, acyloxy, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, oxycarbonylamino, oxythiocarbonylamino, thioamidino, thiocarbonylamino, aminosulfonylamino, aminosulfonyloxy, aminosulfonyl, oxysulfonylamino and oxysulfonyl; and *x* is an integer from 0 to 4; and

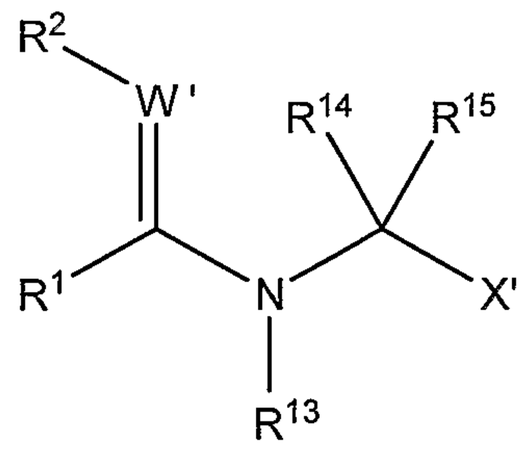
$R^{3'}$ is hydrogen.

In another embodiment, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula VIa and/or VIb:



VIa

and



VIb

wherein, in Formula VIa, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form an aryl, cycloalkenyl, heteroaryl or heterocyclic group having at least five atoms in the aryl, cycloalkenyl, heteroaryl or heterocyclic group and optionally containing or additionally containing in the case of heteroaryl and heterocyclic groups 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heteroaryl or heterocyclic group is mono-cyclic;

in Formula VIb, $R^1$ and $R^2$, together with the carbon atom and W' to which they are bound respectively, are joined to form a cycloalkyl, cycloalkenyl or heterocyclic group having at least five atoms in the cycloalkyl, cycloalkenyl or heterocyclic group and optionally containing or additionally containing in the case the heterocyclic group 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heterocyclic group is mono-cyclic;

and further wherein said aryl, cycloalkyl, cycloalkenyl, heteroaryl or heterocyclic group of Formula VIa or VIb is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, -

$OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-N[S(O)_2-R']_2$ and $-N[S(O)_2-NR']_2$ where each R′ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{13}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, Cy, and Cy-$C_{1-10}$ alkyl, wherein alkyl is optionally substituted with one to four substituents independently selected from $R^a$; and Cy is optionally substituted with one to four substituents independently selected from $R^b$;

$R^{14}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, Cy, Cy-$C_{1-10}$ alkyl, Cy-$C_{2-10}$ alkenyl and Cy-$C_{2-10}$ alkynyl, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents selected from phenyl and $R^X$, and Cy is optionally substituted with one to four substituents independently selected from $R^y$;

or $R^{13}$, $R^{14}$ and the atoms to which they are attached together form a mono- or bicyclic ring containing 0-2 additional heteratoms selected from N, O and S;

$R^{15}$ is selected from the group consisting of $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl, aryl-$C_{1-10}$ alkyl, heteroaryl, heteroaryl-$C_{1-10}$ alkyl, wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from $R^x$, and aryl and heteroaryl are optionally substituted with one to four substituents independently selected from $R^y$;

or $R^{14}$, $R^{15}$ and the carbon to which they are attached form a 3-7 membered mono- or bicyclic ring containing 0-2 heteroatoms selected from N, O and S;

$R^a$ is selected from the group consisting of Cy and a group selected from $R^x$, wherein Cy is optionally substituted with one to four substituents independently selected from $R^c$;

$R^b$ is selected from the group consisting of $R^a$, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl $C_{1-10}$alkyl, heteroaryl $C_{1-10}$ alkyl, wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from $R^c$;

$R^c$ is selected from the group consisting of halogen, $NO_2$, $C(O)OR^f$, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, aryl, aryl $C_{1-4}$ alkyl, aryloxy, heteroaryl, $NR^fR^g$, $R^fC(O)R^g$, $NR^fC(O)NR^fR^g$, and CN;

$R^d$ and $R^e$ are independently selected from hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, Cy and Cy $C_{1-10}$alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from $R^c$;

or $R^d$ and $R^e$ together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

$R^f$ and $R^g$ are independently selected from hydrogen, $C_{1-10}$ alkyl, Cy and Cy-$C_{1-10}$ alkyl wherein Cy is optionally substituted with $C_{1-10}$ alkyl; or $R^f$ and $R^g$ together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

$R^h$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, cyano, aryl, aryl $C_{1-10}$ alkyl, heteroaryl, heteroaryl $C_{1-10}$ alkyl, and $-SO_2R^i$; wherein alkyl, alkenyl, and alkynl are optionally substituted with one to four substitutents independently selected from $R^a$; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from $R^b$;

$R^i$ is selected from the group consisting of $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, and aryl; wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from $R^c$;

$R^x$ is selected from the group consisting of $-OR^d$, $-NO_2$, halogen, $-S(O)_mR^d$, $-SR^d$, $-S(O)_2OR^d$, $-S(O)_mNR^dR^e$, $-NR^dR^e$, $-O(CR^fR^g)_nNR^dR^e$, $-C(O)R^d$, $-CO_2R^d$, $-CO_2(CR^fR^g)_nCONR^dR^e$, $-OC(O)R^d$, -CN, $-C(O)NR^dR^e$, $-NR^dC(O)R^e$, $-OC(O)NR^dR^e$, $-NR^dC(O)OR^e$, $-NR^dC(O)NR^dR^e$, $-CR^d(N-OR^e)$, $CF_3$, oxo, $NR^dC(O)NR^dSO_2R^i$, $NR^dS(O)_mR^e$, $-OS(O)_2OR^d$, and $-OP(O)(OR^d)_2$;

$R^y$ is selected from the group consisting of $R^x$, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl $C_{1-10}$alkyl, heteroaryl $C_{1-10}$ alkyl, cycloalkyl, heterocyclyl; wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substitutents independently selected from $R^x$;

Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

*m* is an integer from 1 to 2;

*n* is an integer from 1 to 10;

W is selected from the group consisting of carbon and nitrogen;

W' is selected from the group consisting of carbon, nitrogen, oxygen, sulfur, S(O) and $S(O)_2$;

X' is selected from the group consisting of $-C(O)OR^d$, $-P(O)(OR^d)(OR^e)$, $-P(O)(R^d)(OR^e)$, $-S(O)_mOR^d$, $-C(O)NR^dR^h$, and -5-tetrazolyl;

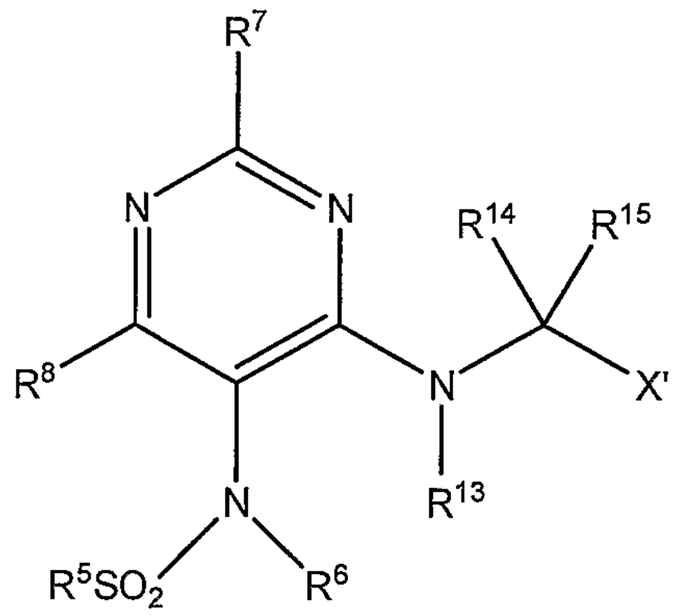
and enantiomers, diastereomers and pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula VIa and/or VIb has a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15μM or less.

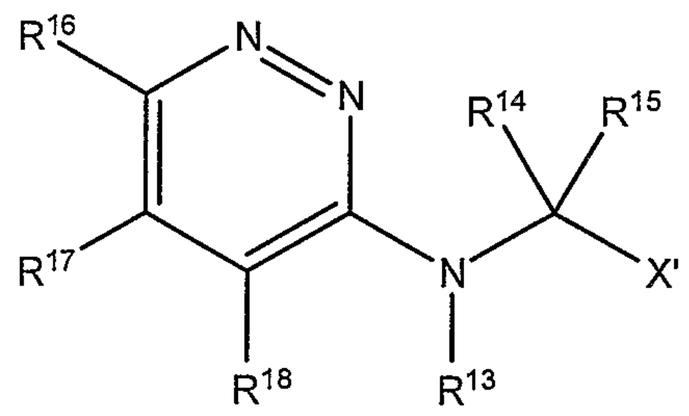
Preferably, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form a heteroaryl or substituted heteroaryl group having two nitrogen atoms in the heteroaryl ring. Optionally, the heteroaryl ring may contain other heteroatoms such as oxygen or sulfur. More preferably, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form a pyridazine, pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or 1,1-dioxo-1,2,5-thiadiazole ring; more preferably, a pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or 1,1-dioxo-1,2,5-thiadiazole ring; wherein the pyridazine, pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or 1,1-dioxo-1,2,5-thiadiazole ring is optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

Preferably, X' is $-C(O)OR^d$.

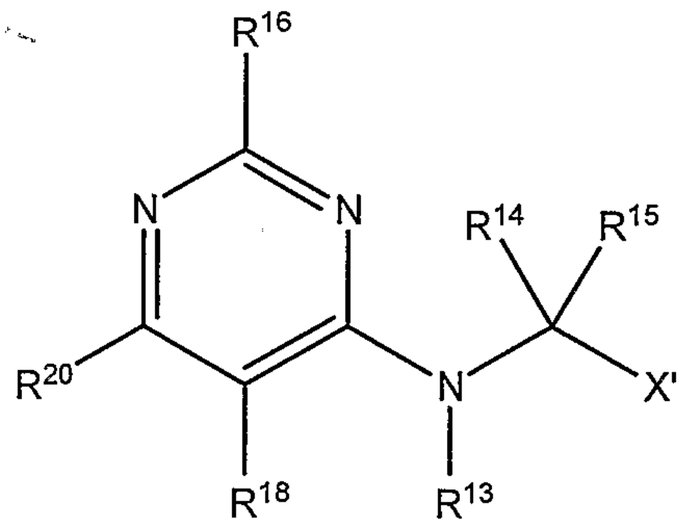
In another preferred embodiment, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula VIIa, VIIb, VIIc, VIId, or VIIe:



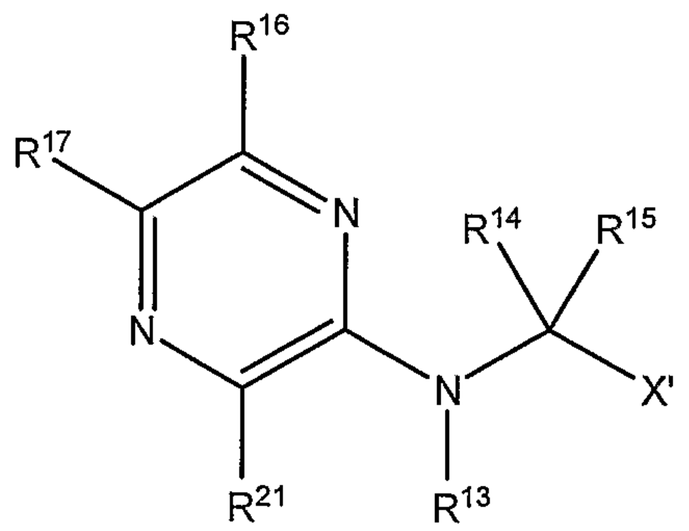
VIIa



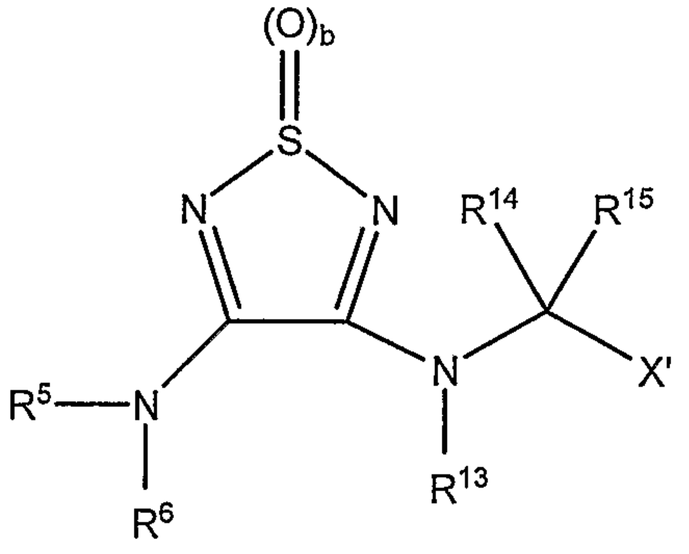
VIIb



VIIc



VIId



VIIe

wherein $R^{13}$, $R^{14}$, $R^{15}$ and X' are as defined herein;

$R^5$ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^6$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-SO_2R^{10}$ where $R^{10}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl; and

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, amino, substituted amino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{16}$ and $R^{17}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

$R^{18}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{20}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

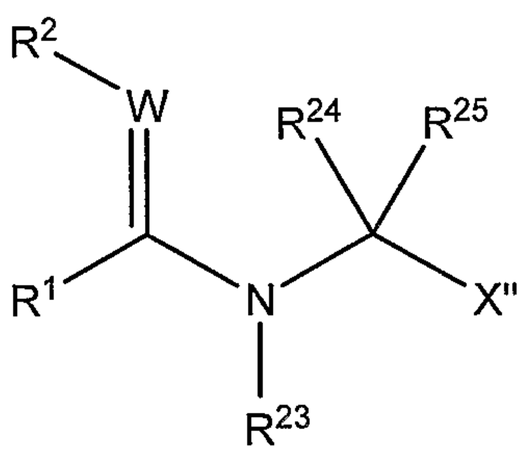
$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

*b* is 1 or 2;

and enatiomers, diastereomers and pharmaceutically acceptable salts thereof.

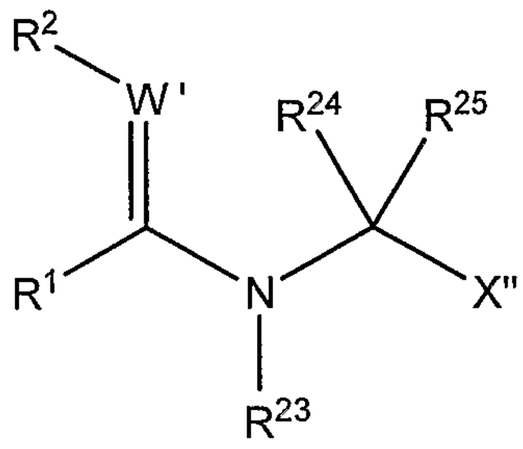
Preferably, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formula VIIa, VIIc, or VIId.

In another embodiment, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula VIIIa and/or VIIIb:



VIIIa

and



VIIIb

wherein, in Formula VIIIa, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form an aryl, cycloalkenyl, heteroaryl or heterocyclic group having at least five atoms in the aryl, cycloalkenyl, heteroaryl or heterocyclic group and optionally containing or additionally containing in the case of heteroaryl and heterocyclic groups 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heteroaryl or heterocyclic group is mono-cyclic;

in Formula VIIIb, $R^1$ and $R^2$, together with the carbon atom and W' to which they are bound respectively, are joined to form a cycloalkyl, cycloalkenyl or heterocyclic group having at least five atoms in the cycloalkyl, cycloalkenyl or heterocyclic group and optionally containing or additionally containing in the case of the heterocyclic group 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heterocyclic group is mono-cyclic;

and further wherein said aryl, cycloalkyl, cycloalkenyl, heteroaryl or heterocyclic group of Formula VIIIa or VIIIb is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino,

aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-N[S(O)_2-R']_2$ and $-N[S(O)_2-NR']_2$ where each R′ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{23}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl optionally substituted with one to four substituents independently selected from $R^{a'}$ and Cy optionally substituted with one to four substituents independently selected from $R^{b'}$;

$R^{24}$ is selected from the group consisting of $Ar^1$-$Ar^2$-$C_{1-10}$ alkyl, $Ar^1$-$Ar^2$-$C_{2-10}$ alkenyl, $Ar^1$-$Ar^2$-$C_{2-10}$ alkynyl, wherein $Ar^1$ and $Ar^2$ are independently aryl or heteroaryl each of which is optionally substituted with one to four substituents independently selected from $R^{b'}$; alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from $R^{a'}$;

$R^{25}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl, aryl $C_{1-10}$alkyl, heteroaryl, and heteroaryl $C_{1-10}$ alkyl, wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from $R^{a'}$, and aryl and heteroaryl are optionally substituted with one to four substituents independently selected from $R^{b'}$;

$R^{a'}$ is selected from the group consisting of Cy, $-OR^{d'}$, $-NO_2$, halogen $-S(O)_mR^{d'}$, $-SR^{d'}$, $-S(O)_2OR^{d'}$, $-S(O)_mNR^{d'}R^{e'}$, $-NR^{d'}R^{e'}$, $-O(CR^{f'}R^{g'})_nNR^{d'}R^{e'}$, $-C(O)R^{d'}$, $-CO_2R^{d'}$, $-CO_2(CR^{f'}R^{g'})_nCONR^{d'}R^{e'}$, $-OC(O)R^{d'}$, -CN, $-C(O)NR^{d'}R^{e'}$, $-NR^{d'}C(O)R^{e'}$, $-OC(O)NR^{d'}R^{e'}$, $-NR^{d'}C(O)OR^{e'}$, $-NR^{d'}C(O)NR^{d'}R^{e'}$, $-CR^{d'}(N-OR^{e'})$, $CF_3$, and $-OCF_3$;

wherein Cy is optionally substituted with one to four substituents independently selected from $R^{c'}$;

$R^{b'}$ is selected from the group consisting of $R^{a'}$, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl $C_{1-10}$ alkyl, heteroaryl $C_{1-10}$alkyl,

wherein alkyl, alkenyl, aryl, heteroaryl are optionally substituted with a group independently selected from $R^{c'}$;

$R^{c'}$ is selected from the group consisting of halogen, amino, carboxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, aryl, aryl $C_{1-4}$alkyl, hydroxy, $CF_3$, and aryloxy;

$R^{d'}$ and $R^{e'}$ are independently selected from hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, Cy and Cy $C_{1-10}$alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from $R^{c'}$; or $R^{d'}$ and $R^{e'}$ together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

$R^{f'}$ and $R^{g'}$ are independently selected from hydrogen, $C_{1-10}$ alkyl, Cy and Cy-$C_{1-10}$ alkyl; or $R^{f'}$ and $R^{g'}$ together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

$R^{h'}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, cyano, aryl, aryl $C_{1-10}$ alkyl, heteroaryl, heteroaryl $C_{1-10}$ alkyl, or $-SO_2R^{i'}$;

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substitutents independently selected from $R^{a'}$; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from $R^{b'}$;

$R^{i'}$ is selected from the group consisting of $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, and aryl;

wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from $R^{c'}$;

Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X" is selected from the group consisting of -C(O)OR$^{d'}$, -P(O)(OR$^{d'}$)(OR$^{e'}$), -P(O)(R$^{d'}$)(OR$^{e'}$), -S(O)$_m$OR$^{d'}$, -C(O)NR$^{d'}$R$^{h'}$, and -5-tetrazolyl;

*m* is an integer from 1 to 2;

*n* is an integer from 1 to 10;

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof;

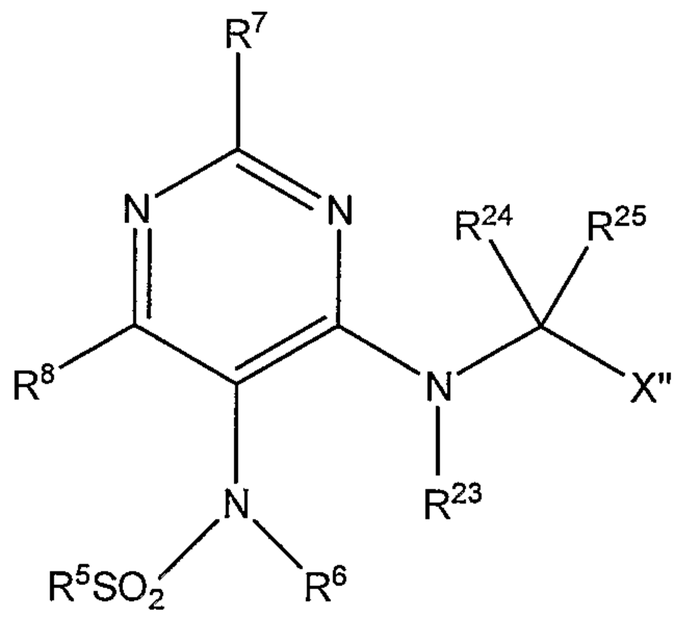
and further wherein the compound of Formula VIIIa and/or VIIIb has a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15μM or less.

Preferably, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form a heteroaryl or substituted heteroaryl group having two nitrogen atoms in the heteroaryl ring. Optionally, the heteroaryl ring may contain other heteroatoms such as oxygen or sulfur. More preferably, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form a pyridazine, pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or 1,1-dioxo-1,2,5-thiadiazole ring; more preferably, a pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or 1,1-dioxo-1,2,5-thiadiazole ring; wherein the pyridazine, pyrimidine, pyrazine, 1-oxo-1,2,5-thiadiazole or 1,1-dioxo-1,2,5-thiadiazole ring is optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

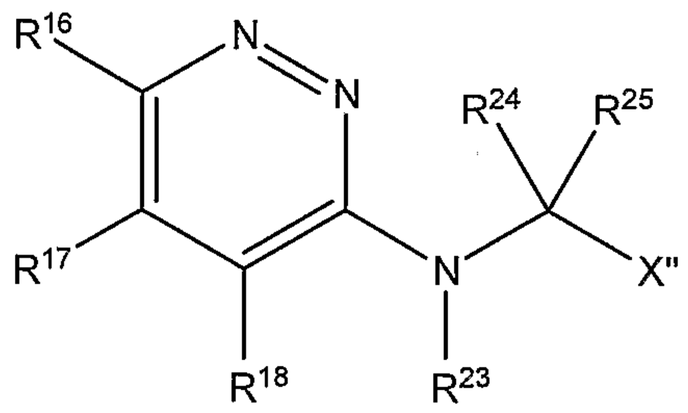
Preferably, X" is -C(O)OR$^{d'}$.

Preferably, $R^{24}$ is -$CH_2$-$Ar^2$-$Ar^1$ and $R^{25}$ is hydrogen.

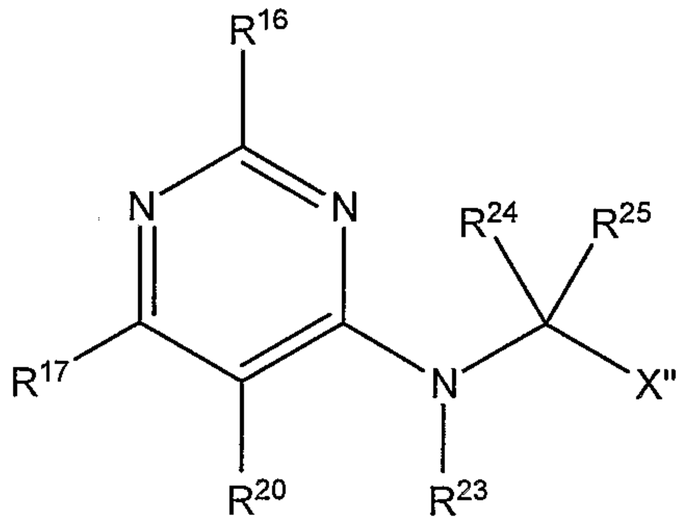
In another preferred embodiment, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula IXa, IXb, IXc, IXd, or IXe:



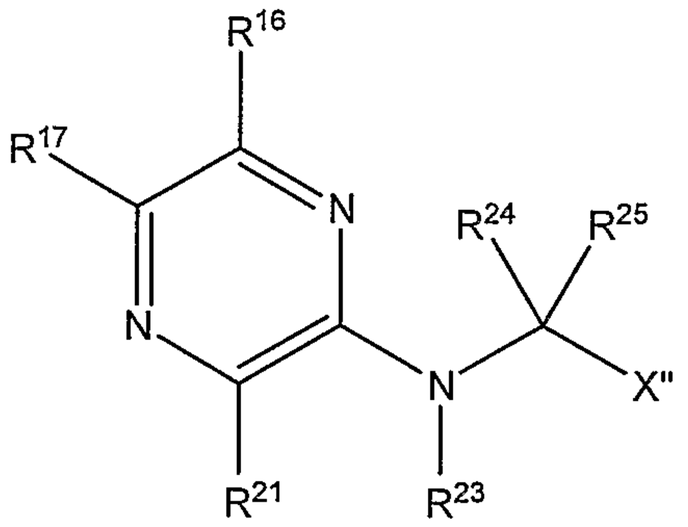
IXa



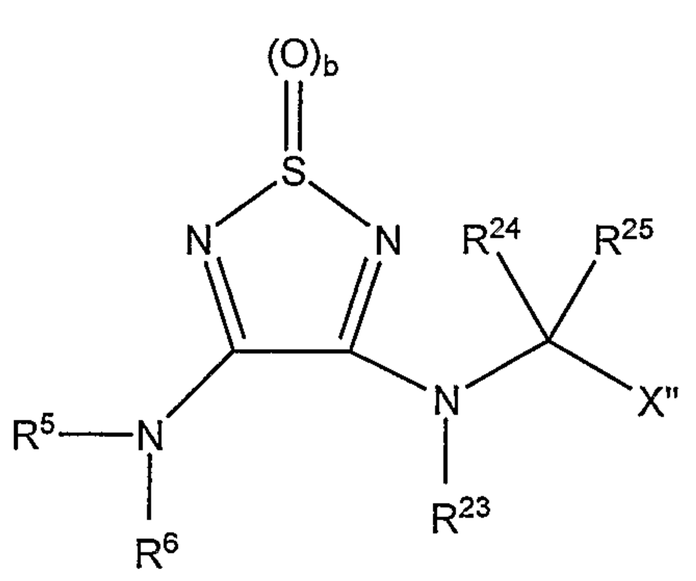
IXb



IXc



IXd



IXe

wherein $R^{23}$, $R^{24}$, $R^{25}$ and X" are as defined herein;

$R^5$ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^6$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-SO_2R^{10}$ where $R^{10}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl; and

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, amino, substituted amino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{16}$ and $R^{17}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

$R^{18}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{20}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

*b* is 1 or 2;

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof.

Preferably, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formula IX a, IXc, or IXd.

In the above compounds, when X is other than -OH or pharmaceutical salts thereof, X is preferably a substituent which will convert (*e.g.*, hydrolyze, metabolize, etc.) *in vivo* to a compound where X is -OH or a salt thereof. Accordingly, suitable X groups are any art recognized pharmaceutically acceptable groups which will hydrolyze or otherwise convert *in vivo* to a hydroxyl group or a salt thereof including, by way of example, esters (X is alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, alkenoxy, substituted alkenoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclooxy, substituted heterocyclooxy, and the like).

Unless otherwise defined, $R^3$ and $R^{15}$ in the above compounds are preferably selected from all possible isomers arising by substitution with the following groups:

4-methylbenzyl,

4-hydroxybenzyl,

4-methoxybenzyl,

4-*t*-butoxybenzyl,

4-benzyloxybenzyl,

4-[φ-$CH(CH_3)O$-]benzyl,

4-[φ-CH(COOH)O-]benzyl,

4-[$BocNHCH_2C(O)NH$-]benzyl,

4-chlorobenzyl,

4-[$NH_2CH_2C(O)NH$-]benzyl,

4-carboxybenzyl,

4-[$CbzNHCH_2CH_2NH$-]benzyl,

3-hydroxy-4-(φ-OC(O)NH-)benzyl,

4-[$HOOCCH_2CH_2C(O)NH$-]benzyl,

benzyl,

4-[2′-carboxylphenoxy-]benzyl,

4-[φ-C(O)NH-]benzyl,

3-carboxybenzyl,

4-iodobenzyl,

4-hydroxy-3,5-diiodobenzyl,

4-hydroxy-3-iodobenzyl,

4-[2′-carboxyphenyl-]benzyl,

φ-$CH_2CH_2$-,

4-nitrobenzyl,

2-carboxybenzyl,

4-[dibenzylamino]-benzyl,

4-[(1′-cyclopropylpiperidin-4′-yl)C(O)NH-]benzyl,

4-[-$NHC(O)CH_2NHBoc$]benzyl,

4-carboxybenzyl,

4-hydroxy-3-nitrobenzyl,

4-[-$NHC(O)CH(CH_3)NHBoc$]benzyl,

4-[-$NHC(O)CH(CH_2φ)NHBoc$]benzyl,

isobutyl,

methyl,

4-[$CH_3C(O)NH$-]benzyl,

-$CH_2$-(3-indolyl),

*n*-butyl,

*t*-butyl-$OC(O)CH_2$-,

*t*-butyl-$OC(O)CH_2CH_2$-,

$H_2NC(O)CH_2$-,

$H_2NC(O)CH_2CH_2$-,

BocNH-$(CH_2)_4$-,

*t*-butyl-OC(O)-$(CH_2)_2$-,

$HOOCCH_2$-,

$HOOC(CH_2)_2$-,

$H_2N(CH_2)_4$-,

isopropyl,

(1-naphthyl)-$CH_2$-,

(2-naphthyl)-$CH_2$-,

(2-thiophenyl)-$CH_2$-,

(φ-$CH_2$-OC(O)NH-$(CH_2)_4$-,

cyclohexyl-$CH_2$-,

benzyloxy-$CH_2$-,

$HOCH_2$-,

5-(3-N-benzyl)imidazolyl-$CH_2$-,

2-pyridyl-$CH_2$-,

3-pyridyl-$CH_2$-,

4-pyridyl-$CH_2$-,

5-(3-N-methyl)imidazolyl-$CH_2$-,

N-benzylpiperid-4-yl-$CH_2$-,

N-Boc-piperidin-4-yl-$CH_2$-,

N-(phenyl-carbonyl)piperidin-4-yl-$CH_2$-,

$H_3CSCH_2CH_2$-,

1-N-benzylimidazol-4-yl-$CH_2$-,

*iso*-propyl-C(O)NH-$(CH_2)_4$-,

*iso*-butyl-C(O)NH-$(CH_2)_4$-,

phenyl-C(O)NH-$(CH_2)_4$-,

benzyl-C(O)NH-$(CH_2)_4$-,

allyl-C(O)NH-$(CH_2)_4$-,

4-(3-N-methylimidazolyl)-$CH_2$-,

4-imidazolyl,

4-[$(CH_3)_2NCH_2CH_2CH_2$-O-]benzyl,

4-[$(benzyl)_2N$-]-benzyl,

4-aminobenzyl,

allyloxy-C(O)NH$(CH_2)_4$-,

allyloxy-C(O)NH$(CH_2)_3$-,

allyloxy-C(O)NH$(CH_2)_2$-,

$NH_2C(O)CH_2$-,

φ-CH=,

2-pyridyl-C(O)NH-$(CH_2)_4$-,

4-methylpyrid-3-yl-C(O)NH-$(CH_2)_4$-,

3-methylthien-2-yl-C(O)NH-$(CH_2)_4$-,

2-pyrrolyl-C(O)NH-$(CH_2)_4$-,

2-furanyl-C(O)NH-$(CH_2)_4$-,

4-methylphenyl-$SO_2$-N($CH_3$)$CH_2$C(O)NH$(CH_2)_4$-,

4-[cyclopentylacetylenyl]-benzyl,

4-[-NHC(O)-(N-Boc)-pyrrolidin-2-yl)]-benzyl-,

1-N-methylimidazol-4-yl-$CH_2$-,

1-N-methylimidazol-5-yl-$CH_2$-,

imidazol-5-yl-$CH_2$-,

6-methylpyrid-3-yl-C(O)NH-$(CH_2)_4$-,

4-[2′-carboxymethylphenyl]-benzyl,

4-[-NHC(O)NH$CH_2CH_2CH_2$-φ]-benzyl,

4-[-NHC(O)NH$CH_2CH_2$-φ]-benzyl,

-$CH_2$C(O)NH$(CH_2)_4$φ,

4-[φ$(CH_2)_4$O-]-benzyl,

4-[-C≡C-φ-4′φ]-benzyl,

4-[-C≡C-$CH_2$-O-S(O)$_2$-4′-$CH_3$-φ]-benzyl,

4-[-C≡C-$CH_2$NHC(O)$NH_2$]-benzyl,

4-[-C≡C-$CH_2$-O-4′-$COOCH_2CH_3$-φ]-benzyl,

4-[-C≡C-CH($NH_2$)-cyclohexyl]-benzyl,

-$(CH_2)_4$NHC(O)$CH_2$-3-indolyl,

-$(CH_2)_4$NHC(O)$CH_2CH_2$-3-indolyl,

-$(CH_2)_4$NHC(O)-3-(5-methoxyindolyl),

-$(CH_2)_4$NHC(O)-3-(1-methylindolyl),

-$(CH_2)_4$NHC(O)-4-(-$SO_2(CH_3)$-φ),

-$(CH_2)_4$NHC(O)-4-(C(O)$CH_3$)-phenyl,

-$(CH_2)_4$NHC(O)-4-fluorophenyl,

-$(CH_2)_4$NHC(O)$CH_2$O-4-fluorophenyl,

4-[-C≡C-(2-pyridyl)]benzyl,

4-[-C≡C-$CH_2$-O-phenyl]benzyl,

4-[-C≡C-$CH_2OCH_3$]benzyl,

4-[-C≡C-(3-hydroxyphenyl)]benzyl,

4-[-C≡C-$CH_2$-O-4′-(-C(O)$OC_2H_5$)phenyl]benzyl,

4-[-C≡C-$CH_2CH(C(O)OCH_3)_2$]benzyl,

4-[-C≡C-$CH_2$NH-(4,5-dihydro-4-oxo-5-phenyl-oxazol-2-yl),

3-aminobenzyl,

4-[-C≡C-$CH_2CH($ NHC(O)$CH_3$)C(O)OH]-benzyl,

-$CH_2$C(O)NHCH($CH_3$)φ,

-$CH_2$C(O)NHC$H_2$-(4-dimethylamino)-φ,

-$CH_2$C(O)NHC$H_2$-4-nitrophenyl,

-$CH_2CH_2$C(O)N($CH_3$)C$H_2$-φ,

-$CH_2CH_2$C(O)NHC$H_2CH_2$-(N-methyl)-2-pyrrolyl,

-$CH_2CH_2$C(O)NHC$H_2CH_2CH_2CH_3$,

-$CH_2CH_2$C(O)NHC$H_2CH_2$-3-indolyl,

-$CH_2$C(O)N($CH_3$)C$H_2$phenyl,

-$CH_2$C(O)NH$(CH_2)_2$-(N-methyl)-2-pyrrolyl,

-$CH_2$C(O)NHC$H_2CH_2CH_2CH_3$,

-$CH_2$C(O)NHC$H_2CH_2$-3-indolyl,

-$(CH_2)_2$C(O)NHCH($CH_3$)φ,

-$(CH_2)_2$C(O)NHC$H_2$-4-dimethylaminophenyl,

-$(CH_2)_2$C(O)NHC$H_2$-4-nitrophenyl,

-$CH_2$C(O)NH-4-[-NHC(O)$CH_3$-phenyl],

-$CH_2$C(O)NH-4-pyridyl,

-$CH_2$C(O)NH-4-[dimethylaminophenyl],

-$CH_2$C(O)NH-3-methoxyphenyl,

-$CH_2CH_2$C(O)NH-4-chlorophenyl,

-$CH_2CH_2$C(O)NH-2-pyridyl,

-$CH_2CH_2$C(O)NH-4-methoxyphenyl,

-$CH_2CH_2$C(O)NH-3-pyridyl,

4-[$(CH_3)_2$N$CH_2CH_2$O-]benzyl,

-$(CH_2)_3$NHC(NH)NH-$SO_2$-4-methylphenyl,

4-[$(CH_3)_2$N$CH_2CH_2$O-]benzyl,

-$(CH_2)_4$NHC(O)NH$CH_2CH_3$,

-$(CH_2)_4$NHC(O)NH-phenyl,

-$(CH_2)_4$NHC(O)NH-4-methoxyphenyl,

4-[4′-pyridyl-C(O)NH-]benzyl,

4-[3′-pyridyl-C(O)NH-]benzyl,

4-[-NHC(O)NH-3′-methylphenyl]benzyl,

4-[-NHC(O)$CH_2$NHC(O)NH-3′-methylphenyl]benzyl,

4-[-NHC(O)-(2′,3′-dihydroindol-2-yl)]benzyl,

4-[-NHC(O)-(2′,3′-dihydro-N-Boc-indol-2-yl)]benzyl,

p-[-$OCH_2CH_2$-1′-(4′-pyrimidinyl)-piperazinyl]benzyl,

4-[-$OCH_2CH_2$-(1′-piperidinyl)benzyl,

4-[-$OCH_2CH_2$-(1′-pyrrolidinyl)]benzyl,

4-[-$OCH_2CH_2CH_2$-(1′-piperidinyl)]benzyl-,

-$CH_2$-3-(1,2,4-triazolyl),

4-[-$OCH_2CH_2CH_2$-4-(3′-chlorophenyl)-piperazin-1-yl]benzyl,

4-[-$OCH_2CH_2N(\varphi)CH_2CH_3$]benzyl,

4-[-$OCH_2$-3′-(N-Boc)-piperidinyl]benzyl,

4-[di-*n*-pentylamino]benzyl,

4-[*n*-pentylamino]benzyl,

4-[di-*iso*-propylamino-$CH_2CH_2O$-]benzyl,

4-[-$OCH_2CH_2$-(N-morpholinyl)]benzyl,

4-[-O-(3′-(N-Boc)-piperidinyl]benzyl,

4-[-$OCH_2CH(NHBoc)CH_2$cyclohexyl]benzyl,

*p*-[$OCH_2CH_2$-(N-piperidinyl]benzyl,

4-[-$OCH_2CH_2CH_2$-(4-*m*-chlorophenyl)-piperazin-1-yl]benzyl,

4-[-$OCH_2CH_2$-(N-homopiperidinyl)benzyl,

4-[-NHC(O)-3′-(N-Boc)-piperidinyl]benzyl,

4-[-$OCH_2CH_2N(benzyl)_2$]benzyl,

-$CH_2$-2-thiazolyl,

3-hydroxybenzyl,

4-[-$OCH_2CH_2CH_2N(CH_3)_2$]benzyl,

4-[-NHC(S)$NHCH_2CH_2$-(N-morpholino)]benzyl,

4-[-$OCH_2CH_2N(C_2H_5)_2$]benzyl,

4-[-$OCH_2CH_2CH_2N(C_2H_5)_2$]benzyl,

4-[$CH_3(CH_2)_4NH$-]benzyl,

4-[N-*n*-butyl,N-*n*-pentylamino-]benzyl,

4-[-NHC(O)-4′-piperidinyl]benzyl,

4-[-NHC(O)CH(NHBoc)$(CH_2)_4$NHCbz]benzyl,

4-[-NHC(O)-(1′,2′,3′,4′-tetrahydro-N-Boc-isoquinolin-1′-yl]benzyl,

p-[-$OCH_2CH_2CH_2$-1′-(4′-methyl)-piperazinyl]benzyl,

-$(CH_2)_4$NH-Boc,

3-[-$OCH_2CH_2CH_2N(CH_3)_2$]benzyl,

4-[-$OCH_2CH_2CH_2N(CH_3)_2$]benzyl,

3-[-$OCH_2CH_2$-(1′-pyrrolidinyl)]benzyl,

4-[-$OCH_2CH_2CH_2N(CH_3)$benzyl]benzyl,

4-[-NHC(S)NH$CH_2CH_2CH_2$-(N-morpholino)]benzyl,

4-[-$OCH_2CH_2$-(N-morpholino)]benzyl,

4-[-$NHCH_2$-(4′-chlorophenyl)]benzyl,

4-[-NHC(O)NH-(4′-cyanophenyl)]benzyl,

4-[-$OCH_2COOH$]benzyl,

4-[-$OCH_2COO$-*t*-butyl]benzyl,

4-[-NHC(O)-5′-fluoroindol-2-yl]benzyl,

4-[-NHC(S)NH$(CH_2)_2$-1-piperidinyl]benzyl,

4-[-N$(SO_2CH_3)(CH_2)_3$-N$(CH_3)_2$]benzyl,

4-[-NHC(O)$CH_2$CH(C(O)$OCH_2\varphi$)-NHCbz]benzyl,

4-[-NHS$(O)_2CF_3$]benzyl,

3-[-O-(N-methylpiperidin-4′-yl]benzyl,

4-[-C(=NH)$NH_2$]benzyl,

4-[-$NHSO_2$-$CH_2Cl$]benzyl,

4-[-NHC(O)-(1′,2′,3′,4′-tetrahydroisoquinolin-2′-yl]benzyl,

4-[-NHC(S)NH$(CH_2)_3$-N-morpholino]benzyl,

4-[-NHC(O)CH($CH_2CH_2CH_2CH_2NH_2$)NHBoc]benzyl,

4-[-C(O)$NH_2$]benzyl,

4-[-NHC(O)NH-3′-methoxyphenyl]benzyl,

4-[-$OCH_2CH_2$-indol-3′-yl]benzyl,

4-[-$OCH_2$C(O)NH-benzyl]benzyl,

4-[-$OCH_2$C(O)O-benzyl]benzyl,

4-[-$OCH_2C(O)OH$]benzyl,

4-[-$OCH_2$-2′-(4′,5′-dihydro)imidazolyl]benzyl,

-$CH_2C(O)NHCH_2$-(4-dimethylamino)phenyl,

-$CH_2C(O)NHCH_2$-(4-dimethylamino)phenyl,

4-[-NHC(O)-L-2′-pyrrolidinyl-N-$SO_2$-4′-methylphenyl]benzyl,

4-[-$NHC(O)NHCH_2CH_2CH_3$]benzyl,

4-aminobenzyl]benzyl,

4-[-$OCH_2CH_2$-1-(4-hydroxy-4-(3-methoxypyrrol-2-yl)-piperazinyl]benzyl,

4-[-O-(N-methylpiperidin-4′-yl)]benzyl,

3-methoxybenzyl,

4-[-NHC(O)-piperidin-3′-yl]benzyl,

4-[-NHC(O)-pyridin-2′-yl]benzyl,

4-[-$NHCH_2$-(4′-chlorophenyl)]benzyl,

4-[-NHC(O)-(N-(4′-CH3-φ-$SO_2$)-L-pyrrolidin-2′-yl)]benzyl,

4-[-$NHC(O)NHCH_2CH_2$-φ]benzyl,

4-[-$OCH_2C(O)NH_2$]benzyl,

4-[-$OCH_2C(O)NH$-*t*-butyl]benzyl,

4-[-$OCH_2CH_2$-1-(4-hydroxy-4-phenyl)-piperidinyl]benzyl,

4-[-$NHSO_2$-$CH=CH_2$]benzyl,

4-[-$NHSO_2$-$CH_2CH_2Cl$]benzyl,

-$CH_2C(O)NHCH_2CH_2N(CH_3)_2$,

4-[(1′-Cbz-piperidin-4′-yl)C(O)NH-]benzyl,

4-[(1′-Boc-piperidin-4′-yl)C(O)NH-]benzyl,

4-[(2′-bromophenyl)C(O)NH-]benzyl,

4-[-NHC(O)-pyridin-4′-yl]benzyl,

4-[(4′-$(CH_3)_2NC(O)O$-)phenyl)-C(O)NH-]benzyl,

4-[-NHC(O)-1′-methylpiperidin-4′-yl-]benzyl,

4-(dimethylamino)benzyl,

4-[-NHC(O)-(1′-N-Boc)-piperidin-2′-yl]benzyl,

3-[-NHC(O)-pyridin-4′-yl]benzyl,

4-[(*tert*-butyl-O(O)$CCH_2$-O-benzyl)-NH-]benzyl,

[Boc$NHCH_2C(O)NH$-]butyl,

4-benzylbenzyl,

2-hydroxyethyl,

4-[$(Et)_2NCH_2CH_2CH_2NHC(S)NH$-]benzyl,

4-[(1′-Boc-4′-hydroxypyrrolidin-2′-yl)C(O)NH-]benzyl,

4-[$\varphi CH_2CH_2CH_2NHC(S)NH$-]benzyl,

4-[(perhydroindolin-2′-yl)C(O)NH-]benzyl,

2-[4-hydroxy-4-(3-methoxythien-2-yl)piperidin-1-yl]ethyl,

4-[(1′-Boc-perhydroindolin-2′-yl)-C(O)NH-]benzyl,

4-[*N*-3-methylbutyl-*N*-trifluoromethanesulfonyl)amino]benzyl,

4-[*N*-vinylsulfonyl)amino]benzyl,

4-[2-(2-azabicyclo[3.2.2]octan-2-yl)ethyl-O-]benzyl,

4-[4′-hydroxypyrrolidin-2′-yl)C(O)NH-]benzyl,

4-($\varphi$NHC(S)NH)benzyl,

4-(EtNHC(S)NH)benzyl,

4-($\varphi CH_2$NHC(S)NH)benzyl,

3-[(1′-Boc-piperidin-2′-yl)C(O)NH-]benzyl,

3-[piperidin-2′-yl-C(O)NH-]benzyl,

4-[(3′-Boc-thiazolidin-4′-yl)C(O)NH-]benzyl,

4-(pyridin-3′-yl-NHC(S)NH)benzyl,

4-($CH_3$-NHC(S)NH)benzyl,

4-($H_2NCH_2CH_2CH_2C(O)NH$)benzyl,

4-($BocHNCH_2CH_2CH_2C(O)NH$)benzyl,

4-(pyridin-4′-yl-$CH_2NH$)benzyl,

4-[(*N*,*N*-di(4-*N*,*N*-dimethylamino)benzyl)amino]benzyl,

4-[(1-Cbz-piperidin-4-yl)C(O)NH-]butyl,

4-[$\varphi CH_2OCH_2(BocHN)CHC(O)NH$]benzyl,

4-[(piperidin-4′-yl)C(O)NH-]benzyl,

4-[(pyrrolidin-2′-yl)C(O)NH-]benzyl,

4-(pyridin-3′-yl-C(O)NH)butyl,

4-(pyridin-4′-yl-C(O)NH)butyl,

4-(pyridin-3′-yl-C(O)NH)benzyl,

4-[$CH_3NHCH_2CH_2CH_2C(O)NH$-]benzyl,

4-[$CH_3N(Boc)CH_2CH_2CH_2C(O)NH$-]benzyl,

4-(aminomethyl)benzyl,

4-[$\varphi CH_2OCH_2(H_2N)CHC(O)NH$]benzyl,

4-[(1′,4′-di(Boc)piperazin-2′-yl)-C(O)NH-]benzyl,

4-[(piperazin-2′-yl)-C(O)NH-]benzyl,

4-[(*N*-toluenesulfonylpyrrolidin-2′-yl)C(O)NH-]butyl,

4-[-NHC(O)-4′-piperidinyl]butyl,

4-[-NHC(O)-1′-N-Boc-piperidin-2′-yl]benzyl,

4-[-NHC(O)-piperidin-2′-yl]benzyl,

4-[(1′-N-Boc-2′,3′-dihydroindolin-2′-yl)-C(O)NH]benzyl,

4-(pyridin-3′-yl-$CH_2NH$)benzyl,

4-[(piperidin-1′-yl)$C(O)CH_2$-O-]benzyl,

4-[$(CH_3)_2CH)_2NC(O)CH_2$-O-]benzyl,

4-[$HO(O)C(Cbz\text{-}NH)CHCH_2CH_2$-C(O)NH-]benzyl,

4-[$\varphi CH_2O(O)C(Cbz\text{-}NH)CHCH_2CH_2$-C(O)NH-]benzyl,

4-[-NHC(O)-2′-methoxyphenyl]benzyl,

4-[(pyrazin-2′-yl)C(O)NH-]benzyl,

4-[$HO(O)C(NH_2)CHCH_2CH_2$-C(O)NH-]benzyl,

4-(2′-formyl-1′,2′,3′,4′-tetrahydroisoquinolin-3′-yl-$CH_2NH$-)benzyl,

*N*-Cbz-$NHCH_2$-,

4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

4-[$CH_3$(*N*-Boc)$NCH_2C(O)NH$-]benzyl,

4-[-NHC(O)-(1′,2′,3′,4′-tetrahydro-N-Boc-isoquinolin-3′-yl]-benzyl,

4-[$CH_3NHCH_2C(O)NH$-]benzyl,

$(CH_3)_2NC(O)CH_2$-,

4-(*N*-methylacetamido)benzyl,

4-(1′,2′,3′,4′-tetrahydroisoquinolin-3′-yl-$CH_2NH$-)benzyl,

4-[$(CH_3)_2NHCH_2C(O)NH$-]benzyl,

(1-toluenesulfonylimidizol-4-yl)methyl,

4-[(1′-Boc-piperidin-4′-yl)C(O)NH-]benzyl,

4-trifluoromethylbenzyl,

4-[(2′-bromophenyl)C(O)NH-]benzyl,

4-[$(CH_3)_2NC(O)NH$-]benzyl,

4-[$CH_3OC(O)NH$-]benzyl,

4-[$(CH_3)_2NC(O)O$-]benzyl,

4-[$(CH_3)_2NC(O)N(CH_3)$-]benzyl,

4-[$CH_3OC(O)N(CH_3)$-]benzyl,

4-(*N*-methyltrifluoroacetamido)benzyl,

4-[(1′-methoxycarbonylpiperidin-4′-yl)C(O)NH-]benzyl,

4-[(4′-phenylpiperidin-4′-yl)C(O)NH-]benzyl,

4-[(4′-phenyl-1′-Boc-piperidin-4′-yl)-C(O)NH-]benzyl,

4-[(piperidin-4′-yl)C(O)O-]benzyl,

4-[(1′-methylpiperidin-4′-yl)-O-]benzyl,

4-[(1′-methylpiperidin-4′-yl)C(O)O-]benzyl,

4-[(4′-methylpiperazin-1′-yl)C(O)NH-]benzyl,

3-[$(CH_3)_2NC(O)O$-]benzyl,

4-[(4′-phenyl-1′-Boc-piperidin-4′-yl)-C(O)O-]benzyl,

4-(*N*-toluenesulfonylamino)benzyl,

4-[$(CH_3)_3CC(O)NH$-]benzyl,

4-[(morpholin-4′-yl)C(O)NH-]benzyl,

4-[$(CH_3CH_2)_2NC(O)NH$-]benzyl,

4-[-C(O)NH-(4′-piperidinyl)]benzyl,

4-[(2′-trifluoromethylphenyl)C(O)NH-]benzyl,

4-[(2′-methylphenyl)C(O)NH-]benzyl,

4-[$(CH_3)_2NS(O)_2O$-]benzyl,

4-[(pyrrolidin-2′-yl)C(O)NH-]benzyl,

4-[-NHC(O)-piperidin-1′-yl]benzyl,

4-[(thiomorpholin-4′-yl)C(O)NH-]benzyl,

4-[(thiomorpholin-4′-yl sulfone)-C(O)NH-]benzyl,

4-[(morpholin-4′-yl)C(O)O-]benzyl,

3-nitro-4-($CH_3OC(O)CH_2O$-)benzyl,

(2-benzoxazolinon-6-yl)methyl-,

(2*H*-1,4-benzoxazin-3(4*H*)-one-7-yl)methyl-,

4-[$(CH_3)_2NS(O)_2NH$-]benzyl,

4-[$(CH_3)_2NS(O)_2N(CH_3)$-]benzyl,

4-[(thiomorpholin-4′-yl)C(O)O-]benzyl,

4-[(thiomorpholin-4′-yl sulfone)-C(O)O-]benzyl,

4-[(piperidin-1′-yl)C(O)O-]benzyl,

4-[(pyrrolidin-1′-yl)C(O)O-]benzyl,

4-[(4′-methylpiperazin-1′-yl)C(O)O-]benzyl,

4-[(2′-methylpyrrolidin-1′-yl)-,

(pyridin-4-yl)methyl-,

4-[(piperazin-4′-yl)-C(O)O-]benzyl,

4-[(1′-Boc-piperazin-4′-yl)-C(O)O-]benzyl,

4-[(4′-acetylpiperazin-1′-yl)C(O)O-]benzyl,

*p*-[(4′-methanesulfonylpiperazin-1′-yl)-benzyl,

3-nitro-4-[(morpholin-4′-yl)-C(O)O-]benzyl,

4-{$[(CH_3)_2NC(S)]_2N$-}benzyl,

*N*-Boc-2-aminoethyl-,

4-[(1,1-dioxothiomorpholin-4-yl)-C(O)O-]benzyl,

4-[$(CH_3)_2NS(O)_2$-]benzyl,

4-(imidazolid-2′-one-1′-yl)benzyl,

4-[(piperidin-1′-yl)C(O)O-]benzyl,

1-N-benzyl-imidazol-4-yl-$CH_2$-,

3,4-dioxyethylenebenzyl (*i.e.*, 3,4-ethylenedioxybenzyl),

3,4-dioxymethylenebenzyl (*i.e.*, 3,4-methylenedioxybenzyl),

4-[$-N(SO_2)(CH_3)CH_2CH_2CH_2N(CH_3)_2$]benzyl,

4-(3′-formylimidazolid-2′-one-1′-yl)benzyl,

4-[$NHC(O)CH(CH_2CH_2CH_2CH_2NH_2)NHBoc$]benzyl,

[2′-[4″-hydroxy-4″-(3‴-methoxythien-2‴-yl)piperidin-2″-yl]ethoxy]benzyl, and

*p*-[$(CH_3)_2NCH_2CH_2N(CH_3)C(O)O$-]benzyl.

Preferably, $R^5$ in the above compounds is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl. Even more preferably $R^5$ is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, *n*-hexyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-

methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

Preferably, $R^{13}$ in the above compounds is selected from hydrogen or $C_{1-6}$ alkyl; more preferably, hydrogen or $C_{1-3}$ alkyl; and still more preferably, hydrogen or methyl.

In a preferred embodiment, $R^{14}$ in the above compounds is preferably hydrogen and $R^{15}$ is preferably $C_{1-10}$ alkyl or Cy-$C_{1-10}$ alkyl, wherein alkyl is optionally substituted with one to four substituents selected from phenyl and $R^x$, and Cy is optionally substituted with one to four substituents independently selected from $R^y$, or $R^{14}$ and $R^{15}$ and the carbon to which they are attached together from a 3-7 membered mono- or bicyclic carbon only ring. For the purpose of $R^{15}$, Cy is preferably aryl, more preferably phenyl. In a preferred embodiment, $R^{15}$ is phenyl-$C_{1-3}$ alkyl, wherein phenyl is optionally substituted with one or two groups selected from $R^y$. Additional preferred embodiments for $R^{14}$ and $R^{15}$ are disclosed in International Patent Application Publication No. WO 98/53814, which application is incorporated herein by reference in its entirety.

In a preferred embodiment of the above compounds, $R^{16}$ is substituted amino; $R^{17}$ and/or $R^{20}$ are hydrogen; and $R^{18}$ and/or $R^{21}$ are alkyl, substituted alkyl, aryl or substituted aryl.

In a preferred embodiment, $R^{23}$ in the above compounds is hydrogen. Preferably, $R^{24}$ in the above compounds is $Ar^1$-$Ar^2$-$C_{1-10}$ alkyl wherein $Ar^1$ and $Ar^2$ are optionally substituted with from 1 to 4 groups independently selected from $R^b$ and $R^{25}$ is hydrogen. More

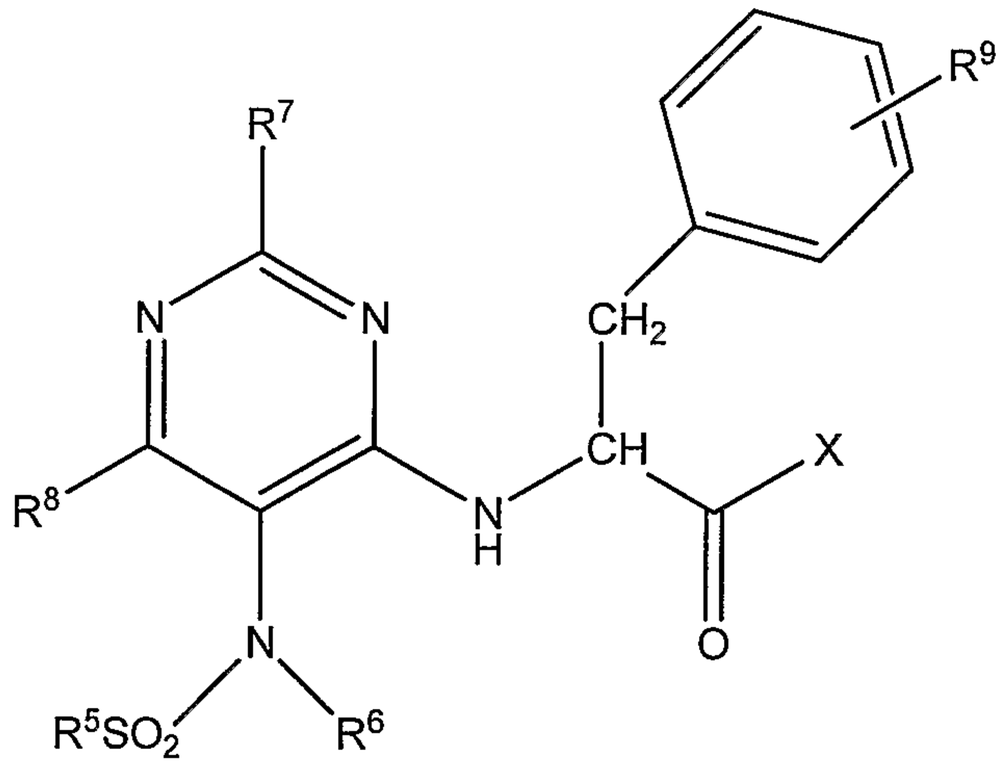
preferably, $R^{24}$ is $Ar^1$-$Ar^2$-$C_{1-3}$ alkyl wherein $Ar^1$ and $Ar^2$ are optionally substituted with from 1 to 4 groups independently selected from $R^b$; still more preferably, $R^{24}$ is -$CH_2$-$Ar^2$-$Ar^1$ and $R^{25}$ is hydrogen. Additional preferred embodiments are disclosed in International Patent Application Publication No. WO 98/53817, which application is incorporated herein by reference in its entirety.

Preferably, $R^3$ and $R^{3'}$, or $R^{14}$ and $R^{15}$, or $R^{24}$ and $R^{25}$ are derived from L-amino acids or other similarly configured starting materials. Alternatively, racemic mixtures can be used.

Preferably, *x* in the above compounds is an integer from 1 to 4.

Preferred compounds include those set forth in Tables 3-6 below:

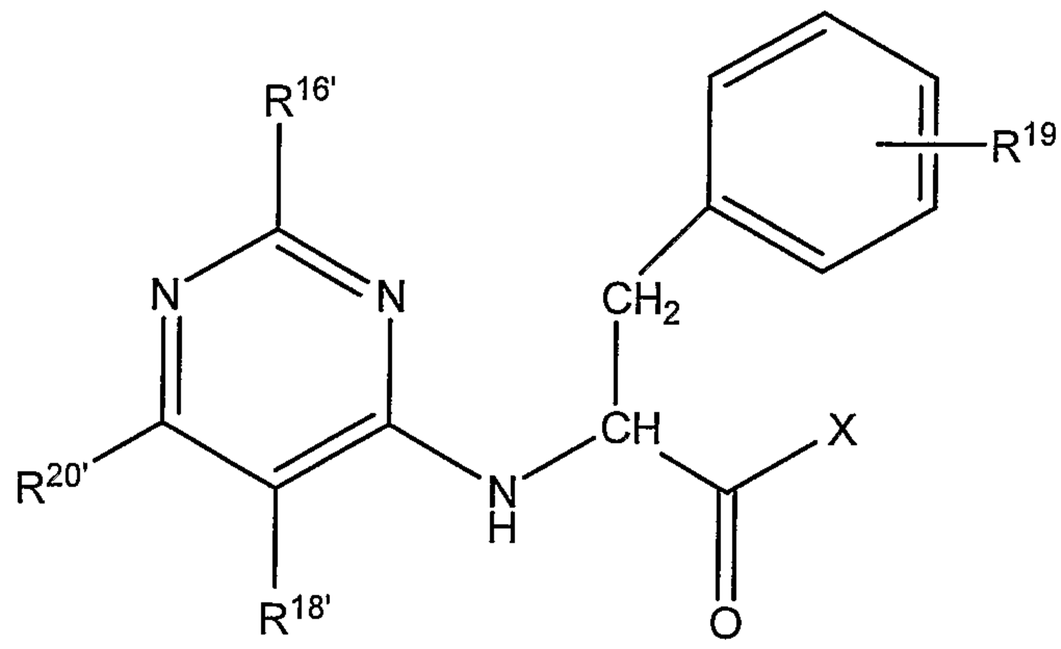
Table 3




| $R^5$ | $R^6$ | $R^7$ | $R^8$ | $R^9$ | X |
|---|---|---|---|---|---|
| 4-$CH_3$-Ph- | H- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OC(CH_3)_3$ |
| 4-$CH_3$-Ph- | H- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 4-$CH_3$-Ph- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OC(CH_3)_3$ |
| 4-$CH_3$-Ph- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 4-$CH_3$-Ph- | 4-$CH_3$-Ph- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 1-$CH_3$-pyrazol-4-yl- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 4-$CH_3$-Ph- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OCH(CH_3)_2$ |
| 3-pyridyl- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OC(CH_3)_3$ |
| 1-($n$-$C_4H_9$)-pyrazol-4-yl- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OC(CH_3)_3$ |
| 4-$CH_3$-Ph- | $CH_3$- | H- | H- | H- | -OH |
| 1-($n$-$C_4H_9$)-pyrazol-4-yl- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 3-pyridyl- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 4-$CH_3$-Ph- | $CH_3$- | $(CH_3)_2N$- | H- | H- | -OH |
| 1-$CH_3$-pyrazol-4-yl- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OCH(CH_3)_2$ |
| 3-pyridyl- | $CH_3$- | H- | H- | 4-(1-$CH_3$-piperazin-4-yl)C(O)O- | -$OCH(CH_3)_2$ |
| 3-pyridyl- | $CH_3$- | H- | H- | 4-(1-$CH_3$-piperazin-4-yl)C(O)O- | -$OC(CH_3)_3$ |
| 3-pyridyl- | $CH_3$- | H- | H- | 4-(1-$CH_3$-piperazin-4-yl)-C(O)O- | -OH |

Ph = phenyl

Table 4




| $R^{16'}$ | $R^{20'}$ | $R^{18'}$ | $R^{19}$ | X |
|---|---|---|---|---|
| Cl- | H- | $NO_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $PhCH_2O$- | H- | -OH |
| H- | H- | $PhCH_2O$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 3-$NO_2$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 3-pyridyl- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$PhCH_2CH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $(CH_3)_2NC(O)$-$(CH_2)_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | Ph- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | 2-$CF_3$-Ph- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | 2-HO$CH_2$Ph- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $CF_3CH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $PhCH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -$OCH(CH_3)_2$ |
| H- | H- | 2-$PhCH_2CH_2$- | 4-$(CH_3)_2NC(O)O$- | -$OCH(CH_3)_2$ |
| H- | H- | 2-$PhCH_2CH_2$- | H- | -$OCH(CH_3)_2$ |
| cyclohexyl-$(CH_3)N$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $CH_3CH_2CH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$CH_3O$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-F-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3)_2CH$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |

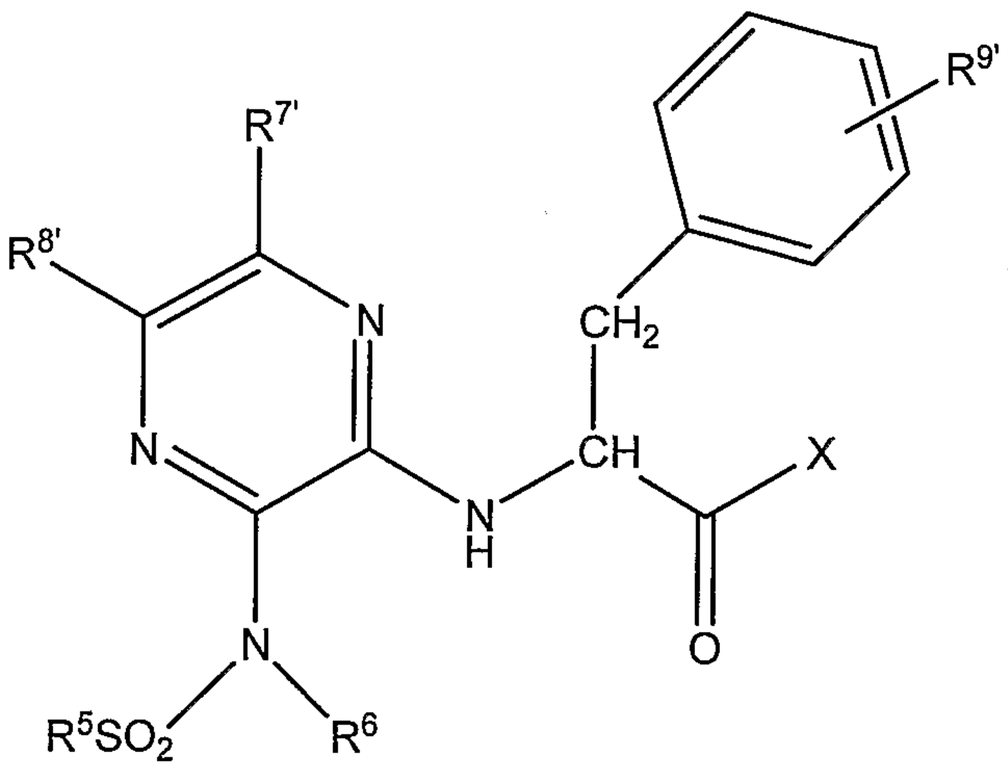
| $R^{16'}$ | $R^{20'}$ | $R^{18'}$ | $R^{19}$ | X |
|---|---|---|---|---|
| $(CH_3)_2CH$-NH- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3)_2CHCH_2$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3CH_2CH_2$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3)_2N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 3-pyridyl- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$PhCF_2CH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | Cl- | 2-$PhCF_2CH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(HOCH_2CH_2)_2N$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(HOCH_2CH_2)_2N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $Ph(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3)_2CHO$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3)_2CHCH_2$-$CH_2(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3NH$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 2-$CH_3$-Ph- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $HOCH_2CH_2$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| cyclohexyl-NH- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 1-$CH_3$-piperidin-4-yl-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3)_2CH$-$(CH_3CH_2$-$)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2,4,6-tri-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $(CH_3)_2CH$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3(CH_2)_3$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3CH_2CH_2$-$(CH_3CH_2$-$)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $(CH_3CH_2)_2N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3CH_2$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | cyclohexyl- | 4-$(CH_3)_2NC(O)O$- | -OH |
| (furan-2-yl)$CH_2$-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 4-Cl-Ph-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | thien-3-yl- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | thien-2-yl- | 4-$(CH_3)_2NC(O)O$- | -OH |
| $HOCH_2CH_2$-$(CH_3)N$- | H- | 2-F-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | piperidin-1-yl- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $(CH_3CH_2CH_2)_2$-CH- | 4-$(CH_3)_2NC(O)O$- | -OH |

| $R^{16'}$ | $R^{20'}$ | $R^{18'}$ | $R^{19}$ | X |
|---|---|---|---|---|
| cyclobutyl-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$HOCH_2$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2,6-di-F-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2,4-di-$CH_3O$-pyrimidin-5-yl | 4-$(CH_3)_2NC(O)O$- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 2-$CF_3$-Ph- | 4-$(CH_3)_2NC(O)O$- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2-$CH_3O$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| $(CH_3)_2CH$-$(CH_3)N$- | H- | 2-F-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| $(CH_3)_2CH$-$(CH_3)N$- | H- | 2-F-Ph- | 2-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2,6-di-F-Ph- | 2,6-di-F-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2-$HOCH_2$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| $(HOCH_2CH_2)_2N$- | H- | 2,4,6-tri-$CH_3$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2-$CF_3$-Ph- | 2-NC-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | thien-3-yl- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | thien-2-yl- | 4-$CF_3$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 3-pyridyl- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2-$NO_2$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2,6-di-Cl-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 4-pyridyl- | 3-$HOCH_2$-Ph- | -OH |
| $(CH_3)_2CH$-$(CH_3CH_2$-$)N$- | H- | 2,6-di-$CH_3O$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-$(CH_3)N$- | H- | 2,6-di-Cl-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| $CH_3CH_2$-$(CH_3)N$- | H- | 2,4,6-tri-$CH_3$-Ph- | 2-NC-Ph- | -OH |
| $(CH_3)_2CH$-$(CH_3)N$- | H- | 2,4,6-tri-$CH_3$-Ph- | 3-pyridyl- | -OH |
| $(HOCH_2CH_2)_2N$- | H- | 2,4,6-tri-$CH_3$-Ph- | 2-NC-Ph- | -OH |
| 1-$CH_3$-piperidin-4-yl-$(CH_3)N$- | H- | 2-NC-Ph- | 2,6-di-F-Ph- | -OH |

| $R^{16'}$ | $R^{20'}$ | $R^{18'}$ | $R^{19}$ | X |
|---|---|---|---|---|
| $(CH_3)_2CH$-<br>$(CH_3CH_2$-$)N$- | H- | 2,4,6-tri-$CH_3$-Ph- | 2-$CH_3$-Ph- | -OH |
| 4-Cl-Ph-$(CH_3)N$- | H- | 2,4,6-tri-$CH_3$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | $PhCH_2CH_2$-$(CH_3)N$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $CH_3(CH_2)_5$-$(CH_3)N$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $(CH_3)_2CH$-$(CH_3)N$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $(CH_3)_3C$-$(CH_3)N$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $(CH_3)_2CH$-<br>$(CH_3CH_2$-$)N$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | 4-pyridyl-$CH_2CH_2$-<br>$(CH_3)N$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $PhCH_2CH_2$-$(CH_3)N$- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | $CH_3(CH_2)_5$-$(CH_3)N$- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | $(CH_3)_2CH$-$(CH_3)N$- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | $(CH_3)_3C$-$(CH_3)N$- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | $(CH_3)_2CH$-<br>$(CH_3CH_2$-$)N$- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | 4-pyridyl-$CH_2CH_2$-<br>$(CH_3)N$- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-<br>$(CH_3)N$- | H- | $CH_3CH_2$- | 4-$(CH_3)_2NC(O)O$- | -OH |
| H- | H- | $CF_3CH_2$- | 2,6-di-$CH_3O$-Ph- | -OH |
| cyclohexyl-<br>$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| H- | H- | 2-F-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |
| $CH_3CH_2CH_2$-<br>$(CH_3)N$- | H- | 2-$CH_3$-Ph- | 2,6-di-$CH_3O$-Ph- | -OH |

Ph = phenyl

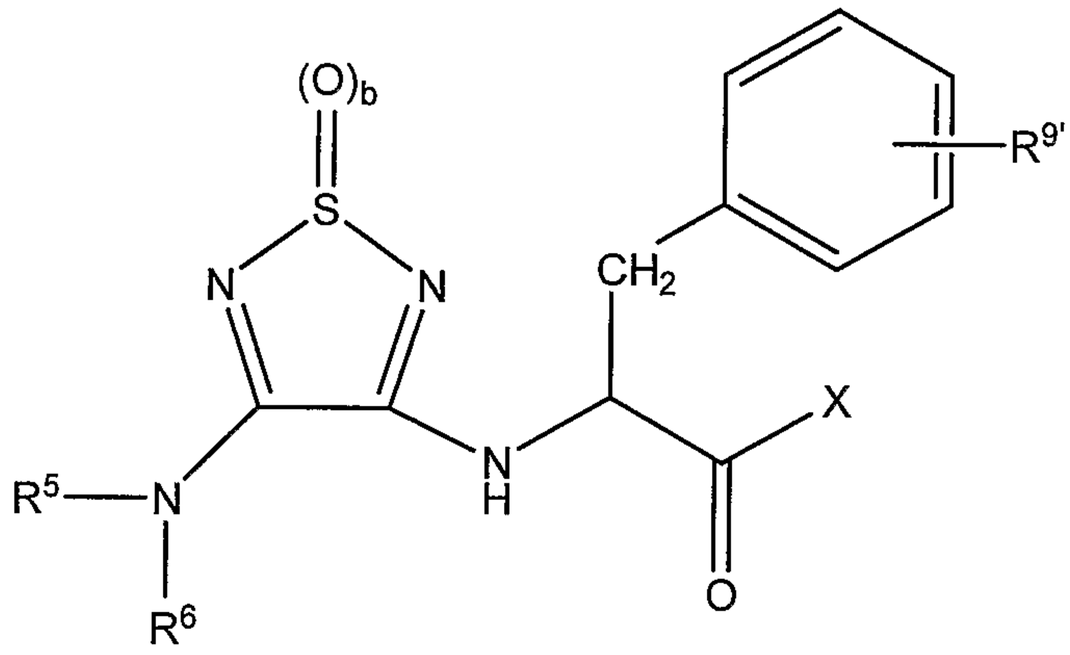
Table 5



| $R^5$ | $R^6$ | $R^{7'}$ | $R^{8'}$ | $R^{9'}$ | X |
|---|---|---|---|---|---|
| 4-$CH_3$-Ph- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -OH |
| 4-$CH_3$-Ph- | $CH_3$- | H- | H- | 4-$(CH_3)_2NC(O)O$- | -$OCH(CH_3)_2$ |

Ph = phenyl

Table 6




| $R^5$ | $R^6$ | *b* | $R^{9'}$ | X |
|---|---|---|---|---|
| $CH_3(CH_2)_5$- | $CH_3(CH_2)_5$- | 2 | 4-HO- | -OH |
| $CH_3(CH_2)_5$- | $CH_3(CH_2)_5$- | 2 | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3$- | $CH_3$- | 1 | 4-$(CH_3)_2NC(O)O$- | -$OC(CH_3)_3$ |
| 3-$CH_3$-PhNH-C(O)NH$(CH_2)_2$- | H- | 2 | 4-$(CH_3)_2NC(O)O$- | -OH |
| $CH_3(CH_2)_5$- | $CH_3(CH_2)_5$- | 2 | 4-(1-$CH_3$-piperazin-4-yl)C(O)O- | -OH |

Ph = phenyl

Accordingly, the following are preferred compounds of Formulae III-IX:

*N*-(2-chloro-5-nitropyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

*N*-[5-(*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

*N*-[5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*,*N*-di-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-[*N*-(1-*N'*-methylpyrazol-4-ylsulfonyl)-*N*-methylamino]pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-[5-(*N*-methyl-*N*-3-pyridylsulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

*N*-(5-(*N*-methyl-*N*-(1-butylpyrazol-4-yl)sulfonylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,4-dimethoxypyrimidin-5-yl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,6-difluorophenyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-hydroxymethylphenyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-cyclohexylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)amino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-ethyl-*N*-isopropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,4-6-trimethylphenyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-isopropylpyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-butylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-ethyl-*N*-propylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*,*N*-diethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-ethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-benzyloxypyrimidin-4-yl)-L-phenylalanine,

*N*-(5-benzyloxypyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl)-L-phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-phenylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(3-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrazin-2-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester,

*N*-(5-benzylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine tert-butyl ester,

*N*-(5-(2-trifluoromethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-*N,N*-dimethylcarbamylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-(1-methylpyrazole)sulfonylamino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-(6-phenylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(6-(2-trifluoromethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(6-(2-hydroxymethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-cyclohexylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-furanmethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-4-chlorophenylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(3-thienyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-thienyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-hydroxyethylamino)-5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(piperidin-1-yl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(1-propylbutyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclobutylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-bis-(2-hydroxyethyl)amino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-bis-(2-hydroxyethyl)amino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-phenylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(isopropoxy)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(N-methyl-N-3-methylbutylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(2-tolyl)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-hydroxyethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-methylpropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-propylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-dimethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-pyridyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenyl-2,2-difluoroethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenyl-2,2-difluoroethyl)-6-chloropyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-propylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-methoxyphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-Methyl-*N*-isopropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-isopropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-(3-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrazin-2-yl)-L-phenylalanine isopropyl ester,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-phenylalanine isopropyl ester,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-ethylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-(5-(3-nitrophenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(3-pyridyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-*N,N*-dimethylamino-5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl)-L-phenylalanine,

N-(5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-methoxyphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-isopropylamino)-5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-isopropylamino)-5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(2-methoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2,6-difluorophenyl)pyrimidin-4-yl)-L-4-(2,6-difluorophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-hydroxymethylphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N,N*-bis-(2-hydroxyethyl)amino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-trifluoromethylphenyl)pyrimidin-4-yl)-L-4-(2-cyanophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-thienyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-thienyl)pyrimidin-4-yl)-L-4-(4-trifluoromethylphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-pyridyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-nitrophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2,6-dichlorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(4-pyridyl)pyrimidin-4-yl)-L-4-(3-hydroxymethylphenyl)phenylalanine,

*N*-(2-(*N*-ethyl-N-isopropylamino)-5-(2,6-dimethoxyphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2,3-dichlorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-ethylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2-cyanophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-isopropylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(3-pyridyl)phenylalanine,

*N*-(2-(*N*,*N*-bis-(2-hydroxyethyl)amino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2-cyanophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)amino)-5-(2-cyanophenyl)pyrimidin-4-yl)-L-4-(2,6-difluorophenyl)phenylalanine,

*N*-(2-(*N*-ethyl-N-isopropylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(o-tolyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-4-chlorophenylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(*N*-methyl-N-2-(phenyl)ethylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-hexylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-*tert*-butylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-ethyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-2-(4-pyridyl)ethyl-pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-2-(phenyl)ethylamino)pyrimidin-4-yl)-L-4-(4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-hexylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-*tert*-butylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-ethyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-2-(4-pyridyl)ethyl-pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-ethylpyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

N-(4-(N,N-di-*n*-hexylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl)-L-tyrosine,

N-(4-(N,N-di-*n*-hexylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

N-(4-(N,N-dimethylamino)-1-oxo-1,2,5-thiadiazol-3-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

N-[4-(2-(3-methylphenylaminocarbonylamino)eth-1-ylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

N-(4-(N,N-di-*n*-hexylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

*N*-(5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(N-cyclohexyl-N-methyl)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

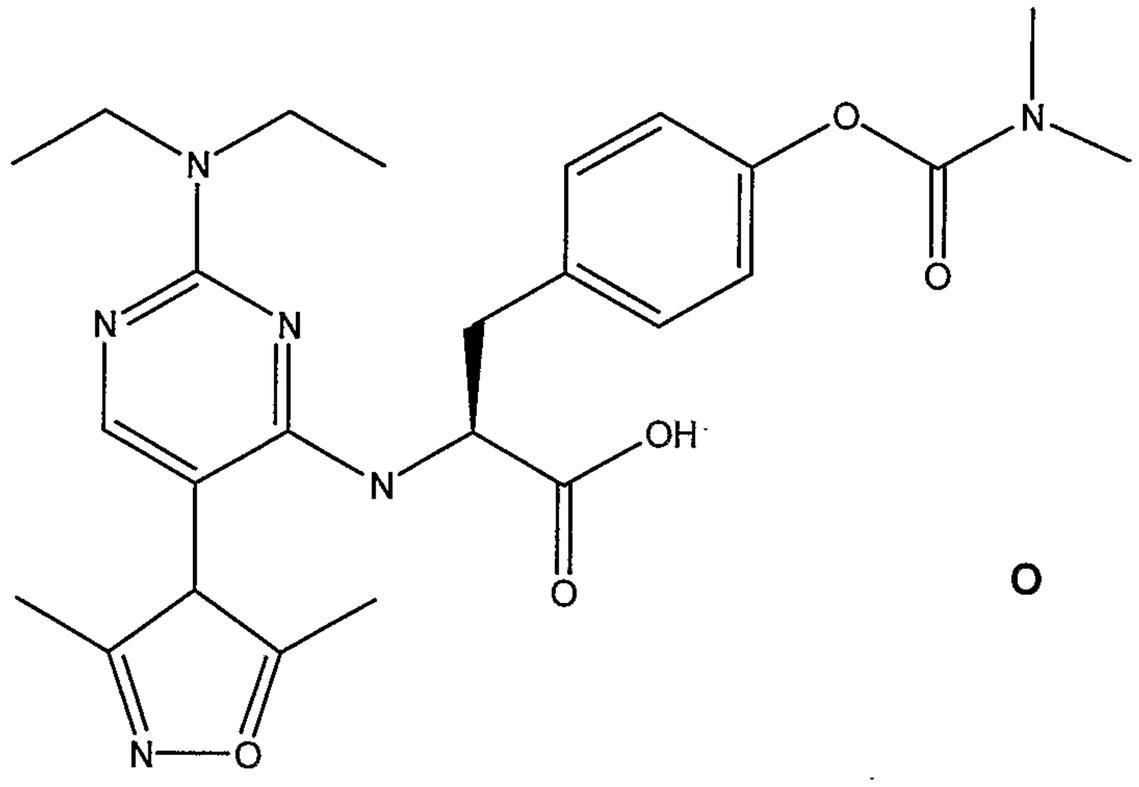
*N*-(5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(N-methyl-N-propyl)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(3-chloropyrazin-2-yl)-L-4-[1-(*tert*-butoxycarbonyl)piperidin-4-ylcarbonylamino]phenylalanine ethyl ester,

and pharmaceutically acceptable salts thereof.

Preferably, the compound is the compound of Formula O below:



O

Further description of the compounds of the above Formulae III-IX procedures and reaction conditions for preparing these compounds are described in U.S.S.N. 09/489,377 (filed January 21, 2000, and issued as U.S. Patent No. 6,492,372), herein incorporated by reference in its entirety.

Further description of these type of compounds is described in U.S. Patent Publication 20030139402, a divisional application of U.S.S.N. 09/489,377, herein incorporated by reference in its entirety.

Compound Preparation for Compounds of Formulae III-IX

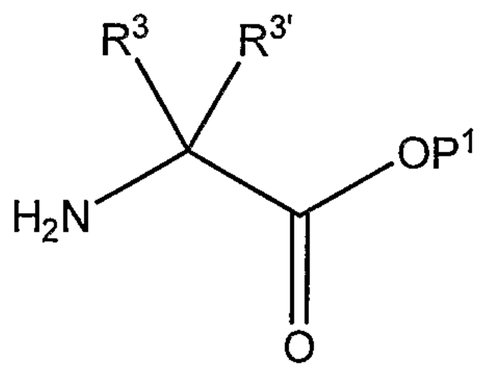
The compounds of Formulae III-IX can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants

or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Furthermore, the compounds of Formulae III-IX will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, *i.e.*, as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

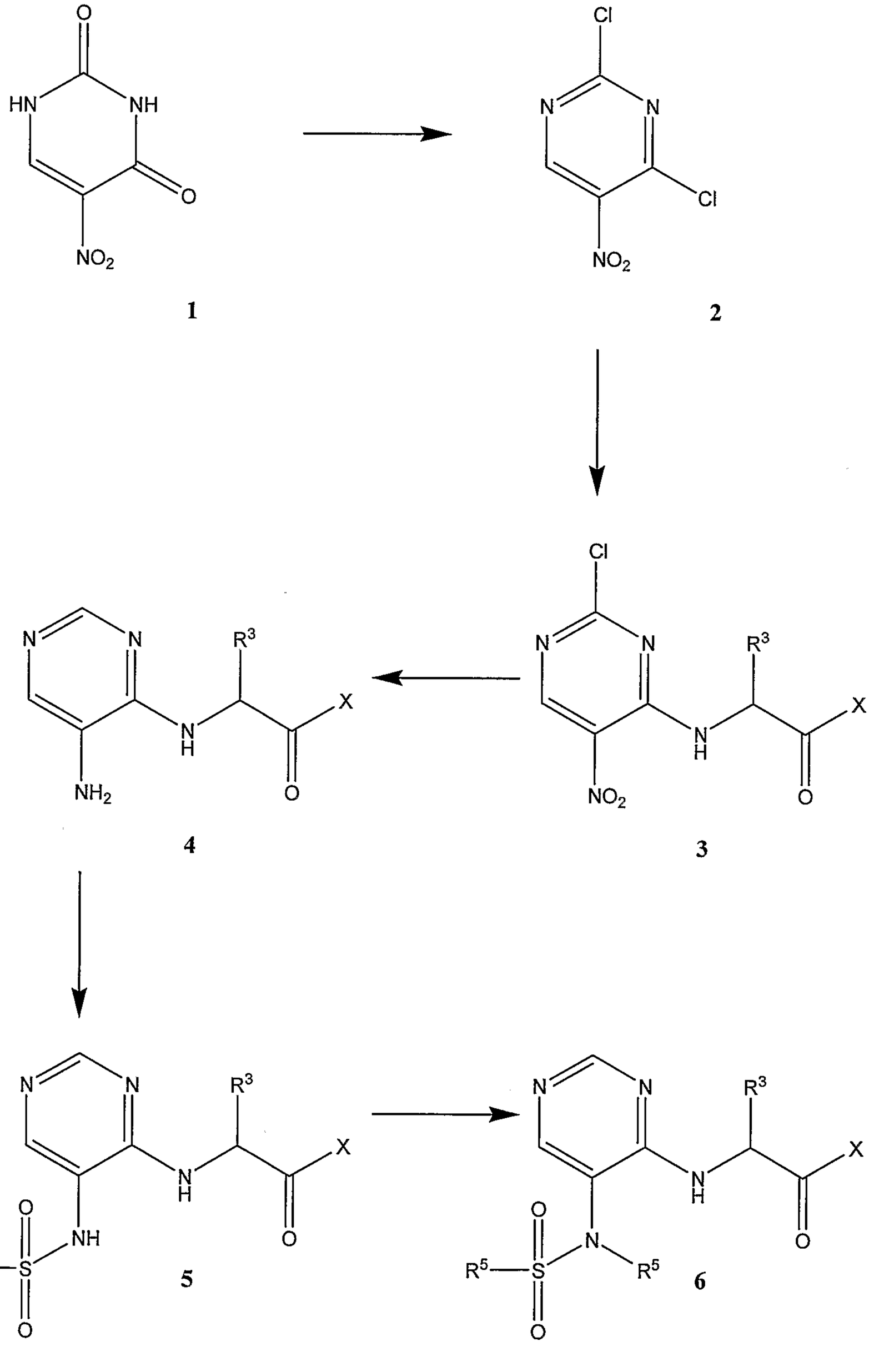
In a preferred method of synthesis, the compounds of Formulae III-IX are prepared by coupling an amino acid derivative of the formula:




where $R^3$ and $R^{3'}$ are as defined herein and $P^1$ is a carboxylic acid protecting group (such as an alkyl group, *i.e.*, methyl, ethyl and the like), with a suitably functionalized heteroaryl or heterocyclic intermediate. For example, such coupling reactions may be performed by displacing a leaving group, such as chloro, bromo, iodo, tosyl and the like, from the heteroaryl or heterocyclic intermediate with the amino group of the amino acid derivative; or by reductive alkylation of the amino group of amino acid derivative with a carbonyl-

functionalized intermediate. Such coupling reactions are well-known to those skilled in the art.

By way of illustration, the synthesis of a representative compound of Formula III is shown in Scheme 1.



As shown in Scheme 1, 5-nitrouracil, **1**, (commercially available from Aldrich Chemical Company, Milwaukee, Wisconsin USA) is treated with phosphorus oxychloride and *N,N*-dimethylaniline according to the procedure described in Whittaker, *J. Chem. Soc.* **1951**, 1565 to give 1,3-dichloro-4-nitropyrimidine, **2**.

1,3-Dichloro-4-nitropyrimidine, **2**, is then reacted with about one molar equivalent of an amino acid derivative of the formula $H_2N$-CH($R^3$)C(O)X where $R^3$ and X are as defined herein or X is -$OP^1$ where $P^1$ is a carboxylic acid protecting group, in the presence of a trialkylamine, such as diisopropylethylamine (DIEA). Typically, this reaction is conducted in an inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 10°C for about 5 min. to about 6 hours to afford intermediate **3**.

The nitro group of intermediate **3** is then reduced using a conventional reducing agent, such as hydrogen and a palladium on carbon catalyst. When hydrogen and palladium on carbon are employed as the reducing agent, the chloro group of intermediate **3** is also removed. This reaction is typically conducted by contacting **3** with a Degussa-type palladium on carbon catalyst (typically 20%) and excess sodium bicarbonate in an inert diluent, such as methanol, under hydrogen (typically about 55 psi) for about 12 to 36 hours at ambient temperature to afford amino intermediate **4**.

Amino intermediate **4** is then reacted with a sulfonyl chloride of the formula $R^5$-$S(O)_2$-Cl, where $R^5$ is as defined herein, to provide sulfonamide intermediate **5**. This reaction is typically conducted by reacting the amino intermediate **4** with at least one equivalent, preferably about 1.1 to about 2 equivalents, of the sulfonyl chloride in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting sulfonamide **5** is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Other heteroaryl intermediates may also be employed in the above described reactions including, but not limited to, 2-chloro-3-nitropyrazine (*J. Med. Chem.* **1984**, *27*, 1634); 4-chloro-5-nitroimidazole (*J. Chem. Soc.* **1930**, 268); and the like.

The amino acid derivatives employed in the above reactions are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. For example, amino acid derivatives can be prepared by *C*-alkylating commercially available diethyl 2-acetamidomalonate (Aldrich, Milwaukee, Wisconsin, USA) with an alkyl or substituted alkyl halide. This reaction is typically conducted by treating the diethyl 2-acetamidomalonate with at least one equivalent of sodium ethoxide and at least one equivalent of an alkyl or substituted alkyl halide in refluxing ethanol for about 6 to about 12 hours. The resulting C-alkylated malonate is then deacetylated, hydrolyzed and decarboxylated by heating in aqueous hydrochloric acid at reflux for about 6 to about 12 hours to provide the amino acid, typically as the hydrochloride salt.

Examples of amino acid derivatives suitable for use in the above reactions include, but are not limited to, L-alanine methyl ester, L-isoleucine methyl ester, L-leucine methyl ester, L-valine methyl ester, β-*tert*-butyl-L-aspartic acid methyl ester, L-asparagine *tert*-butyl ester, ε-Boc-L-lysine methyl ester, ε-Cbz-L-lysine methyl ester, γ-*tert*-butyl-L-glutamic acid methyl ester, L-glutamine *tert*-butyl ester, L-(*N*-methyl)histidine methyl ester, L-(*N*-benzyl)histidine methyl ester, L-methionine methyl ester, L-(*O*-benzyl)serine methyl ester, L-tryptophan methyl ester, L-phenylalanine methyl ester, L-phenylalanine isopropyl ester, L-phenylalanine benzyl ester, L-phenylalaninamide, *N*-methyl-L-phenylalanine benzyl ester, 3-carboxy-D,L-phenylalanine methyl ester, 4-carboxy-D,L-phenylalanine methyl ester, L-4-chlorophenylalanine methyl ester, L-4-(3-dimethylaminopropyloxy)-phenylalanine methyl ester, L-4-iodophenylalanine methyl ester, L-3,4-methylenedioxyphenylalanine methyl ester, L-3,4-ethylenedioxyphenylalanine methyl ester, L-4-nitrophenylalanine methyl ester, L-tyrosine methyl ester, D,L-homophenylalanine methyl ester, L-(*O*-methyl)tyrosine methyl ester, L-(*O*-*tert*-butyl)tyrosine methyl ester, L-(*O*-benzyl)tyrosine methyl ester, L-3,5-diiodotyrosine methyl ester, L-3-iodotyrosine methyl ester, β-(1-naphthyl)-L-alanine methyl ester, β-(2-naphthyl)-L-alanine methyl ester, β-(2-thienyl)-L-alanine methyl ester, β-cyclohexyl-L-alanine methyl ester, β-(2-pyridyl)-L-alanine methyl ester, β-(3-pyridyl)-L-alanine methyl ester, β-(4-pyridyl)-L-alanine methyl ester, β-(2-thiazolyl)-D,L-alanine

methyl ester, β-(1,2,4-triazol-3-yl)-D,L-alanine methyl ester, and the like. If desired, of course, other esters or amides of the above-described compounds may also be employed.

Additionally, α-hydroxy and α-thio carboxylic acids may also be employed in the above-described reactions. Such compounds are well-known in the art and are either commercially available or may be prepared from commercially available starting materials using conventional reagents and reaction conditions.

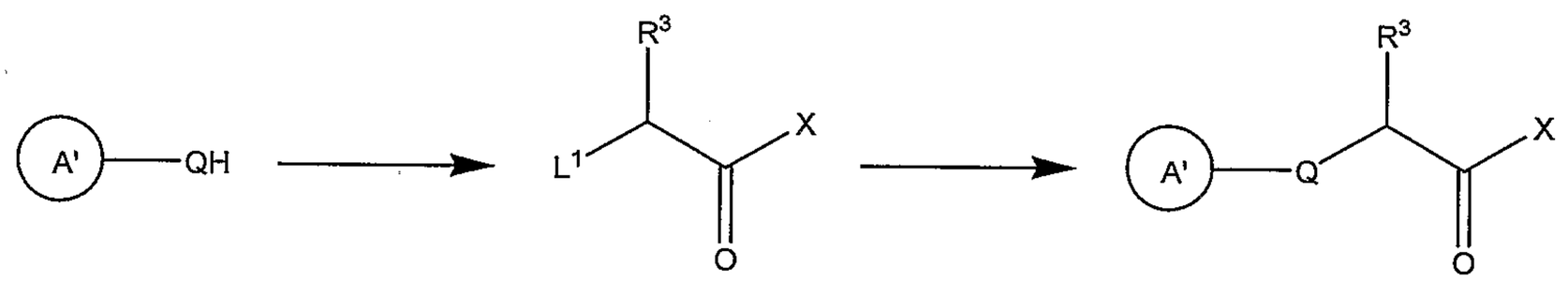
The sulfonyl chlorides employed in the above reaction are also either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, *i.e.*, from compounds of the formula $R^5$-$SO_3H$ where $R^5$ is as defined above, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the sulfonyl chloride can be prepared from the corresponding thiol compound, *i.e.*, from compounds of the formula $R^5$-SH where $R^5$ is as defined herein, by treating the thiol with chlorine ($Cl_2$) and water under conventional reaction conditions.

Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, *p*-toluenesulfonyl chloride, α-toluenesulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-amidinobenzenesulfonyl chloride, 4-*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethylbenzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-dichloro-4-thiophenesulfonyl chloride,

2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the sulfonamide intermediate **5**.

If desired, sulfonamide intermediate **5** can be alkylated at the sulfonamide nitrogen atom to provide compound **6**. For example, **5** can be contacted with excess diazomethane (generated, for example, using 1-methyl-3-nitro-1-nitrosoguanidine and sodium hydroxide) to afford **6** where $R^6$ is methyl. Other conventional alkylation procedures and reagents may also be employed to prepare various compounds of this invention.

In another preferred embodiment, compounds of Formulae III-IX may be prepared by displacement of a leaving group as shown in Scheme 2:

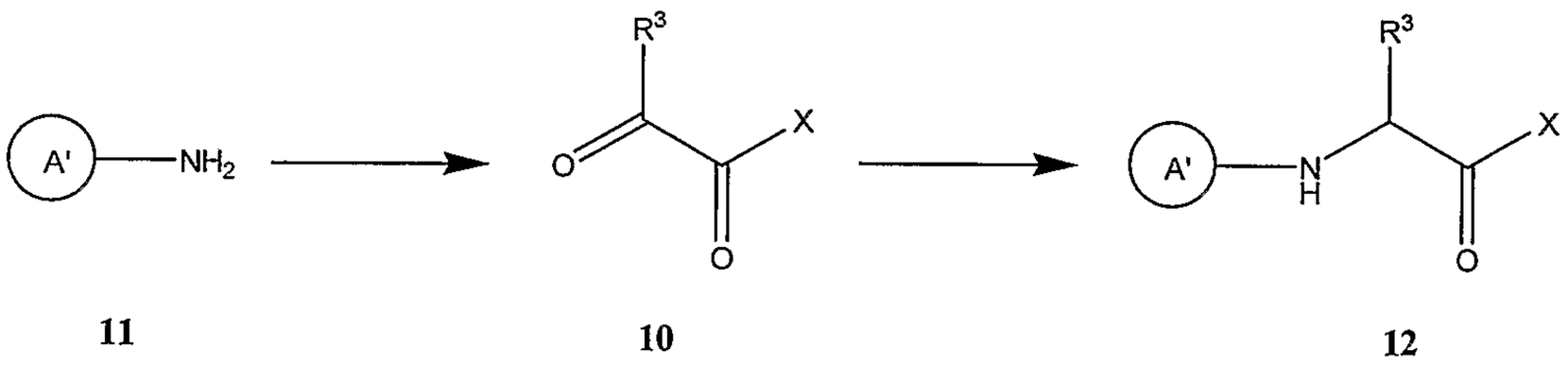



**7** **8** **9**

where $R^3$, Q and X are as defined herein; A' is heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic containing two nitrogen atoms in the heteroaryl or heterocyclic ring; and $L^1$ is a leaving group, such as chloro, bromo, iodo, sulfonate ester and the like.

Typically, this reaction is conducted by combining approximately stoichiometric equivalents of **7** and **8** in a suitable inert diluent such as water, dimethylsulfoxide (DMSO) and the like, with an excess of a suitable base such as sodium bicarbonate, sodium hydroxide, etc. to scavenge the acid generated by the reaction. The reaction is preferably conducted at from about 25°C to about 100°C until reaction completion which typically occurs within 1 to about 24 hours. This reaction is further described in U.S. Patent No. 3,598,859, which is incorporated herein by reference in its entirety. Upon reaction completion, the product **9** is recovered by conventional methods including precipitation, chromatography, filtration and the like.

In still another alternative embodiment, compounds of Formulae III-IX in which Q is $NR^4$ can be prepared by reductive amination of a suitable 2-oxocarboxylic acid ester, **10**, such as a pyruvate ester, as shown in Scheme 3:

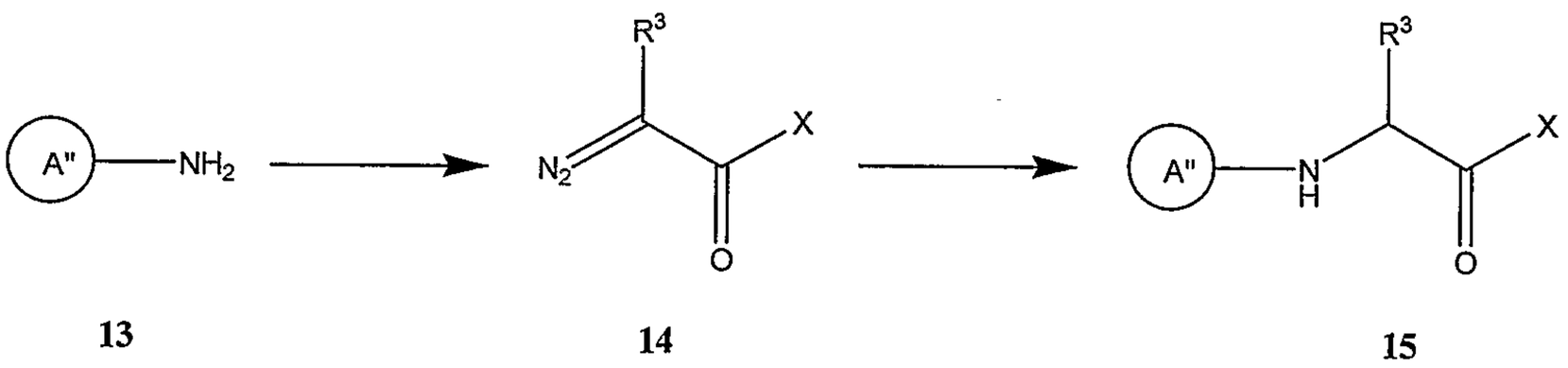



**11** **10** **12**

where A', $R^3$ and X are as defined herein.

Generally, this reaction is conducted by combining equamolar amounts of **10** and **11** in an inert diluent such as methanol, ethanol and the like under conditions which provide for imine formation (not shown). The imine formed is then reduced under conventional conditions by a suitable reducing agent such as sodium cyanoborohydride, $H_2$/palladium on carbon and the like to form the product **12**. In a particularly preferred embodiment, the reducing agent is $H_2$/palladium on carbon which is incorporated into the initial reaction medium thereby permitting imine reduction *in situ* in a one pot procedure to provide **12**. The reaction is preferably conducted at from about 20°C to about 80°C at a pressure of from 1 to 10 atmospheres until reaction completion which typically occurs within 1 to about 24 hours. Upon reaction completion, the product **12** is recovered by conventional methods including chromatography, filtration and the like.

Alternatively, certain compounds of Formulae III-IX can be prepared via a rhodium-catalyzed insertion reaction as shown in Scheme 4:

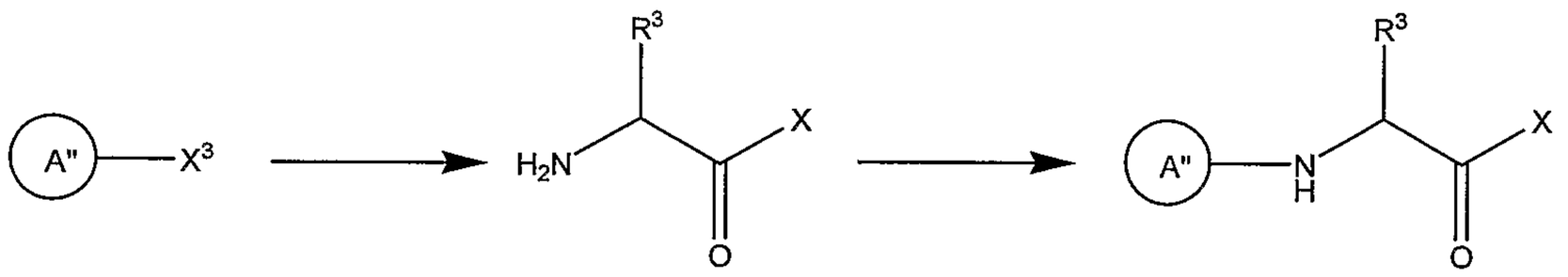



**13** **14** **15**

where A" is heteroaryl or substituted heteroaryl containing two nitrogen atoms in the heteroaryl ring, and $R^3$ and X (preferably alkoxy) are as defined herein. Typically, this

reaction is conducted using rhodium acetate dimer, $Rh_2(OAc)_4$, in an inert diluent such as toluene at a temperature ranging from about 25°C to about 80°C for about 1 to 12 hours to afford **15**. This reaction is described further in B. R. Henke et. al., *J. Med. Chem.* **1998**, *41*, 5020-5036 and references cited therein.

Similarly, certain compounds of Formulae III-IX can be prepared by the copper-catalyzed coupling reaction shown in Scheme 5:




**16** **17** **18**

where A" is as defined herein, $X^3$ is halogen, such as chloro, bromo or iodo (preferably iodo), and $R^3$ and X (preferably alkoxy) are as defined herein. Typically, this reaction is conducted using copper iodide (CuI) and potassium carbonate in an inert diluent such as *N*,*N*-dimethyl acetamide (DMA) at a temperature ranging from about 60°C to about 120°C for about 12 to 36 hours to afford **15**. This reaction is described further in D. Ma et. al., *J. Am. Chem. Soc.* **1998**, *120*, 12459-12467 and references cited therein.

For ease of synthesis, the compounds of Formulae III-IX are typically prepared as an ester, *i.e.*, where X is an alkoxy or substituted alkoxy group and the like. If desired, the ester group can be hydrolysed using conventional conditions and reagents to provide the corresponding carboxylic acid. Typically, this reaction is conducted by treating the ester with at least one equivalent of an alkali metal hydroxide, such as lithium, sodium or potassium hydroxide, in an inert diluent, such as methanol or mixtures of methanol and water, at a temperature ranging about 0°C to about 24°C for about 1 to about 12 hours. Alternatively, benzyl esters may be removed by hydrogenolysis using a palladium catalyst, such as palladium on carbon, and *tert*-butyl esters can be removed using formic acid to afford the corresponding carboxylic acid.

As will be apparent to those skilled in the art, other functional groups present on any of the substituents of the compounds of Formulae III-IX can be readily modified or derivatized either before or after the above-described synthetic reactions using well-known

synthetic procedures. For example, a nitro group present on a substituent of a compound of Formulae III-IX or an intermediate thereof may be readily reduced by hydrogenation in the presence of a palladium catalyst, such as palladium on carbon, to provide the corresponding amino group. This reaction is typically conducted at a temperature of from about 20°C to about 50°C for about 6 to about 24 hours in an inert diluent, such as methanol. Compounds having a nitro group on the $R^3$ and/or $R^{3'}$ substituent can be prepared, for example, by using a 4-nitrophenylalanine derivative and the like in the above-described coupling reactions.

Similarly, a pyridyl group can be hydrogenated in the presence of a platinum catalyst, such as platinum oxide, in an acidic diluent to provide the corresponding piperidinyl analogue. Generally, this reaction is conducted by treating the pyridine compound with hydrogen at a pressure ranging from about 20 psi to about 60 psi, preferably about 40 psi, in the presence of the catalyst at a temperature of about 20°C to about 50°C for about 2 to about 24 hours in an acidic diluent, such as a mixture of methanol and aqueous hydrochloric acid.

Additionally, when the $R^3$ and/or $R^{3'}$ substituent of a compound of Formulae III-IX or an intermediate thereof contains a primary or secondary amino group, such amino groups can be further derivatized either before or after the above coupling reactions to provide, by way of example, amides, sulfonamides, ureas, thioureas, carbamates, secondary or tertiary amines and the like. Compounds having a primary amino group on the $R^3$ and/or $R^{3'}$ substituent may be prepared, for example, by reduction of the corresponding nitro compound as described above.

By way of illustration, a compound of Formulae III-IX or an intermediate thereof having a substituent containing a primary or secondary amino group, such as where $R^3$ is a (4-aminophenyl)methyl group, can be readily *N*-acylated using conventional acylating reagents and conditions to provide the corresponding amide. This acylation reaction is typically conducted by treating the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of a carboxylic acid in the presence of a coupling reagent such as a carbodiimide, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphonate) and the like, in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N*,*N*-dimethylformamide and the like, at a temperature ranging from about 0°C to about 37°C for about 4 to about 24 hours. Preferably, a promoter, such as *N*-hydroxysuccinimide, 1-hydroxy-benzotriazole and the like, is used to facilitate the acylation reaction. Examples of carboxylic acids suitable for use in this reaction

include, but are not limited to, *N*-*tert*-butyloxycarbonylglycine, *N*-*tert*-butyloxycarbonyl-L-phenylalanine, *N*-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester, benzoic acid, *N*-*tert*-butyloxycarbonylisonipecotic acid, *N*-methylisonipecotic acid, *N*-*tert*-butyloxycarbonylnipecotic acid, *N*-*tert*-butyloxycarbonyl-L-tetrahydroisoquinoline-3-carboxylic acid, *N*-(toluene-4-sulfonyl)-L-proline and the like.

Alternatively, a compound of Formulae III-IX or an intermediate thereof containing a primary or secondary amino group can be *N*-acylated using an acyl halide or a carboxylic acid anhydride to form the corresponding amide. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the acyl halide or carboxylic acid anhydride in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. If desired, an acylation catalyst such as 4-(*N*,*N*-dimethylamino)pyridine may be used to promote the acylation reaction. The acylation reaction is preferably conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like.

Examples of acyl halides and carboxylic acid anhydrides suitable for use in this reaction include, but are not limited to, 2-methylpropionyl chloride, trimethylacetyl chloride, phenylacetyl chloride, benzoyl chloride, 2-bromobenzoyl chloride, 2-methylbenzoyl chloride, 2-trifluoro-methylbenzoyl chloride, isonicotinoyl chloride, nicotinoyl chloride, picolinoyl chloride, acetic anhydride, succinic anhydride, and the like. Carbamyl chlorides, such as *N*,*N*-dimethylcarbamyl chloride, *N*,*N*-diethylcarbamyl chloride and the like, can also be used in this reaction to provide ureas. Similarly, dicarbonates, such as di-*tert*-butyl dicarbonate, may be employed to provide carbamates.

In a similar manner, a compound of Formulae III-IX or an intermediate thereof containing a primary or secondary amino group may be *N*-sulfonated to form a sulfonamide using a sulfonyl halide or a sulfonic acid anhydride. Sulfonyl halides and sulfonic acid anhydrides suitable for use in this reaction include, but are not limited to, methanesulfonyl chloride, chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride,

trifluoromethanesulfonic anhydride, and the like. Similarly, sulfamoyl chlorides, such as dimethylsulfamoyl chloride, can be used to provide sulfamides (*e.g.*, >N-$SO_2$-N<).

Additionally, a primary and secondary amino group present on a substituent of a compound of Formulae III-IX or an intermediate thereof can be reacted with an isocyanate or a thioisocyanate to give a urea or thiourea, respectively. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the isocyanate or thioisocyanate in an inert diluent, such as toluene and the like, at a temperature ranging from about 24°C to about 37°C for about 12 to about 24 hours. The isocyanates and thioisocyanates used in this reaction are commercially available or can be prepared from commercially available compounds using well-known synthetic procedures. For example, isocyanates and thioisocyanates are readily prepared by reacting the appropriate amine with phosgene or thiophosgene. Examples of isocyanates and thioisocyanates suitable for use in this reaction include, but are not limited to, ethyl isocyanate, *n*-propyl isocyanate, 4-cyanophenyl isocyanate, 3-methoxyphenyl isocyanate, 2-phenylethyl isocyanate, methyl thioisocyanate, ethyl thioisocyanate, 2-phenylethyl thioisocyanate, 3-phenylpropyl thioisocyanate, 3-(*N*,*N*-diethylamino)propyl thioisocyanate, phenyl thioisocyanate, benzyl thioisocyanate, 3-pyridyl thioisocyanate, fluorescein isothiocyanate (isomer I) and the like.

Furthermore, when a compound of Formulae III-IX or an intermediate thereof contains a primary or secondary amino group, the amino group can be reductively alkylated using aldehydes or ketones to form a secondary or tertiary amino group. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of an aldehyde or ketone and at least one equivalent based on the amino compound of a metal hydride reducing agent, such as sodium cyanoborohydride, in an inert diluent, such as methanol, tetrahydrofuran, mixtures thereof and the like, at a temperature ranging from about 0°C to about 50°C for about 1 to about 72 hours. Aldehydes and ketones suitable for use in this reaction include, by way of example, benzaldehyde, 4-chlorobenzaldehyde, valeraldehyde and the like.

In a similar manner, when a compound of Formulae III-IX or an intermediate thereof has a substituent containing a hydroxyl group, the hydroxyl group can be further modified or derivatized either before or after the above coupling reactions to provide, by way of example, ethers, carbamates and the like. Compounds having a hydroxyl group on the $R^3$ substituent,

for example, can be prepared using an amino acid derivative derived from tyrosine and the like in the above-described reactions.

By way of example, a compound of Formulae III-IX or an intermediate thereof having a substituent containing a hydroxyl group, such as where $R^3$ is a (4-hydroxyphenyl)methyl group, can be readily *O*-alkylated to form ethers. This *O*-alkylation reaction is typically conducted by contacting the hydroxy compound with a suitable alkali or alkaline earth metal base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, to form the alkali or alkaline earth metal salt of the hydroxyl group. This salt is generally not isolated, but is reacted *in situ* with at least one equivalent of an alkyl or substituted alkyl halide or sulfonate, such as an alkyl chloride, bromide, iodide, mesylate or tosylate, to afford the ether. Generally, this reaction is conducted at a temperature ranging from about 60°C to about 150°C for about 24 to about 72 hours. Preferably, a catalytic amount of sodium or potassium iodide is added to the reaction mixture when an alkyl chloride or bromide is employed in the reaction.

Examples of alkyl or substituted alkyl halides and sulfonates suitable for use in this reaction include, but are not limited to, *tert*-butyl bromoacetate, *N*-*tert*-butyl chloroacetamide, 1-bromoethylbenzene, ethyl α-bromophenylacetate, 2-(*N*-ethyl-*N*-phenylamino)ethyl chloride, 2-(*N*,*N*-ethylamino)ethyl chloride, 2-(*N*,*N*-diisopropylamino)ethyl chloride, 2-(*N*,*N*-dibenzylamino)ethyl chloride, 3-(*N*,*N*-ethylamino)propyl chloride, 3-(*N*-benzyl-*N*-methylamino)propyl chloride, *N*-(2-chloroethyl)morpholine, 2-(hexamethyleneimino)ethyl chloride, 3-(*N*-methylpiperazine)propyl chloride, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, 2-(4-hydroxy-4-phenylpiperidine)ethyl chloride, *N*-*tert*-butyloxycarbonyl-3-piperidinemethyl tosylate, and the like.

Alternatively, a hydroxyl group present on a substituent of a compound of Formulae III-IX or an intermediate thereof can be *O*-alkylating using the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(*N*,*N*-dimethylamino)-1-propanol and the like, is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as *N*-*tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the *O*-alkylated product.

In a similar manner, a compound of Formulae III-IX or an intermediate thereof containing an aryl hydroxy group can be reacted with an aryl iodide to provide a diaryl ether. Generally, this reaction is conducted by forming the alkali metal salt of the hydroxyl group using a suitable base, such as sodium hydride, in an inert diluent such as xylenes at a temperature of about -25°C to about 10°C. The salt is then treated with about 1.1 to about 1.5 equivalents of cuprous bromide dimethyl sulfide complex at a temperature ranging from about 10°C to about 30°C for about 0.5 to about 2.0 hours, followed by about 1.1 to about 1.5 equivalents of an aryl iodide, such as sodium 2-iodobenzoate and the like. The reaction is then heated to about 70°C to about 150°C for about 2 to about 24 hours to provide the diaryl ether.

Additionally, a hydroxy-containing compound can also be readily derivatized to form a carbamate. In one method for preparing such carbamates, a hydroxy compound of Formulae III-IX or an intermediate thereof is contacted with about 1.0 to about 1.2 equivalents of 4-nitrophenyl chloroformate in an inert diluent, such as dichloromethane, at a temperature ranging from about -25°C to about 0°C for about 0.5 to about 2.0 hours. Treatment of the resulting carbonate with an excess, preferably about 2 to about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5 to 2 hours, followed by about 1.0 to about 1.5 equivalents of a primary or secondary amine provides the carbamate. Examples of amines suitable for using in this reaction include, but are not limited to, piperazine, 1-methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine, pyrrolidine, piperidine and the like.

Alternatively, in another method for preparing carbamates, a hydroxy-containing compound is contacted with about 1.0 to about 1.5 equivalents of a carbamyl chloride in an inert diluent, such as dichloromethane, at a temperature ranging from about 25°C to about 70°C for about 2 to about 72 hours. Typically, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Additionally, at least one equivalent (based on the hydroxy compound) of 4-(*N*,*N*-dimethylamino)pyridine is preferably added to the reaction mixture to facilitate the reaction. Examples of carbamyl chlorides suitable for use in this reaction include, by way of example, dimethylcarbamyl chloride, diethylcarbamyl chloride and the like.

Likewise, when a compound of Formulae III-IX or an intermediate thereof contains a primary or secondary hydroxyl group, such hydroxyl groups can be readily converted into a leaving group and displaced to form, for example, amines, sulfides and fluorides. Generally, when a chiral compound is employed in these reactions, the stereochemistry at the carbon atom attached to the derivatized hydroxyl group is typically inverted.

These reactions are typically conducted by first converting the hydroxyl group into a leaving group, such as a tosylate, by treatment of the hydroxy compound with at least one equivalent of a sulfonyl halide, such as *p*-toluenesulfonyl chloride and the like, in pyridine. This reaction is generally conducted at a temperature of from about 0°C to about 70°C for about 1 to about 48 hours. The resulting tosylate can then be readily displaced with sodium azide, for example, by contacting the tosylate with at least one equivalent of sodium azide in an inert diluent, such as a mixture of *N*,*N*-dimethylformamide and water, at a temperature ranging from about 0°C to about 37°C for about 1 to about 12 hours to provide the corresponding azido compound. The azido group can then be reduced by, for example, hydrogenation using a palladium on carbon catalyst to provide the amino ($-NH_2$) compound.

Similarly, a tosylate group can be readily displaced by a thiol to form a sulfide. This reaction is typically conducted by contacting the tosylate with at least one equivalent of a thiol, such as thiophenol, in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in an inert diluent, such as *N*,*N*-dimethylformamide, at a temperature of from about 0°C to about 37°C for about 1 to about 12 hours to provide the sulfide. Additionally, treatment of a tosylate with morpholinosulfur trifluoride in an inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours affords the corresponding fluoro compound.

Furthermore, a compound of Formulae III-IX or an intermediate thereof having a substituent containing an iodoaryl group, for example, when $R^3$ is a (4-iodophenyl)methyl group, can be readily converted either before or after the above coupling reactions into a biaryl compound. Typically, this reaction is conducted by treating the iodoaryl compound with about 1.1 to about 2 equivalents of an arylzinc iodide, such as 2-(methoxycarbonyl)phenylzinc iodide, in the presence of a palladium catalyst, such as palladium tetra(triphenylphosphine), in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 24°C to about 30°C until reaction completion. This reaction is further described, for example, in Rieke, *J. Org. Chem.* **1991**, *56*, 1445. Additional

methods for preparing biaryl derivatives are disclosed in International Publication Number WO 98/53817, published December 3, 1998, the disclosure of which is incorporated herein by reference in its entirety.

In some cases, the compounds of Formulae III-IX or intermediates thereof may contain substituents having one or more sulfur atoms. When present, such sulfur atoms can be oxidized either before or after the above coupling reactions to provide a sulfoxide or sulfone compound using conventional reagents and reaction conditions. Suitable reagents for oxidizing a sulfide compound to a sulfoxide include, by way of example, hydrogen peroxide, 3-chloroperoxybenzoic acid (MCPBA), sodium periodate and the like. The oxidation reaction is typically conducted by contacting the sulfide compound with about 0.95 to about 1.1 equivalents of the oxidizing reagent in an inert diluent, such as dichloromethane, at a temperature ranging from about -50°C to about 75°C for about 1 to about 24 hours. The resulting sulfoxide can then be further oxidized to the corresponding sulfone by contacting the sulfoxide with at least one additional equivalent of an oxidizing reagent, such as hydrogen peroxide, MCPBA, potassium permanganate and the like. Alternatively, the sulfone can be prepared directly by contacting the sulfide with at least two equivalents, and preferably an excess, of the oxidizing reagent. Such reactions are described further in March, "*Advanced Organic Chemistry*," 4th Ed., pp. 1201-1202, Wiley Publisher, 1992.

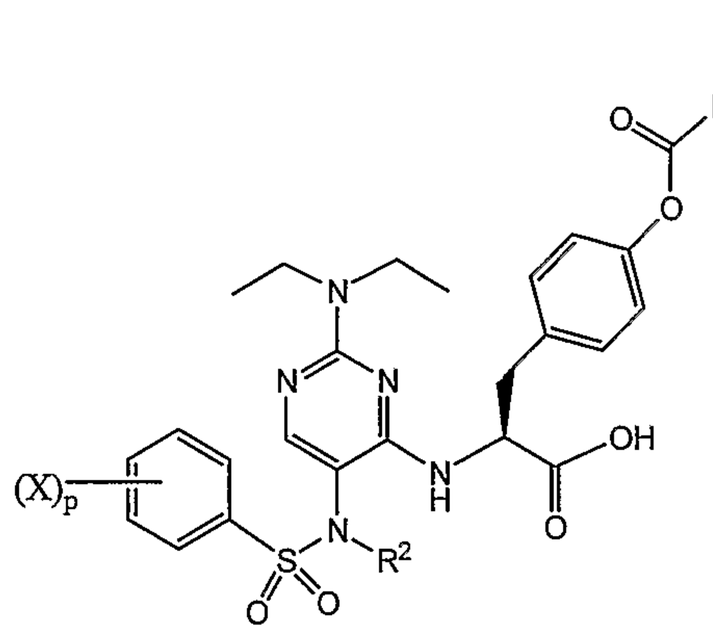
Other procedures and reaction conditions for preparing the compounds of this invention are described in the examples set forth below. Additionally, other procedures for preparing compounds useful in certain aspects of this invention are disclosed in U.S. Serial No. 09/489,378, filed on January 21, 2000, entitled "Compounds Which Inhibit Leucocyte Adhesion Mediated by VLA-4," now issued as U.S. Patent No. 6,479,492, the disclosure of which is incorporated herein by reference in its entirety.

Compounds of Formulae X-XV

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formulae X, XI, XII, XIII, XIV, and XV.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula X below. These

compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



X

wherein each X is independently fluoro, chloro or bromo;

p is an integer from 0 to 3;

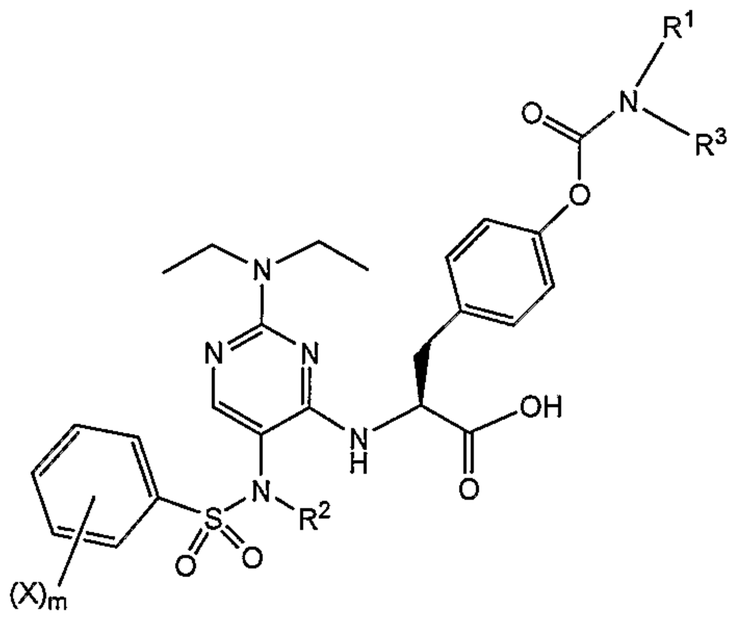
$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, pyrrolyl, 2,5-dihydopyrrol-1-yl, piperidinyl, or 1,2,3,6-tetrahydropyridin-1-yl;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

In a preferred embodiment, $R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XI below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XI

wherein each X is independently selected from the group consisting of fluoro and chloro;

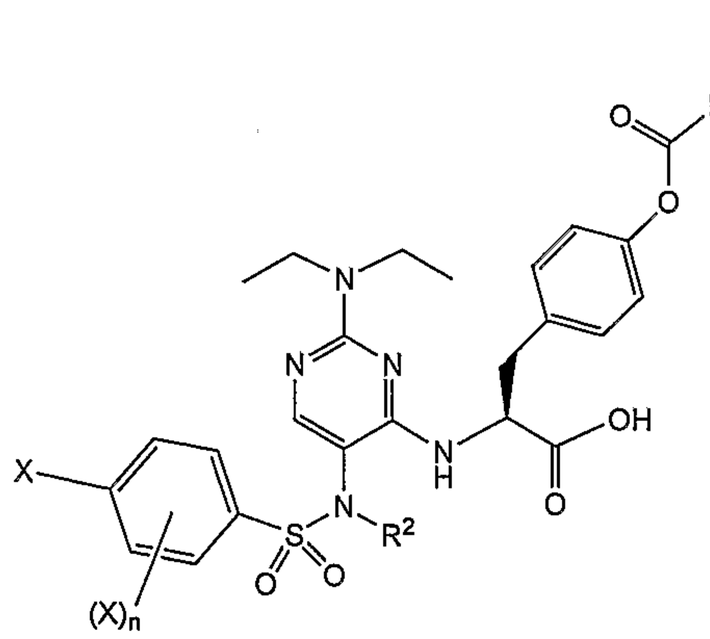
*m* is an integer equal to 1 or 2;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XII below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XII

wherein each X is independently fluoro or chloro;

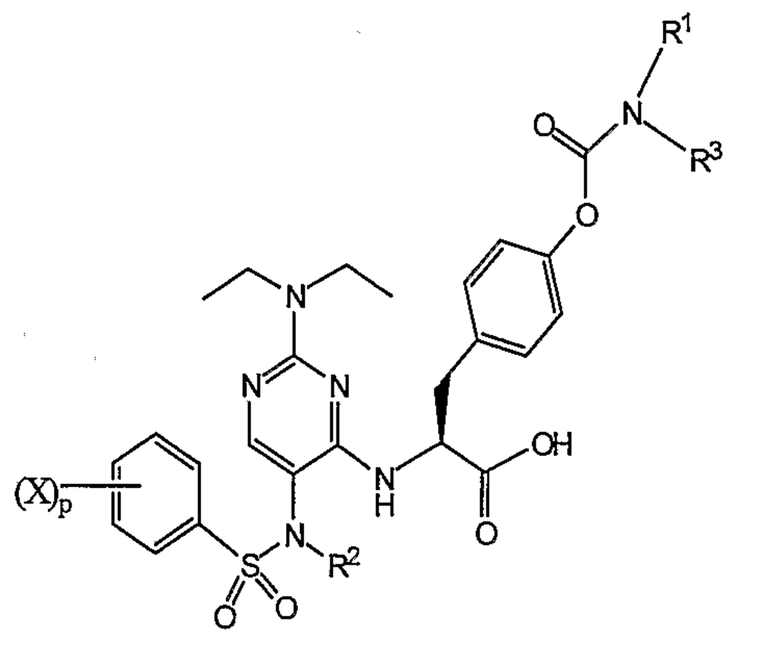
*n* is zero or one;

$R^2$ is -$CH_2$-R' where R' is selected from the group consisting of hydrogen, methyl or -CH=$CH_2$;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XIII below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XIII

wherein each X is independently fluoro, chloro or bromo;

p is an integer from 0 to 3;

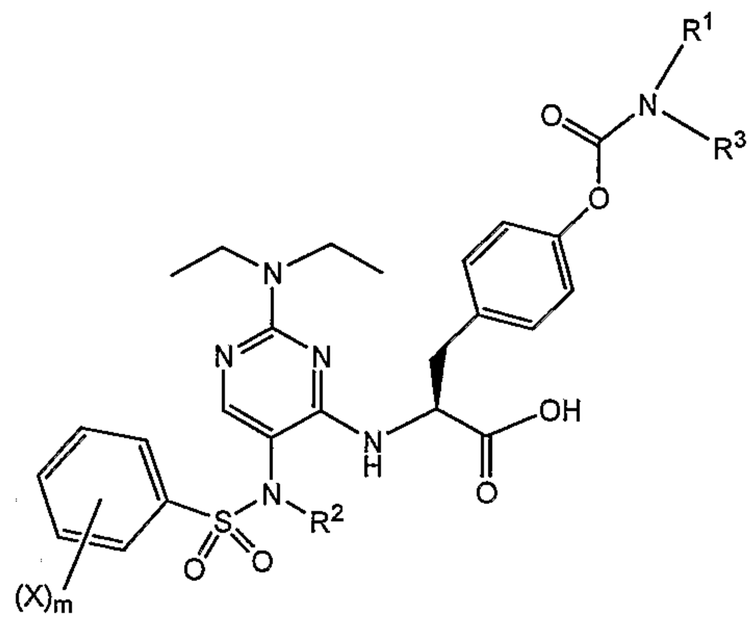
$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, pyrrolyl, 2,5-dihydopyrrol-1-yl, piperidinyl, or 1,2,3,6-tetrahydropyridin-1-yl;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

In a preferred embodiment, $R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group and $R^2$ is propargyl.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XIV below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XIV

wherein each X is independently selected from the group consisting of fluoro and chloro;

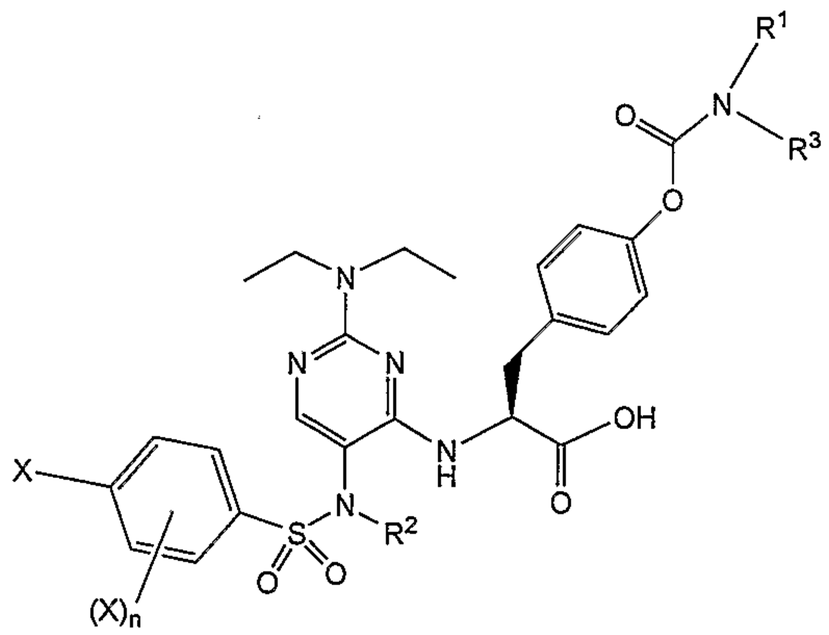
*m* is an integer equal to 1 or 2;

$R^2$ is lower alkynyl;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XV below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XV

wherein each X is independently fluoro or chloro;

*n* is zero or one;

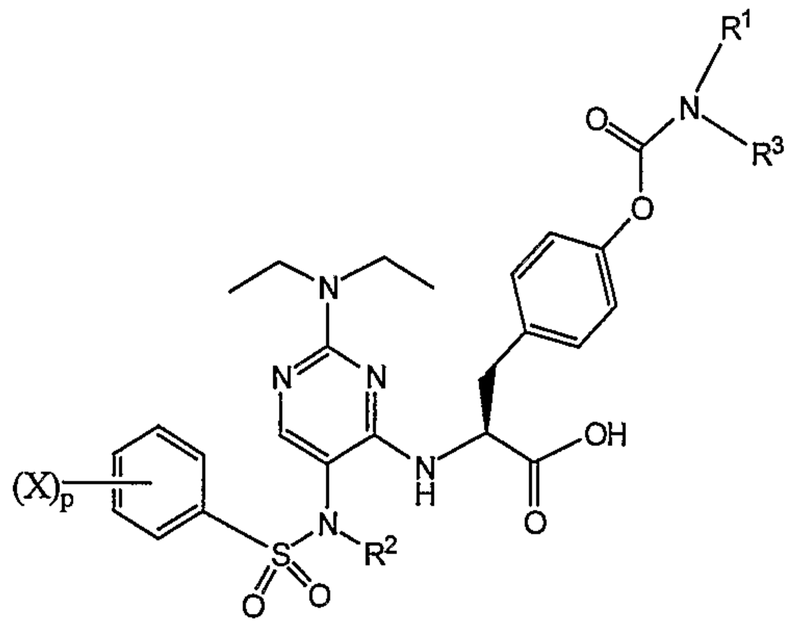
$R^2$ is lower alkynyl;

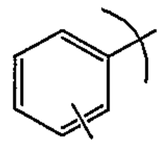
$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

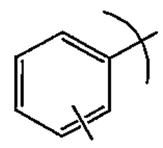
and pharmaceutically acceptable salts thereof.

N-[2-N′,N′-diethylamino-5-aminosulfonylphenylpyrimidin-4-yl]-*p*-carbomyloxy-phenylalanine compounds within the scope of this invention include those set forth in Table 7 as follows:

Table 7



| $R^1$ and $R^3$ | $R^2$ |  | Example No. |
|---|---|---|---|

| $R^1$ and $R^3$ | $R^2$ |  | Example No. |
|---|---|---|---|
| pyrrolidinyl | ethyl | 4-chlorophenyl | 505 |
| pyrrolidinyl | ethyl | 4-fluorophenyl | 506 |
| pyrrolidinyl | methyl | 4-fluorophenyl | 507 |
| pyrrolidinyl | methyl | 4-chlorophenyl | 508 |
| piperidinyl | methyl | 4-fluorophenyl | 509 |
| piperidinyl | ethyl | 4-fluorophenyl | 510 |
| azetidinyl | ethyl | 4-fluorophenyl | 511 |
| azetidinyl | methyl | 4-fluorophenyl | 512 |
| azetidinyl | methyl | 4-chlorophenyl | 513 |
| azetidinyl | ethyl | 4-chlorophenyl | 514 |
| pyrrolidinyl | methyl | 2,4-difluorophenyl | 515 |
| pyrrolidinyl | ethyl | 2,4-difluorophenyl | 516 |
| azetidinyl | methyl | 2,4-difluorophenyl | 517 |
| azetidinyl | ethyl | 2,4-difluorophenyl | 518 |
| pyrrolidinyl | propargyl | 4-fluorophenyl | 519 |
| pyrrolidinyl | progargyl | 2,4-difluorophenyl | 520 |
| azetidinyl | propargyl | 2,4-difluorophenyl | 521 |
| azetidinyl | propargyl | 4-fluorophenyl | 522 |
| pyrrolidinyl | progargyl | 4-chlorophenyl | 523 |

Specific compounds within the scope of this invention include the following compounds. As used below, these compounds are named based on phenylalanine derivatives but, alternatively, these compounds could have been named based on N-[2-N',N'-diethylamino-5-aminosulfonylphenyl-pyrimidin-4-yl]-*p*-carbomyloxyphenylalanine derivatives or 2-{2-diethylamino-5-[(benzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-*p*-carbamoyloxy-phenyl)propionic acid derivatives.

N-(2-[N',N'-diethylamino]-5-[N''-(4-chlorophenylsulfonyl)-N''-ethylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N''-(4-fluorophenylsulfonyl)-N''-ethylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(pyrrolidin -1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(piperidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(piperidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

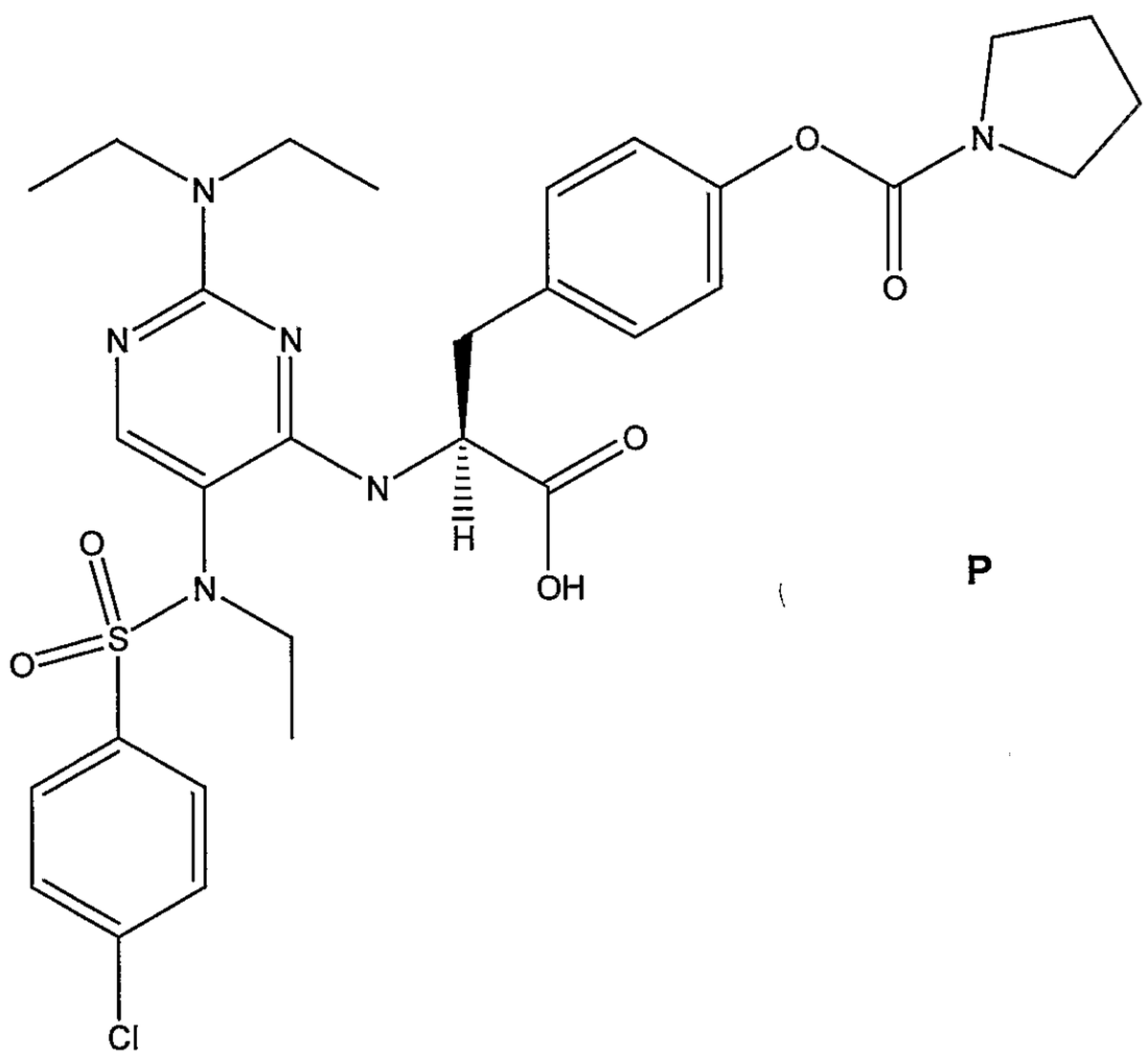
N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine; and

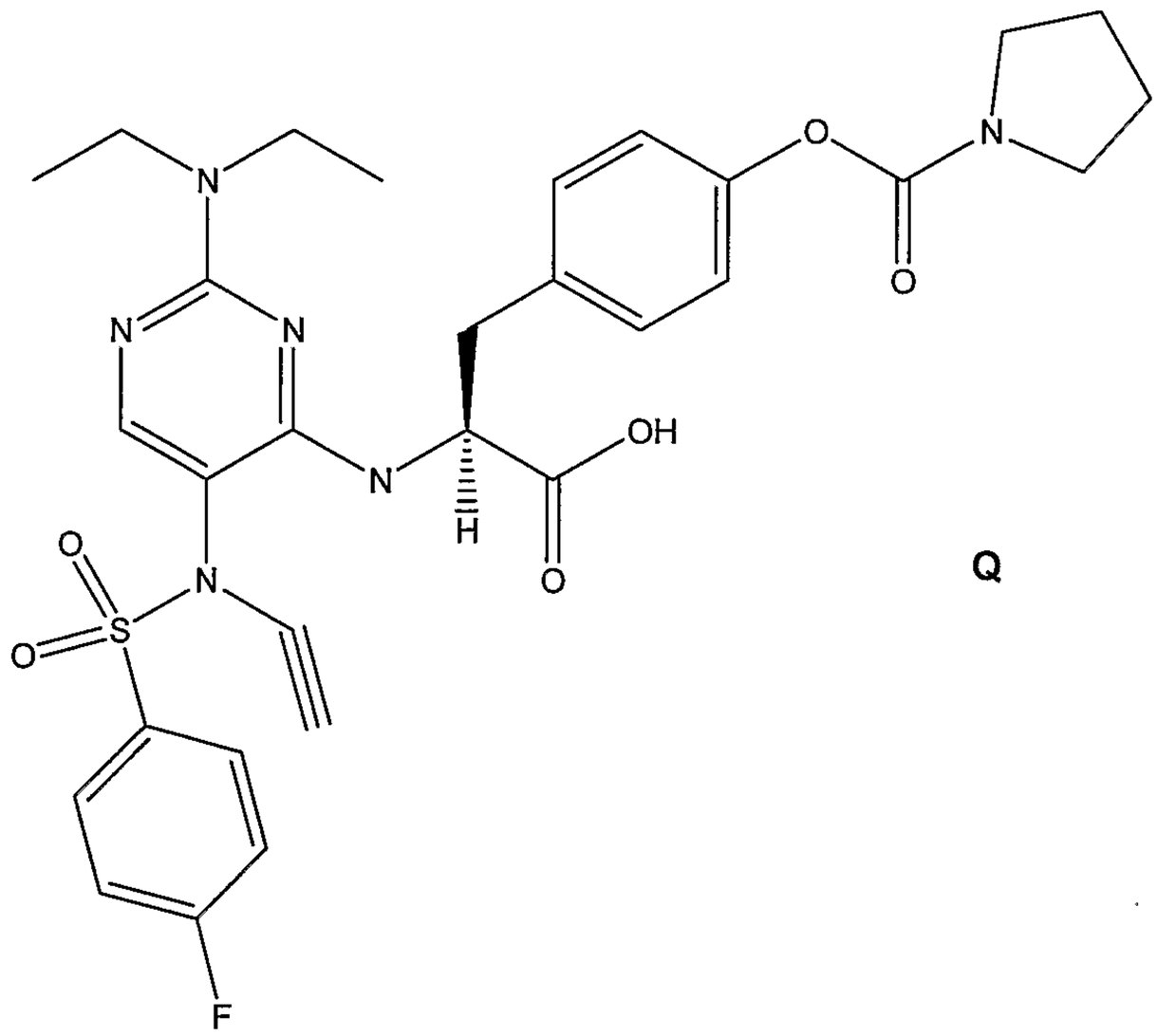
pharmaceutically acceptable salts thereof.

Preferably, the compound is the compound of Formula P below:



**P**

In another embodiment, preferably the compound is the compound of Formula Q below:



Q

Compound Preparation of Compounds of Formulae X-XV

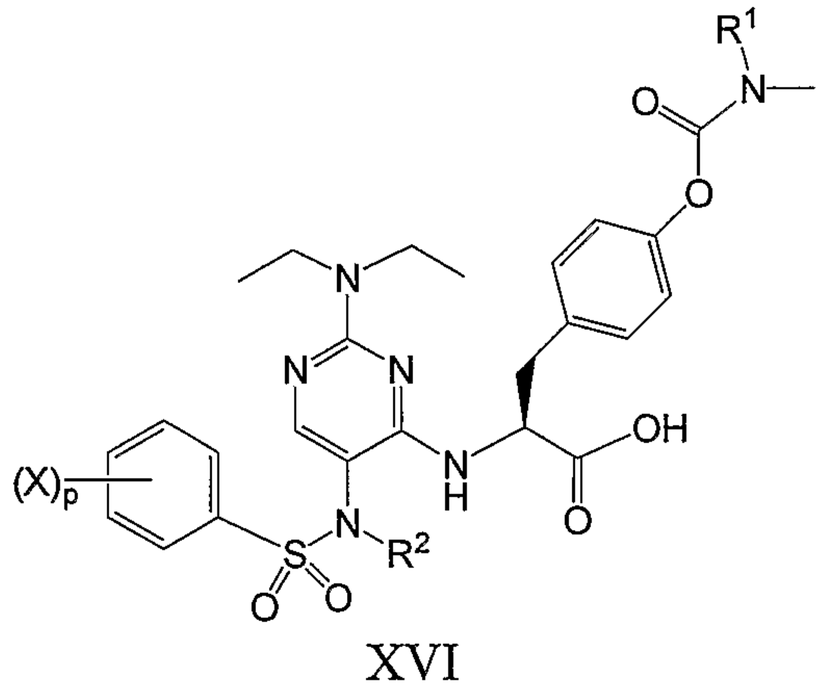
The compounds of Formulae X-XV can be prepared from readily available starting materials using the methods and procedures set forth in the examples below. These methods and procedures outline specific reaction protocols for preparing N-[2-N′,N′-diethylamino-5-aminosulfonylphenyl-yrimidin-4-yl]-*p*-carbomyloxy-phenylalanine compounds. Compounds within the scope not exemplified in these examples and methods are readily prepared by appropriate substitution of starting materials which are either commercially available or well known in the art.

Other procedures and reaction conditions for preparing the compounds of this invention are described in the examples set forth below. Additionally, other procedures for preparing compounds useful in certain aspects of this invention are disclosed in U.S. Patent 6,492,372, issued December 10, 2002; the disclosure of which is incorporated herein by reference in its entirety.

Compounds of Formulae XVI-XXI

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds of Formulae XVI, XVII, XVIII, XIX, XX, and XXI.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XVI below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XVI

wherein each X is independently fluoro, chloro or bromo;

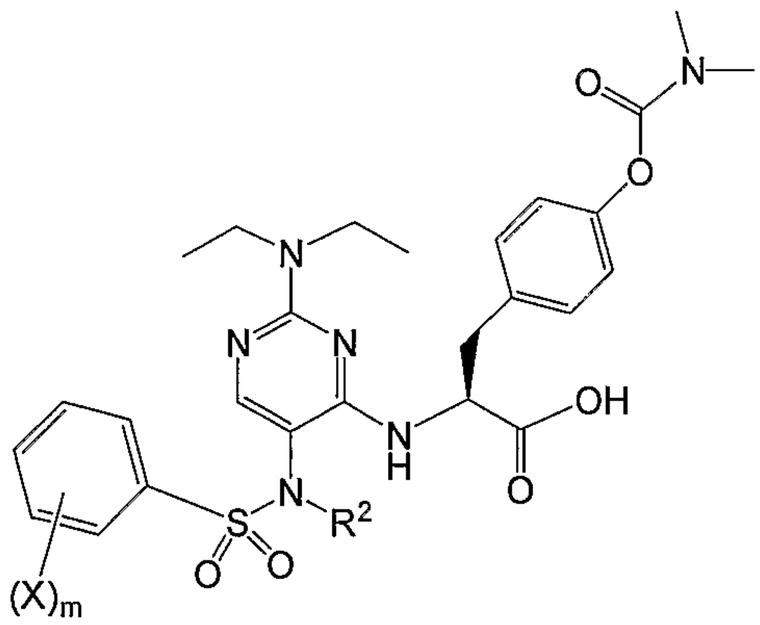
p is 0 or an integer from 1 - 3;

$R^1$ is selected from the group consisting of methyl and ethyl;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XVII below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XVII

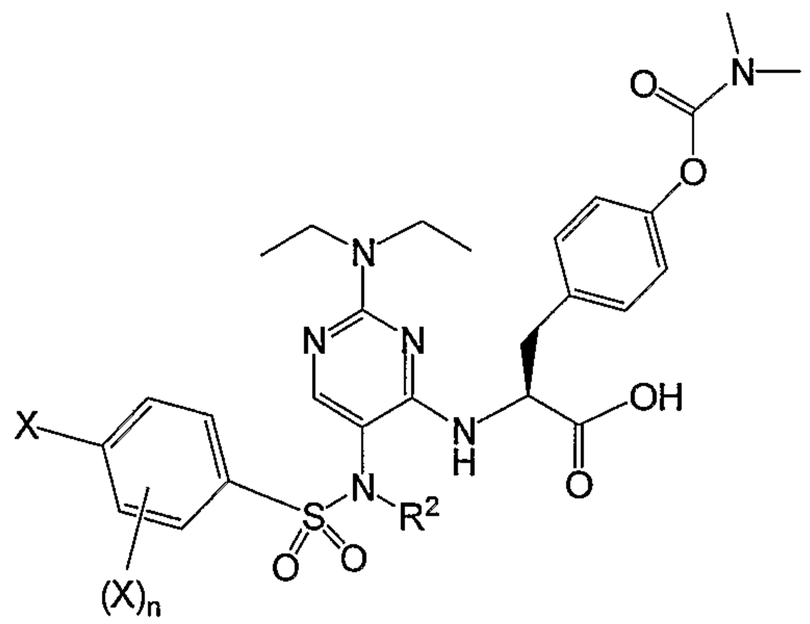
wherein each X is independently selected from the group consisting of fluoro and chloro,

*m* is an integer equal to 1 or 2;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XVIII below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XVIII

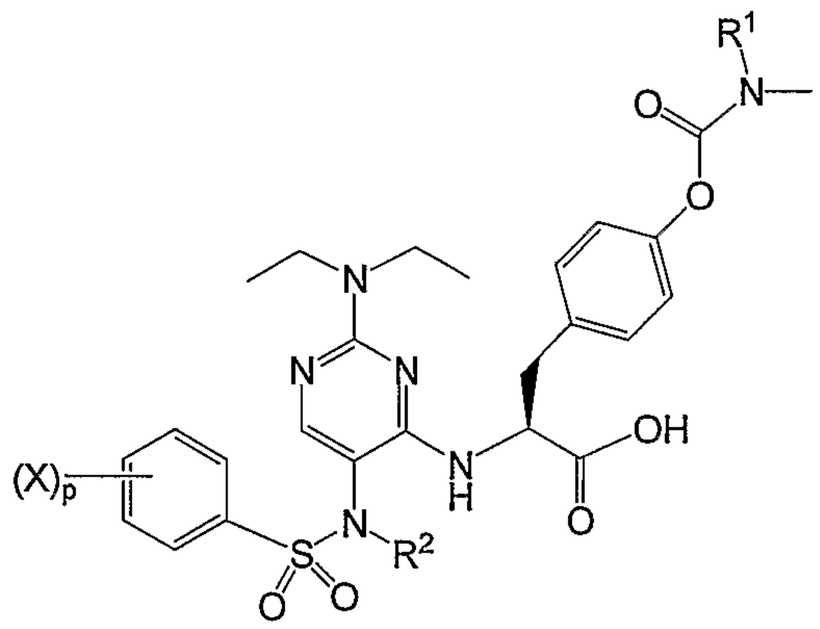
wherein each X is independently fluoro or chloro;

*n* is zero or one;

$R^2$ is -$CH_2$-R' where R' is selected from the group consisting of hydrogen, methyl or -CH=$CH_2$;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XIX below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XIX

wherein each X is independently fluoro, chloro or bromo;

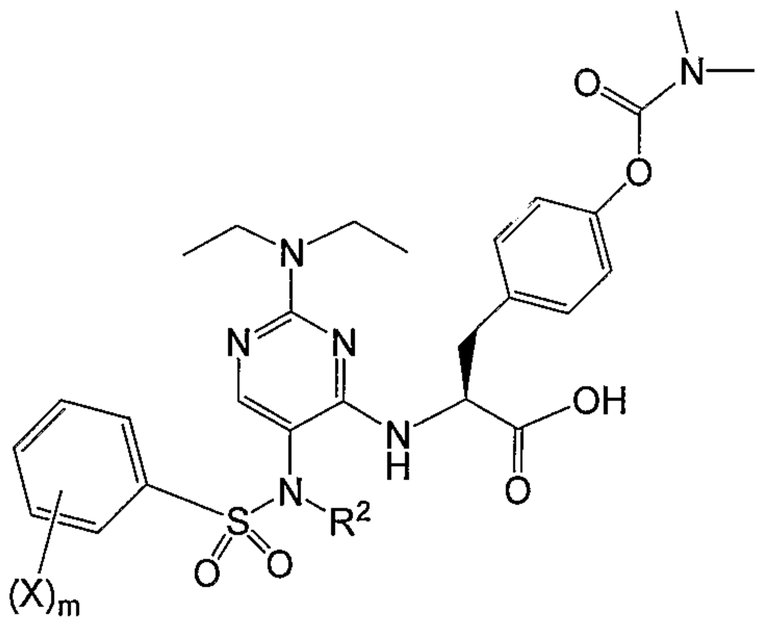
p is 0 or an integer from 1 - 3;

$R^1$ is selected from the group consisting of methyl and ethyl;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XX below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XX

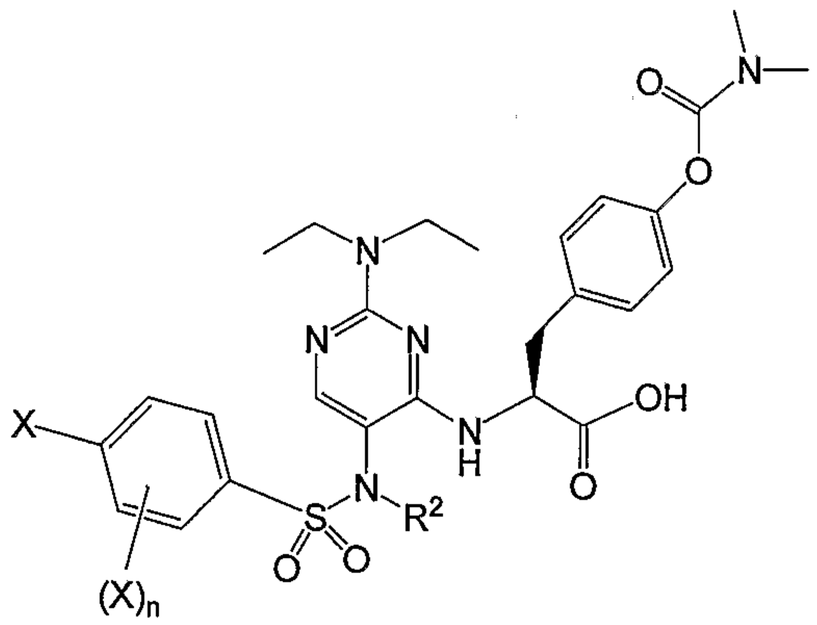
wherein each X is independently selected from the group consisting of fluoro and chloro,

*m* is an integer equal to 1 or 2;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

In one aspect, the compounds that can be utilized as combination therapies with methotrexate for the treatment of RA are compounds defined by Formula XXI below. These compounds have a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15 μM or less (measured as described in Example A below):



XXI

wherein each X is independently fluoro or chloro;

*n* is zero or one;

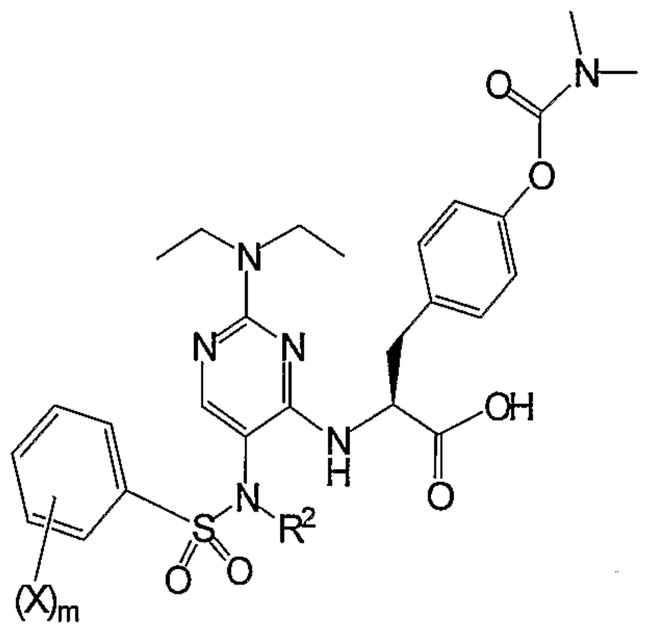
$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

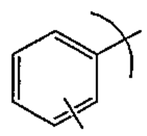
$R^2$ is preferably propargyl in any of one of Formula XIX, XX or XXI.

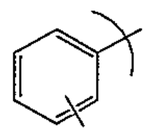
N-[2-N′,N′-diethylamino-5-aminosulfonylphenylpyrimidin-4-yl]-*p*-carbomyloxyphenylalanine compounds within the scope of this invention include those set forth in Table 8 as follows:

Table 8



XVII

| Example No. |  | $R^2$ |
|---|---|---|
| 524 | 4-fluorophenyl | methyl |
| 525 | 4-chlorophenyl | methyl |
| 526 | 3,4 -difluorophenyl | methyl |
| 527 | 3,4-dichlorophenyl | methyl |
| 528 | phenyl | methyl |
| 529 | 2-fluorophenyl | methyl |
| 530 | 3-fluorophenyl | methyl |
| 531 | 4-fluorophenyl | isopropyl |
| 532 | 4-fluorophenyl | ethyl |
| 533 | 3,4-difluorophenyl | isopropyl |
| 534 | 4-chlorophenyl | isopropyl |
| 535 | 3,4-difluorophenyl | ethyl |
| 536 | 4-chlorophenyl | ethyl |
| 537 | 4-fluorophenyl | cyclopropylmethyl |
| 538 | 3,5-difluorophenyl | methyl |

| Example No. |  | $R^2$ |
|---|---|---|
| 539 | 3,5-difluorophenyl | ethyl |
| 540 | 2,4-difluorophenyl | methyl |
| 541 | 2,4-difluorophenyl | ethyl |
| 542 | 3,5-dichlorophenyl | methyl |
| 543 | 3,5-dichlorophenyl | ethyl |
| 544 | 4-fluorophenyl | n-propyl |
| 545 | 4-fluorophenyl | allyl |
| 546 | 4-fluorophenyl | isobutyl |
| 547 | 4-fluorophenyl | n-butyl |
| 548 | 2,6-difluorophenyl | Methyl |
| 549 | 2,3-difluorophenyl | methyl |
| 550 | 4-fluorophenyl | propargyl |
| 551 | 2,4-difluorophenyl | propargyl |
| 552 | 4-fluorophenyl | 2-trisfluoroethyl |

Specific compounds within the scope of this invention include the following. As used below, these compounds are named based on propionic acid derivatives but, alternatively, these compounds could have been named based on N-[2-N′,N′-diethylamino-5-aminosulfonylphenylpyrimidin-4-yl]-*p*-carbomyloxy-phenylalanine derivatives.

2-{2-diethylamino-5-[(4-chlorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-dichlorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(benzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2-fluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3-fluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)isopropylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-difluorobenzenesulfonyl)isopropylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-chlorobenzenesulfonyl)isopropylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-chlorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)cylclopropylmethyl-amino]pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,4-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,4-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-dichlorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-dichlorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)-n-propylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)allylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)isobotylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)-n-butylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,6-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,3-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-Diethylamino-5-[(4-fluorobenzenesulfonyl)propargylamino] pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-Diethylamino-5-[(2,4-difluorobenzenesulfonyl)propargylamino] pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-Diethylamino-5-[(4-fluorobenzenesulfonyl)-(2-trisfluoroethyl)-amino]pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

and pharmaceutically acceptable salts thereof.

Compound Preparation for Compounds of Formulae XVI-XXI

The compounds of Formulae XVI-XXI can be prepared from readily available starting materials using the methods and procedures set forth in the examples below. These methods and procedures outline specific reaction protocols for preparing N-[2-N′,N′-diethylamino-5-aminosulfonylphenyl-yrimidin-4-yl]-*p*-carbomyloxy-phenylalanine compounds. Compounds within the scope not exemplified in these examples and methods are readily prepared by appropriate substitution of starting materials which are either commercially available or well known in the art.

Other procedures and reaction conditions for preparing the compounds of this invention are described in the examples set forth below. Additionally, other procedures for preparing compounds useful in certain aspects of this invention are disclosed in U.S. Patent 6,492,372 the disclosure of which is incorporated herein by reference in its entirety.

Pharmaceutical Formulations of the Compounds

In general, the compounds of the subject invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for these

compounds. The compounds can be administered by a variety of routes, including, but not limited to, oral, parenteral (*e.g.*, subcutaneous, subdural, intravenous, intramuscular, intrathecal, intraperitoneal, intracerebral, intraarterial, or intralesional routes of administration), topical, intranasal, localized (*e.g.*, surgical application or surgical suppository), rectal, and pulmonary (*e.g.*, aerosols, inhalation, or powder). Accordingly, these compounds are effective as both injectable and oral compositions. The compounds can be administered continuously by infusion or by bolus injection. Preferably, the compounds are administered by parenteral routes. More preferably, the compounds are administered by intravenous routes. Such compositions are prepared in a manner well known in the pharmaceutical art.

The actual amount of the compound of the subject invention, *i.e.*, the active ingredient, will depend on a number of factors, such as the severity of the disease, *i.e.*, the condition or disease to be treated, age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the $LD_{50}$ (the dose lethal to 50% of the population) and the $ED_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio $LD_{50}/ED_{50}$. Compounds that exhibit large therapeutic indices are preferred.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the $ED_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the $IC_{50}$ (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. The

effective blood level of the compounds of the subject invention is preferably greater than or equal to 10 ng/ml.

The amount of the pharmaceutical composition administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient are in the form of pharmaceutical compositions described *supra*. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically or therapeutically effective amount. The therapeutic dosage of the compounds of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the range of about 0.5 mg to about 100 mg per kilogram body weight, preferably about 3 mg to about 50 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Typically, the clinician will administer the compound until a dosage is reached that achieves the desired effect.

According to one aspect of the invention, the compounds are administered in combination with methotrexate, to treat, ameliorate, or palliate the symptoms of rheumatoid arthritis. When administered in combination, the compounds may be administered in the same formulation as the methotrexate, or in a separate formulation. The compounds may be administered prior to, following, or concurrently with the methotrexate such that the benefitsd of the combination therapy are achieved. The calculation of appropriate dosages will be well within the purvue of the skilled artisan. Standard doses of methotrexate for the treatment of rheumatoid arthritis range from 2 mg to 20 mg per dose per week. Dosages of the compounds are as set forth above. The methotrexate dosage may be administered as a single dose or as a divided dose. Once a response has been achieved, the dosage may be reduced if possible to the lowest effective dose. The maximum recommended dose is 20 mg/week. Preferably, methotrexate is administered orally or via injection.

When employed as pharmaceuticals, the compounds of the subject invention are usually administered in the form of pharmaceutical compositions. This invention also includes pharmaceutical compositions, which contain as the active ingredient, one or more of the compounds of the subject invention above, associated with one or more pharmaceutically acceptable carriers or excipients. The excipient employed is typically one suitable for administration to human subjects or other mammals. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally

adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The quantity of active compound in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the manner or introduction, the potency of the particular compound, and the desired concentration. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. The concentration of therapeutically active compound may vary from about 1 mg/ml to 250 g/ml.

Preferably, the compound can be formulated for parenteral administration in a suitable inert carrier, such as a sterile physiological saline solution. For example, the concentration of compound in the carrier solution is typically between about 1-100 mg/ml. The dose administered will be determined by route of administration. Preferred routes of administration include parenteral or intravenous administration. A therapeutically effective dose is a dose effective to produce a significant steroid tapering. Preferably, the amount is sufficient to produce a statistically significant amount of steroid tapering in a subject.

Administration of therapeutic agents by intravenous formulation is well known in the pharmaceutical industry. An intravenous formulation should possess certain qualities aside from being just a composition in which the therapeutic agent is soluble. For example, the formulation should promote the overall stability of the active ingredient(s), also, the manufacture of the formulation should be cost effective. All of these factors ultimately determine the overall success and usefulness of an intravenous formulation.

Other accessory additives that may be included in pharmaceutical formulations of compounds of the present invention as follow: solvents: ethanol, glycerol, propylene glycol; stabilizers: EDTA (ethylene diamine tetraacetic acid), citric acid; antimicrobial preservatives: benzyl alcohol, methyl paraben, propyl paraben; buffering agents: citric acid/sodium citrate, potassium hydrogen tartrate, sodium hydrogen tartrate, acetic acid/sodium acetate, maleic acid/sodium maleate, sodium hydrogen phthalate, phosphoric acid/potassium dihydrogen phosphate, phosphoric acid/disodium hydrogen phosphate; and tonicity modifiers: sodium chloride, mannitol, dextrose.

The presence of a buffer is necessary to maintain the aqueous pH in the range of from about 4 to about 8 and more preferably in a range of from about 4 to about 6. The buffer system is generally a mixture of a weak acid and a soluble salt thereof, *e.g.*, sodium citrate/citric acid; or the monocation or dication salt of a dibasic acid, *e.g.*, potassium hydrogen tartrate; sodium hydrogen tartrate, phosphoric acid/potassium dihydrogen phosphate, and phosphoric acid/disodium hydrogen phosphate.

The amount of buffer system used is dependent on (1) the desired pH; and (2) the amount of drug. Generally, the amount of buffer used is in a 0.5:1 to 50:1 mole ratio of buffer:alendronate (where the moles of buffer are taken as the combined moles of the buffer ingredients, *e.g.*, sodium citrate and citric acid) of formulation to maintain a pH in the range of 4 to 8 and generally, a 1:1 to 10:1 mole ratio of buffer (combined) to drug present is used.

A useful buffer in the invention is sodium citrate/citric acid in the range of 5 to 50 mg per ml. sodium citrate to 1 to 15 mg per ml. citric acid, sufficient to maintain an aqueous pH of 4-6 of the composition.

The buffer agent may also be present to prevent the precipitation of the drug through soluble metal complex formation with dissolved metal ions, *e.g.*, Ca, Mg, Fe, Al, Ba, which may leach out of glass containers or rubber stoppers or be present in ordinary tap water. The agent may act as a competitive complexing agent with the drug and produce a soluble metal complex leading to the presence of undesirable particulates.

In addition, the presence of an agent, *e.g.*, sodium chloride in an amount of about of 1-8 mg/ml, to adjust the tonicity to the same value of human blood may be required to avoid the swelling or shrinkage of erythrocytes upon administration of the intravenous formulation leading to undesirable side effects such as nausea or diarrhea and possibly to associated blood disorders. In general, the tonicity of the formulation matches that of human blood which is in

the range of 282 to 288 mOsm/kg, and in general is 285 mOsm/kg , which is equivalent to the osmotic pressure corresponding to a 0.9% solution of sodium chloride.

The intravenous formulation can be administered by direct intravenous injection, i.v. bolus, or can be administered by infusion by addition to an appropriate infusion solution such as 0.9% sodium chloride injection or other compatible infusion solution.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner

component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The compounds of this invention can be administered in a sustained release form. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the protein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, *J. Biomed. Mater. Res.* 15: 167-277 (1981) and Langer, *Chem. Tech.* 12: 98-105 (1982) or poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, *Biopolymers* 22: 547-556, 1983), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (*i.e.*, injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

The compounds of this invention can be administered in a sustained release form, for example a depot injection, implant preparation, or osmotic pump, which can be formulated in such a manner as to permit a sustained release of the active ingredient. Implants for sustained release formulations are well-known in the art. Implants may be formulated as, including but not limited to, microspheres, slabs, with biodegradable or non-biodegradable polymers. For example, polymers of lactic acid and/or glycolic acid form an erodible polymer that is well-tolerated by the host. The implant is placed in proximity to the site of protein deposits (*e.g.*, the site of formation of amyloid deposits associated with neurodegenerative disorders), so that the local concentration of active agent is increased at that site relative to the rest of the body.

The following formulation examples illustrate pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 30.0 |
| Starch | 305.0 |
| Magnesium stearate | 5.0 |

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 25.0 |
| Cellulose, microcrystalline | 200.0 |
| Colloidal silicon dioxide | 10.0 |
| Stearic acid | 5.0 |

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

| Ingredient | Weight % |
|---|---|
| Active Ingredient | 5 |
| Lactose | 95 |

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 30.0 mg |
| Starch | 45.0 mg |
| Microcrystalline cellulose | 35.0 mg |
| Polyvinylpyrrolidone (as 10% solution in water) | 4.0 mg |
| Sodium carboxymethyl starch | 4.5 mg |
| Magnesium stearate | 0.5 mg |
| Talc | 1.0 mg |
| Total | 120 mg |

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules, which after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 40.0 mg |
| Starch | 109.0 mg |
| Magnesium stearate | 1.0 mg |
| Total | 150.0 mg |

The active ingredient, cellulose, starch, an magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

| Ingredient | Amount |
|---|---|
| Active Ingredient | 25 mg |
| Saturated fatty acid glycerides | to 2,000 mg |

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

| Ingredient | Amount |
|---|---|
| Active Ingredient | 50.0 mg |
| Xanthan gum | 4.0 mg |
| Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%) | 50.0 mg |
| Sucrose | 1.75 g |
| Sodium benzoate | 10.0 mg |
| Flavor and Color | q.v. |
| Purified water | to 5.0 ml |

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and

color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Hard gelatin tablets, each containing 15 mg of active ingredient are made as follows:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 15.0 mg |
| Starch | 407.0 mg |
| Magnesium stearate | 3.0 mg |
| Total | 425.0 mg |

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Formulation Example 9

An intravenous formulation may be prepared as follows:

| Ingredient | Quantity |
|---|---|
| Active Ingredient | 250.0 mg |
| Isotonic saline | 1000 ml |

Therapeutic compound compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle or similar sharp instrument.

Formulation Example 10

A topical formulation may be prepared as follows:

| Ingredient | Quantity |
|---|---|
| Active Ingredient | 1-10 g |
| Emulsifying Wax | 30 g |
| Liquid Paraffin | 20 g |
| White Soft Paraffin | to 100 g |

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Example 11

An aerosol formulation may be prepared as follows:

A solution of the candidate compound in 0.5% sodium bicarbonate/saline (w/v) at a concentration of 30.0 mg/mL is prepared using the following procedure:

A. Preparation of 0.5% Sodium Bicarbonate / Saline Stock Solution: 100.0 mL

| Ingredient | Gram / 100.0 mL | Final Concentration |
|---|---|---|
| Sodium Bicarbonate | 0.5 g | 0.5% |
| Saline | q.s. ad 100.0 mL | q.s. ad 100% |

Procedure:

1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
2. Add approximately 90.0 mL saline and sonicate until dissolved.
3. Q.S. to 100.0 mL with saline and mix thoroughly.

B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL

| Ingredient | Gram / 10.0 mL | Final Concentration |
|---|---|---|
| Candidate Compound | 0.300 g | 30.0 mg/mL |
| 0.5% Sodium Bicarbonate / Saline Stock Solution | q.s. ad 10.0 mL | q.s ad 100% |

Procedure:

1. Add 0.300 g of the candidate compound into a 10.0 mL volumetric flask.
2. Add approximately 9.7 mL of 0.5% sodium bicarbonate / saline stock solution.
3. Sonicate until the candidate compound is completely dissolved.
4. Q.S. to 10.0 mL with 0.5% sodium bicarbonate / saline stock solution and mix thoroughly.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to

provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent No. 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Direct or indirect placement techniques may be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent No. 5,011,472, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

According to one aspect of the invention, the compound may be administered alone with methotrexate, as a combination of compounds and with methotrexate, or in combination with anti-alpha-4-antibodies and methotrexate. The compounds of the present invention may also be administered in combination with an immunosuppressant, wherein the immunosuppressant is typically used to treat the condition or disease for which the compound of the present invention is being administered. The immunosuppressant may b,e, but is not limited to, azathioprine, 6-mercaptopurine, or mycophenolate.

When administered in combination, the small compounds may be administered in the same formulation as these other compounds or compositions, or in a separate formulation. When administered in combinations, the compounds may be administered prior to, following, or concurrently with the other compounds and methotrexate.

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in

*Remington's Pharmaceutical Sciences,* Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

In order to enhance serum half-life, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, *e.g.*, Szoka *et al.*, U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

Polymer conjugates

Compounds of the present invention may be formulated and administered as polymer conjugates, preferably PEG derivatives. Polymer conjugates may exhibit benefits over non-conjugated polymers, such as improved solubility and stability.

As such, single polymer molecules may be employed for conjugation with the compounds of the present invention, although it is also contemplated that more than one polymer molecule can be attached as well. The conjugated compounds of the present invention may find utility in both *in vivo* as well as non-*in vivo* applications. Additionally, it will be recognized that the conjugating polymer may utilize any other groups, moieties, or other conjugated species, as appropriate to the end use application. By way of example, it may be useful in some applications to covalently bond to the polymer a functional moiety imparting UV-degradation resistance, or antioxidation, or other properties or characteristics to the polymer. As a further example, it may be advantageous in some applications to functionalize the polymer to render it reactive and enable it to cross-link to a drug molecule and to enhance various properties or characteristics of the overall conjugated material. Accordingly, the polymer may contain any functionality, repeating groups, linkages, or other constitutent structures which do not preclude the efficacy of the conjugated the compounds of the present invention composition for its intended purpose.

Illustrative polymers that may usefully be employed to achieve these desirable characteristics are described *supra*, as well as in PCT WO 01/54690 (to Zheng *et al.*) incorporated by reference herein in its entirety. The polymer may be coupled to the compounds of the present invention (preferably via a linker moiety) to form stable bonds that are not significantly cleavable by human enzymes. Generally, for a bond to be not "significantly" cleavable requires that no more than about 20% of the bonds connecting the

polymer and the compounds of the present invention to which the polymer is linked, are cleaved within a 24 hour period, as measured by standard techniques in the art including, but not limited to, high pressure liquid chromatography (HPLC).

The compounds of the present inventions are conjugated most preferably via a terminal reactive group on the polymer although conjugations can also be branched from non-terminal reactive groups. The polymer with the reactive group(s) is designated herein as "activated polymer". The reactive group selectively reacts with reactive groups on the compounds of the present invention. The activated polymer(s) is reacted so that attachment may occur at any available functional group on compounds of the present invention. Amino, carbon, free carboxylic groups, suitably activated carbonyl groups, hydroxyl, guanidyl, oxidized carbohydrate moieties, amino, carbon and mercapto groups of the compounds of the present invention (if available) can be used as attachment sites.

Generally, about 1.0 to about 10 moles of activated polymer per mole of the compounds of the present invention, depending on concentration, is employed. The final amount is a balance between maximizing the extent of the reaction while minimizing non-specific modifications of the product and, at the same time, defining chemistries that will maintain optimum activity, while at the same time optimizing the half-life of the compounds of the present invention. Preferably, at least about 50% of the biological activity of the compounds of the present invention is retained, and most preferably 100% is retained.

The reactions may take place by any suitable art-recognized method used for reacting biologically active materials with inert polymers. Generally, the process involves preparing an activated polymer and thereafter reacting the compounds of the present invention with the activated polymer to produce a soluble compound suitable for formulation. This modification reaction can be performed by several methods, which may involve one or more steps. The polymeric substances included herein are preferably water-soluble at room temperature. A non-limiting list of such polymers includes polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained.

In the preferred practice of the present invention, polyalkylene glycol residues of $C_1$-$C_4$ alkyl polyalkylene glycols, preferably polyethylene glycol (PEG), or poly(oxy)alkylene glycol residues of such glycols are advantageously incorporated in the polymer systems of

interest. Thus, the polymer to which the compounds of the present invention are attached may be a homopolymer of polyethylene glycol (PEG) or is a polyoxyethylated polyol, provided in all cases that the polymer is soluble in water at room temperature. Non-limiting examples of such polymers include polyalkylene oxide homopolymers such as PEG or polypropylene glycols, polyoxyethylenated glycols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymer is maintained.

Examples of polyoxyethylated polyols include, but are not limited to, polyoxyethylated glycerol, polyoxyethylated sorbitol, polyoxyethylated glucose, or the like. The glycerol backbone of polyoxyethylated glycerol is the same backbone occurring naturally in, for example, animals and humans in mono-, di-, and triglycerides. Therefore, this branching would not necessarily be seen as a foreign agent in the body.

Those of ordinary skill in the art will recognize that the foregoing list is merely illustrative and that all polymer materials having the qualities described herein are contemplated. The polymer need not have any particular molecular weight, but it is preferred that the molecular weight be between about 300 and 100,000, more preferably between 10,000 and 40,000. In particular, sizes of 20,000 or more are most effective at preventing loss of the product due to filtration in the kidneys.

Polyethylene glycol (PEG) and related polyalkylene oxides (PAOs) are known in the art as being useful adjuncts for the preparation of drugs. See for example, PCT WO 93/24476. PEG has also been conjugated to proteins, peptides and enzymes to increase aqueous solubility and circulating life *in vivo* as well as reduce antigenicity. See, for example, U.S. Patent Nos. 5,298,643 and 5,321,095, both to Greenwald *et al.* PCT WO 93/24476 discloses using an ester linkage to covalently bind an organic molecule to water-soluble polyethylene glycols. Thus, the compounds of the invention are preferably administered as polyethylene glycol (PEG) derivatives. Further description of polyethylene glycol derivatives of the compounds of the present invention and reaction conditions for preparing these derivatives are described in U.S.S.N. 60/538,573, entitled "Polyethylene Glycol Conjugates of Dipeptides," filed January 23, 2004, herein incorporated by reference in its entirety.

As such, the compounds or conjugates of this invention may contain one or more polyethylene glycol (PEG) substituents covalently attached thereto. Such conjugates demonstrate improved serum half-life, as compared to compounds lacking polyethylene

glycol substituents. Without being limited to any theory, the improved serum half-life is believed to be associated with the covalent conjugation of at least one polyethylene glycol entity onto the structure of the compound.

The term "PEG" refers to polymers comprising multiple oxyalkylene units. Such polymers are optionally mono-capped with a substituent preferably selected from alkyl, aryl, substituted alkyl, and substituted aryl. Inclusive of such polymers are those diamino capped polyoxyalkylene polymers which are known in the art as Jeffamines®. Still further, such polymers can optionally contain one or more non-oxyalkylene units such as the commercially available poly[di(ethylene glycol)adipates, poly[di(ethylene glycol)phthalate diols, and the like.

By PEG derivative is meant a polyethylene glycol polymer in which one or both of the terminal hydroxyl groups found in polyethylene glycol itself has been modified. Examples of suitable modifications include replacing one or both hydroxyl group(s) with alternative functional groups, which may be protected or unprotected, with low molecular weight ligands, or with another macromolecule or polymer. Modification of the terminal hydroxyl groups in the polyethylene glycol may be achieved by reacting the polyethylene glycol with compounds comprising complementary reactive functional groups, including functional groups which are able to undergo a reaction with the hydroxyl groups in polyethylene glycol. The PEG derivatives of the compounds of this invention may contain one or more polyethylene glycol (PEG) substituents covalently attached thereto by a linking group.

"Linking group" or "linker" refers to a group or groups that covalently links a non-PEG substituted compound of the present invention with one or more PEG groups. Each linker may be chiral or achiral, linear, branched or cyclic and may be homogenous or heterogeneous in its atom content (*e.g.*, linkers containing only carbon atoms or linkers containing carbon atoms as well as one or more heteroatoms present on the linker.

The PEG group or groups are covalently attached to the linker using conventional chemical techniques providing for covalent linkage of the PEG group to the linker. The linker, in turn, may be covalently attached to the otherwise, non-PEG substituted compounds of the present invention. Reaction chemistries resulting in such linkages are well known in the art. Such reaction chemistries involve the use of complementary functional groups on the linker, the non-PEG substituted compound of the present invention and the PEG groups.

Preferably, the complementary functional groups on the linker are selected relative to the functional groups available on the PEG group for bonding or which can be introduced onto the PEG group for bonding. Again, such complementary functional groups are well known in the art.

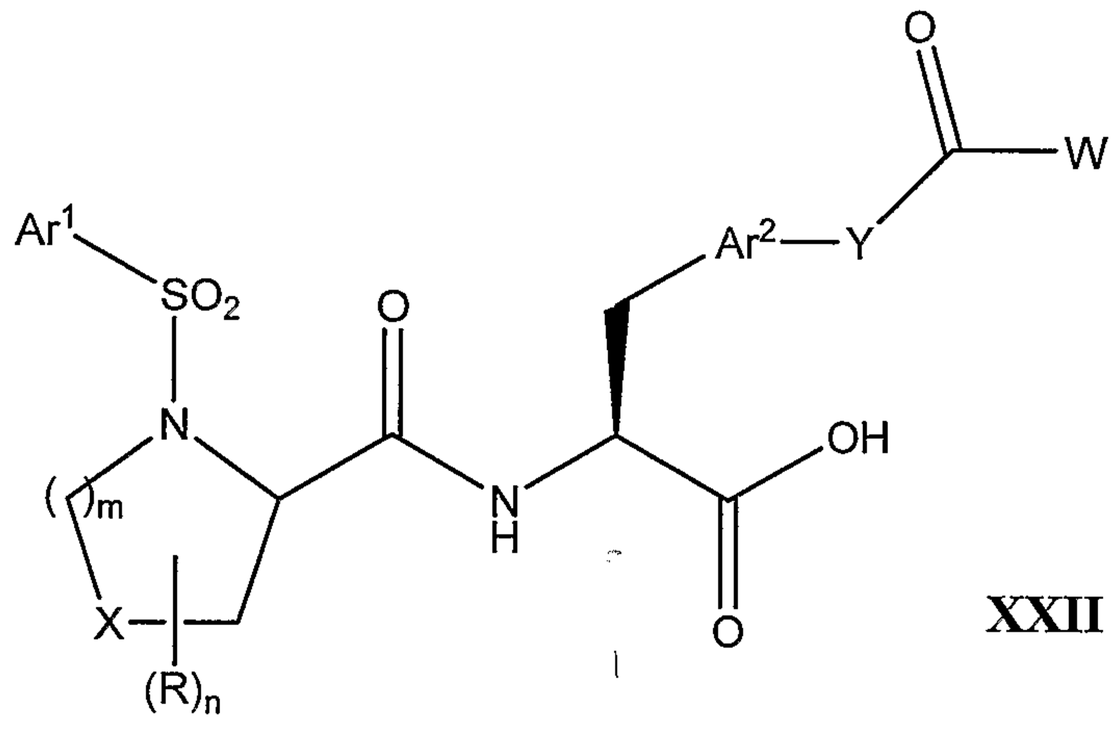
Such polymers have a number average molecular weight of from about 100 to 100,000; preferably from about 1,000 to 50,000; more preferably from about 10,000 to about 40,000.

The polymer conjugates of the invention may provide enhanced *in vivo* retention as compared to the non-conjugated compounds. The improved retention of the conjugate within the body results in lower required dosages of the drug, which in turn results in fewer side effects and reduced likelihood of toxicity. In addition, the drug formulation comprising these polymer conjugates may be administered less frequently to the patient while achieving a similar or improved therapeutic effect. The conjugates of this invention have improved inhibition, *in vivo*, of adhesion of leukocytes to endothelial cells mediated by VLA-4 by competitive binding to VLA-4. Preferably, the compounds of this invention can be used in I.V. formulations.

The therapeutic dosage of the polymer conjugates of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the range of about 20 μg to about 2000 μg per kilogram body weight, preferably about 20 μg to about 500 μg, more preferably about 100 μg to about 300 μg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.1 pg to 1 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

When formulated and administered as polymer conjugates, the compounds or conjugates of this invention are characterized as containing one or more polyethylene glycol substituents covalently attached thereto. Without being limited to any theory, the improved serum half-life is believed to be associated with covalent conjugation of at least one polyethylene glycol entity onto the structure of the compound.

Accordingly, the compounds of the present invention may be PEG derivatives of formula XXII below:



**XXII**

wherein

R is selected from the group consisting of a PEG moiety, amino, substituted amino, alkyl and substituted alkyl wherein each amino, substituted amino, alkyl and substituted alkyl is optionally substituted with a PEG moiety wherein, in each case, the PEG moiety optionally comprises a linker which covalently links the PEG moiety;

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

$Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^2$;

X is selected from the group consisting of -S-, -SO-, $-SO_2$ and optionally substituted -$CH_2$-;

Y is selected from the group consisting of -O- and $-NR^1$- wherein $R^1$ is selected from the group consisting of hydrogen and alkyl;

W is selected from the group consisting of a PEG moiety which optionally comprises a linker and $-NR^2R^3$ wherein $R^2$ and $R^3$ are independently selected from the group consisting of alkyl, substituted alkyl, and where $R^2$ and $R^3$, together with the nitrogen atom bound thereto, form a heterocyclic ring or a substituted heterocyclic ring wherein each of alkyl,

substituted alkyl, heterocyclic and substituted heterocyclic is optionally substituted with a PEG moiety which further optionally comprises a linker;

*m* is an integer equal to 0, 1 or 2;

*n* is an integer equal to 0 to 2; and

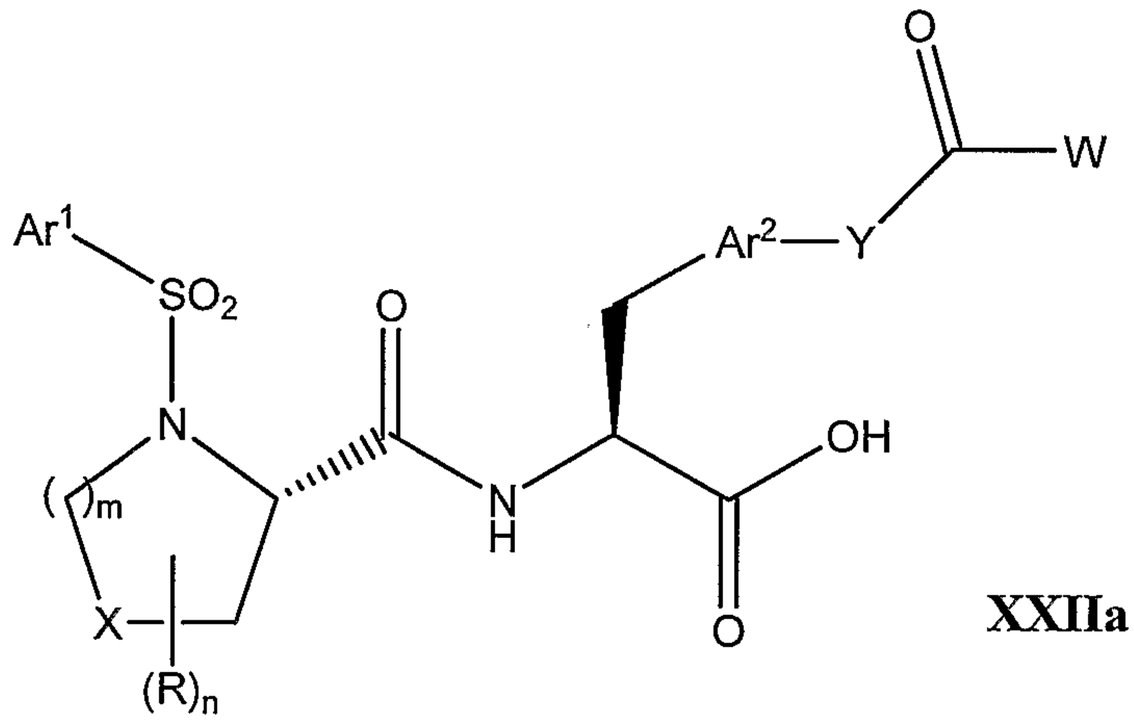
pharmaceutically acceptable salts thereof;

provided that at least one of R, $Ar^1$, $Ar^2$, W and $-NR^2R^3$ contains a PEG moiety;

further provided that when R is a PEG moiety, *n* is one and X is not -S-, -SO-, or -$SO_2$-;

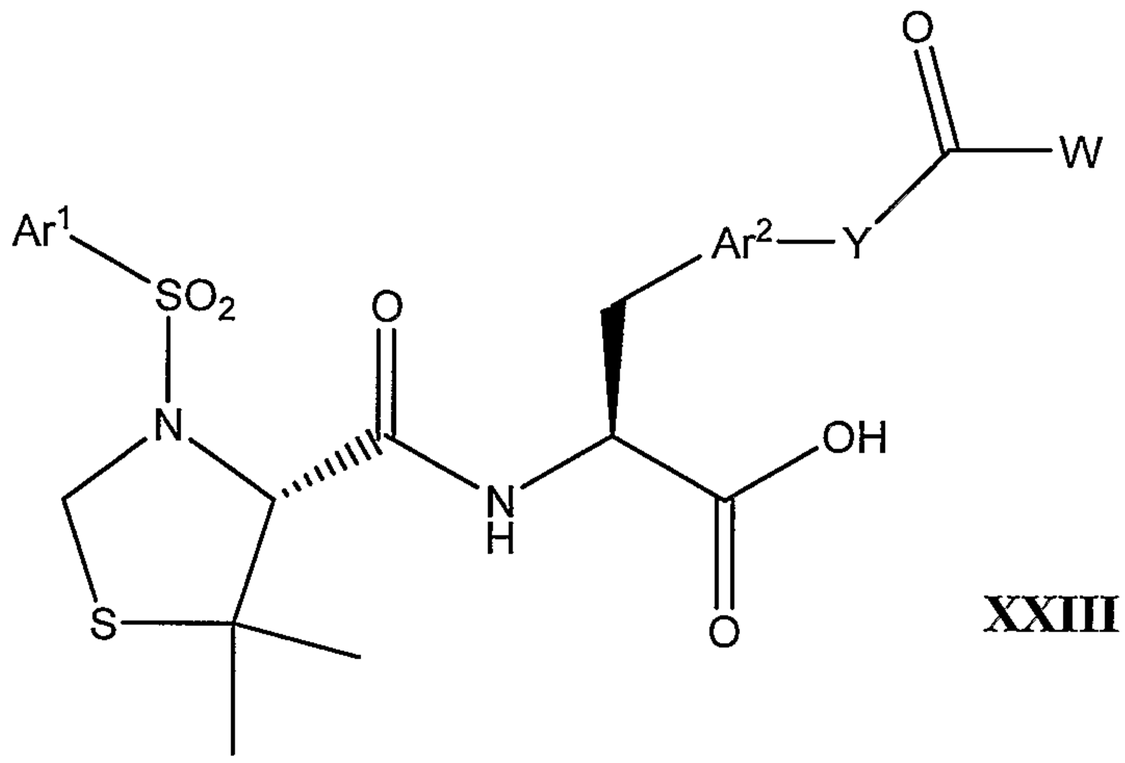
and still further provided that the compound of formula XXII has a molecular weight of no more than 100,000.

Preferably the PEG derivates of formula XXII are the of the L isomer as shown below:



**XXIIa**

In another aspect, the compounds of the present invention may be PEG derivatives of formula XXIII below:



**XXIII**

wherein

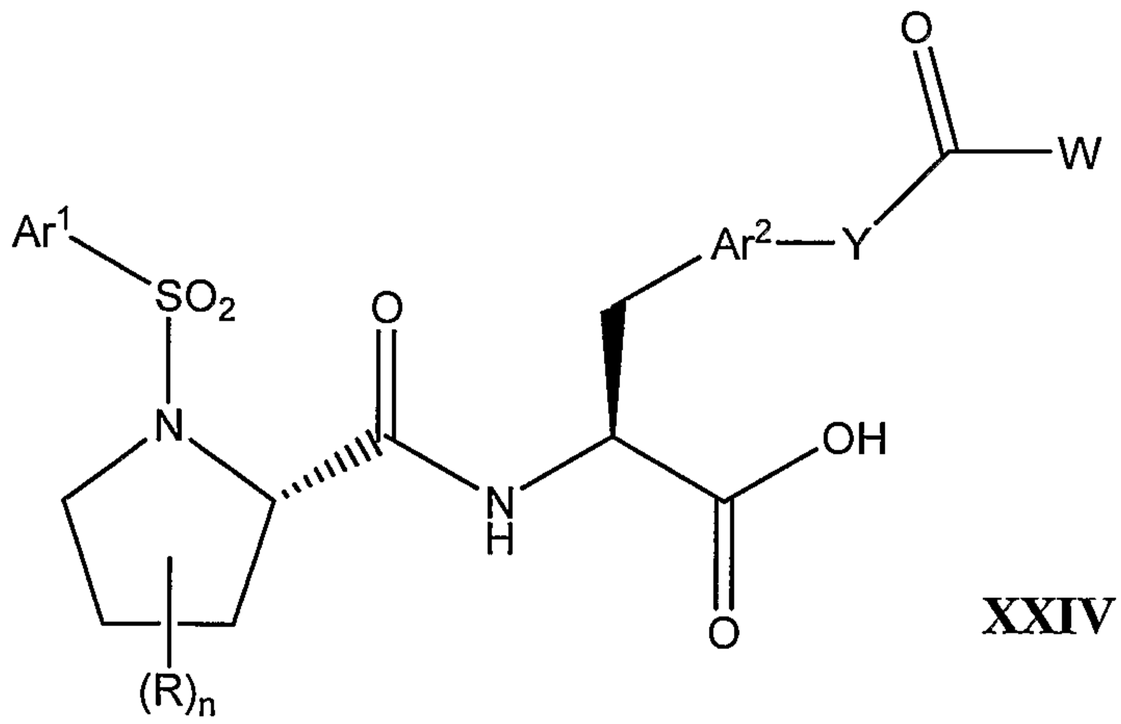
$Ar^1$, $Ar^2$, Y and W are as defined above; and

pharmaceutically acceptable salts thereof;

provided that at least one of $Ar^1$, $Ar^2$, W and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of formula XXIII has a molecular weight of no more than 100,000.

In another aspect, the compounds of the present invention may be PEG derivatives of formula XXIV below:



**XXIV**

wherein

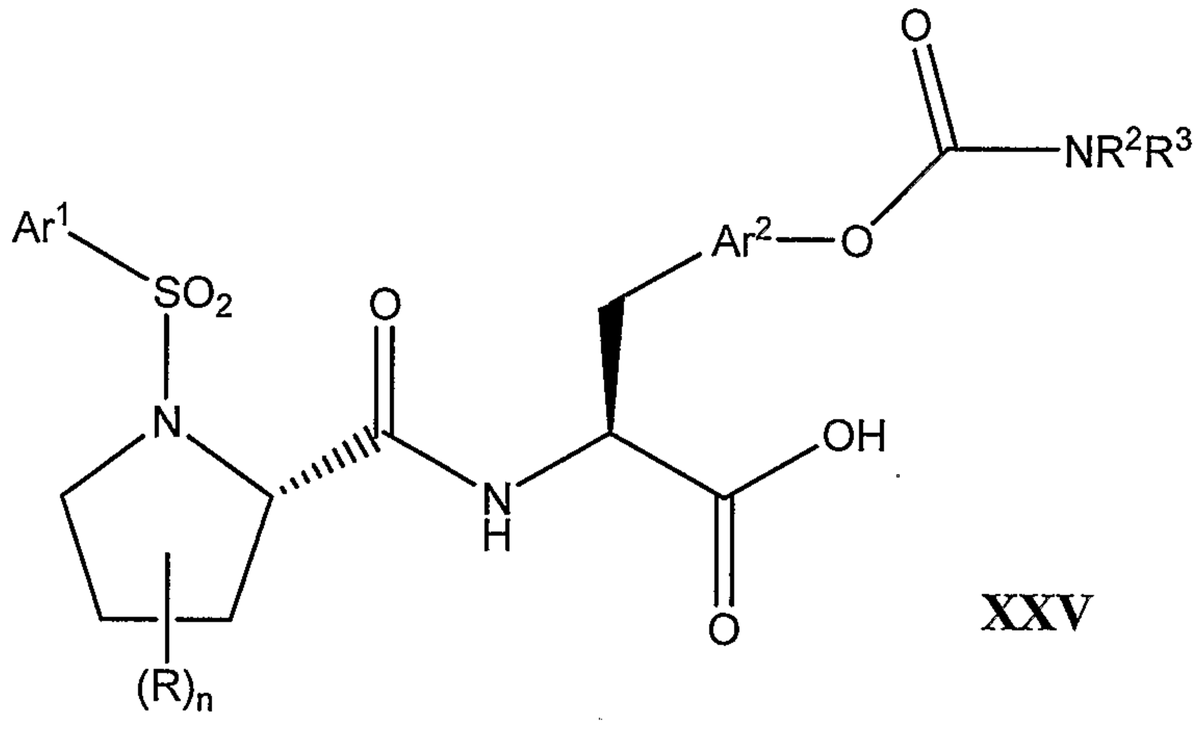
R, $Ar^1$, $Ar^2$, Y, W and *n* are as defined above; and

pharmaceutically acceptable salts thereof;

provided that at least one of R, $Ar^1$, $Ar^2$, W and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of formula XXVI has a molecular weight of no more than 100,000.

In another aspect, the compounds of the present invention may be PEG derivatives of formula XXV below:



**XXV**

wherein

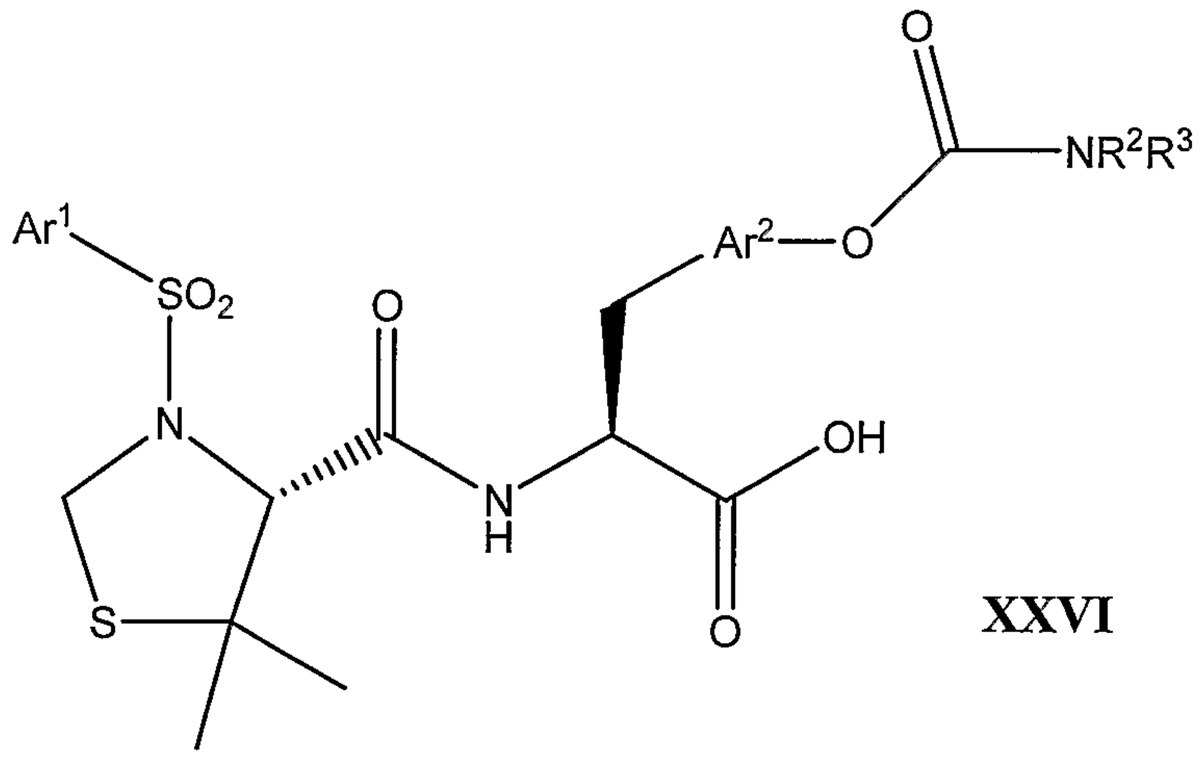
R, $R^2$, $R^3$, $Ar^1$, $Ar^2$ and *n* are as defined above; and

pharmaceutically acceptable salts thereof;

provided that at least one of R, $Ar^1$, $Ar^2$, and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of formula XXV has a molecular weight of no more than 100,000.

In another of its aspects, the compound of this invention is directed to a PEG derivative of formula XXVI below:



XXVI

wherein

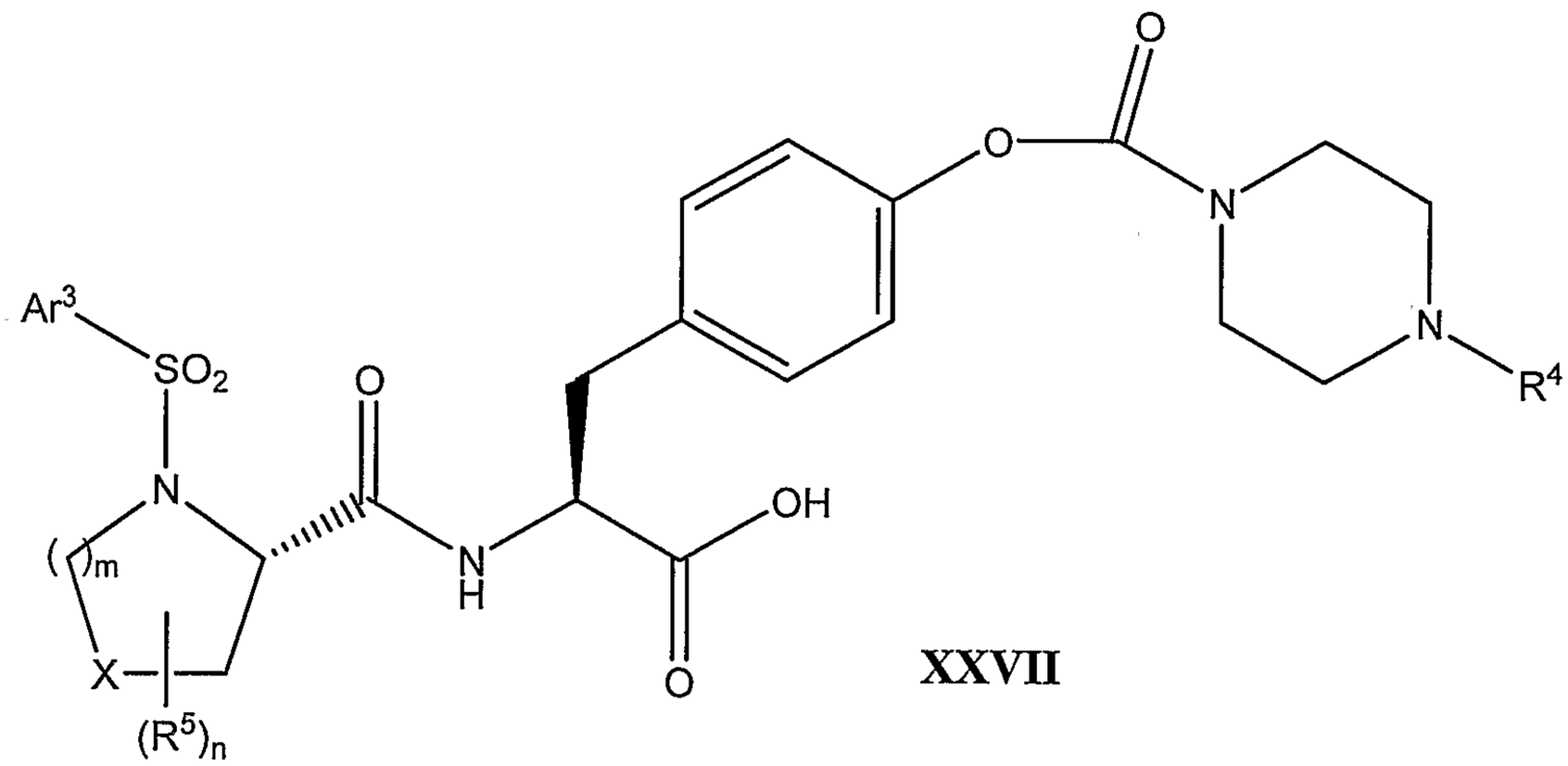
$R^2$, $R^3$, $Ar^1$, and $Ar^2$ are as defined above; and

pharmaceutically acceptable salts thereof;

provided that at least one of $Ar^1$, $Ar^2$ and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of formula XXVI has a molecular weight of no more than 100,000.

In another aspect, the compounds of this invention can be PEG derivatives of formula XXVII:



XXVII

wherein

$R^4$ is a PEG moiety which optionally comprises a linker;

$R^5$ is selected from the group consisting of alkyl and substituted alkyl;

$Ar^3$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

X is selected from the group consisting of -S-, -SO-, and -$SO_2$- or optionally substituted -$CH_2$-;

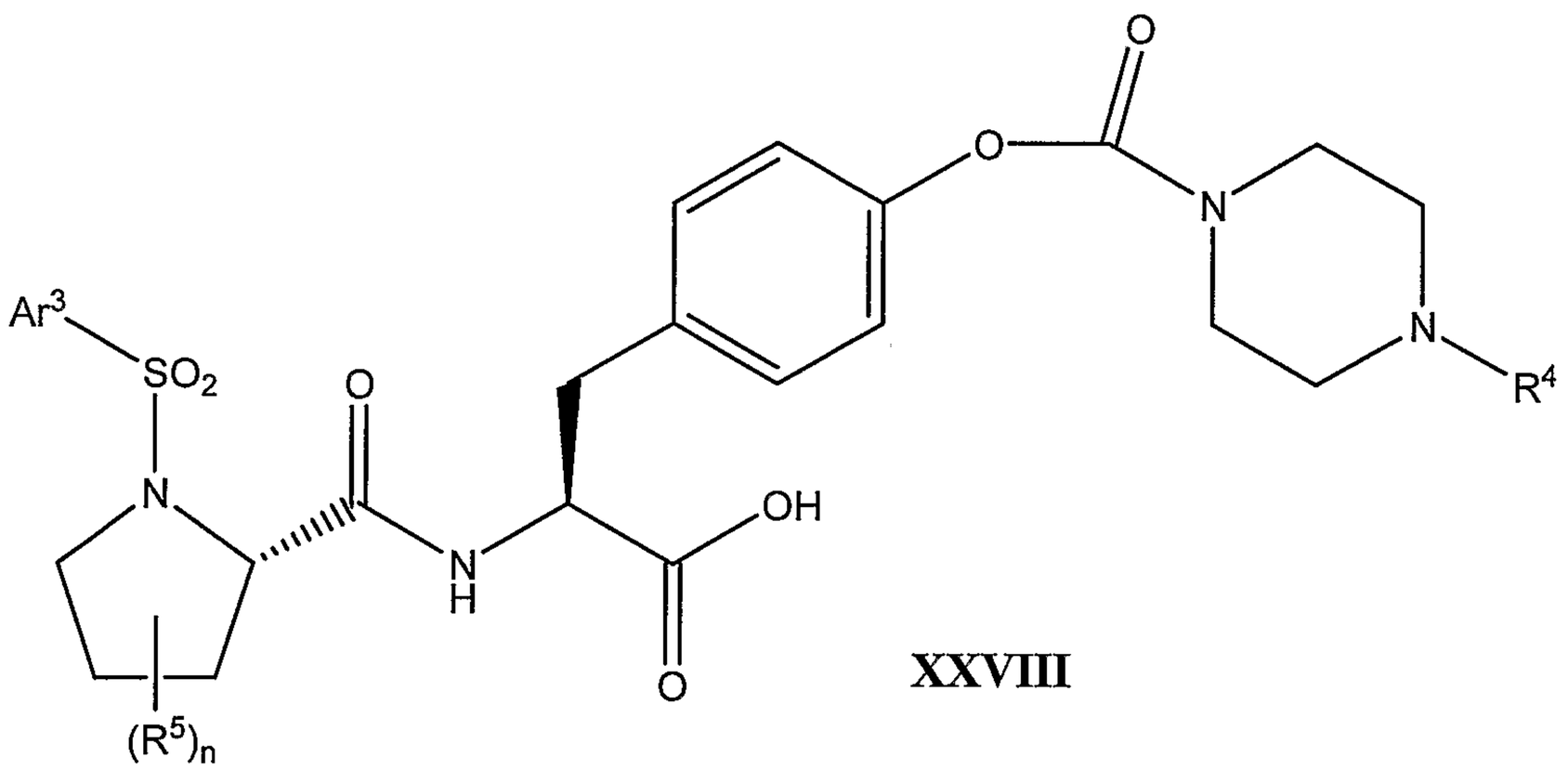
*m* is an integer equal to 0, 1 or 2;

*n* is an integer equal to 0 to 2; and

pharmaceutically acceptable salts thereof;

provided that the compound of formula XXVII has a molecular weight of no more than 100,000.

In another aspect, the compound of the invention can be a PEG derivative of formula XXVIII:




**XXVIII**

wherein

$R^4$ is a PEG moiety which optionally comprises a linker;

$R^5$ is selected from the group consisting of alkyl and substituted alkyl;

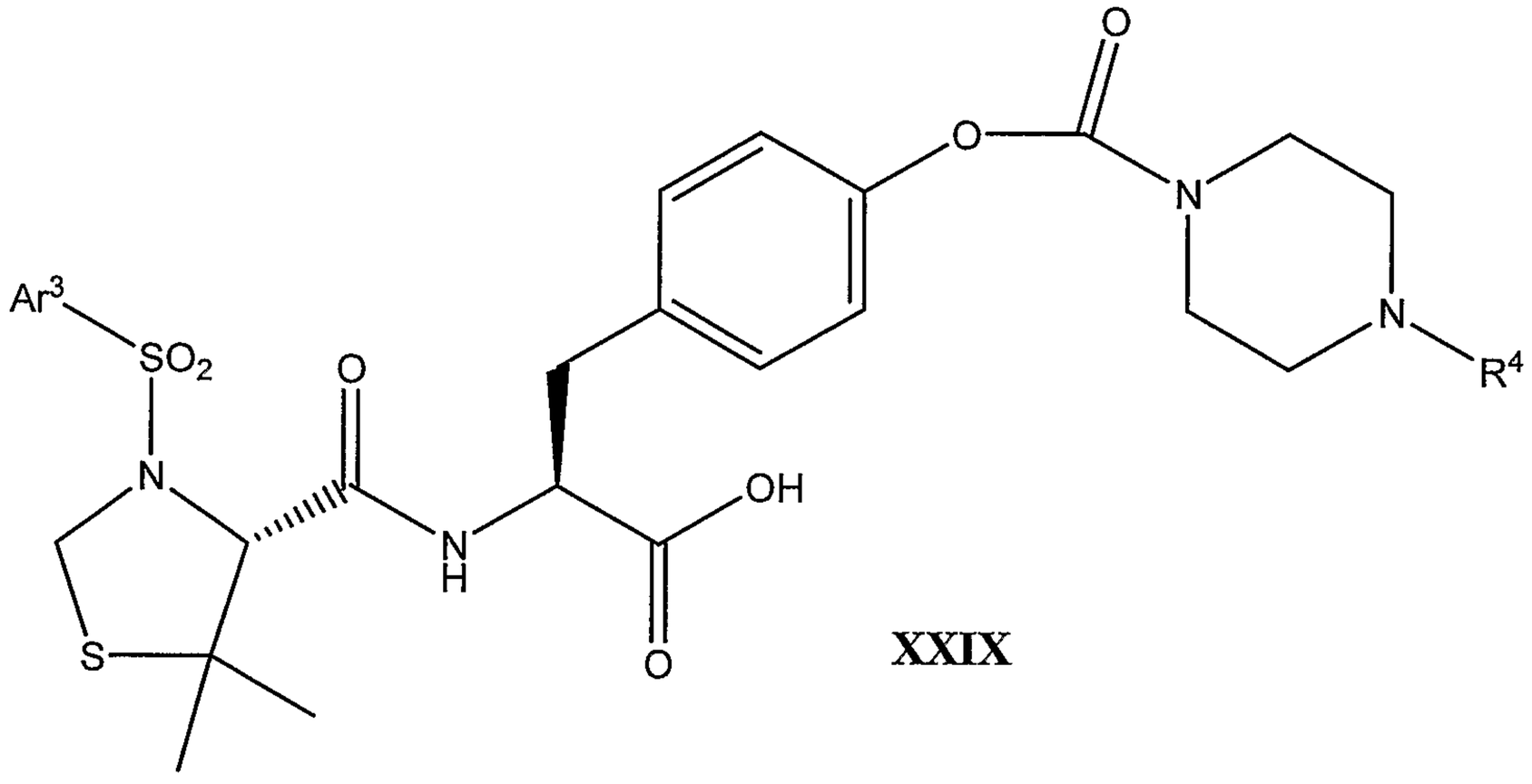
$Ar^3$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

*n* is an integer equal to 0 to 2; and

pharmaceutically acceptable salts thereof;

provided that the compound of formula XXVIII has a molecular weight of no more than 100,000.

In another aspect, the compound of the invention can be a PEG derivative of formula XXIX:



**XXIX**

wherein

$R^4$ is a PEG moiety which optionally comprises a linker;

$Ar^3$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

pharmaceutically acceptable salts thereof;

provided that the compound of formula XXIX has a molecular weight of no more than 100,000.

Preferably, when $Ar^1$ does not contain a PEG moiety, $Ar^1$ in formulas XXII-XXVI and $Ar^3$ in formulas XXVII-XXIX is selected from the group consisting of:

phenyl,

4-methylphenyl,

4-*t*-butylphenyl,

2,4,6-trimethylphenyl,

2-fluorophenyl,

3-fluorophenyl,

4-fluorophenyl,

2,4-difluorophenyl,

3,4-difluorophenyl,

3,5-difluorophenyl,

2-chlorophenyl,

3-chlorophenyl,

4-chlorophenyl,

3,4-dichlorophenyl,

3,5-dichlorophenyl,

3-chloro-4-fluorophenyl,

4-bromophenyl,

2-methoxyphenyl,

3-methoxyphenyl,

4-methoxyphenyl,

3,4-dimethoxyphenyl,

4-*t*-butoxyphenyl,

4-(3'-dimethylamino-*n*-propoxy)-phenyl,

2-carboxyphenyl,

2-(methoxycarbonyl)phenyl,

4-($H_2NC(O)$-)phenyl,

4-($H_2NC(S)$-)phenyl,

4-cyanophenyl,

4-trifluoromethylphenyl,

4-trifluoromethoxyphenyl,

3,5-di-(trifluoromethyl)phenyl,

4-nitrophenyl,

4-aminophenyl,

4-($CH_3C(O)NH$-)phenyl,

4-(PhNHC(O)NH-)phenyl,

4-amidinophenyl,

4-methylamidinophenyl,

4-[$CH_3SC(=NH)$-]phenyl,

4-chloro-3-[$H_2NS(O)_2$-]phenyl,

1-naphthyl,

2-naphthyl,

pyridin-2-yl,

pyridin-3-yl,

pyridine-4-yl,

pyrimidin-2-yl,

quinolin-8-yl,

2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl,

2-thienyl,

5-chloro-2-thienyl,

2,5-dichloro-4-thienyl,

1-*N*-methylimidazol-4-yl,

1-*N*-methylpyrazol-3-yl,

1-*N*-methylpyrazol-4-yl,

1-*N*-butylpyrazol-4-yl,

1-*N*-methyl-3-methyl-5-chloropyrazol-4-yl,

1-*N*-methyl-5-methyl-3-chloropyrazol-4-yl,

2-thiazolyl, and

5-methyl-1,3,4-thiadiazol-2-yl.

When $Ar^1$ contains a PEG group, $Ar^1$ is preferably of the formula:

$$-Ar^1-Z-(CH_2CHR^7O)_pR^8$$

wherein

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

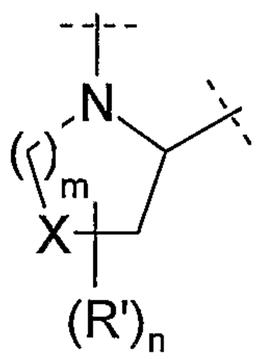
Z is selected from the group consisting of a covalent bond, a linking group of from 1 to 40 atoms, -O-, and $-NR^9-$, where $R^9$ is selected from the group consisting of hydrogen and alkyl,

$R^7$ is selected from the group consisting of hydrogen and methyl;

$R^8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and $-CH_2CHR^7NR^{10}R^{11}$ where $R^7$ is as defined above and $R^{10}$ and $R^{11}$ are independently selected from the group consisting of hydrogen and alkyl; and

*p* is an integer such that the molecular weight of the PEG moiety ranges from 100 to 100,000.

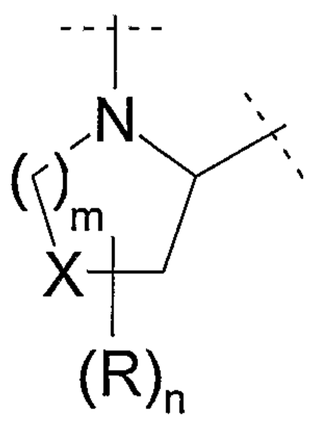
Preferably, when R does not contain a PEG moiety, the substituent of the formula:



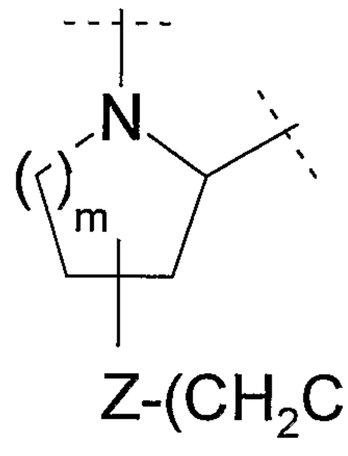

where X, *m* and *n* are as defined above, and R' is alkyl or substituted alkyl is preferably selected from the group consisting of:

azetidinyl, thiazolidinyl, piperidinyl, piperazinyl, thiomorpholinyl, pyrrolidinyl, 4-hydroxypyrrolidinyl, 4-oxopyrrolidinyl, 4-fluoropyrrolidinyl, 4,4-difluoropyrrolidinyl, 4-(thiomorpholin-4-ylC(O)O-)pyrrolidinyl, 4-[$CH_3S(O)_2O$-]pyrrolidinyl, 3-phenylpyrrolidinyl, 3-thiophenylpyrrolidinyl, 4-aminopyrrolidinyl, 3-methoxypyrrolidinyl, 4,4-dimethylpyrrolidinyl, 4-*N*-Cbz-piperazinyl, 4-[$CH_3S(O)_2$-]piperazinyl, 5,5-dimethylthiazolindin-4-yl, 1,1-dioxo-thiazolidinyl, 1,1-dioxo-5,5-dimethylthiazolidin-2-yl and 1,1-dioxothiomorpholinyl.

When the substituent of the formula:



contains a PEG moiety, then preferably the substituent is of the formula:




wherein

*m* is an integer equal to zero, one or two;

Z is selected from the group consisting of a covalent bond, a linking group of from 1 to 40 atoms, -O-, and -$NR^9$-, where $R^9$ is selected from the group consisting of hydrogen and alkyl,

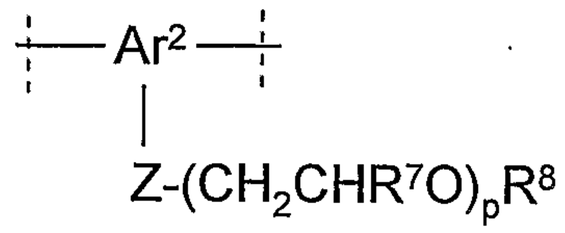
$R^7$ is selected from the group consisting of hydrogen and methyl;

$R^8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and -$CH_2CHR^7NR^{10}R^{11}$ where $R^7$ is as defined above and $R^{10}$ and $R^{11}$ are independently selected from the group consisting of hydrogen and alkyl; and

*p* is an integer such that the molecular weight of the PEG moiety ranges from 100 to 100,000.

Preferably, when $Ar^2$ does not contain a PEG moiety, $Ar^2$ in formulas I-V is preferably selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and 4-pyrid-2-onyl.

When $Ar^2$ contains a PEG moiety, $Ar^2$ in formulas XXII-XXVI is preferably represented by the formula:



where $Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

Z is selected from the group consisting of a covalent bond, a linking group of from 1 to 40 atoms, -O-, and $-NR^9-$, where $R^9$ is selected from the group consisting of hydrogen and alkyl,

$R^7$ is selected from the group consisting of hydrogen and methyl;

$R^8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and $-CH_2CHR^7NR^{10}R^{11}$ where $R^7$ is as defined above and $R^{10}$ and $R^{11}$ are independently selected from the group consisting of hydrogen and alkyl; and

*p* is an integer such that the molecular weight of the PEG moiety ranges from 100 to 100,000.

Preferably, in formulas XXII-XXIV, -YC(O)W is $-OC(O)NR^2R^3$. When $R^2$ and $R^3$ do not contain a PEG moiety, $-OC(O)NR^2R^3$ in formulas XXII-XXVI is preferably selected from the group:

$(CH_3)_2NC(O)O-$,

(piperidin-1-yl)C(O)O-,

(4-hydroxypiperidin-1-yl)C(O)O-,

(4-formyloxypiperidin-1-yl)C(O)O-,

(4-ethoxycarbonylpiperidin-1-yl)C(O)O-,

(4-carboxylpiperidin-1-yl)C(O)O-,

(3-hydroxymethylpiperidin-1-yl)C(O)O-,

(4-hydroxymethylpiperidin-1-yl)C(O)O-,

(4-piperidon-1-yl ethylene ketal)C(O)O-,

(piperazin-1-yl)-C(O)O-,

(1-Boc-piperazin-4-yl)-C(O)O-,

(4-methylpiperazin-1-yl)C(O)O-,

(4-methylhomopiperazin-1-yl)C(O)O-,

(4-(2-hydroxyethyl)piperazin-1-yl)C(O)O-,

(4-phenylpiperazin-1-yl)C(O)O-,

(4-(pyridin-2-yl)piperazin-1]-yl)C(O)O-,

(4-(4-trifluoromethylpyridin-2-yl)piperazin-1-yl)C(O)O-,
(4-(pyrimidin-2-yl)piperazin-1-yl)C(O)O-,
(4-acetylpiperazin-1-yl)C(O)O-,
(4-(phenylC(O)-)piperazin-1-yl)C(O)O-,
(4-(pyridin-4'-ylC(O)-)piperazin-1-yl)C(O)O,
(4-(phenylNHC(O)-)piperazin-1-yl)C(O)O-,
(4-(phenylNHC(S)-)piperazin-1-yl)C(O)O-,
(4-methanesulfonylpiperazin-1-yl-C(O)O-,
(4-trifluoromethanesulfonylpiperazin-1-yl-C(O)O-,
(morpholin-4-yl)C(O)O-,
(thiomorpholin-4-yl)C(O)O-,
(thiomorpholin-4'-yl sulfone)-C(O)O-,
(pyrrolidin-1-yl)C(O)O-,
(2-methylpyrrolidin-1-yl)C(O)O-,
(2-(methoxycarbonyl)pyrrolidin-1-yl)C(O)O-,
(2-(hydroxymethyl)pyrrolidin-1-yl)C(O)O-,
(2-(N,N-dimethylamino)ethyl)($CH_3$)NC(O)O-,
(2-(N-methyl-N-toluene-4-sulfonylamino)ethyl)($CH_3$)N-C(O)O-,
(2-(morpholin-4-yl)ethyl)($CH_3$)NC(O)O-,
(2-(hydroxy)ethyl)($CH_3$)NC(O)O-,
bis(2-(hydroxy)ethyl)NC(O)O-,
(2-(formyloxy)ethyl)($CH_3$)NC(O)O-,
($CH_3OC(O)CH_2$)HNC(O)O-, and
2-[(phenylNHC(O)O-)ethyl-]HNC(O)O-.

When $R^2$ and/or $R^3$ comprise a PEG moiety, the PEG moiety is preferably represented by the formula:

$$-Z'-(CH_2CHR^7O)_pR^8$$

Z' is selected from the group consisting of a covalent bond and a linking group of from 1 to 40 atoms;

$R^7$ is selected from the group consisting of hydrogen and methyl;

$R^8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and $-CH_2CHR^7NR^{10}R^{11}$ where $R^7$ is as defined above and $R^{10}$ and $R^{11}$ are independently selected from the group consisting of hydrogen and alkyl; and

*p* is an integer such that the molecular weight of the PEG moiety ranges from 100 to 100,000.

Preferred -YC(O)W substituents comprising a PEG moiety include the following:

$-OC(O)NH(CH_2CH_2O)_pCH_2CH_2NH_2$;

$-OC(O)NH(CH_2CH(CH_3)O)_pCH_2CH(CH_3)NH_2$;

$-NHC(O)O(CH_2CH_2O)_pH$;

$-NHC(O)O(CH_2CH(CH_3)O)_pH$;

$-NHC(O)O(CH_2CH_2O)_pCH_3$;

$-NHC(O)O(CH_2CH(CH_3)O)_pCH_3$;

$-NHC(O)O(CH_2CH_2O)_p$-φ;

$-NHC(O)O(CH_2CH(CH_3)O)_p$-φ;

$-NHC(O)NH(CH_2CH_2O)_pCH_2CH_2NH_2$;

$-NHC(O)NH(CH_2CH(CH_3)O)_pCH_2CH(CH_3)NH_2$;

-OC(O)NH-(1,4)-φ-O-$(CH_2CH_2O)_pH$;

-OC(O)NH-(1,4)-φ-O-$(CH_2CH(CH_3)O)_pH$;

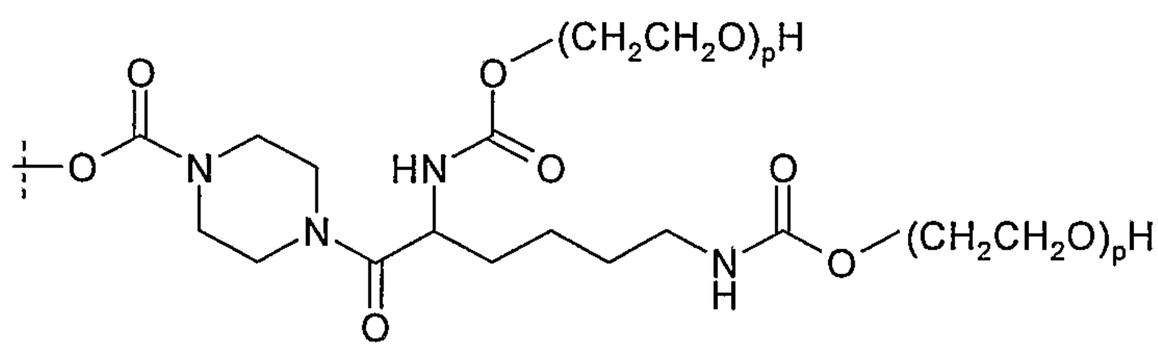
-OC(O)NH-(1,4)-φ-O-$(CH_2CH_2O)_pCH_3$;

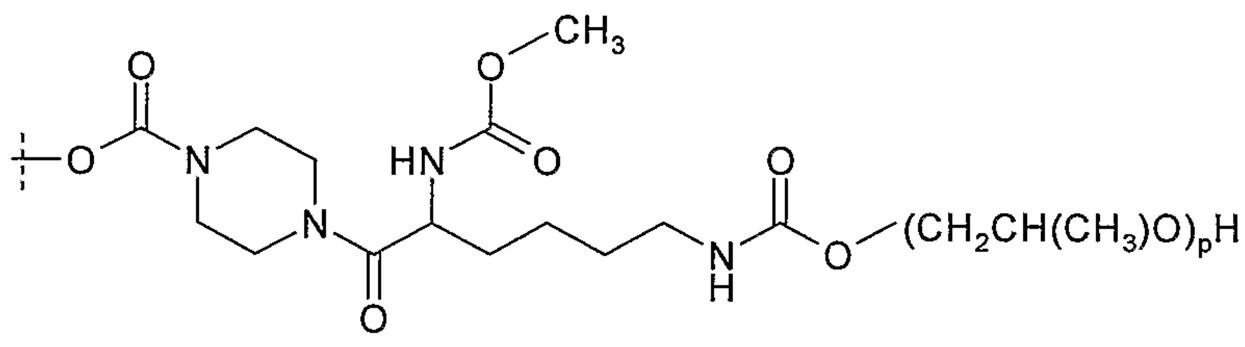
-OC(O)NH-(1,4)-φ-O-$(CH_2CH(CH_3)O)_pCH_3$;

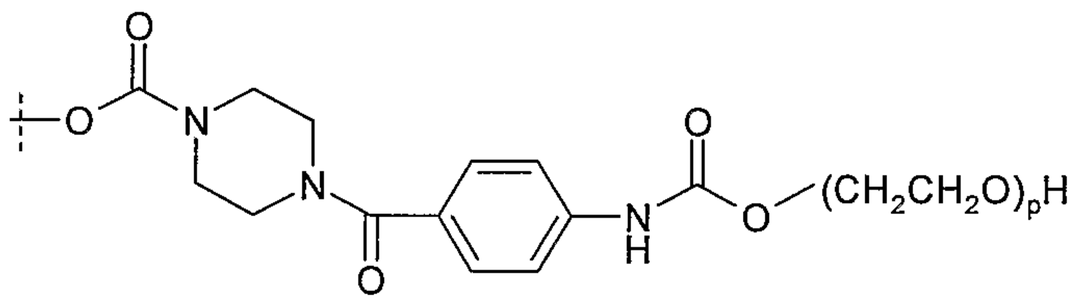
$-OC(O)NH(CH_2CH(CH_3)O)_pCH_2CH(CH_3)OCH_3$;

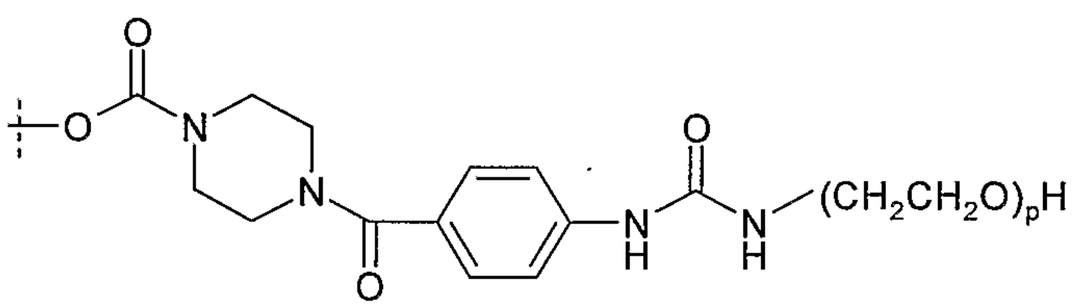
$-NHC(O)NH(CH_2CH_2O)_pCH_3$;

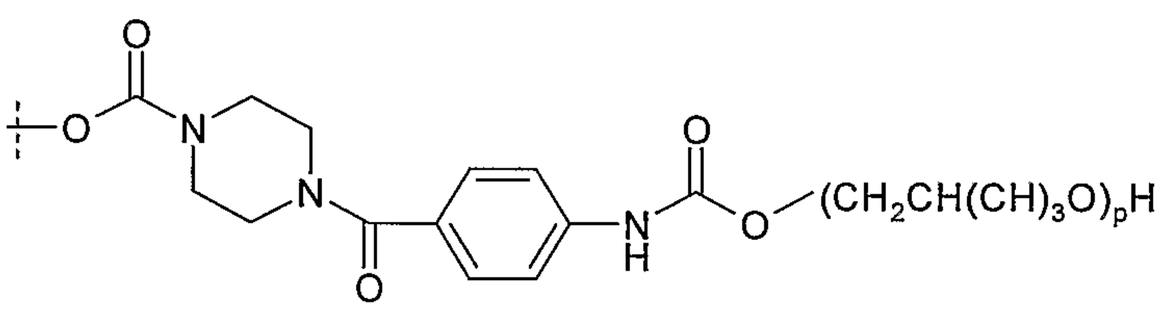
$-NHC(O)NH(CH_2CH(CH_3)O)_pCH_3$;

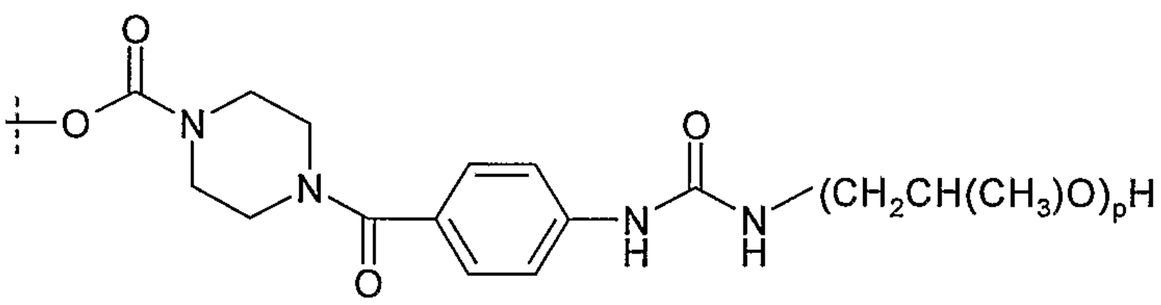


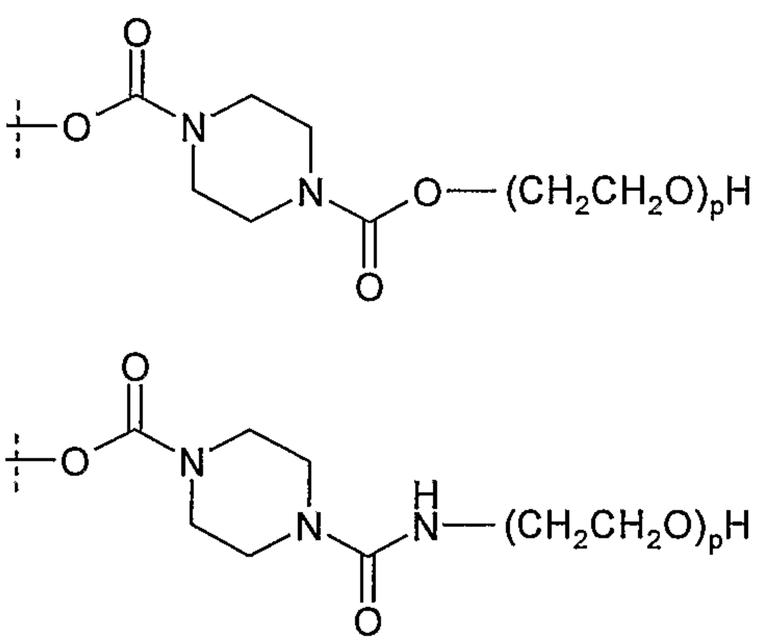


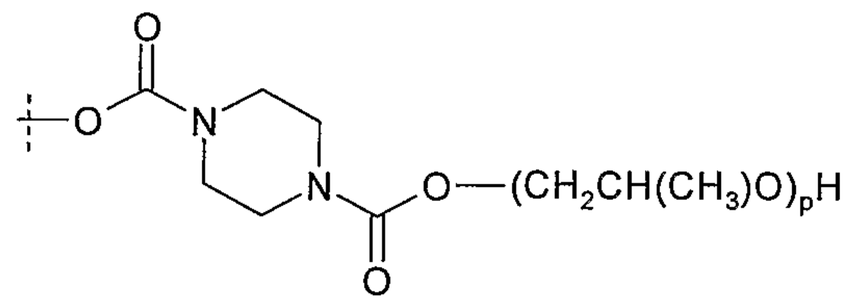


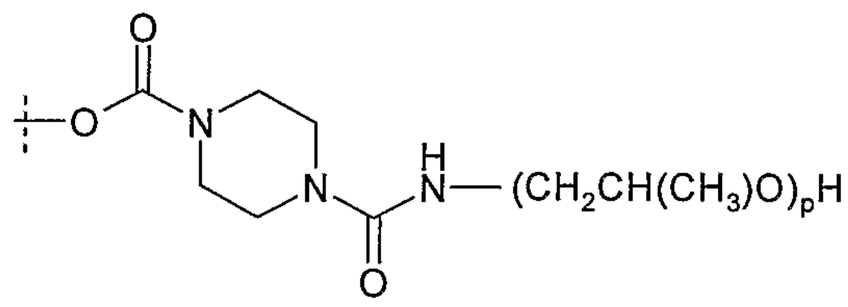


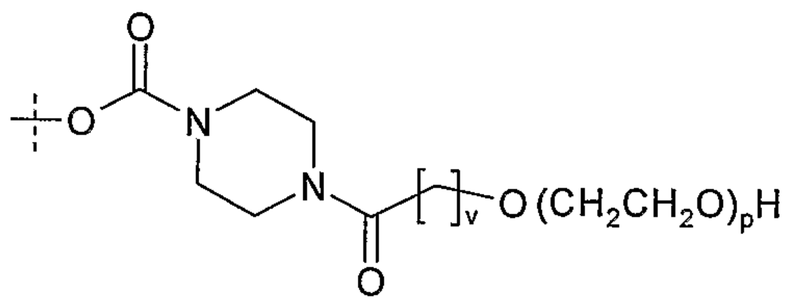


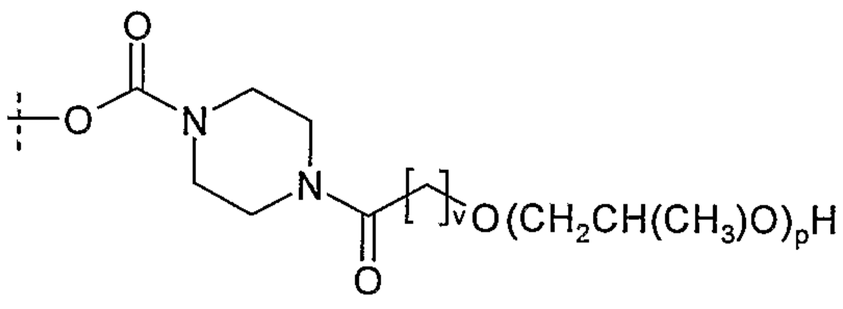


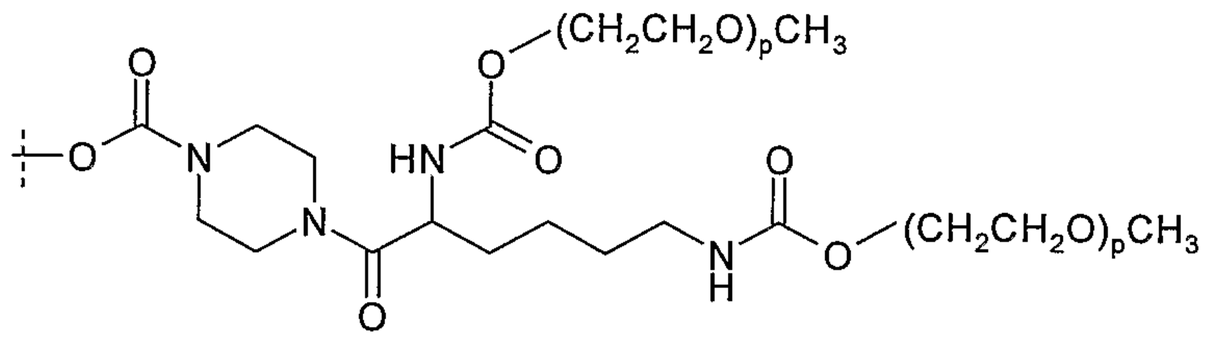


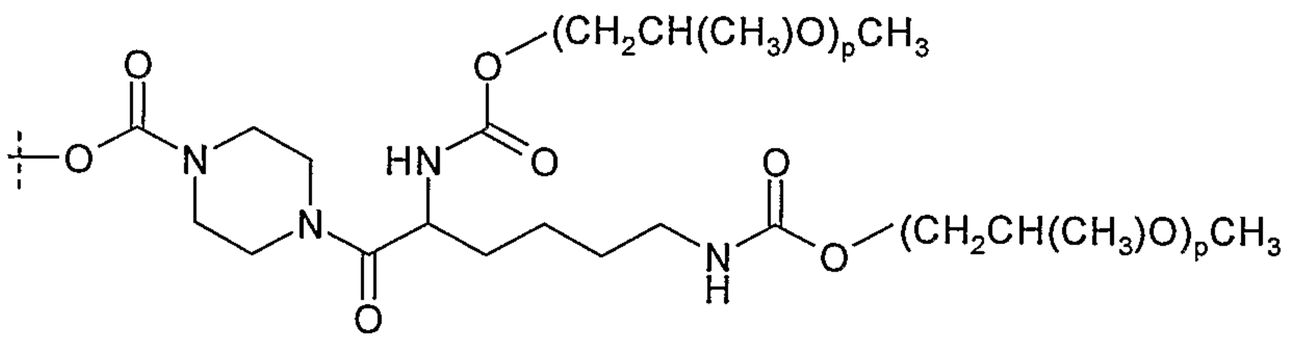


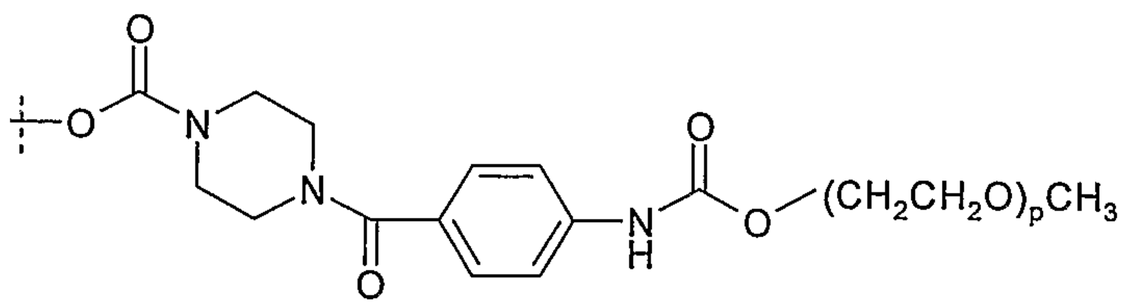


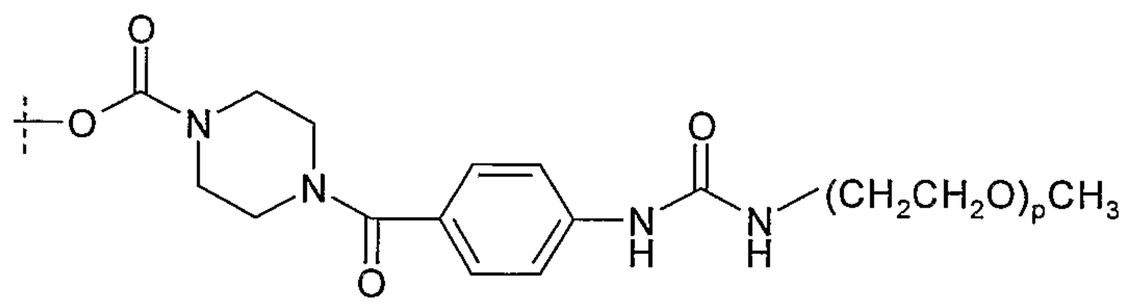


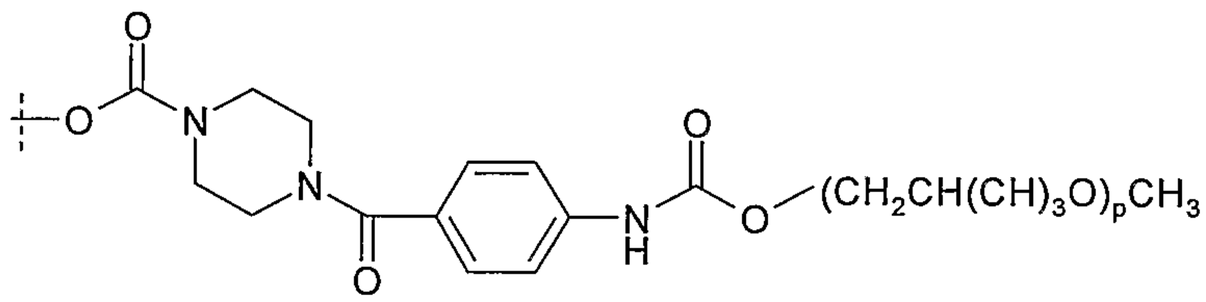


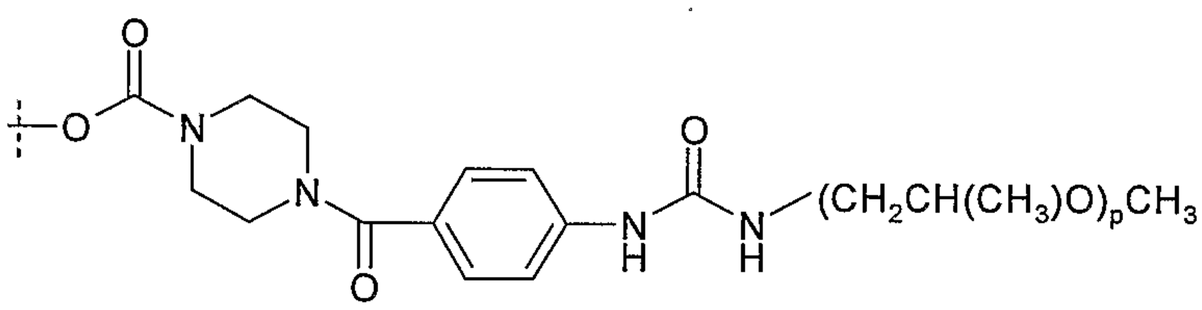


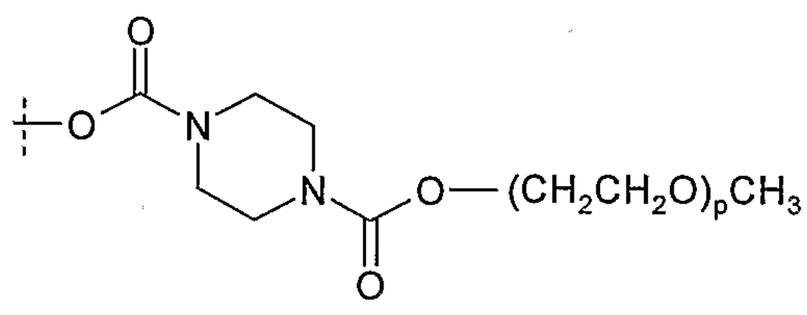


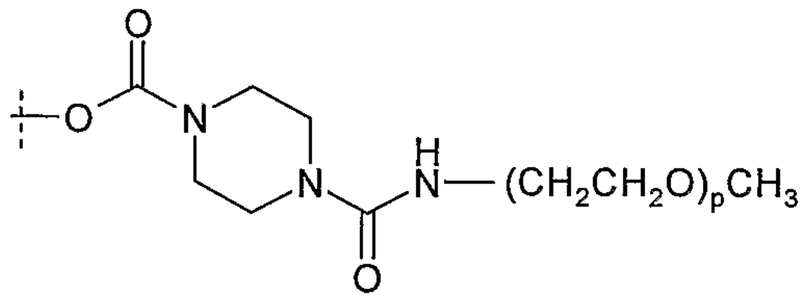


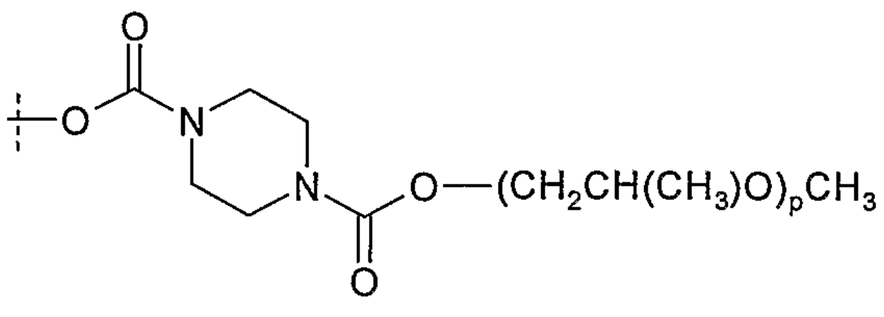


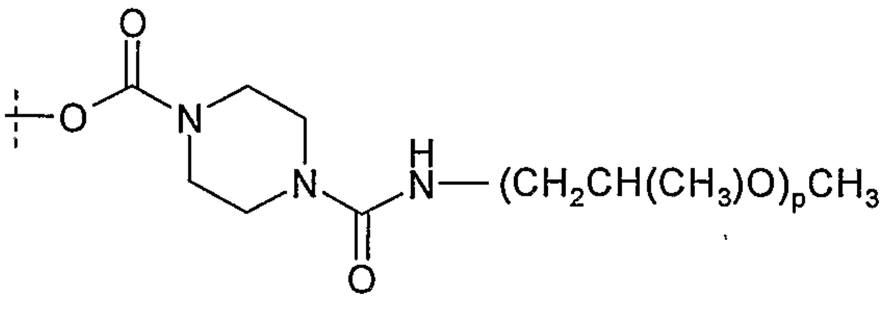


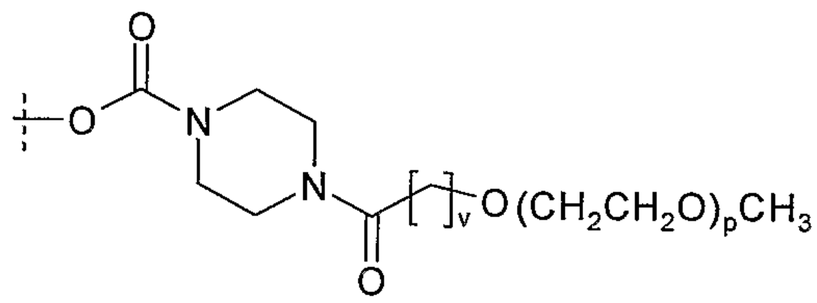


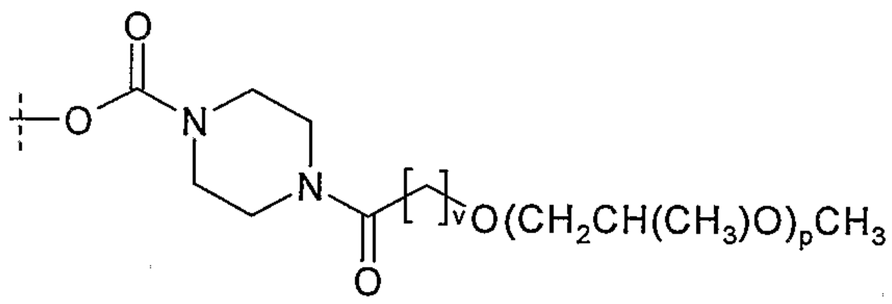


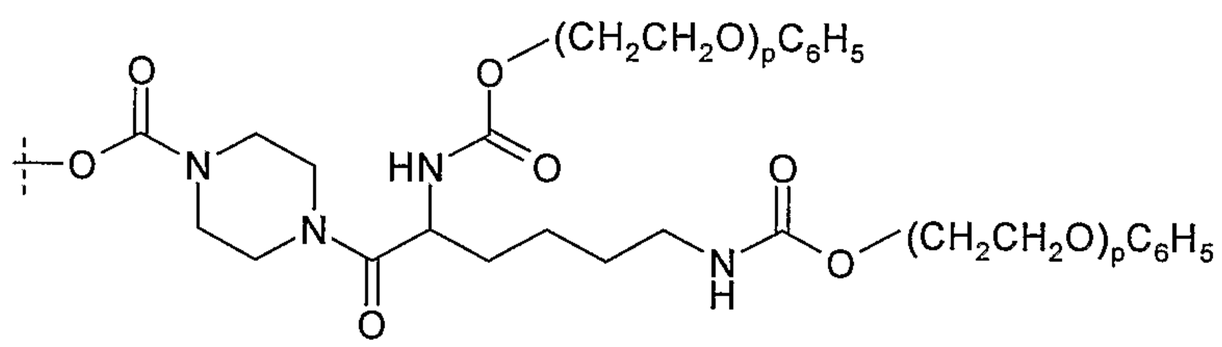


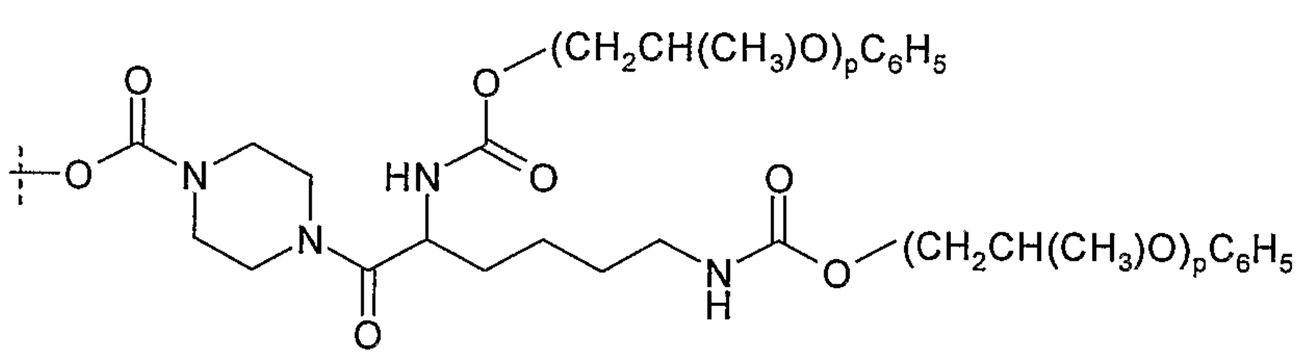


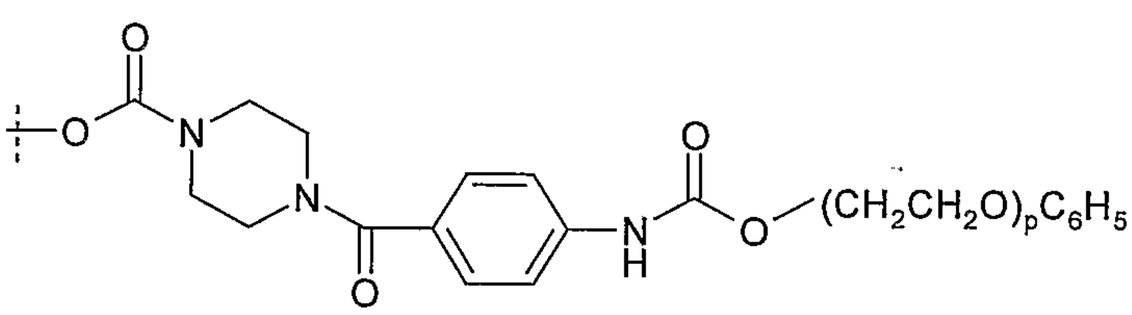


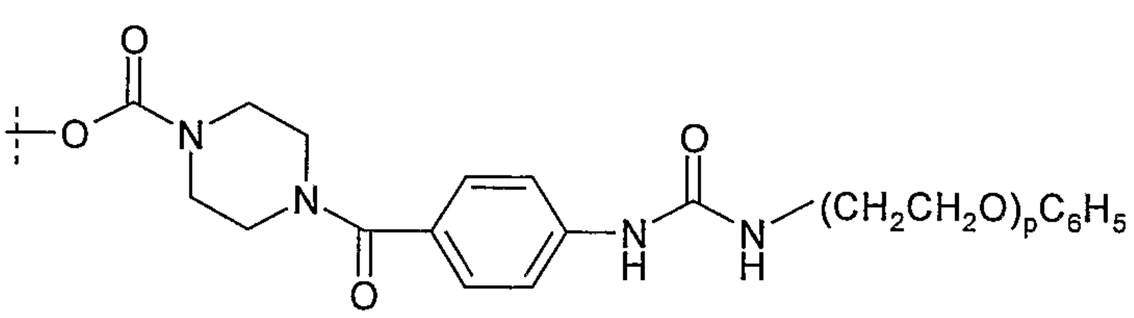


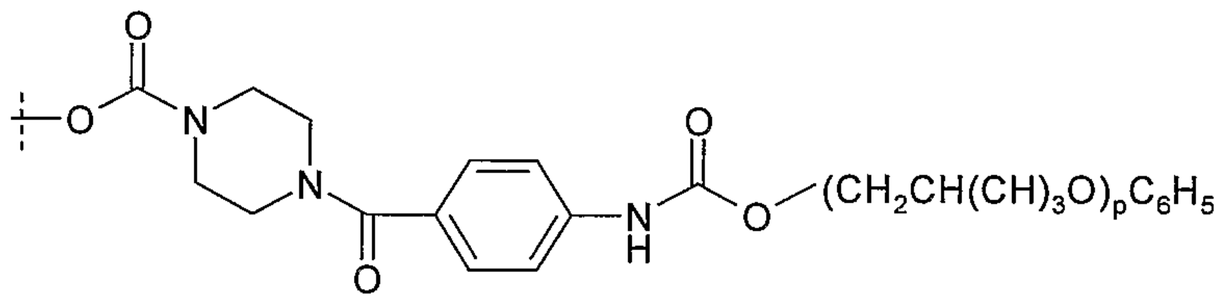


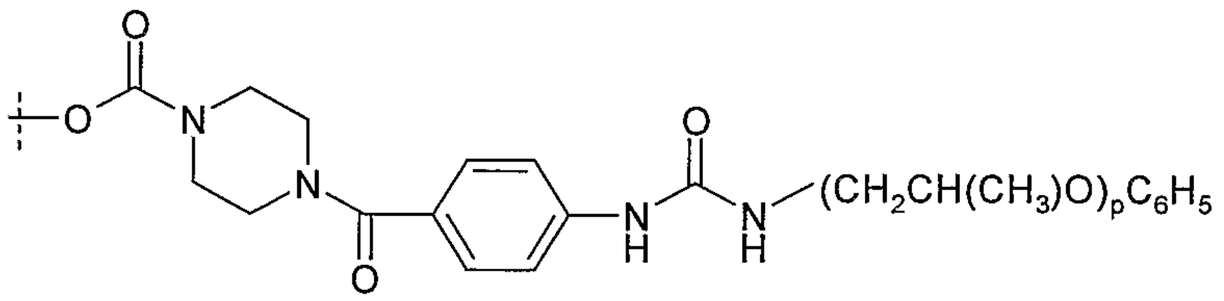


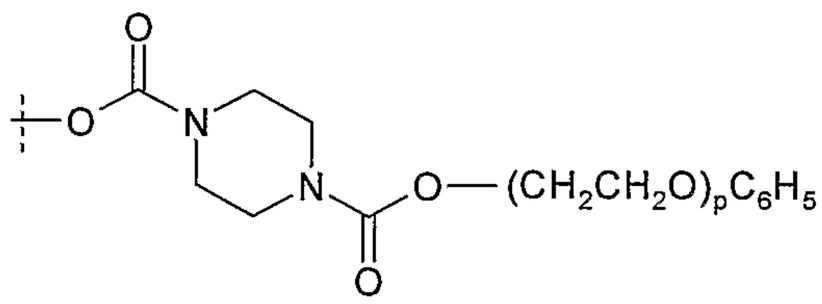


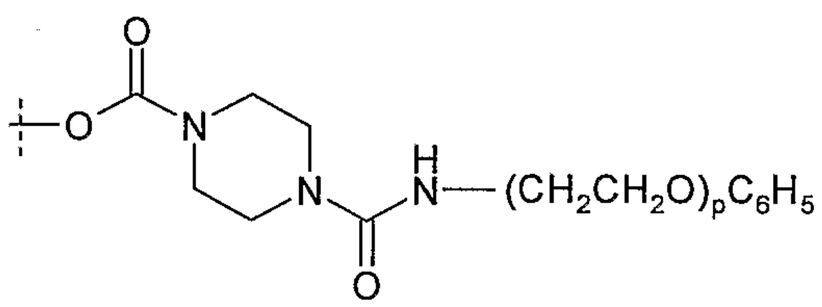


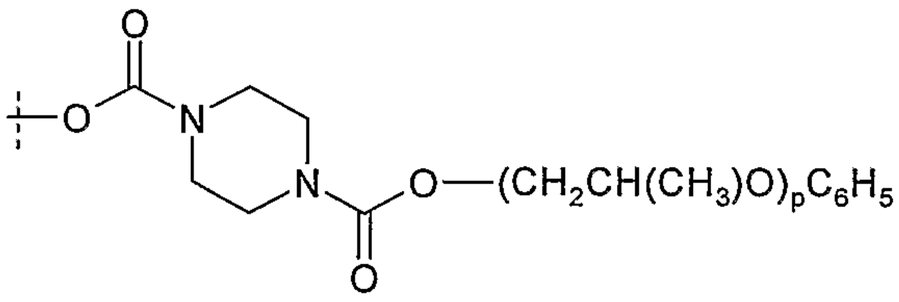


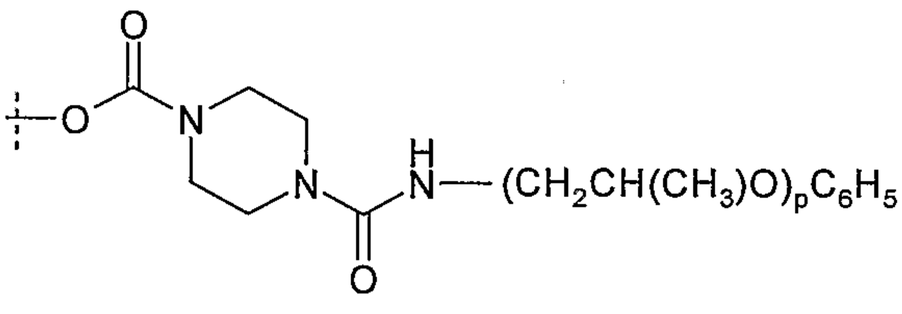


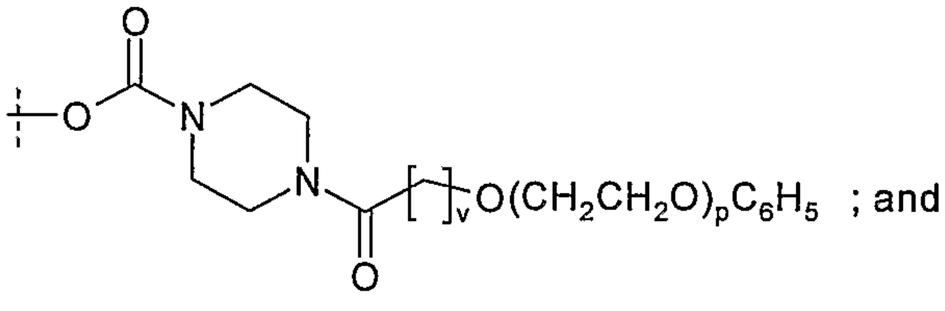




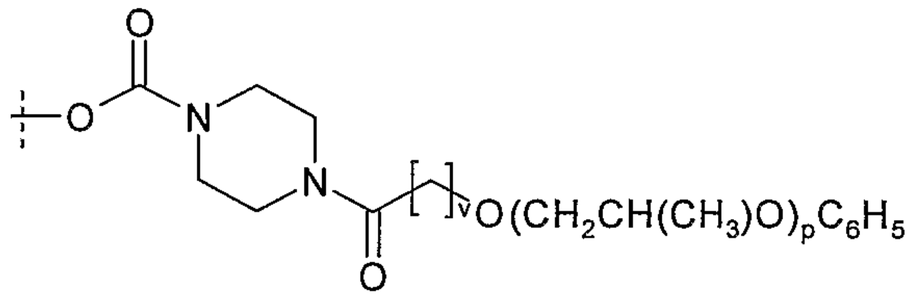






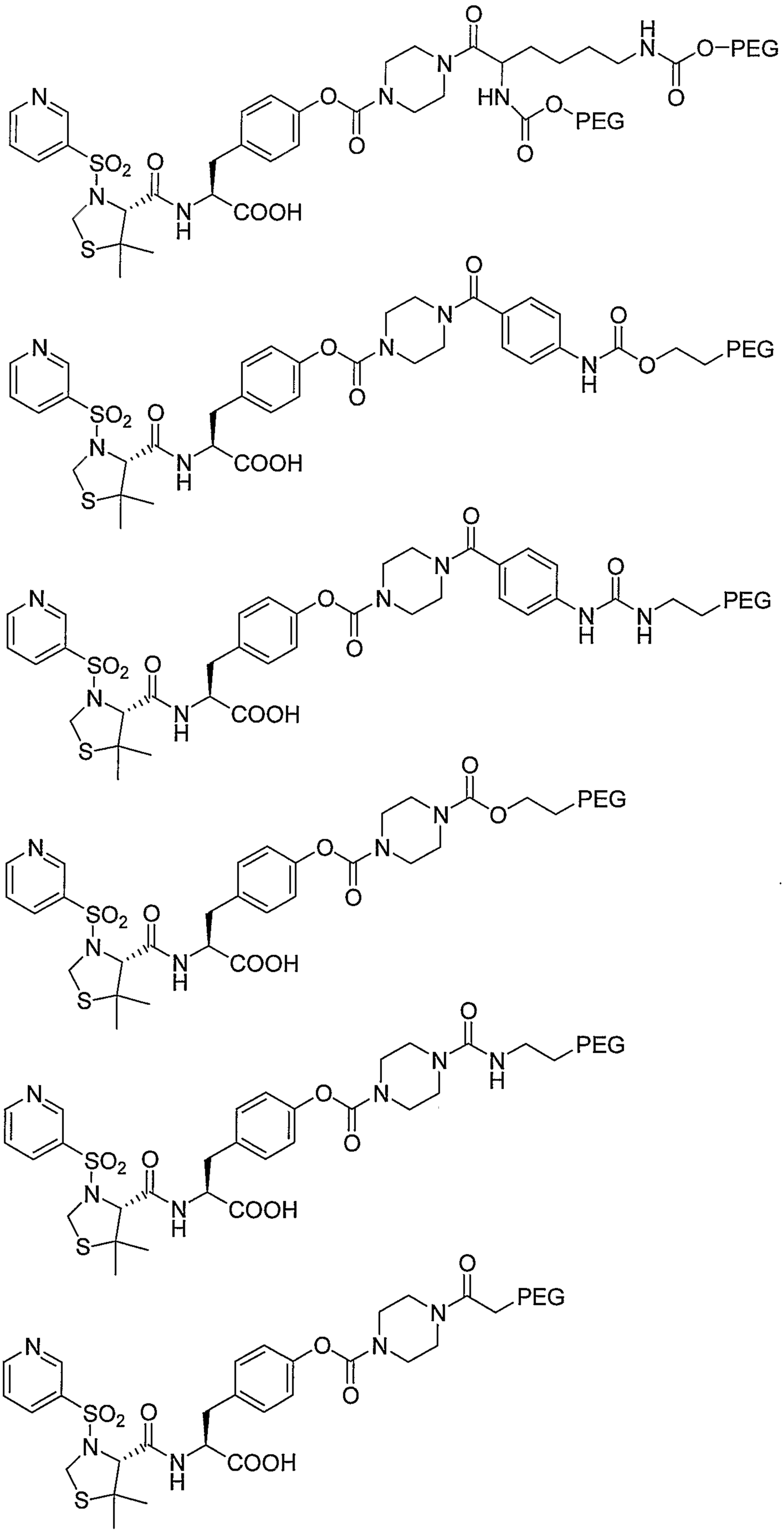


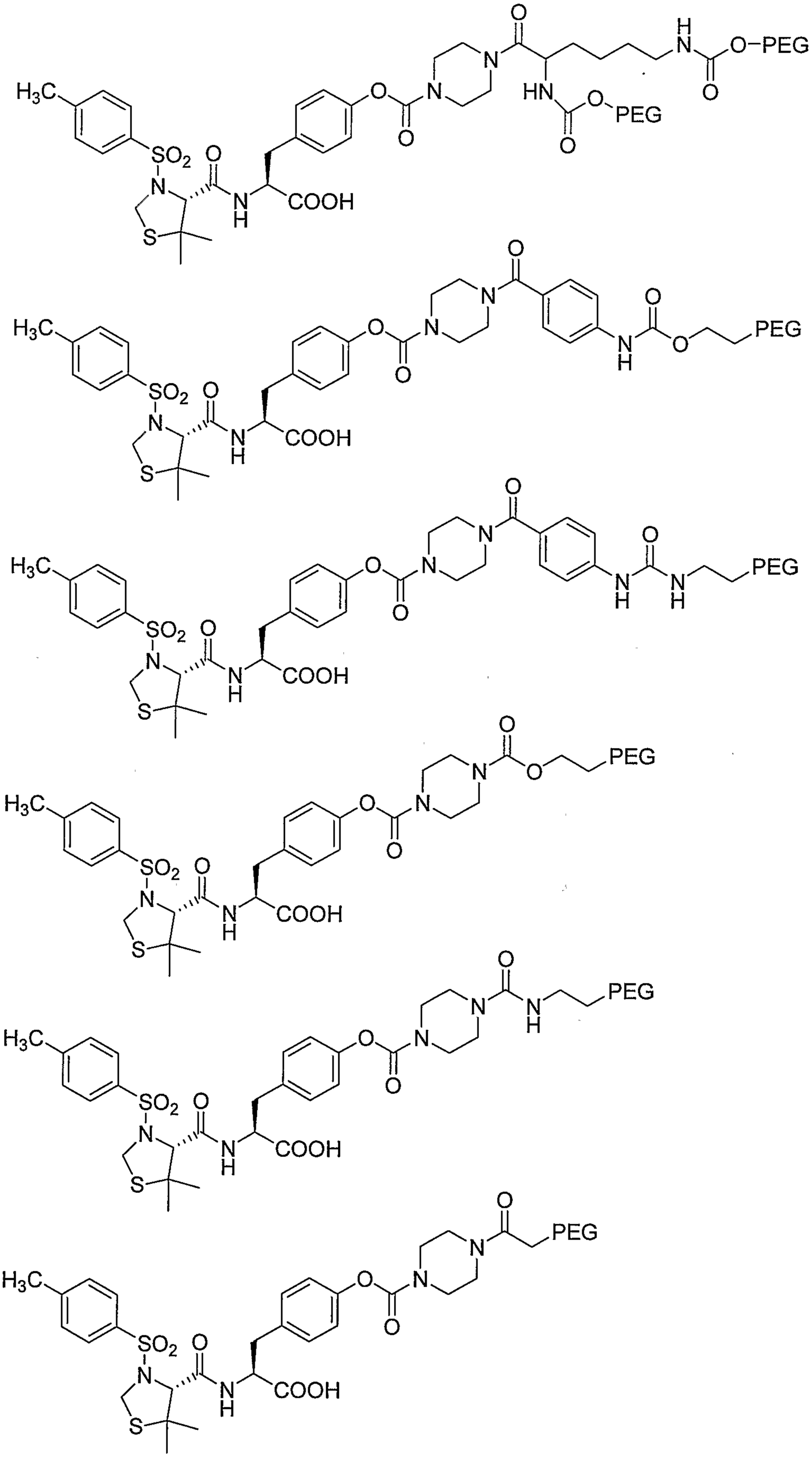
; and



where φ or $C_6H_5$ is phenyl and *p* is an integer such that the molecular weight of the PEG moiety ranges from about 100 to 100,000 and *v* is 1 to 5.

Preferred PEG derivatives of this invention include those set forth below:





where, in each case, PEG is a methyl capped polyoxyethylene group having a molecular weight (Mw) of approximately 20,000.

"Linking group" or "linker" of from 1 to 40 atoms is a di- to hexavalent group or groups that covalently links a non-PEG substituted compound of formula I (*i.e.*, none of $Ar^1$, $Ar^2$, R or -Y-C(O)-W- contain a PEG group) with 1 to 5 PEG groups. Each linker may be chiral or achiral, linear, branched or cyclic and may be homogenous or heterogeneous in its atom content (*e.g.*, linkers containing only carbon atoms or linkers containing carbon atoms as well as one or more heteroatoms present on the linker in the form of alcohols, ketones, aldehydes, carboxyl groups, amines, amides, carbamates, ureas, thiols, ethers, etc., or residues thereof) Preferably, the linker contains 1 to 25 carbon atoms and 0 to 15 heteroatoms selected from oxygen, $NR^{22}$, sulfur, -S(O)- and $-S(O)_2-$, where $R^{22}$ is as defined above.

The PEG group or groups are covalently attached to the linker using conventional chemical techniques providing for covalent linkage of the PEG group to the linker. The linker, in turn, is covalently attached to the otherwise, non-PEG substituted compound of formula I. Reaction chemistries resulting in such linkages are well known in the art. Such reaction chemistries involve the use of complementary functional groups on the linker, the non-PEG substituted compound of formula XXII and the PEG groups. Preferably, the complementary functional groups on the linker are selected relative to the functional groups available on the PEG group for bonding or which can be introduced onto the PEG group for bonding. Again, such complementary functional groups are well known in the art. For example, reaction between a carboxylic acid of either the linker or the PEG group and a primary or secondary amine of the PEG group or the linker in the presence of suitable, well-known activating agents results in formation of an amide bond covalently linking the PEG group to the linker; reaction between an amine group of either the linker or the PEG group and a sulfonyl halide of the PEG group or the linker results in formation of a sulfonamide bond covalently linking the PEG group to the linker; and reaction between an alcohol or phenol group of either the linker or the PEG group and an alkyl or aryl halide of the PEG

group or the linker results in formation of an ether bond covalently linking the PEG group to the linker.

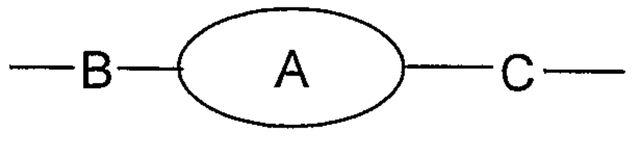
Table 9 below illustrates numerous complementary reactive groups and the resulting bonds formed by reaction therebetween.

TABLE 9

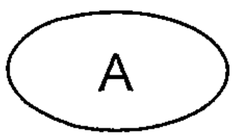
Representative Complementary Binding Chemistries

| First Reactive Group | Second Reactive Group | Linkage |
|---|---|---|
| Hydroxyl | Isocyanate | urethane |
| Amine | Epoxide | β-hydroxyamine |
| sulfonyl halid | Amine | sulfonamide |
| Carboxyl | Amine | amide |
| Hydroxyl | alkyl/aryl halide | ether |

Preferred linkers include, by way of example, the following -O-, -$NR^{22}$-, -$NR^{22}$C(O)O-, -OC(O)$NR^{22}$-, -$NR^{22}$C(O)-, -C(O)$NR^{22}$-, -$NR^{22}$C(O)$NR^{22}$-, -alkylene-$NR^{22}$C(O)O-,-alkylene-$NR^{22}$C(O)$NR^{22}$-, -alkylene-OC(O) $NR^{22}$-, -alkylene-$NR^{22}$-, -alkylene-O-, -alkylene-$NR^{22}$C(O)-, -alkylene-C(O)$NR^{22}$-, -$NR^{3}$C(O)O-alkylene-, -$NR^{22}$C(O)$NR^{22}$-alkylene-, -OC(O) $NR^{22}$-alkylene, -$NR^{22}$-alkylene-, -O-alkylene-, -$NR^{22}$C(O)-alkylene-, -C(O)$NR^{22}$-alkylene-, -alkylene-$NR^{22}$C(O)O-alkylene-, -alkylene-$NR^{3}$C(O)$NR^{22}$-alkylene-, -alkylene-OC(O)$NR^{22}$-alkylene-, -alkylene-$NR^{22}$-alkylene-, alkylene-O-alkylene-, -alkylene-$NR^{22}$C(O)-alkylene-, -C(O)$NR^{22}$-alkylene-, and




where




is selected from the group consisting of aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted

heterocyclic, and B and C are independently selected from the group consisting of a bond, -O-, CO, -$NR^{22}$-, -$NR^{22}$C(O)O-, -OC(O)$NR^{22}$-, -$NR^{22}$C(O)-, -C(O)$NR^{22}$-, -$NR^{22}$C(O)$NR^{22}$-, -alkylene-$NR^{22}$C(O)O-, -alkylene-$NR^{22}$C(O)$NR^{22}$-, -alkylene-OC(O) $NR^{22}$-, -alkylene-$NR^{22}$-, -alkylene-O-, -alkylene-$NR^{22}$C(O)-, alkylene-C(O)$NR^{22}$-, -$NR^{22}$C(O)O-alkylene-, -$NR^{22}$C(O)$NR^{22}$-alkylene-, -OC(O) $NR^{22}$-alkylene-, -$NR^{22}$-alkylene-, -O-alkylene-, -$NR^{22}$C(O)-alkylene-, -C(O)$NR^{22}$-alkylene-, -alkylene-$NR^{22}$C(O)O-alkylene-, -alkylene-$NR^{22}$C(O)$NR^{22}$-alkylene-, -alkylene-OC(O) $NR^{22}$-alkylene-, -alkylene-$NR^{22}$-alkylene-, alkylene-O-alkylene-, -alkylene-$NR^{22}$C(O)-alkylene-, and -C(O)$NR^{22}$-alkylene-, where $R^{22}$ is as defined above.

"PEG" or "PEG moiety" refers to polymers comprising multiple oxyalkylene units. Such polymers are optionally mono-capped with a substituent preferably selected from alkyl, aryl, substituted alkyl, and substituted aryl. Inclusive of such polymers are those diamino capped polyoxyalkylene polymers which are known in the art as Jeffamines®. Still further, such polymers can optionally contain one or more non-oxyalkylene units such as the commercially available poly[di(ethylene glycol)adipates, poly[di(ethylene glycol)phthalate diols, and the like. Also included are block copolymers of oxyalkylene, polyethylene glycol, polypropylene glycol, and polyoxyethylenated polyol units.

Such polymers have a number average molecular weight of from about 100 to 100,000; preferably from about 1,000 to 50,000; more preferably from about 10,000 to about 40,000. In a particularly preferred embodiment, the molecular weight of the total amount of PEG arising from single or multiple PEG moieties bound in the molecule does not exceed 100,000; more preferably 50,000 and even more preferably 40,000.

In a preferred embodiment, the -[linking group]$_u$-PEG group where *u* is zero or one can be represented by the formula:

$$-Z'-[(CH_2CHR^7O)_pR^8]_t$$

where Z' is selected from the group consisting of a covalent bond, a linking group of from 1 to 40 atoms, -O-, -S-, -$NR^{22}$-, -C(O)O-, -$C(O)NR^{22}$-, and -C(O)- where $R^{22}$ is selected from the group consisting of hydrogen and alkyl,

$R^7$ is selected from the group consisting of hydrogen and methyl;

$R^8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -$CH_2CHR^7SR^7$ and -$CH_2CHR^7NR^{10}R^{11}$ where $R^7$ is as defined above and $R^{10}$ and $R^{11}$ are independently selected from the group consisting of hydrogen and alkyl;

*p* is an integer such that the molecular weight of the PEG moiety ranges from 100 to 100,000; and

*t* is an integer from 1 to 5 provided that *t* is one less than the valency of the linking group and is one when there is no linking group.

When Z' is linking group, multiple PEG groups can be present. For example, if the linking group is trivalent, then 2 PEG groups can be attached and the remaining valency is employed to link to the molecule of formula XXII. Preferably the number of PEG groups is 1 or 2. In any event, when multiple PEG groups are present, the total aggregate molecular weight of the PEG groups does not exceed 100,000.

PEG Derivative Preparation

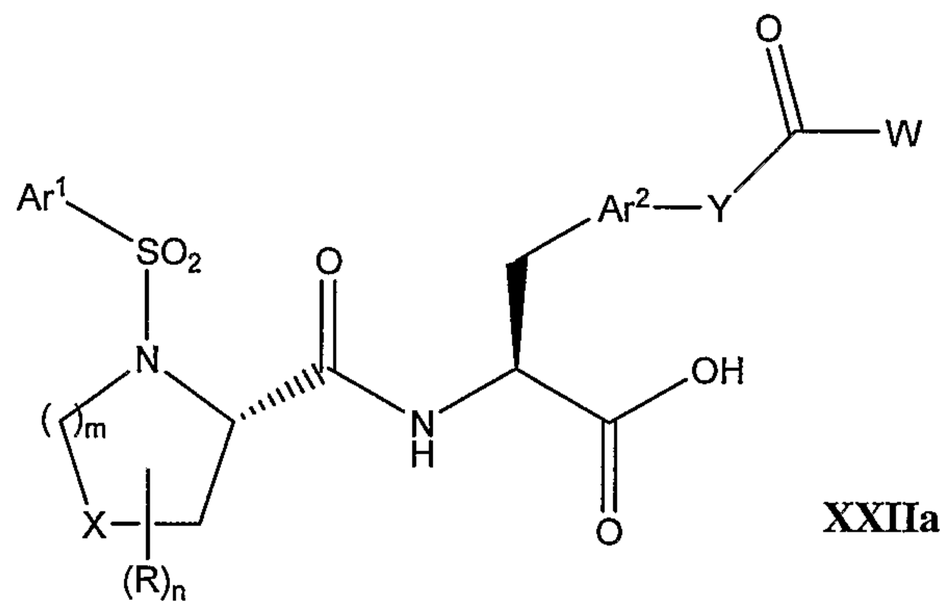
The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.,* reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M.

Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, *i.e.*, as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

The compounds of this invention are preferably characterized by containing one or more PEG moieties at one of several sites of a compound of formula XXIIa:



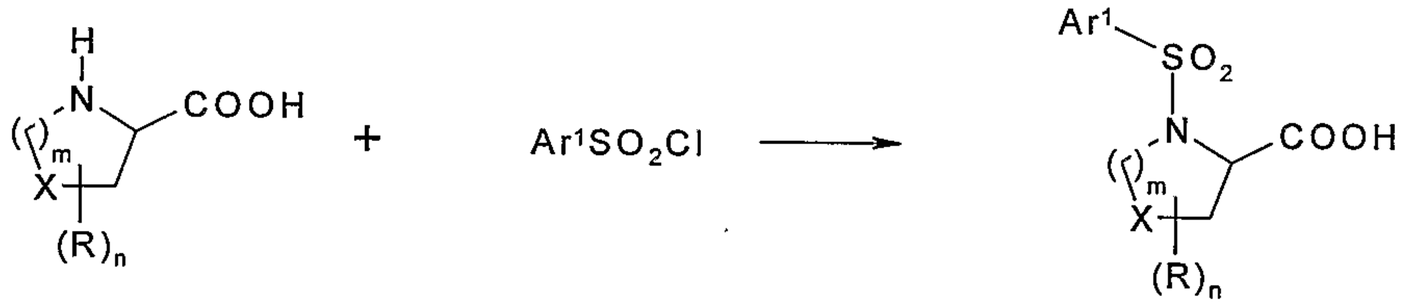
**XXIIa**

Specifically, the PEG moiety can be incorporated into the $Ar^1$ substituent, the R substituent, the $Ar^2$ substituent and/or in the -YC(O)W substituent wherein the PEG moiety is either directly attached or is attached via a linker. The synthetic protocol for insertion of a PEG moiety at each of these positions is similar and entails reaction of a functional group on the PEG moiety or the linking group covalently bound to the PEG moiety with a complementary functional group on the non-PEG substituted compounds of formula XXIIa.

Initially, non-PEG substituted compounds of formula XXIIa are well known in the art and are exemplified in a number of issued patents including, without limitation, U.S. Patent Nos. 6,489,300 and 6,436,904 both of which are incorporated herein by reference in their entirety. Non-PEG variants of compounds of formula Ia include those having complementary functional groups or groups derivatizable to complementary functional groups on one or more of the $Ar^1$, R, $Ar^2$ and -YC(O)W moieties. For illustrative purposes,

compounds having a complementary functional group (-OH) on the $Ar^2$ moiety (*e.g.*, tyrosine) are recited below as a suitable starting point for addition of a PEG group to the molecule either directly or through a linker.

Such compounds can be prepared by first coupling a heterocyclic amino acid, 1, with an appropriate aryl sulfonyl chloride as illustrated in Scheme 1 below:




1 2 3

Scheme 1

where R, $Ar^1$, X, *m* and *n* are as defined above.

Specifically, in Scheme 1 above, heterocyclic amino acid, 1, is combined with a stoichiometric equivalent or excess amount (preferably from about 1.1 to about 2 equivalents) of arylsulfonyl halide, 2, in a suitable inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about -70°C to about 40°C until the reaction is substantially complete, which typically occurs within 1 to 24 hours. Preferably, the reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, N-methyl-morpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using an aqueous alkali solution such as an aqueous solution of sodium hydroxide, an aqueous phosphate solution buffered to pH 7.4, and the like. The resulting product, 3, can be recovered by conventional methods, such as chromatography, filtration, evaporation, crystallization, and the like or, alternatively, used in the next step without purification and/or isolation.

Heterocyclic amino acids, 1, employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Examples of suitable amino acids for use in this reaction include, but are not limited to, L-proline, *trans*-4-hydroxyl-L-proline, *cis*-4-hydroxyl-L-proline, *trans*-3-

phenyl-L-proline, *cis*-3-phenyl-L-proline, L-(2-methyl)proline, L-pipecolinic acid, L-azetidine-2-carboxylic acid, L-thiazolidine-4-carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid. If desired, the corresponding carboxylic acid esters of the amino acids, 1, such as the methyl esters, ethyl esters, *t*-butyl esters, and the like, can be employed in the above reaction with the arylsulfonyl chloride. Subsequent hydrolysis of the ester group to the carboxylic acid using conventional reagents and conditions, *i.e.*, treatment with an alkali metal hydroxide in an inert diluent such as methanol/water, then provides the N-sulfonyl amino acid, 3.

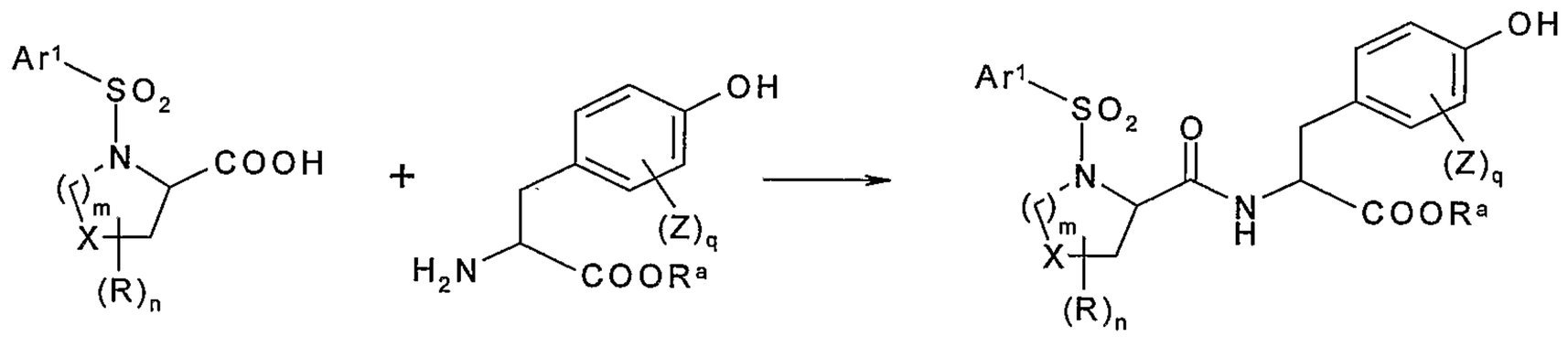
Similarly, the arylsulfonyl chlorides, 2, employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, *i.e.,* from compounds of the formula $Ar^1SO_3H$ where $Ar^1$ is as defined above, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the arylsulfonyl chlorides, 2, can be prepared from the corresponding thiol compound, *i.e.*, from compounds of the $Ar^1$-SH where $Ar^1$ is as defined herein, by treating the thiol with chlorine ($Cl_2$) and water under conventional reaction conditions.

Alternatively, arylsulfonyl chlorides, 2, employed in the above reaction may be prepared by chlorosulfonylation of substituted benzene or heterocycloalkyl group using Cl-$SO_3H$.

Examples of arylsulfonyl chlorides suitable for use in this invention include, but are not limited to, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, p-toluenesulfonyl chloride, *o*-toluenesulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamido-benzenesulfonyl chloride, 4-

nitrobenzenesulfonyl chloride, 4-trifluoromethyl-benzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the N-sulfonyl amino acid, 3.

The N-arylsulfonyl amino acid, 3, is then coupled to commercially available tyrosine esters as shown in Scheme 2 below:




3 4 5

Scheme 2

where R, $Ar^1$, X, *m* and *n* are as defined above, $R^a$ is hydrogen or alkyl but preferably is an alkyl group such as *t*-butyl, Z represents optional substitution on the aryl ring and *q* is zero, one or two.

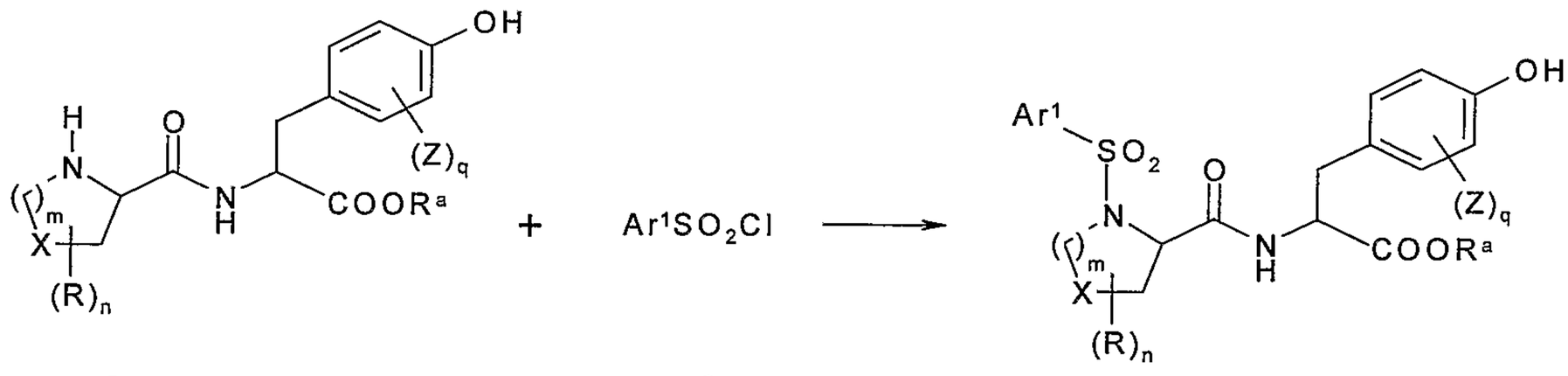
This coupling reaction is typically conducted using well-known coupling reagents such as carbodiimides, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphonate) and the like. Suitable carbodiimides include, by way of example, dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and the like. If desired, polymer supported forms of carbodiimide coupling reagents may also be used including, for example, those described in Tetrahedron Letters, 34(48), 7685 (1993). Additionally, well-known coupling promoters, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be used to facilitate the coupling reaction.

This coupling reaction is typically conducted by contacting the N-sulfonylamino acid, 3, with about 1 to about 2 equivalents of the coupling reagent and at least one equivalent, preferably about 1 to about 1.2 equivalents, of tyrosine derivative, 4, in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, N,N-dimethylformamide and the like. Generally, this reaction is conducted at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours. Upon completion of the reaction, the compound 5 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the N-sulfonyl amino acid, 3, can be converted into an acid halide which is then coupled with compound, 4, to provide compound 5. The acid halide can be prepared by contacting compound 3 with an inorganic acid halide, such as thionyl chloride, phosphorous trichloride, phosphorous tribromide or phosphorous pentachloride, or preferably, with oxalyl chloride under conventional conditions. Generally, this reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either neat or in an inert solvent, such as dichloromethane or carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, such as DMF, may also be used in this reaction.

The acid halide of N-sulfonyl amino acid, 3, is then contacted with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of the tyrosine derivative, 4, in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, N-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like. Upon completion of the reaction, compound 5 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like.

Aternatively, compound 5 can be prepared by first forming a diamino acid derivative and then coupling the diamino acid to the arylsulfonyl halide, 2, as shown in scheme 3 below:



6 2 7

Scheme 3

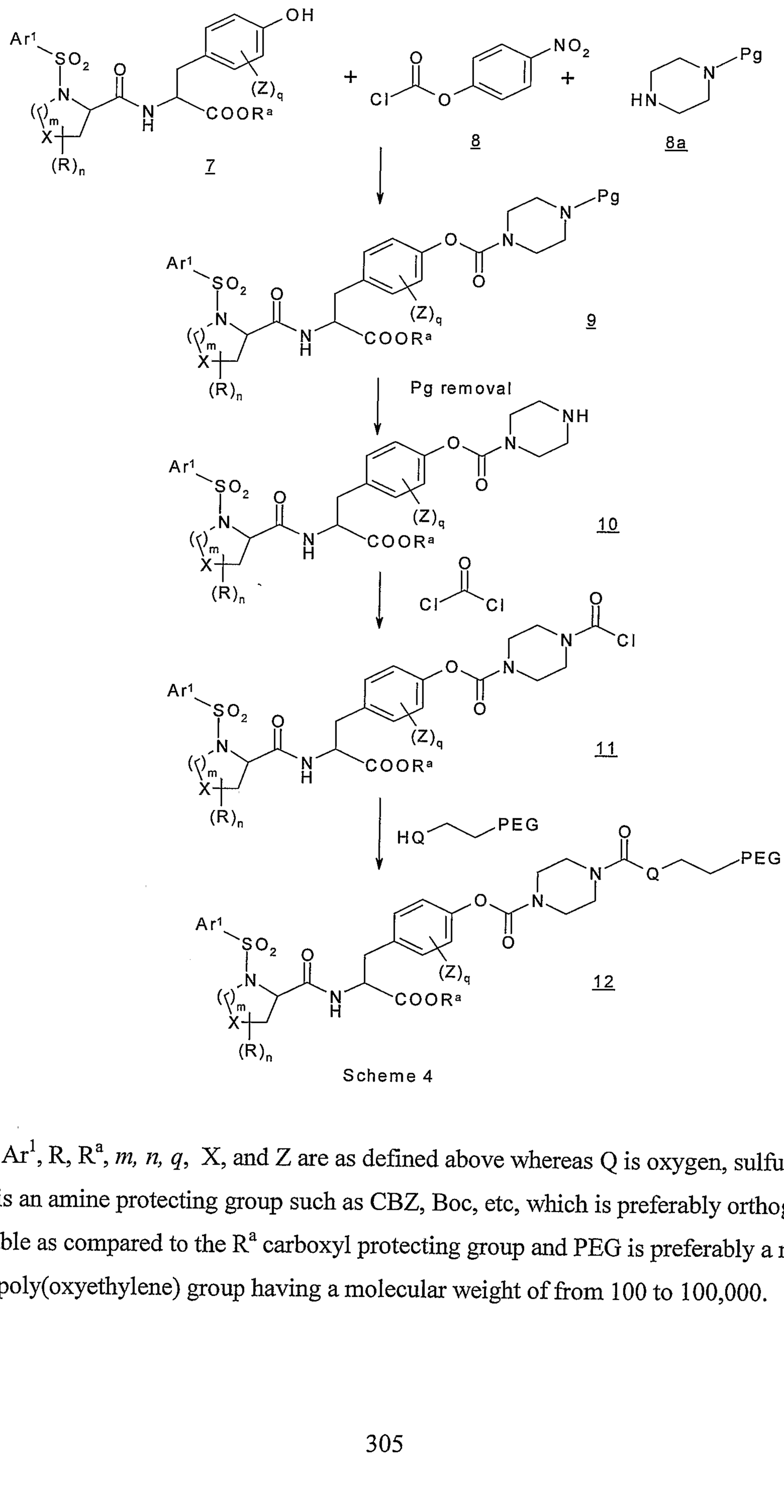
where R, $R^a$, $Ar^1$, X, Z, *m, n* and *q* are as defined above.

The diamino acid, 6, can be readily prepared by coupling amino acid, 1, with amino acid, 4, using conventional amino acid coupling techniques and reagents, such carbodiimides, BOP reagent and the like, as described above. Diamino acid, 6, can then be sulfonated using sulfonyl chloride, 2, and using the synthetic procedures described above to provide compound 7.

The tyrosine derivatives, 4, employed in the above reactions are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. For example, tyrosine derivatives, 4, suitable for use in the above reactions include, but are not limited to, L-tyrosine methyl ester, L-tyrosine *t*-butyl ester, L-3,5-diiodotyrosine methyl ester, L-3-iodotyrosine methyl ester, β-(4-hydroxy-naphth-1-yl)-L-alanine methyl ester, β-(6-hydroxy-naphth-2-yl)-L-alanine methyl ester, and the like. If desired, of course, other esters or amides of the above-described compounds may also be employed.

The N-arylsulfonyl-heterocyclic amino acid-tyrosine derivative, 7, can be used as a starting point to prepare PEG derivatives at the $Ar^2$ group by coupling reactions shown in Schemes 4-14 below which coupling reactions are illustrative only in demonstrating how PEG moieties can be introduced. In some cases, the PEG moiety can be directly introduced onto the phenoxy group and, in other cases, the PEG moiety can be introduced by linkage through a linker moiety.

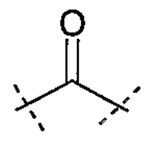
Specifically, Scheme 4 illustrates the following:




Scheme 4

wherein $Ar^1$, R, $R^a$, *m, n, q,* X, and Z are as defined above whereas Q is oxygen, sulfur and NH, Pg is an amine protecting group such as CBZ, Boc, etc, which is preferably orthogonally removeable as compared to the $R^a$ carboxyl protecting group and PEG is preferably a methyl capped poly(oxyethylene) group having a molecular weight of from 100 to 100,000.

In Scheme 4, the PEG moiety is covalently attached to the N-piperazinylcarbonyltyrosine moiety ($R^2/R^3$ are joined together with the nitrogen atom attached thereto to form a piperazine ring) via a linker entity which constitutes the group:



Specifically, in Scheme 4, compound 7, prepared as above, is combined with at least an equivalent and preferably an excess of 4-nitrophenyl chloroformate, 8, in a suitable solvent such as methylene chloride, chloroform and the like and preferably under an inert atmosphere. The reaction is preferably conducted at a temperature of from about -40° to about 0°C in the presence of a suitable base to scavenge the acid generated. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, and the like. After formation of the intermediate mixed carbonate (not shown), at least an approximately equimolar amount of N-Pg piperazine, 8a, is added to the reaction solution. This reaction is allowed to continue at room temperature for about 1 to 24 hours. Upon completion of the reaction, the compound 9 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like, or, alternatively, is used in the next reaction without purification and/or isolation.

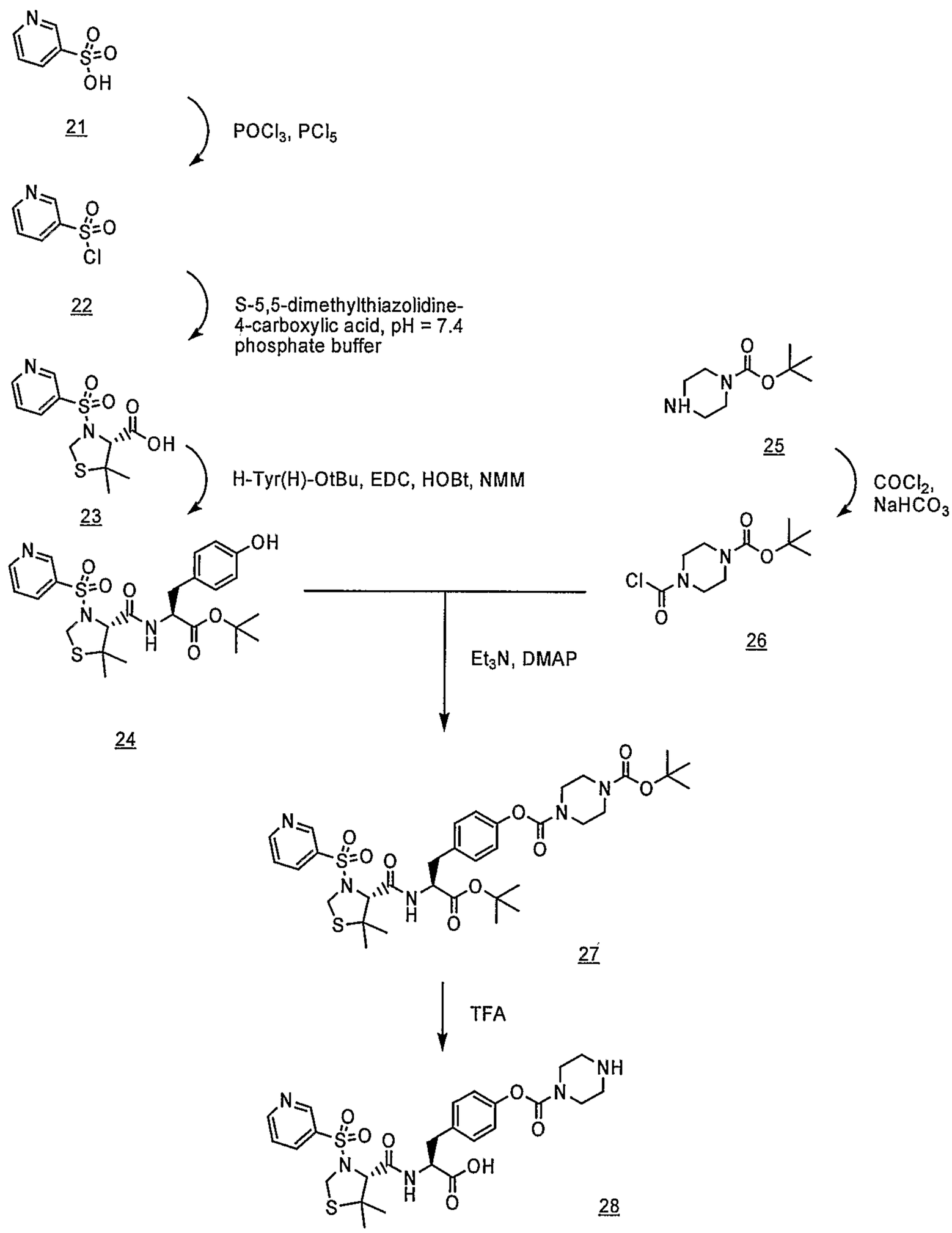
Conventional removal of the protecting group provides for the free piperazine derivative, 10. Removal is accomplished in accordance with the blocking group employed. For example, a trifluoromethylcarbonyl protecting group is readily removed via an aqueous solution of potassium carbonate. Further, suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. See, for example, T.W. Greene and G. M. Wuts, *Protecting Groups in Organic Chemistry*, Second Edition, Wiley, New York, 1991, and references cited therein.

The free piperazine derivative, 10, is then converted to the corresponding carbamyl chloride, 11, by reaction in a biphasic reaction mixture of phosgene in toluene (Fluka), dichloromethane and aqueous bicarbonate solution. Subsequent reaction of the carbamyl chloride, 11, with a mono-capped PEG compound such as commercially available $CH_3(OCH_2CH_2)_pOH$ provides for PEG derivative 12. The reaction is conducted in a suitable

solvent such as methylene chloride, chloroform, etc. typically in the presence of a catalytic amount of DMAP and a base to scavenge the acid generated during reaction. The reaction is continued until substantially complete which typically occurs within 4 to 24 hours.

When $R^a$ is alkyl, subsequent hydrolysis of the ester derivative provides for the free carboxyl group or a salt thereof.

A specific example of this reaction scheme up to formation of the piperazine derivative 10 is illustrated in Scheme 5 below:



Scheme 5

Specifically, commercially available 3-pyridinesulfonic acid, 21, is converted under conventional conditions to the corresponding sulfonyl chloride, 22, by contact with $POCl_3/PCl_5$ using conditions well known in the art. Coupling of sulfonyl chloride, 22, with commercially available S-5,5-dimethylthiazolidine-4-carboxylic acid, 23, is accomplished under conventional conditions preferably in the presence of a phosphate buffer (pH 7.4) using an excess of sulfonyl chloride. The reaction is preferably conducted at a temperature of from about -10 to 20 °C until the reaction is substantially complete, which typically occurs within 0.5 to 5 hours. The resulting product, 24, can be recovered by conventional methods, such as chromatography, filtration, evaporation, crystallization, and the like or, alternatively, used in the next step without purification and/or isolation.

The N-pyridyl sulfonyl-5,5-dimethylthiazolidine-4-carboxylic acid compound, 23, is next coupled to *t*-butyl tyrosine using conventional amino acid coupling conditions. Specifically, this coupling reaction is conducted using well known coupling reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), 1-hydroxy-benzotriazole (HOBt) and N-methylmorpholine to facilitate the coupling reaction.

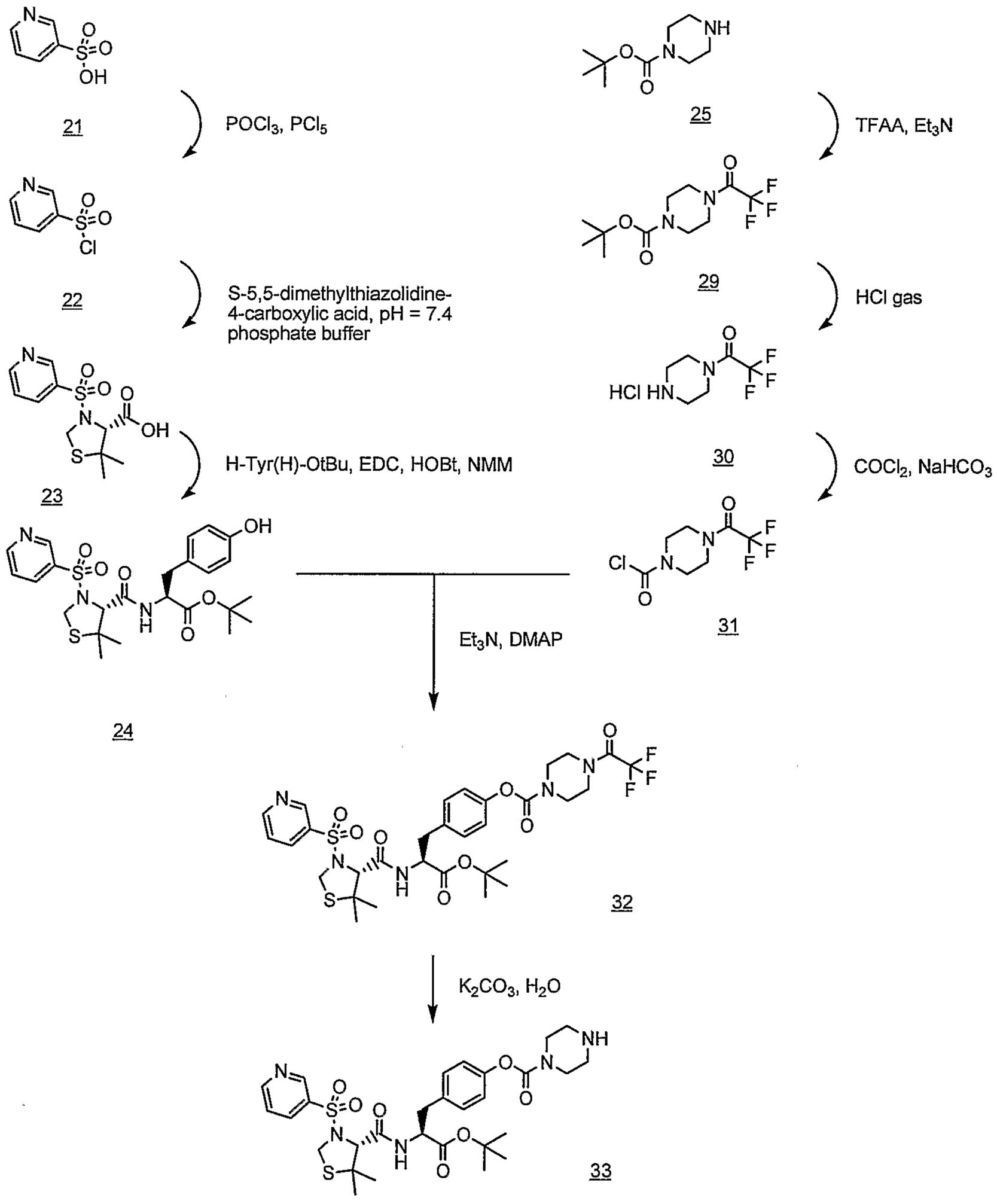
This coupling reaction is typically conducted by contacting the N-sulfonylamino acid, 23, with about 1 to about 2 equivalents of the coupling reagent and at least one equivalent, preferably about 1 to about 1.2 equivalents, of tyrosine *t*-butyl ester in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, N,N-dimethylformamide and the like. Generally, this reaction is conducted at a temperature ranging from about 0°C to about 22°C for about 12 to about 24 hours. Upon completion of the reaction, the compound 24 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Separately, mono-N-Boc-piperazine, 25, is converted to the corresponding carbamyl chloride, 26, by reaction with phosgene in the manner described above. Upon completion of the reaction, the compound 26 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Coupling of compound 24 with compound 26 to provide for compound 27 proceeds under conventional conditions in an inert diluent such as dichloromethane, with a catalytic amount of DMAP and preferably in the presence of a base to scavenge the acid generate. The reaction is run at a temperature of about -20 to about 22°C for about 2 to about 24 hours. Upon completion of the reaction, compound 27 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Removal of both the amino Boc protecting group and the t-butyl ester proceeds in the presence of trifluoroacetic acid to provide for compound 28 which can be recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like.

Scheme 6 below illustrates the preparation of a piperazine compound orthogonally protected on one of the amine groups relative to the carboxyl protecting group found on the phenylalanine compound such that after coupling, the piperazine protecting group can be removed differentially from that of the carboxyl protecting group. Such orthogonal protection is necessary if subsequent reactions on the resulting compound require a carboxyl protecting group to avoid undesired side reactions.




Scheme 6

Specifically, in Scheme 6, compound 24 is prepared in the manner described above. N-*t*-Boc-piperazine, 25, is conventionally converted to N-*t*-Boc-N'-trifluoromethyl-carbonylpiperazine, 29, by contact with an excess of trifluoroacetic anhydride in the presence of a suitable amine such as triethylamine to scavenge the acid generated during reaction in a suitable solvent such as dichloromethane. Generally, this reaction is conducted at a temperature ranging from about -20°C to about 22°C for about 1 to about 24 hours. Upon completion of the reaction, compound 29 can be recovered by conventional methods

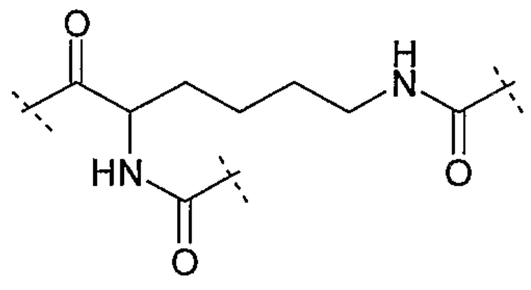
including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively and preferably, is employed in the next step without purification and/or isolation.

In turn, removal of the *t*-Boc protecting group on the N-*t*-Boc-N'-trifluoromethylcarbonylpiperazine, 29, proceeds under conventional conditions using gaseous HCl bubbled through an inert solvent such as methylene chloride, EtOAc, $EtO_2$, and the like under ambient conditions to provide for the hydrochloride salt of N'-trifluoromethylcarbonylpiperazine, 30. Generally, this reaction is conducted at a temperature ranging from about -20°C to about 22°C for about 0.5 to about 4 hours. Upon completion of the reaction, compound 30 can be recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively and preferably, is employed in the next step without purification and/or isolation.

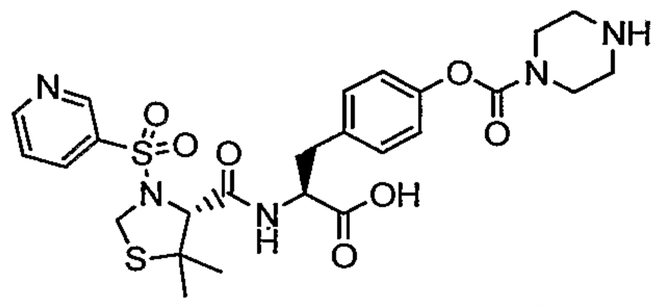
Conversion of N'-trifluoromethylcarbonylpiperazine, 30, to the N-carbamyl chloride derivative, 31, conventionally proceeds by contact with phosgene in the manner described above. Upon completion of the reaction, compound 31 can be recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively and preferably, is employed in the next step without purification and/or isolation.

Compounds 31 and 24 are coupled under conditions similar to those described above to provide for compound 32 which is orthogonally protected at the amino moiety of the piperazine group as well as the carboxyl moiety of the phenylalanine group. Selective removal of the trifluoromethylcarbonyl amino protecting group proceeds under conventional conditions using an aqueous solution of potassium carbonate to provide for compound 33.

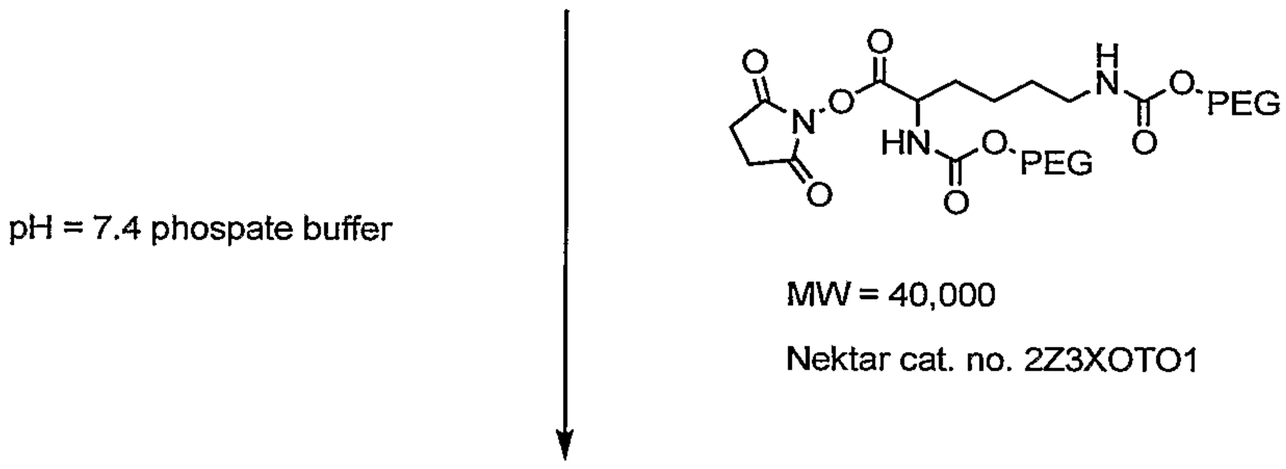
Scheme 7 below illustrates a first route for derivatization of compound 28 to provide for PEG substitution. In this scheme, the amino moiety of the piperazine group is employed as a complementary functional group to the activated carboxyl group of the lysine derivative to form a covalent amide bond thereby introducing two PEG moieties into the compound through a linker of the formula

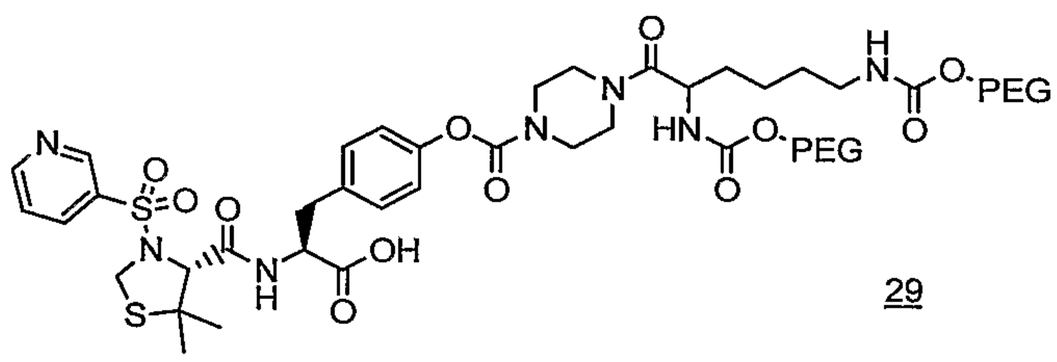


which linker comprises 8 carbon atoms and 5 heteroatoms.



28



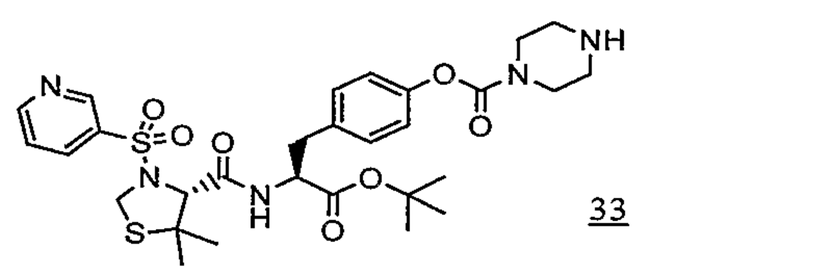
29

Scheme 7

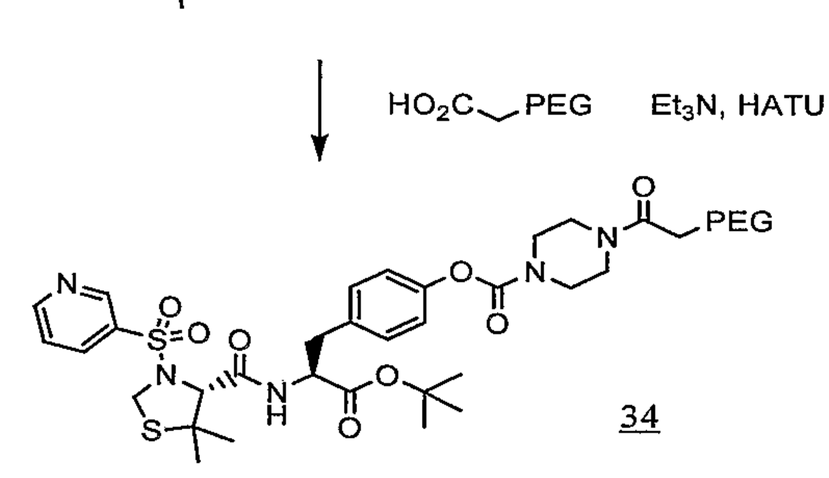
Specifically, in Scheme 7, conjugation of an excess of compound 28 (1.1 to 10 eq) with commercially available N-hydroxysuccinimidyl ester of a di-PEG substituted lysine derivative, in the presence of phosphate buffered aqueous solution provides for compound 29 which is recovered by dialysis. The commercially available N-hydroxy-succinimidyl ester of a di-PEG substituted lysine derivative has a weight average molecular weight of about 40,000

which means that each PEG moiety has a number average molecular weight of about 20,000. The reaction is run at a temperature of about 0 to about 22°C.

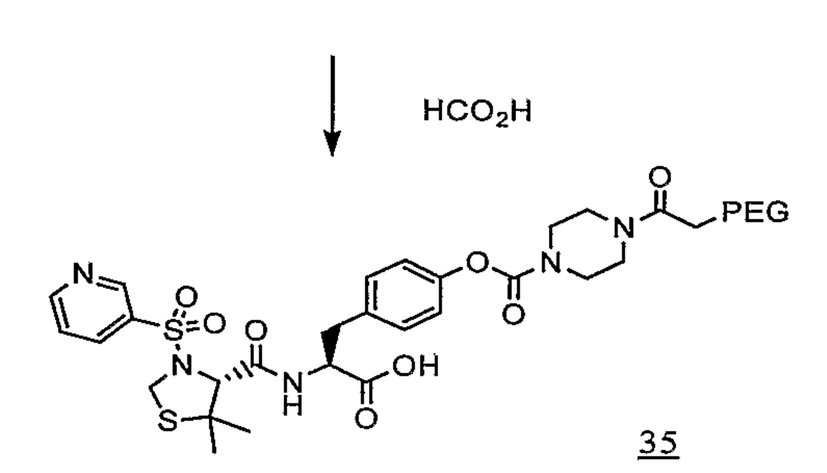
Scheme 8 illustrates a second route for derivatization to provide for PEG substitution. In this scheme, the amino moiety of the piperazine group is employed as a complementary functional group to an *in situ* formed activated carboxyl group of a commercially available carboxyl-PEG compound which under conventional reactive conditions forms a covalent amide bond thereby introducing a single PEG moiety into the compound. In this embodiment, the carboxyl-PEG compound is represented by the formula $HOOC(CH_2)_v(OCH_2CH_2)_pOCH_3$ where *p* and *v* are as defined above and the resulting linker to the PEG group is represented by $-C(O)(CH_2)_v-$. Carboxylated PEG compounds can be made by oxidation of the hydroxy terminated PEG compounds using conventional methods and reagents.



33




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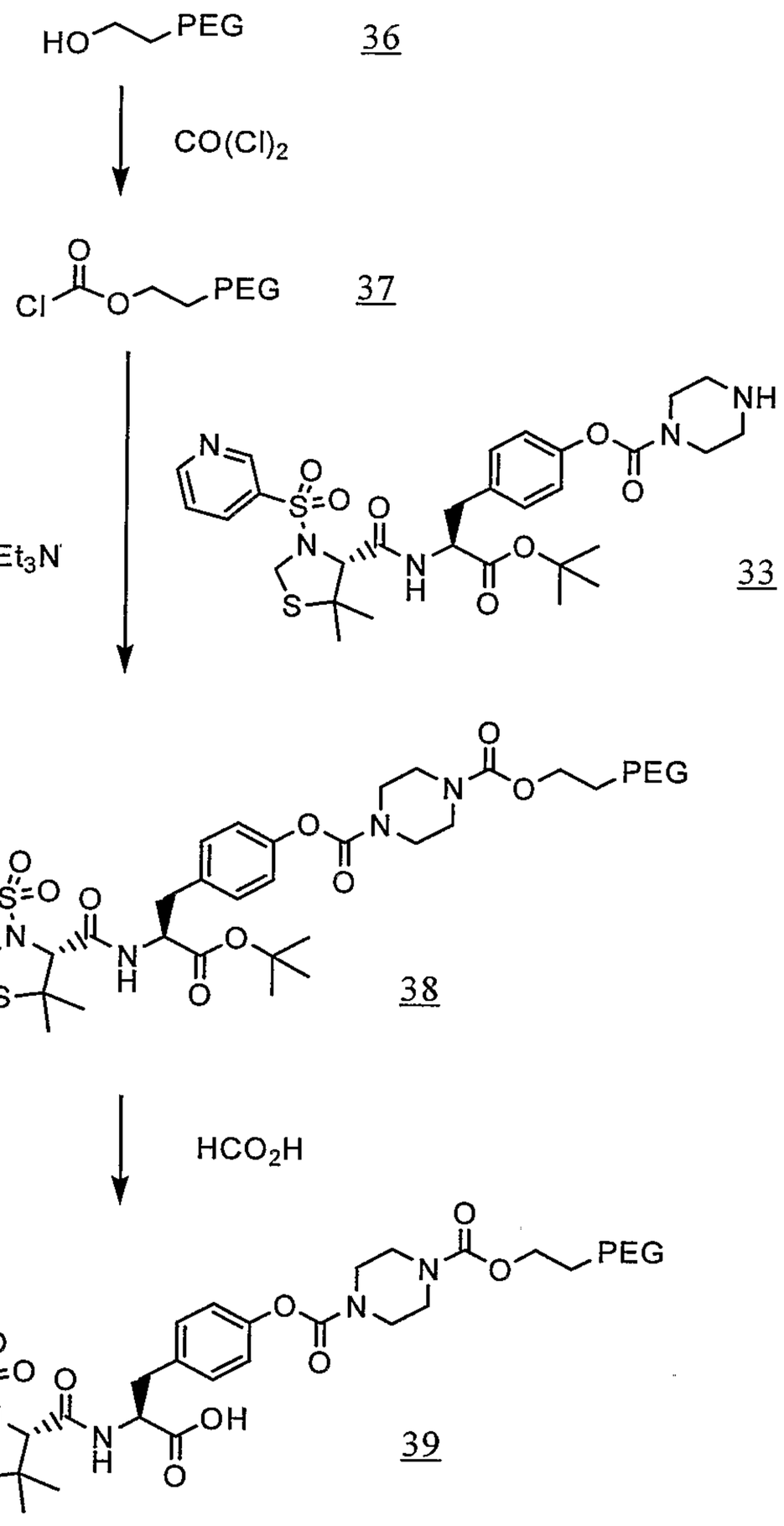
Scheme 8

Specifically, in Scheme 8, an excess (1.1 to 10 equiv) of compound 33, prepared as in Scheme 7, is added to at least an equivalent of a commercially available carboxyl-PEG compound which is convertd *in situ* to an activated ester (not shown) by contact with at least

an equivalent and preferably an excess of HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] in the presence of a suitable amine such as triethylamine. Coupling of the carboxyl-PEG compound to compound 33 preferably proceeds at a temperature of from about 0 to about 22°C for about 2 to about 24 hours. Upon completion of the reaction, the compound 34 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Conventional removal of the *t*-butyl carboxyl protecting group with an excess of formic acid provides for a mono-PEG compound of formula XXII of this invention.

Scheme 9 illustrates a third route for derivatization to provide for PEG substitution. In this scheme, the amino moiety of the piperazine group is employed as a complementary functional group to an *in situ* formed chloroformate of a commercially available mono-hydroxy-PEG compound which under conventional reactive conditions forms a covalent carbamate bond thereby introducing a single PEG moiety into the compound. In this embodiment, the mono-hydroxy-PEG compound is represented by the formula $HOCH_2CH_2(OCH_2CH_2)_pOCH_3$ where *p* is as defined above and the resulting linker is represented by -C(O)-.




Scheme 9

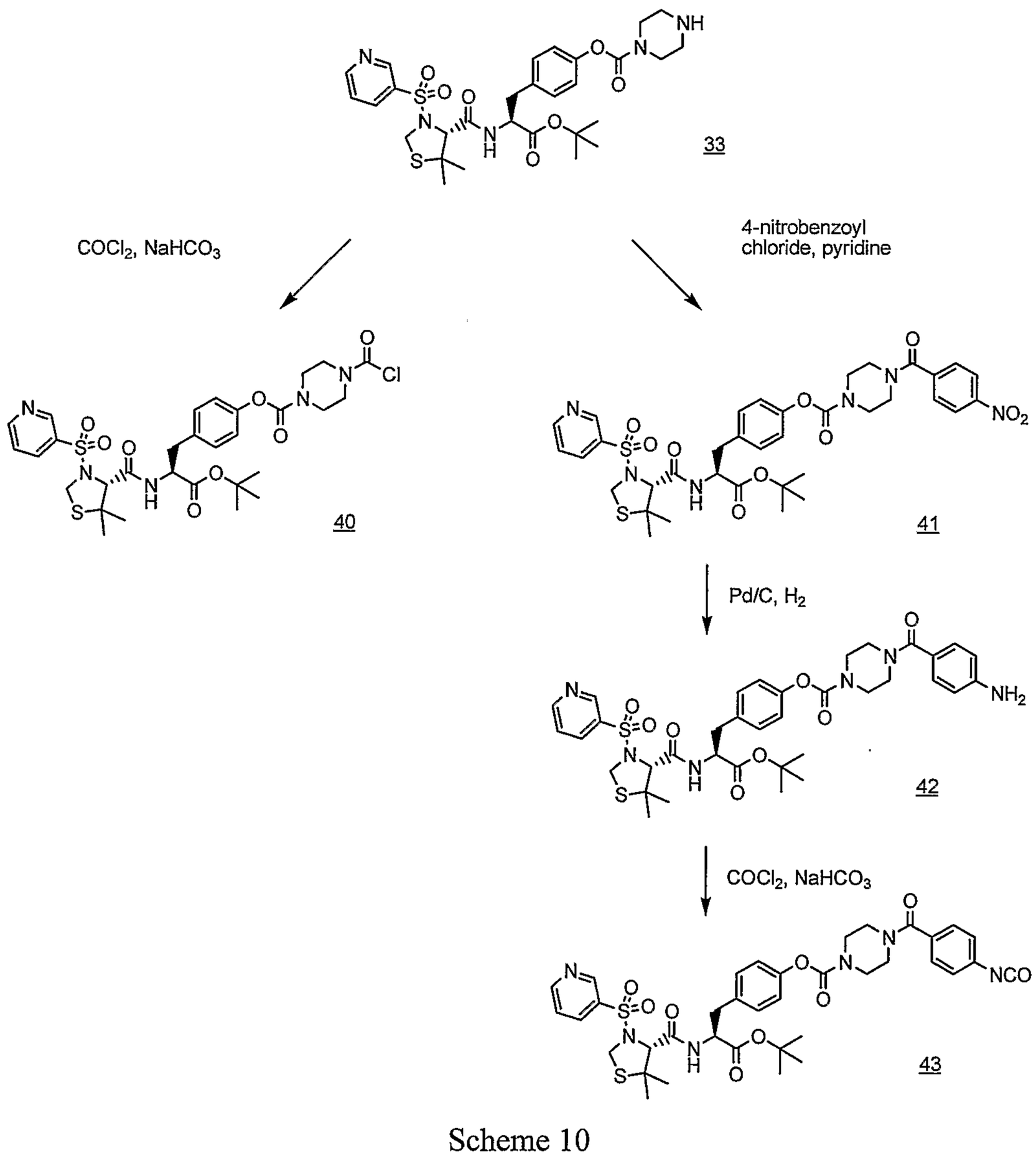
Specifically, in Scheme 9, the hydroxyl group of a commercially available mono-hydroxy PEG, 36, is converted to the corresponding chloroformate, 37, by reaction with phosgene in toluene (Fluka), in dichloromethane. The product is isolated by evaporation and is employed in the next step without further purification.

A slight excess (1.1 to 10 eq) of chloroformate 37 is contacted with compound 33, prepared as above, in the presence of a suitable base such as triethylamine to scavenge the acid generated. Coupling of the chloroformate-PEG compound to compound 33 preferably proceeds at a temperature of from about 0 to about 22°C for about 2 to about 4 hours. Upon completion of the reaction, the compound 38 is recovered by conventional methods including

neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Conventional removal of the *t*-butyl carboxyl protecting group with an excess of formic acid provides for a mono-PEG compound, 39, of formula XXII of this invention.

Scheme 10 illustrates the synthesis of two intermediates useful for subsequent PEG substitution. In this scheme, the amino moiety of the piperazine group is employed as a complementary functional group which is derivatized for subsequent PEG substitution.




Scheme 10

Specifically, in Scheme 10, conversion of amino moiety of the piperazine group to the corresponding N-carbamyl chloride derivative, 40, proceeds by contact with an excess of

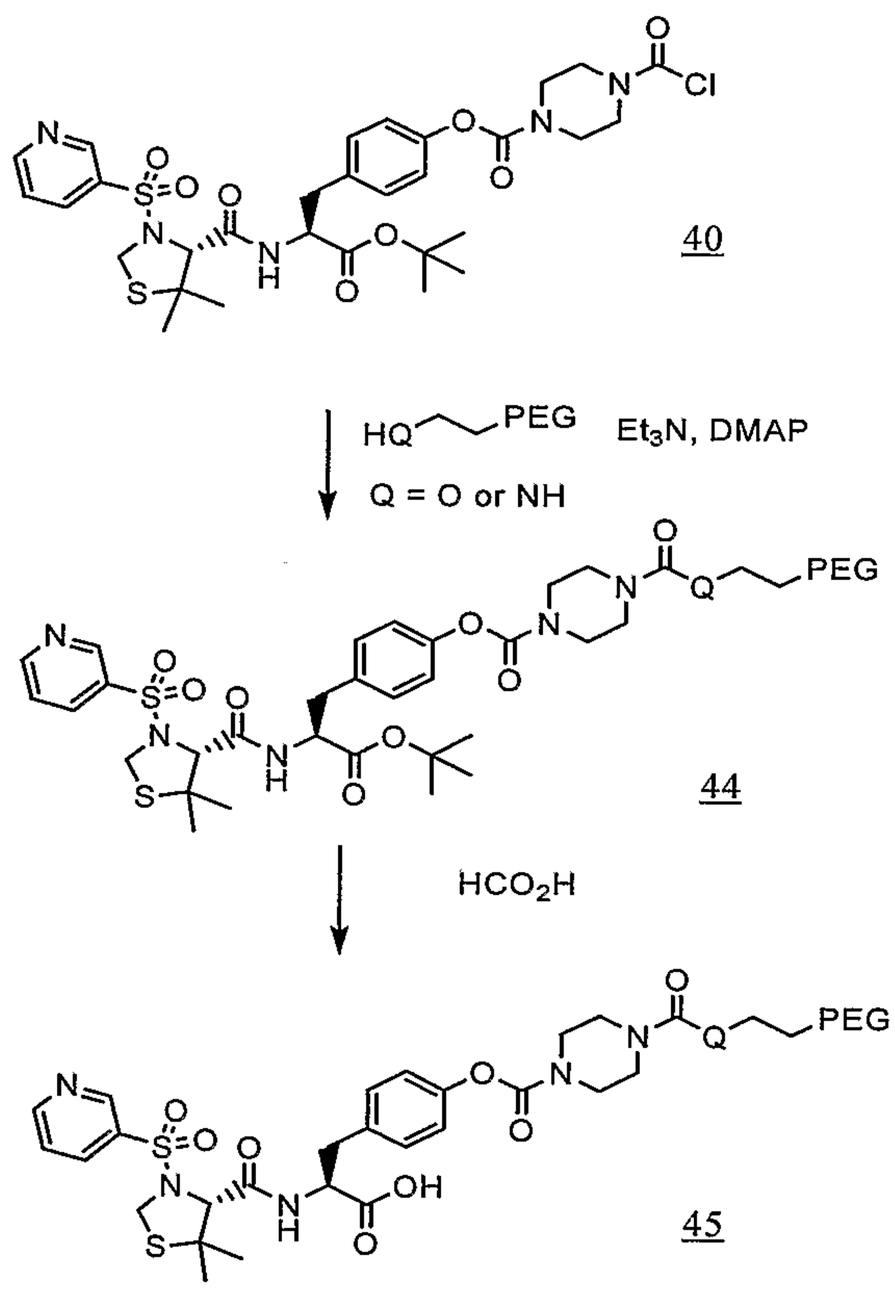
phosgene in the presence of a suitable base such as sodium bicarbonate to scavenge the acid generated during reaction. Upon completion of the reaction, compound 40 can be recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively and preferably, is employed in the next step (illustrated in Scheme 11) without purification and/or isolation.

Alternatively, the amino moiety of the piperazine group of compound 33 can be converted to the corresponding amide, compound 41, by reaction with at least an equivalent and preferably an excess of 4-nitrobenzoyl chloride in the presence of a base such as pyridine (which can also act as a solvent) to scavenge the acid generated during reaction. The reaction preferably proceeds at a temperature of from about 0 to about 22 °C for about 1 to about 24 hours. Upon completion of the reaction, compound 41 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Subsequent reduction of the *para*-nitro substituent of the phenyl group provides for the amine substituent in compound 42. Reduction is conventionally conducted using palladium/carbon under a hydrogen atmosphere typically at elevated pressures in a suitable diluent such as methanol. The reaction proceeds until substantial completion which typically occurs within about 24 to about 72 hours. During the reaction, additional catalyst is added as required to affect reaction completion. Upon completion of the reaction, the compound 42 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Conversion of the *para*-amino substituent of the phenyl group of compound 42 to the corresponding isocyanate, 43, occurs by reaction with an excess of phosgene in the presence of a suitable base such as sodium bicarbonate which scavenges the acid generated. The reaction proceeds until substantial completion which typically occurs within about 0.5 to about 5 hours at about 0°C to about 22°C. Upon completion of the reaction, the compound 43 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

Scheme 11 illustrates a fourth route for derivatization to provide for PEG substitution. In this scheme, the carbamyl chloride moiety of the piperazine group of compound 40 is employed as a complementary functional group to form a carbamate or urea bond with a commercially available mono-hydroxy- or mono-amino-PEG compound which under conventional reactive conditions. In this embodiment, the PEG compound is represented by the formula $HQCH_2CH_2(OCH_2CH_2)_pOCH_3$ where *p* and Q are as defined above and the resulting linker is represented by -C(O)-.




Scheme 11

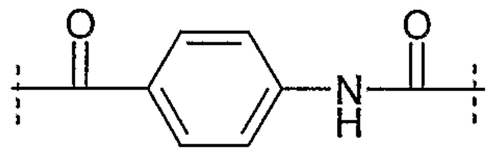
Specifically, in Scheme 11, an excess (1.1 to 10 eq) of carbamyl chloride, 40, is contacted in an inert solvent such as dichloromethane with a suitable mono-hydroxy- or mono-amino-PEG compound preferably in the presence of a suitable base such as triethylamine and/or catalytic amounts of 4-N,N-dimethylaminopyridine (DMAP). The reaction proceeds until substantial completion which typically occurs within about 4 to about 48hours. Upon completion of the reaction, the compound 44 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography,

filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

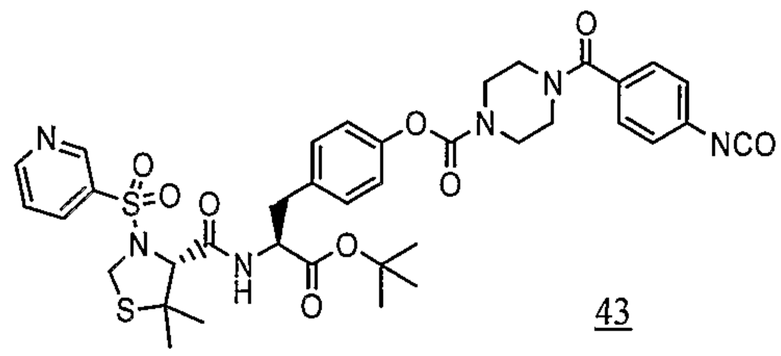
When Q is a hydroxyl group, the resulting product contains a carbamate functionality covalently linking the PEG group to the VLA-4 antagonist through a linker represented by -C(O)-. When Q is an amino group, the resulting product contains a urea functionality covalently linking the PEG group to the VLA-4 antagonist through a linker represented by -C(O)-.

Conventional removal of the *t*-butyl carboxyl protecting group with an excess of formic acid provides for a mono-PEG compound, 45, of formula XXIIa of this invention.

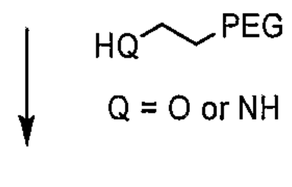
Scheme 12 illustrates a fifth route for derivatization to provide for PEG substitution. In this scheme, the isocyanate moiety of the phenyl group of compound 43 is employed as a complementary functional group to form a carbamate or urea bond with a commercially available mono-hydroxy- or mono-amino-PEG compound which under conventional reactive conditions. In this embodiment, the PEG compound is represented by the formula $HQCH_2CH_2(OCH_2CH_2)_pOCH_3$ where *p* and Q are as defined above and the resulting linker is represented by:

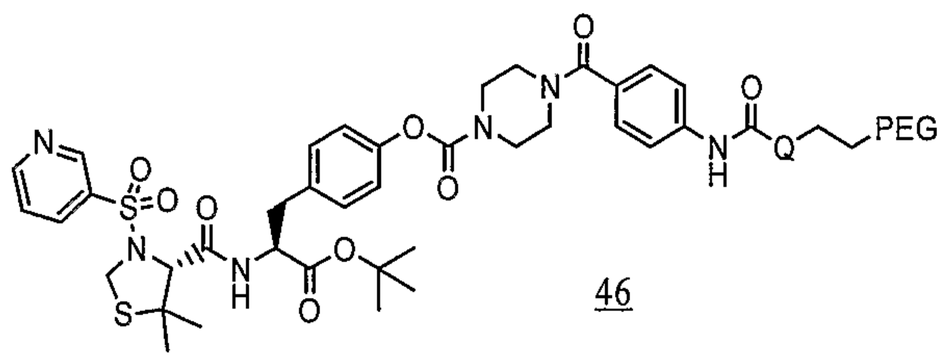


where the linker comprises 8 carbon atoms and 3 heteroatoms.

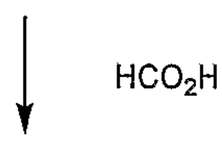


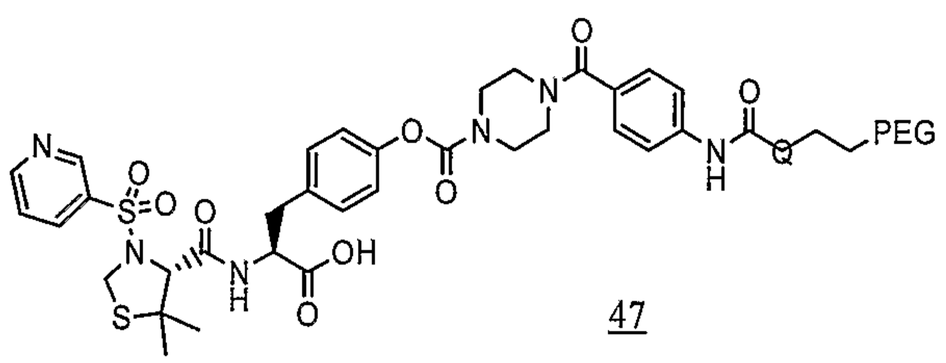
43



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Scheme 12

Specifically, in Scheme 12, an excess (1.1 to 10 eq) isocyanate, 43, is contacted with a suitable mono-hydroxy- or mono-amino-PEG compound in a suitable inert diluent such as dichloromethane or toluene. The reaction is preferably maintained at a temperature of from about 0° to about 105°C until substantial completion which typically occurs within about 1 to about 24 hours. Upon completion of the reaction, compound 46 is recovered by conventional methods including neutralization, evaporation, extraction, precipitation, chromatography, filtration, and the like or, alternatively, is employed in the next step without purification and/or isolation.

When Q is a hydroxyl group, the resulting product contains a carbamate functionality covalently linking the PEG group to the VLA-4 antagonist through a -C(O)- linking group. When Q is an amino group, the resulting product contains a urea functionality covalently linking the PEG group to the VLA-4 antagonist through a -C(O)- linking group.

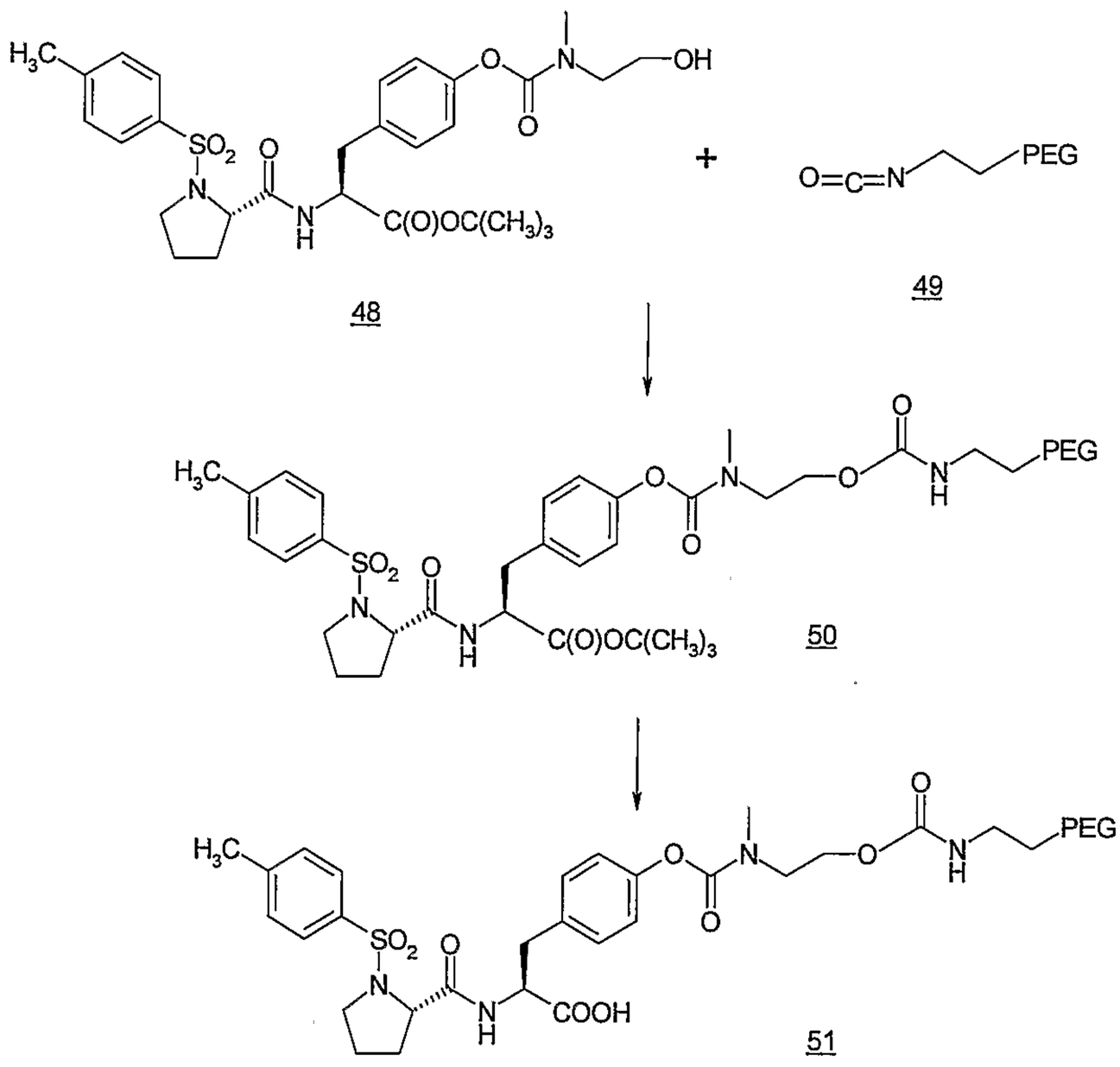
Conventional removal of the *t*-butyl carboxyl protecting group with an excess of formic acid provides for a mono-PEG compound, 47, of formula XXII of this invention.

In the Schemes above, amine moieties located on other portions of the molecule can be employed in the manner described above to covalently link a PEG group to the molecule. For example, amines located on $Ar^1$, on the heterocyclic amino acid or on $Ar^2$ can be similarly derivatized to provide for PEG substitution. The amine moieties can be included in these substituents during synthesis and appropriately protected as necessary. Alternatively, amine precursors can be employed. For example, as shown in Scheme 10, reduction of a nitro group provides for the corresponding amine. Similarly, reduction of a cyano group provides for a $H_2NCH_2$- group. Nitro and cyano substituted $Ar^1$ groups are provided in U.S. Patent No. 6,489,300 as is an amino substituted $Ar^1$ group.

Further, the amino substitution can be incorporated into the heterocyclic amino acid functionality and then derivatized to include a PEG moiety found in formula XXII as R. For example, the heterocyclic amino acid functionality can be 2-carboxylpiperazine depicted in U.S. Patent No. 6,489,300. Alternatively, commercially available 3- or 4-hydroxyproline can be oxidized to the corresponding ketone and then reductively aminated with ammonia in the presence of sodium cyanoborohydride to form the corresponding amine moiety. Still further, 4-cyanoproline can be reduced to provide for a substituted alkyl group of the formula - $CH_2NH_2$ which can be derivatized through the amine.

Still further, the amine moiety can be incorporated into the $Ar^2$ functionality. Preferably, the amine moiety is present as an amine precursor such as a nitro or cyano group bound to $Ar^2$.

In the schemes above, the reactions of the amine with a complementary functional group can be reversed such that the carboxyl or hydroxyl group is on the VLA-4 antagonist of formula XXIIa (without any PEG substituents) and the amine group could be part of the PEG moiety. In such cases, the amine group, preferably terminating the PEG moiety, can be converted to an isocyanate, using phosgene and $Et_3N$, and reacted with the hydroxyl group to form a carbamate as illustrated in Scheme 13 below:

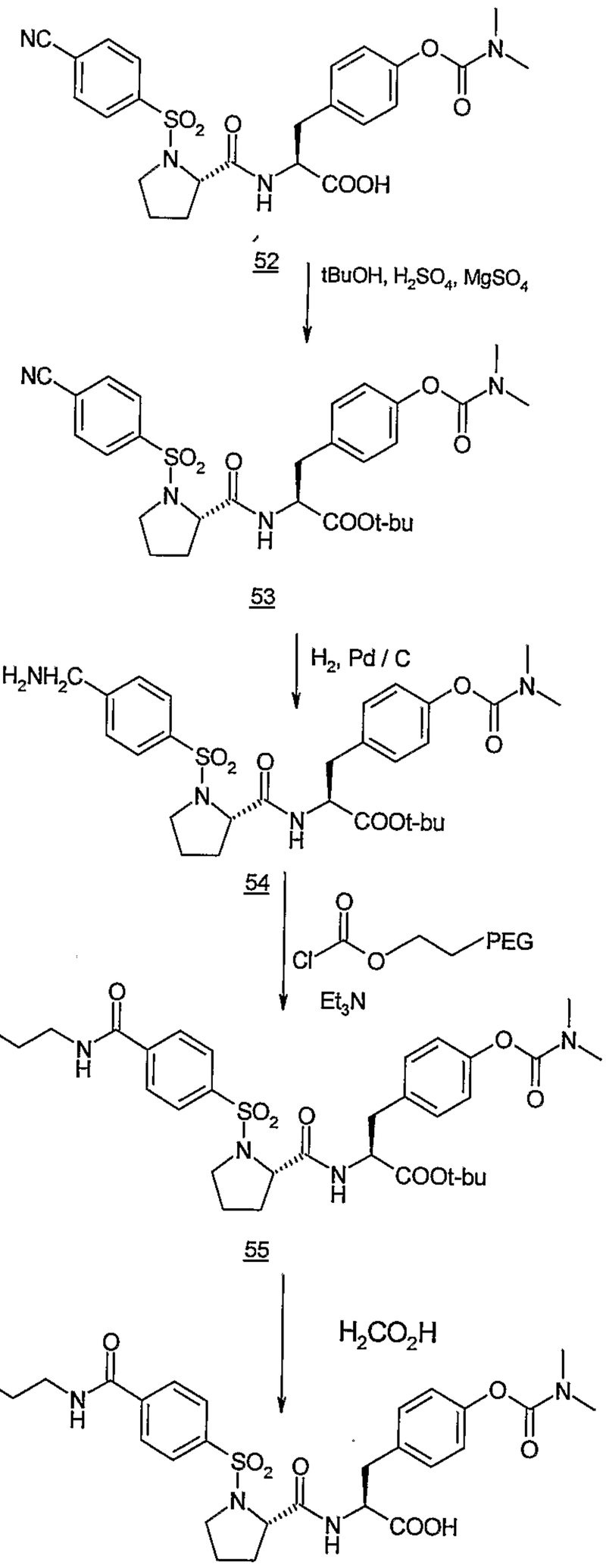



Scheme 13

Specifically, compound 48 described in U.S. Patent No. 6,489,300 is contacted with at least an equivalent and preferably an excess of 49 in the manner described above to provide for the corresponding carbamate, 50. Deprotection, as described above, then provides for compound 51.

Alternatively, in Scheme 13, the hydroxyl functionality can be reacted with phosgene to provide for the chlorocarbonyloxy derivative which reacts with an amine group of a monoamine compound to provide for the carbamate.

Carboxyl functionality, for example on the $Ar^1$ moiety, can be converted to the corresponding amide by reaction with a mono-amino-PEG compound in the manner described above in Scheme 8.




Scheme 14

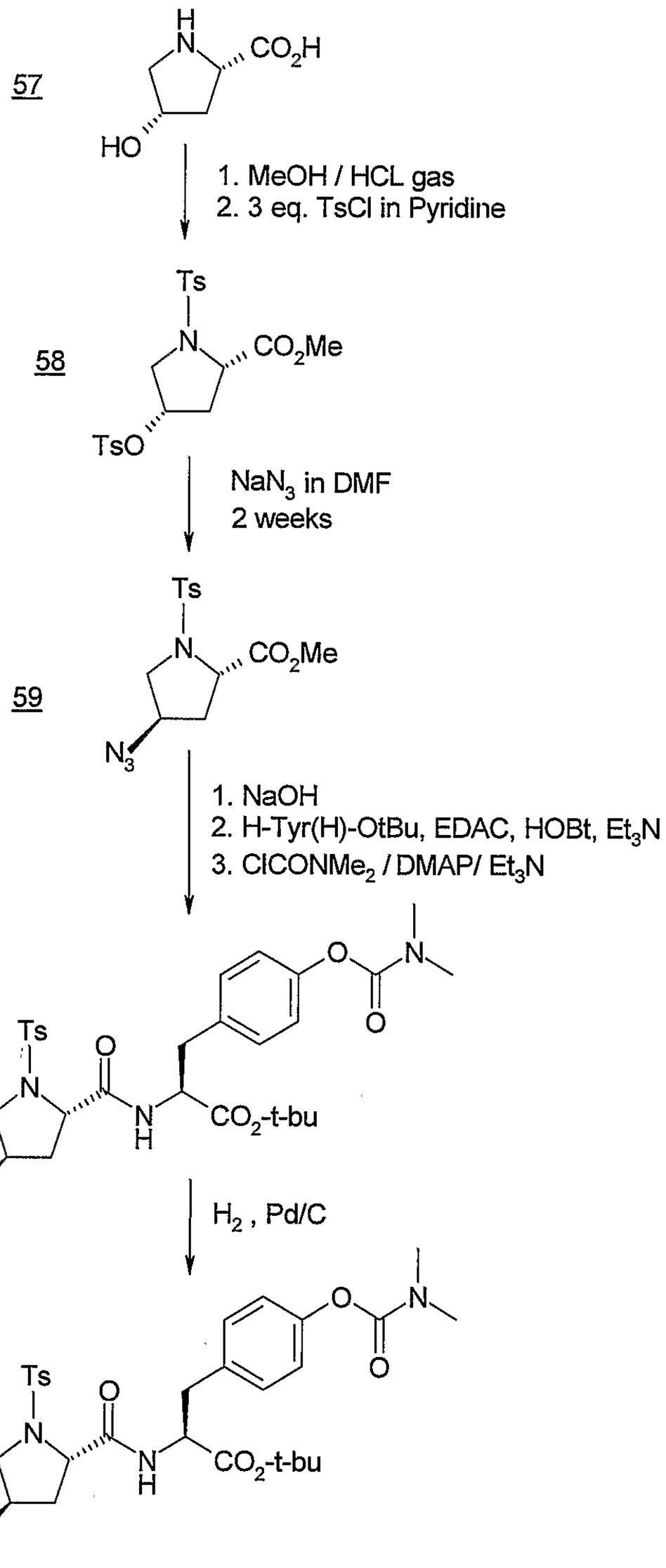
Specifically, in Scheme 14, known compound 52, described in U.S. Patent No. 6,489,300, is t-butyl protected under convention conditions to provide the cyano compound 53, which is hydrogenated under conventional conditions to provide the aminomethyl compound 54. The aminomethyl group is reacted with $Et_3N$ and a PEG chloroformate, as illustrated previously in Scheme 9, to provide the carbamate-linked conjugate t-butyl ester 55. Treatment of the t-butyl ester with $HCO_2H$ provides the conjugate carboxylic acid 56.

Suitable PEG compounds are commercially available or can be prepared by art recognized procedures. For example, mono-capped linear PEGs with one terminal amine are available in varying molecular weights (*e.g.*, 2 kilodaltons (kDa), 5 kDa, 10 kDa and 20 kDa from Nektar, San Carlos, CA). Preferred mono-capped PEGs having one terminal amine group can be represented by the formula $H_2NCH_2CH_2(OCH_2CH_2)_pOCH_3$.

Mono-capped linear PEGs with one terminal alcohol are available in varying molecular weights (*e.g.*, 2 kilodaltons (kDa), 5 kDa, 10 kDa and 20 kDa from Nektar, San Carlos, CA). Preferred mono-capped linear PEGs having one terminal alcohol can be represented by the formula $HOCH_2CH_2(OCH_2CH_2)_pOCH_3$.

Diamino-capped linear PEGs having an amino group at both termini are commercially available and are sometimes referred to as "Jeffamines" (tradename of Huntsman). Preferred diamino-capped linear PEGs having an amino group at both termini can be represented by the formula: $H_2NCH_2CH_2(OCH_2CH_2)_pNH_2$.

Scheme 15 below illustrates an alternative synthesis of 3-aminopyrrolidinyl derivatives useful as starting materials in this invention for subsequent PEG substitution at the amino group.




Scheme 15

Using conventional methods, commercially available cis-4-hydroxy L-proline, 57, is treated with methanolic hydrogen chloride for several hours at reflux, followed by evaporation, and the so generated methyl ester hydrochloride is treated with excess tosyl chloride in pyridine for two days at room temperature, giving the product, 58. Compound 58 is isolated by neutralizing the pyridine using weak aqueous acid and extracting the product

with an organic solvent such as EtOAc. The product 58 may be purified by crystallization, flash chromatography, or more preferably be used in subsequent steps without purification.

Reaction of 58 with a saturated solution of excess sodium azide in DMF at room temperature for 15 days affords compound 59. Compound 59 is isolated by dilution of the reaction mixture with water, followed by extraction with an organic solvent such as EtOAc. The product 59 may be purified by crystallization, flash chromatography, or more preferably be used in subsequent steps without purification.

Compound 59 is treated with sodium hydroxide, in a mixture of water and methanol, thus hydrolyzing the methyl ester and generating a carboxylic acid, which is isolated by acidification and extraction with an organic solvent such as EtOAc. The carboxylic acid is treated with L-tyrosine t-butyl ester [H-Tyr(H)-OtBu], EDAC, HOBt, and Et3N in DMF, generating a dipeptide, which is isolated by dilution with water and extraction with an organic solvent such as EtOAc. The dipeptide is treated with ClCONMe2, Et3N, and DMAP in DCM at reflux for 24 hours, generating the carbamate, 60, which is isolated by dilution with EtOAc, sequential washing with weak aqueous acid and base, and then evaporation. Compound 60 is rigorously purified by flash chromatography.

Finally, compound 61 is prepared by shaking of a solution of 60 in methanol, with a Pd/C catalyst under an atmosphere of hydrogen. The product, 61, is isolated by removal of the catalyst by filtration and evaporation.

Still further, the synthesis of varying mono-capped mono-hydroxy PEGs are described in detail by Campbell, U.S. Patent No. 4,604,103 which is incorporated herein by reference in its entirety. If a mono-capped mono-amino PEG is preferred, the mono-capped mono-hydroxy PEGs can readily be converted to the corresponding chloride by conventional methods and subsequently converted to an amine by contact with an excess of ammonia.

The PEGs of this invention comprise, for example, the following:

| | |
|---|---|
| $HO(alkylene\text{-}O)_pH$ | dihydroxy-PEG |
| $HO(alkylene\text{-}O)_pR^b$ | mono-capped mono-hydroxy PEG |
| $H_2N(alkylene\text{-}O)_pR^b$ | mono-capped mono-amino PEG |
| $H_2N(alkylene\text{-}O)_pCH_2CH_2NH_2$ | Jeffamines |

where *p* and alkylene are as defined herein and $R^b$ is preferably selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl.

The PEG derivatives described herein can be used in the pharmaceuticals formulations described above. Preferably, the formulations are administered orally or parenterally to a subject in need thereof.

**Antibodies & Immunoglobulins**

In one specific embodiment, the agents of the invention are immunoglobulins that selectively bind to an alpha-4 integrin or a dimer comprising alpha-4 integrin, such as alpha-4 beta-1 or alpha-4 beta-7. The immunoglobulins are preferably antibodies or fragments thereof that bind to an alpha-4 integrin or dimer thereof. Also contemplated herein are immunoglobulin molecules that bind to VCAM-1 in a manner such that they inhibit VCAM-1 interaction with VLA-4. By antibodies is meant to include complete immunoglobulins such as IgG1 or IgM, or inhibitors derived from antibodies, such as Antegren™. Preferably, the immunoglobulins recognize epitopes on VLA-4 and by recognizing and binding to these epitopes, the immunoglobulines inhibit VLA-4 from interacting with VCAM-1.

When the agent of the invention is an antibody, a monoclonal antibody is the preferred antibody. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different epitopes, each monoclonal antibody is directed against a single epitope on the antigen. A second advantage of monoclonal antibodies is that they are synthesized by means that are uncontaminated by other immunoglobulins, *e.g.,* by phage display or isolation from a hybridoma. Although the present invention intends to encompass both polyclonal and monoclonal antibodies as agents of the invention, monoclonal antibodies are preferred as they are highly specific, and the invention is thus discussed primarily in terms of monoclonal antibodies.

"Native antibodies and immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 Daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain ($V_H$) followed by a number of constant domains. Each light chain has a variable domain at one and ($V_L$) and a

constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains (Clothia *et al.*, 1985, *J. Mol. Biol.*, 186: 651-63; Novotny *et al.*, 1985, *Proc. Natl. Acad. Sci. USA*, 82: 4592-6).

In addition, other antibodies can be identified using techniques available in the art. For example, monoclonal antibodies of the present invention can be produced using phage display technology. Antibody fragments, which selectively bind to an alpha-4 integrin or a dimer comprising an alpha-4 integrin, are then isolated. Exemplary preferred methods for producing such antibodies via phage display are disclosed in U.S. Pat. Nos. 6,225,447; 6,180,336; 6,172,197; 6,140,471; 5,969,108; 5,885,793; 5,872,215; 5,871,907; 5,858,657; 5,837,242; 5,733,743 and 5,565,332.

A "variant" antibody, refers herein to an immunoglobulin molecule that differs in amino acid sequence from a "parent" antibody amino acid sequence by virtue of addition, deletion and/or substitution of one or more amino acid residue(s) in the parent antibody sequence. The parent antibody or immunoglobulin can be a polyclonal antibody, monoclonal antibody, humanized antibody, Primatized® antibody or any antibody fragment. In the preferred embodiment, the variant comprises one or more amino acid substitution(s) in one or more hypervariable region(s) of the parent antibody. For example, the variant may comprise at least one, *e.g.,* from about one to about ten, and preferably from about two to about five, substitutions in one or more hypervariable regions of the parent antibody. Ordinarily, the variant will have an amino acid sequence having at least 75% amino acid sequence identity with the parent antibody heavy or light chain variable domain sequences, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the parent antibody residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. No N-terminal, C-terminal, or internal extensions, deletions, or insertions into the antibody sequence shall be construed as affecting sequence identity or homology. The variant retains the ability to bind the receptor and preferably has properties that are superior to those of the parent antibody. For example, the variant may have a stronger binding affinity, enhanced ability to activate the receptor, *etc.* To analyze

such properties, one should compare a Fab form of the variant to a Fab form of the parent antibody or a full-length form of the variant to a full-length form of the parent antibody. The variant antibody of particular interest herein is one which displays at least about 10 fold, preferably at least about 20 fold, and most preferably at least about 50 fold, enhancement in biological activity when compared to the parent antibody. The "parent" antibody herein is one that is encoded by an amino acid sequence used for the preparation of the variant. Preferably, the parent antibody has a human framework region and has human antibody constant region(s). For example, the parent antibody may be a humanized or human antibody. An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibodies will be prepared by at least one purification step.

***Monoclonal Antibodies.*** Monoclonal antibodies can also be produced using the conventional hybridoma methods. These methods have been widely applied to produce hybrid cell lines that secrete high levels of monoclonal antibodies against many specific antigens, and can also be used to produce monoclonal antibodies of the present invention. For example, mice (*e.g.,* Balb/c mice) can be immunized with an antigenic alpha-4 epitope by intraperitoneal injection. After sufficient time has passed to allow for an immune response, the mice are sacrificed and the spleen cells obtained and fused with myeloma cells, using techniques well known in the art. The resulting fused cells, hybridomas, are then grown in a selective medium, and the surviving cells grown in such medium using limiting dilution conditions. After cloning and recloning, hybridomas can be isolated that secrete antibodies

(for example, of the IgG or IgM class or IgG1 subclass) that selectively bind to the target, alpha-4 or a dimer comprising an alpha-4 integrin. To produce agents specific for human use, the isolated monoclonal can then be used to produce chimeric and humanized antibodies. Antibodies can also be prepared that are anti-peptide antibodies. Such anti-peptide antibodies would be prepared against peptides of alpha-4 integrin.

Chimeric, Primatized® and humanized antibodies can be produced from non-human antibodies, and can have the same or similar binding affinity as the antibody from which they are produced. Techniques developed for the production of chimeric antibodies (Morrison *et al.*, 1984 *Proc. Natl. Acad. Sci.* 81: 6851; Neuberger *et al.*, 1984 *Nature* 312: 604; Takeda *et al.*, 1985 *Nature* 314: 452) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from, for example, a human antibody molecule of appropriate biological activity can be used; such antibodies are within the scope of this invention. For example, a nucleic acid encoding a variable (V) region of a mouse monoclonal antibody can be joined to a nucleic acid encoding a human constant (C) region, *e.g.*, IgG1 or IgG4. The resulting antibody is thus a species hybrid, generally with the antigen binding domain from the non-human antibody and the C or effector domain from a human antibody.

Humanized antibodies are antibodies with variable regions that are primarily from a human antibody (the acceptor antibody), but which have complementarity determining regions substantially from a non-human antibody (the donor antibody). See, *e.g.*, Queen *et al.*, 1989 *Proc. Natl Acad. Sci. USA* 86: 10029-33; WO 90/07861; and U.S. Patent Nos. 6,054,297; 5,693,761; 5,585,089; 5,530,101 and 5,224,539. The constant region or regions of these antibodies are generally also from a human antibody. The human variable domains are typically chosen from human antibodies having sequences displaying a high homology with the desired non-human variable region binding domains. The heavy and light chain variable residues can be derived from the same antibody, or a different human antibody. In addition, the sequences can be chosen as a consensus of several human antibodies, such as described in WO 92/22653.

Specific amino acids within the human variable region are selected for substitution based on the predicted conformation and antigen binding properties. This can be determined using techniques such as computer modeling, prediction of the behavior and binding properties of amino acids at certain locations within the variable region, and observation of

effects of substitution. For example, when an amino acid differs between a non-human variable region and a human variable region, the human variable region can be altered to reflect the amino acid composition of the non-human variable region.

In a specific embodiment, the antibodies used in the chronic dosage regime of the present invention are humanized antibodies as disclosed in U.S. Pat. No. 5,840,299, which is incorporated herein by reference.

In another embodiment, transgenic mice containing human antibody genes can be immunized with an antigenic alpha-4 structure and hybridoma technology can be used to generate human antibodies that selectively bind to alpha-4.

Chimeric, human and/or humanized antibodies can be produced by recombinant expression, *e.g.,* expression in human hybridomas (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985)), in myeloma cells or in Chinese Hamster Ovary (CHO) cells. Alternatively, antibody-coding sequences can be incorporated into vectors suitable for introducing into the genome of animal thereby producing a transgenic animal. One example would be to produce such antibodies in the milk of a transgenic animal such as a bovine. *See, e.g.,* U.S. Pat Nos. 5,849,992 and 5,304,489. Suitable transgenes include trangenes having a promoter and/or enhancer from a mammary gland specific gene, for example casein or β-lactoglobulin.

Natalizumab And Related Humanized Antibodies

The invention provides for a method of using humanized immunoglobulins that specifically bind to a VLA-4 ligand either alone or in combination to diagnose and/or treat rheumatoid arthritis. One preferred antibody for use in such methods of treatment and in medicaments includes that described in U.S. Patent No. 5,840,299 assigned to Elan Pharmaceuticals, which is herein incorporated in its entirety. Another aspect contemplates the use of fragments of these antibodies as assessed *in vivo*.

The humanized antibodies comprise a humanized light chain and a humanized heavy chain. In one aspect, the humanized light chain can comprise three complementarity determining regions (*i.e.*, CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of a mouse 21-6 immunoglobulin light chain, and a variable region framework from a human kappa light chain variable region framework sequence except in at least one position selected from a first group consisting of

positions L45, L49, L58 and L69, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21.6 immunoglobulin light chain variable region framework.

The humanized heavy chain comprises three complementarity determining regions (*i.e.*, CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of a mouse 21-6 immunoglobulin heavy chain, and a variable region framework from a human heavy chain variable region framework sequence except in at least one position selected from a group consisting of H27, H28, H29, H30, H44, H71, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin heavy chain variable region framework. The immunoglobulins specifically bind to VLA-4 with an affinity having a lower limit of about $10^7$ $M^{-1}$ and an upper limit of about five times the affinity of the mouse 21-6 immunoglobulin.

Usually, the humanized light and heavy chain variable region frameworks are from RE1 and 21/28'CL variable region framework sequences respectively. When the humanized light chain variable region framework is from RE1, at least two framework amino acids are replaced. One amino acid is from the first group of positions described *supra*. The other amino acids are from a third group consisting of positions L104, L105 and L107. This position is occupied by the same amino acid present in the equivalent position of a kappa light chain from a human immunoglobulin other than RE1.

Some humanized immunoglobulins have a mature light chain variable region sequence designated La or Lb, or a mature heavy chain variable region sequence designated Ha, Hb or Hc (FIG. 13). Preferred humanized immunoglobulins include those having a La light chain and an Ha, Hb or Hc heavy chain.

The humanized immunoglobulins have variable framework regions substantially from a human immunoglobulin (termed an acceptor immunoglobulin) and complementarity determining regions substantially from a mouse immunoglobulin termed mu MAb 21.6 (referred to as the donor immunoglobulin). The constant region(s), if present, are also substantially from a human immunoglobulin. The humanized antibodies exhibit a specific binding affinity for VLA-4 of at least $10^7$, $10^8$, $10^9$, or $10^{10}$ $M^{-1}$. Usually the upper limit of binding affinity of the humanized antibodies for VLA-4 is within a factor of three or five of

that of mu MAb 21.6 (about $10^9$ $M^{-1}$). Often the lower limit of binding affinity is also within a factor of three or five of that of mu MAb 21.6.

Humanized antibodies can be produced as exemplified, for example, with the mouse MAb 21.6 monoclonal antibody. The starting material for production of humanized antibodies is mu MAb 21.6. The isolation and properties of this antibody are described in U.S. Patent No. 6,033,655 (assigned to Elan Pharmaceuticals, Inc.), which is herein incorporated by reference in its entirety. Briefly, mu MAb 21.6 is specific for the $\alpha_4$ subunit of VLA-4 and has been shown to inhibit human lymphocyte binding to tissue cultures of rat brain cells stimulated with tumor necrosis factor. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the numbering convention of Kabat.

The next step involved selecting human antibodies to supply framework residues. The substitution of mouse CDRs into a human variable domain framework is most likely to result in retention of their correct spatial orientation if the human variable domain framework adopts the same or similar conformation to the mouse variable framework from which the CDRs originated. This is achieved by obtaining the human variable domains from human antibodies whose framework sequences exhibit a high degree of sequence identity with the murine variable framework domains from which the CDRs were derived. The heavy and light chain variable framework regions can be derived from the same or different human antibody sequences. The human antibody sequences can be the sequences of naturally occurring human antibodies or can be consensus sequences of several human antibodies. *See* Kettleborough *et al.*, *Protein Engineering* 4: 773 (1991); Kolbinger *et al.*, *Protein Engineering* 6: 971 (1993).

Suitable human antibody sequences are identified by computer comparisons of the amino acid sequences of the mouse variable regions with the sequences of known human antibodies. The comparison is performed separately for heavy and light chains but the principles are similar for each. This comparison reveals that the mu 21.6 light chain shows greatest sequence identity to human light chains of subtype kappa 1; the mu 21.6 heavy chain shows greatest sequence identity to human heavy chains of subtype one, as defined by Kabat, *supra*. Thus, light and heavy human framework regions are usually derived from human antibodies of these subtypes, or from consensus sequences of such subtypes. The preferred

light and heavy chain human variable regions showing greatest sequence identity to the corresponding regions from mu MAb 21.6 are from antibodies RE1 and 21/28'CL respectively.

Computer modeling can then be used to further enhance the humanized antibody's ability to bind to its cognate antigen. The unnatural juxtaposition of murine CDR regions with human variable framework region can result in unnatural conformational restraints, which, unless corrected by substitution of certain amino acid residues, lead to loss of binding affinity. The selection of amino acid residues for substitution is determined, in part, by computer modeling. Computer hardware and software for producing three-dimensional images of immunoglobulin molecules are widely available. In general, molecular models are produced starting from solved structures for immunoglobulin chains or domains thereof. The chains to be modeled are compared for amino acid sequence similarity with chains or domains of solved three dimensional structures, and the chains or domains showing the greatest sequence similarity is/are selected as starting points for construction of the molecular model. For example, for the light chain of mu MAb 21.6, the starting point for modeling the framework regions, CDR1 and CDR2 regions, was the human light chain RE1. For the CDR3 region, the starting point was the CDR3 region from the light chain of a different human antibody HyHEL-5. The solved starting structures are modified to allow for differences between the actual amino acids in the immunoglobulin chains or domains being modeled, and those in the starting structure. The modified structures are then assembled into a composite immunoglobulin. Finally, the model is refined by energy minimization and by verifying that all atoms are within appropriate distances from one another and that bond lengths and angles are within chemically acceptable limits.

As noted *supra*, the humanized antibodies of the invention comprise variable framework regions substantially from a human immunoglobulin and complementarity determining regions substantially from a mouse immunoglobulin termed mu MAb 21.6. Having identified the complementarity determining regions (CDRs) of mu MAb 21.6 and appropriate human acceptor immunoglobulins, the next step is to determine which, if any, residues from these components should be substituted to optimize the properties of the resulting humanized antibody. In general, substitution of human amino acid residues with murine should be minimized, because introduction of murine residues increases the risk of the antibody eliciting a HAMA response in humans. Amino acids are selected for

# DEMANDE OU BREVET VOLUMINEUX

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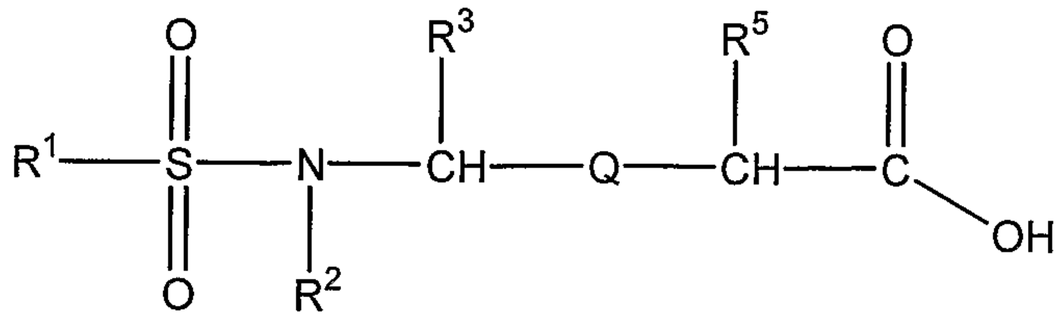
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We claim:

1. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula I below:



I

wherein

$R^1$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^2$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $R^1$ and $R^2$ together with the nitrogen atom bound to $R^2$ and the $SO_2$ group bound to $R^1$ can form a heterocyclic or a substituted heterocyclic group;

$R^3$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when $R^2$ does not form a heterocyclic group with $R^1$, $R^2$ and $R^3$ together with the nitrogen atom bound to $R^2$ and the carbon atom bound to $R^3$ can form a heterocyclic or a substituted heterocyclic group;

$R^5$ is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z- $R^{8''}$ wherein $R^8$ and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where $R^8$ and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, $R^{8''}$ is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2$-;

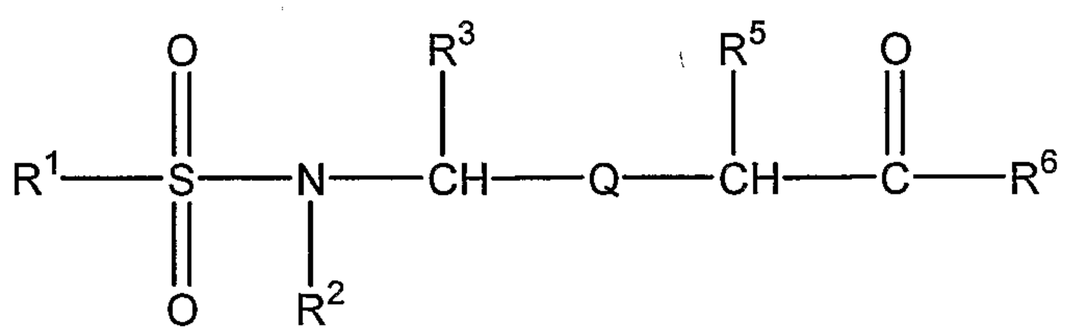
Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

*x* is an integer of from 1 to 4;

Q is -C(X)NR$^7$- wherein R$^7$ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

2. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula IA below:



IA

wherein:

R$^1$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R$^2$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R$^1$ and R$^2$ together with the nitrogen atom bound to R$^2$ and the $SO_2$ group bound to R$^1$ can form a heterocyclic or a substituted heterocyclic group;

R$^3$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R$^2$ does not form a heterocyclic group with R$^1$, R$^2$ and R$^3$ together with the nitrogen atom bound to R$^2$ and the carbon atom bound to R$^3$ can form a heterocyclic or a substituted heterocyclic group;

R$^5$ is - $(CH_2)_x$-Ar-R$^{5'}$ where R$^{5'}$ is selected from the group consisting of -O-Z-NR$^8$R$^{8'}$ and -O-Z- R$^{8''}$ wherein R$^8$ and R$^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R$^8$ and R$^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R$^{8''}$ is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -$SO_2$-;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

*x* is an integer of from 1 to 4;

$R^6$ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where $R^9$ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and $R^{10}$ is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where $R^{11}$ is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein $R^7$ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof

with the following provisos

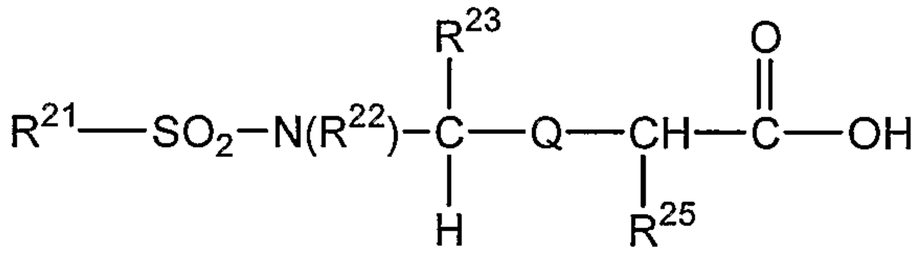
(A) when $R^1$ and $R^2$ together with the $SO_2$ group pendent to $R^1$ and the nitrogen pendent to $R^2$ form a saccharin-2-yl group, $R^3$ is $-CH_3$, $R^5$ is *p*-[$(CH_3)_2NC(O)O$-]benzyl and Q is -C(O)NH- then $R^6$ is not $-OC(CH_3)_3$;

(B) when $R^1$ is *p*-methylphenyl, $R^2$ and $R^3$ together with the nitrogen atom pendent to $R^2$ and the carbon atom pendent to $R^3$ form a pyrrodinyl ring derived from D-proline; $R^5$ is *p*-[(4-methylpiperazin-1-yl)NC(O)O-]benzyl derived from D-phenylalanine and Q is -C(O)NH- then $R^6$ is not $-OC(CH_3)_3$;

(C) when $R^1$ is pyrimidin-2-yl, $R^2$ and $R^3$ together with the nitrogen atom bound to $R^2$ and the carbon atom bound to $R^3$ form a pyrrolidinyl ring, $R^5$ is *p*-[$(CH_3)_2NC(O)O$-]benzyl and Q is -C(O)NH- then $R^6$ is not $-OC(CH_3)_3$; and

(D) when $R^1$ is *p*-methylphenyl, $R^2$ and $R^3$ together with the nitrogen atom pendent to $R^2$ and the carbon atom pendent to $R^3$ form a (2S)-piperazin-2-carbonyl ring; $R^5$ is *p*-[$(CH_3)_2NC(O)O$-]benzyl and Q is -C(O)NH- then $R^6$ is not $-OC(CH_3)_3$.

3. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula II below:



II

wherein:

$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^{22}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $R^{21}$ and $R^{22}$ together with the nitrogen atom bound to $R^{22}$ and the $SO_2$ group bound to $R^{21}$ can form a heterocyclic or a substituted heterocyclic group;

$R^{23}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where $R^{22}$ and $R^{23}$ together with the nitrogen atom bound to $R^{22}$ and the carbon atom bound to $R^{23}$ can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

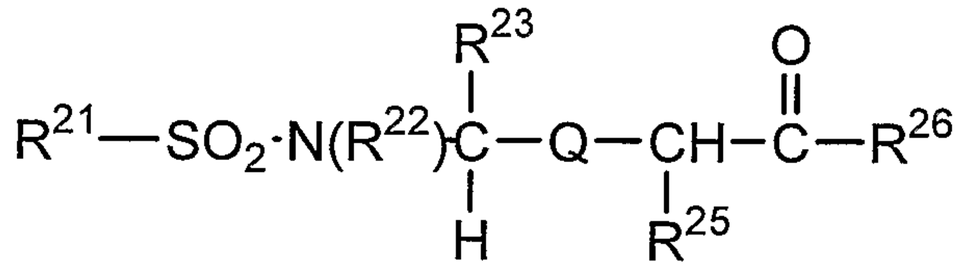
Q is $-C(X)NR^7-$ wherein $R^7$ is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur; and

$R^{25}$ is $-CH_2Ar^{22}-R^{25'}$ where $Ar^{22}$ is aryl or heteroaryl and $R^{25'}$ is selected from the group consisting of aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclic-O-, substituted heterocyclic-O-, heteroaralkoxy, and substituted heteroaralkoxy ;

and pharmaceutically acceptable salts thereof.

4. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula IIA below:



IIA

where

$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^{22}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and $R^{21}$ and $R^{22}$ together with the nitrogen atom bound to $R^{22}$ and the $SO_2$ group bound to $R^{21}$ can form a heterocyclic or a substituted heterocyclic group;

$R^{23}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and $R^{22}$ and $R^{23}$ together with the nitrogen atom bound to $R^{22}$ and the carbon atom bound to $R^{23}$ can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl;

$R^{25}$ is $-CH_2Ar^{22}-R^{25'}$ where $Ar^{22}$ is aryl or heteroaryl and $R^{25'}$ is selected from the group consisting of aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy, , heterocyclic-O-, substituted heterocyclic-O-, heteroaralkoxy, and substituted heteroaralkoxy ;

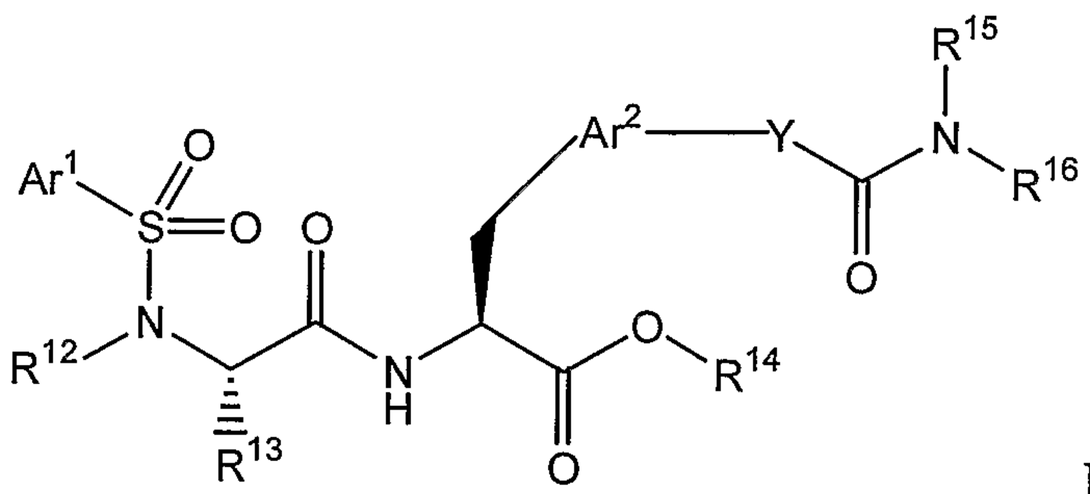
$R^{26}$ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^{29}R^{30}$ where $R^{29}$ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and $R^{30}$ is selected from the group consisting of hydrogen and $-CH_2COOR^{31}$ where $R^{31}$ is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is -C(X)NR$^7$- wherein R$^7$ is selected from the group consisting of hydrogen and alkyl; and

X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

5. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula IB below:



IB

wherein:

Ar$^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

Ar$^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R$^{12}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl or R$^{12}$ and R$^{13}$ together with the nitrogen atom bound to R$^{12}$ and the carbon atom bound to R$^{13}$ form a heterocyclic or substituted heterocyclic group;

R$^{13}$ is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or R$^{12}$ and R$^{13}$ together with the nitrogen atom bound to R$^{12}$ and the carbon atom bound to R$^{13}$ form a heterocyclic or substituted heterocyclic group;

R$^{14}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl;

R$^{15}$ is selected from the group consisting of alkyl, and substituted alkyl, or R$^{15}$ and R$^{16}$ together with the nitrogen atom to which they are bound form a heterocyclic or substituted heterocyclic group;

$R^{16}$ is selected from the group consisting of alkyl and substituted alkyl or $R^{15}$ and $R^{16}$ together with the nitrogen atom to which they are bound form a heterocyclic or substituted heterocyclic group; and

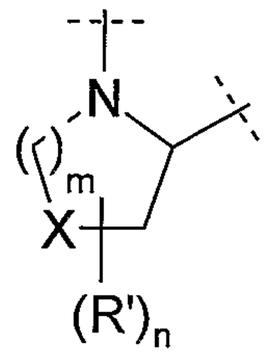
Y is selected from the group consisting of -O-, -$NR^{100}$-, and -$CH_2$- wherein $R^{100}$ is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof.

6. The use according to claim 5, wherein $R^{12}$ is alkyl, substituted alkyl, or $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic group; and $R^{14}$ is hydrogen or alkyl.

7. The use according to claim 5, wherein $Ar^1$ is selected from the group consisting of phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-*t*-butoxyphenyl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, 2-carboxyphenyl, 2-(methoxycarbonyl)phenyl, 4-($H_2NC(O)$-)phenyl, 4-($H_2NC(S)$-)phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, 4-($CH_3C(O)NH$-)phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$-]phenyl, 4-chloro-3-[$H_2NS(O)_2$-]phenyl, 1-naphthyl, 2-naphthyl, pyridin-2-yl, pyridin-3-yl, pyridine-4-yl, pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-*N*-methylimidazol-4-yl, 1-*N*-methylpyrazol-3-yl, 1-*N*-methylpyrazol-4-yl, 1-*N*-butylpyrazol-4-yl, 1-*N*-methyl-3-methyl-5-chloropyrazol-4-yl, 1-*N*-methyl-5-methyl-3-chloropyrazol-4-yl, 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

8. The use according to claim 5, wherein $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic of the formula:



wherein

X is selected from the group consisting of -S-, -SO-, -$SO_2$, and optionally substituted -$CH_2$-;

*m* is an integer of 0 to 12;

*n* is an integer of 0 to 2; and

R' is selected from the group consisting of alkyl, substituted alkyl, and amino.

9. The use according to claim 8, wherein m is 1, X is -S- or -$CH_2$-, R' is alkyl or substituted alkyl.

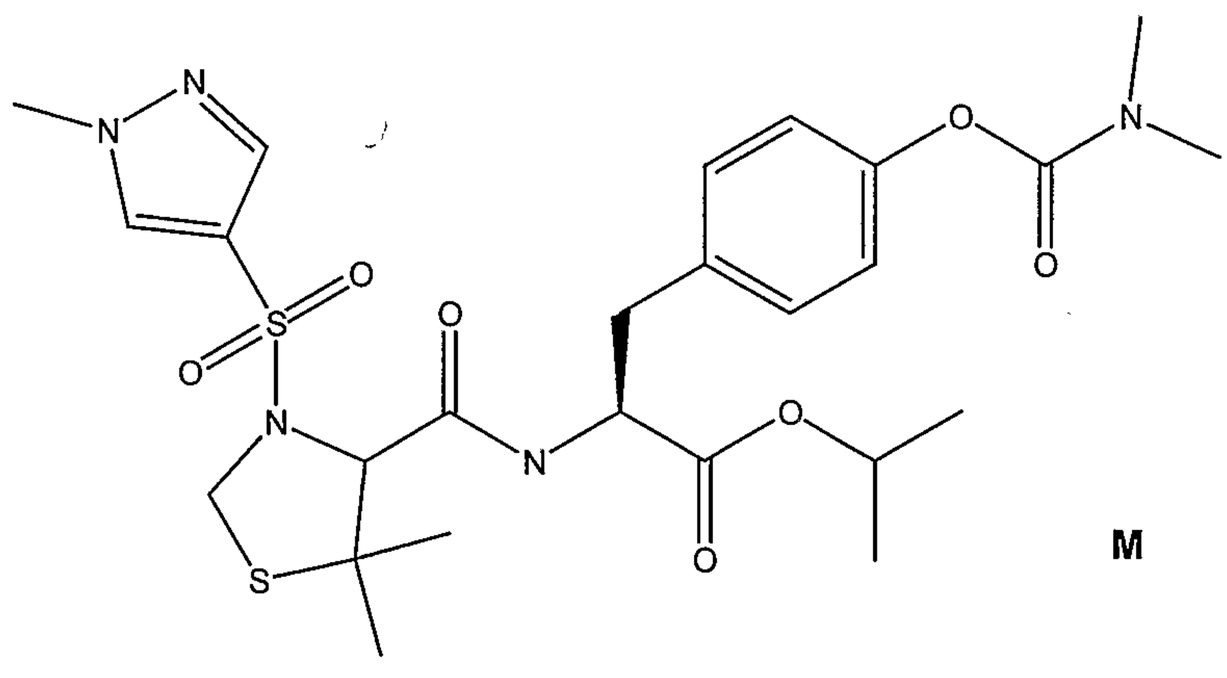
10. The use according to claim 8, wherein $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic selected from the group consisting of azetidinyl, thiazolidinyl, piperidinyl, piperazinyl, thiomorpholinyl, pyrrolidinyl, 4-hydroxypyrrolidinyl, 4-oxopyrrolidinyl, 4-fluoropyrrolidinyl, 4,4-difluoropyrrolidinyl, 4-(thiomorpholin-4-ylC(O)O-)pyrrolidinyl, 4-[$CH_3S(O)_2O$-]pyrrolidinyl, 3-phenylpyrrolidinyl, 3-thiophenylpyrrolidinyl, 4-aminopyrrolidinyl, 3-methoxypyrrolidinyl, 4,4-dimethylpyrrolidinyl, 4-*N*-Cbz-piperazinyl, 4-[$CH_3S(O)_2$-]piperazinyl, thiazolidin-3-yl, 5,5-dimethyl-thiazolidin-3-yl, 5,5-dimethylthiazolindin-4-yl, 1,1-dioxo-thiazolidinyl, 1,1-dioxo-5,5-dimethylthiazolidin-2-yl and 1,1-dioxothiomorpholinyl.

11. The use according to claim 5, wherein $Ar^2$ is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and 4-pyrid-2-onyl.

12. The use according to claim 5, wherein Y is -O-, and when Y is -O-, the moiety -$OC(O)NR^{15}R^{16}$ is selected from the group consisting of $(CH_3)_2NC(O)O$-, (piperidin-1-yl)C(O)O-, (4-hydroxypiperidin-1-yl)C(O)O-, (4-formyloxypiperidin-1-yl)C(O)O-, (4-ethoxycarbonylpiperidin-1-yl)C(O)O-, (4-carboxylpiperidin-1-yl)C(O)O-, (3-

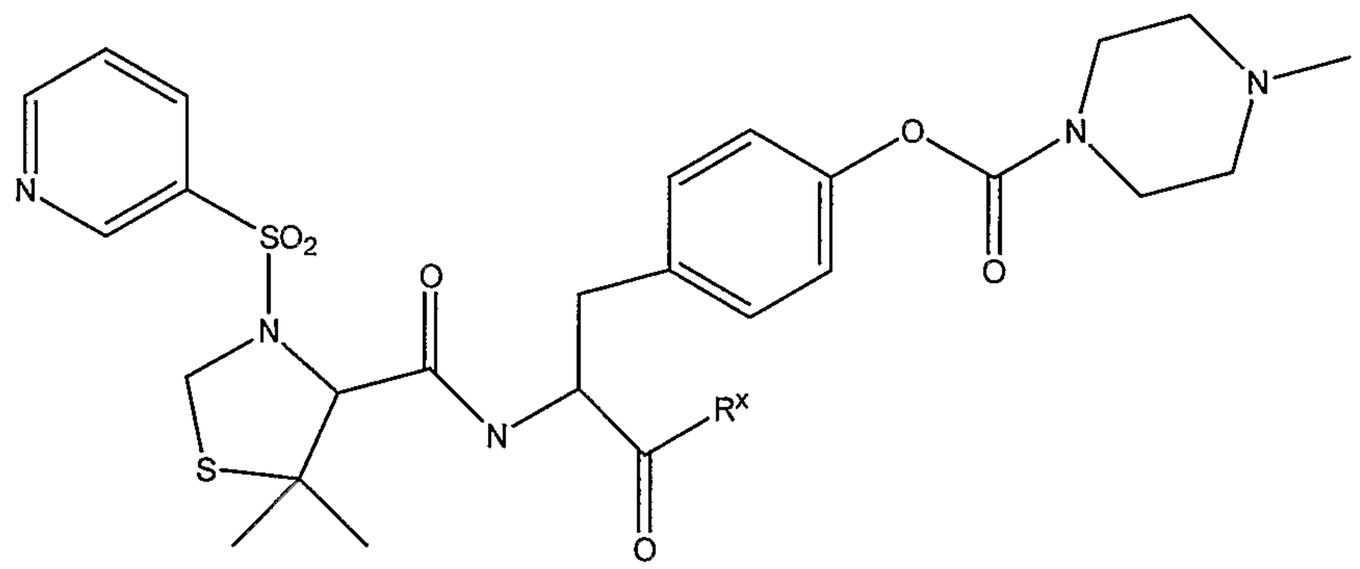
hydroxymethylpiperidin-1-yl)C(O)O-, (4-hydroxymethylpiperidin-1-yl)C(O)O-, (4-piperidon-1-yl ethylene ketal)C(O)O-, (piperazin-1-yl)-C(O)O-, (1-Boc-piperazin-4-yl)-C(O)O-, (4-methylpiperazin-1-yl)C(O)O-, (4-methylhomopiperazin-1-yl)C(O)O-, (4-(2-hydroxyethyl)piperazin-1-yl)C(O)O-, (4-phenylpiperazin-1-yl)C(O)O-, (4-(pyridin-2-yl)piperazin-1]-yl)C(O)O-, (4-(4-trifluoromethylpyridin-2-yl)piperazin-1-yl)C(O)O-, (4-(pyrimidin-2-yl)piperazin-1-yl)C(O)O-, (4-acetylpiperazin-1-yl)C(O)O-, (4-(phenylC(O)-)piperazin-1-yl)C(O)O-, (4-(pyridin-4'-ylC(O)-)piperazin-1-yl)C(O)O, (4-(phenylNHC(O)-)piperazin-1-yl)C(O)O-, (4-(phenylNHC(S)-)piperazin-1-yl)C(O)O-, (4-methanesulfonylpiperazin-1-yl-C(O)O-, (4-trifluoromethanesulfonylpiperazin-1-yl-C(O)O-, (morpholin-4-yl)C(O)O-, (thiomorpholin-4-yl)C(O)O-, (thiomorpholin-4'-yl sulfone)-C(O)O-, (pyrrolidin-1-yl)C(O)O-, (2-methylpyrrolidin-1-yl)C(O)O-, (2-(methoxycarbonyl)pyrrolidin-1-yl)C(O)O-, (2-(hydroxymethyl)pyrrolidin-1-yl)C(O)O-, (2-(N,N-dimethylamino)ethyl)($CH_3$)NC(O)O-, (2-(N-methyl-N-toluene-4-sulfonylamino)ethyl)($CH_3$)N-C(O)O-, (2-(morpholin-4-yl)ethyl)($CH_3$)NC(O)O-, (2-(hydroxy)ethyl)($CH_3$)NC(O)O-, bis(2-(hydroxy)ethyl)NC(O)O-, (2-(formyloxy)ethyl)($CH_3$)NC(O)O-, ($CH_3OC(O)CH_2$)HNC(O)O-, and 2-[(phenylNHC(O)O-)ethyl-]HNC(O)O-.

13. The use according to claim 5, wherein the compound is the compound of Formula M below:



M

14. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula IC below:



IC

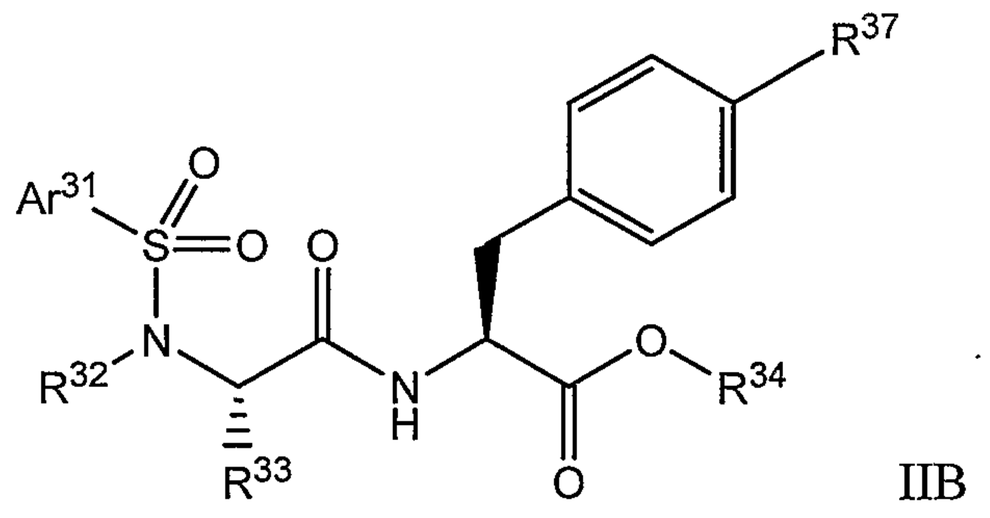
wherein

$R^x$ is hydroxy or $C_{1-5}$ alkoxy; and

pharmaceutically acceptable salts thereof.

15. The use according to claim 14, wherein the compound is *N*-[*N*-(3-pyridinesulfonyl)-L-3,3-dimethyl-4-thiaprolyl]-*O*-[1-methylpiperazin-4-ylcarbonyl]-L-tyrosine isopropyl ester.

16. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula IIB below:



IIB

wherein:

$Ar^{31}$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

$R^{32}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group;

$R^{33}$ is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group;

$R^{34}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl; and

$R^{37}$ is aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy;

and pharmaceutically acceptable salts thereof.

17. The use according to claim 16, wherein $R^{32}$ is alkyl, substituted alkyl, or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group; and $R^{34}$ is hydrogen or alkyl.

18. The use according to claim 16, wherein $R^{37}$ is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic.

19. The use according to claim 18, wherein $R^{37}$ is substituted aryl, wherein the aryl is substituted with one to three substituents independently selected from the group consisting alkyl and alkoxy, or a substituted heteroaryl, wherein the heteroaryl is substituted with one to three substituents independently selected from the group consisting alkyl, alkoxy, and oxo.

20. The use according to claim 18, wherein $R^{37}$ is substituted aryl or substituted heteroaryl wherein aryl or heteroaryl is 2,6-di-substituted.

21. The use according to claim 20, wherein $R^{37}$ is selected from the group consisting of 2,6-dialkoxyaryl, 2,6-dialkoxyheteroaryl, 2-alkyl-6-alkoxyaryl, 2-alkyl-6-alkoxyheteroaryl, 2-oxo-6-alkoxyheteroaryl, 2-oxo-6-alkylheteroaryl, and optionally substituted imidazolidin-2,4-dion-3-yl.

22. The use according to claim 16, wherein $Ar^{31}$ is selected from the group consisting of 4-methylphenyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl,

phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

23. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of selected from the group consisting of:

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *n*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine cyclopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *n*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine cyclopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine ethyl ester

*N*-(α-toluenesulfonyl)-L-prolyl-L-4-(*N*-methylisonipecotoyloxy)phenylalanine ethyl ester

*N*-(α-toluenesulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-3-(*N*,*N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butylcarbonyloxy-4-phenylpiperidin-4-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(α-toluenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(piperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(α-toluenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(piperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-benzyloxycarbonylpiperazin-2-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(isonipecotoyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-D-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyrrolidin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine neopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine neopentyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)sarcosyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-*N*-methylalanyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyrimidine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-acetylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)-3-nitrophenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1-*tert*-butyloxycarbonylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*N*-methyl-2-(*tert*-butyl)glycinyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-*tert*-butyloxycarbonyl-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidin-2-one

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyrimidine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-carboxy-2-(*N*,*N*-dimethylcarbamyloxy)phenylethyl]azetidin-2-one

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(1,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(1,1-dioxo)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-acetamidobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-*tert*-butylbenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(2-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-acetamidobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(3,3-dimethyl)prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(3,3-dimethyl)prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *iso*-propyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-acetylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-phenylpiperazin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine (N′-*tert*-butoxycarbonyl-2-amino-2-methylpropyl) ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-acetylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-hydroxypiperidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-(morpholin-4′-yl)ethyl)carbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(1,4-dioxa-8-aza-spiro[4.5]decan-8-yl)carbonyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-hydroxyethyl)-N-methylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-4-(4′-(2-hydroxyethyl)piperazin-1-ylcarbonyloxy)-L-phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-formyloxyethyl)-N-methylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N-(2′-hydroxyethyl)-N-methylcarbamyloxy)phenylalanine isopropyl ester

N-(toulene-4-sulfonyl)-L-prolyl-L-4-(N-(methoxycarbonylmethyl)carbamyloxy)phenylalanine *tert*-butyl ester

N-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(4-N,N-dimethylcarbamyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methoxypiperidin-1-ylcarbonyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-methoxypiperidin-1-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-*trans*-4-hydroxyprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(3-fluorobenzenesulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(morpholino-sulfonyl)-L-prolyl-L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(morpholino-sulfonyl)-L-prolyl-L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl-thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-*tert*-butylbenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-(3,3-dimethyl)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-methoxybenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-methoxybenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-oxo-thiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(1-oxo-thiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-prolyl-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-prolyl-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-2-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-2-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-2-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,5-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-chlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,5-dichlorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-chlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2-methoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dimethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(3,4-dichlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3-chlorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(3-chloro-4-fluorobenzenesulfonyl)-L-(1,1-dioxothiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thioprolyl-L-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(3,4-difluorobenzenesulfonyl)-L-(thiamorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(2,5-dichlorothiophene-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(8-quinolinesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(8-quinolinesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(8-quinolinesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isoproplyl ester

*N*-(8-quinolinesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4′-(ethoxycarbonyl)piperidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(3-sulfonamido-4-chloro-benzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-oxothiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(2,4-difluorobenzenefulfonyl)-L-(1-oxothiomorpholin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine cyclopropylmethyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester

*N*-(pyridine-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine cyclopropylmethyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-methoxyphenyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *n*-butyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *n*-propyl ester

*N*-(1-methylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2,2-dimethylpropionyloxymethyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-(4'-(2'-aminoethyl)morpholino)carbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[4-(carboxy)piperidin-1-ylcarbonyloxy]phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N,N*-bis-(2-hydroxyethyl)carbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[3-(hydroxymethyl)piperidin-1-ylcarbonyloxy]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-trifluoromethanesulfonylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-(*N*-phenylurea)benzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(pyridine-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(pyridine-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-methyl-N-(2-dimethylaminoethyl)carbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiapropyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N*-methyl-*N*-(2-dimethylaminoethyl)carbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethycarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-methylpiperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2'-pyridyl)-piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2'-pyridyl)-piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylcarbamylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-phenylcarbamylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-*n*-butylpyrazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(pyridin-4-ylcarbonyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-*trans*-4-hydroxyprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-aminobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[3-(hydroxymethyl)piperidin-1-ylcarbonyloxy]phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4,4-difluoro)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(4,4-difluoro)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-benzoylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methyl-1H-imidazole-4-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-4-(thiomorpholin-4-ylcarbonyloxy)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-cyanobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester

*N*-(toluene-4-sulfonyl)-L-4-oxoprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-4-hydroxyprolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-(4-benzoylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine methyl ester

*N*-(3-fluorobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[*N*-methyl-*N*-(2-(*N*'-methyl-*N*'-toluenesulfonyl-amino)ethyl)carbamyloxy]phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-[*N*-(2-(*N*'-phenylaminocarbonyloxy)ethyl)carbamyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-4-(*trans*-hydroxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-4-(*trans*-hydroxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(pyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(2-hydroxymethylpyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(2-hydroxymethylpyrrolidin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(2-methoxycarbonylpyrrolidin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-hydroxy)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-(2-methoxyethoxy)ethyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyrimidyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-fluoro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(toluene-4-sulfonyl)-L-(1-methanesulfonylpyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4-hydroxy)prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyrimidyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(4-oxo)prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-(4-oxo)prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine *tert*-butyl ester

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(*N*-phenylthiocarbonyl)piperazin-1-ylcarbonyloxy)]phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-methylhomopiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-4-(methanesulfonyloxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-aminocarbonylbenzenesulfonyl)-L-prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-aminocarbonylbenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-amidinobenzenesulfonyl)-L-prolyl-L-4-(thiomorpholin-4-ylcarbonyloxy)phenylalanine

*N*-(4-nitrobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)]phenylalanine ethyl ester

*N*-(4-fluorobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)thiazolidinyl-2-carbonyl-L-4-(4-methylhomopiperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(toluene-4-sulfonyl)-L-(1-methanesulfonylpyrazin-3-carbonyl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(toluene-4-sulfonyl)-L-4-(methanesulfonyloxy)prolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-bromobenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(4-fluorobenzenesulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-fluorobenzenesulfonyl)-L-(4-hydroxy)prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(4-trifluoromethoxybenzenesulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylimidazole-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-prolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

*N*-(1-methylimidazole-4-sulfonyl)-L-prolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine 2-phenoxyethyl ester

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

*N*-(1-methylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine ethyl ester

*N*-(3-chloro-1,5-dimethylpyrazole-3-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-3-chloro-4-(4-(5-trifluoromethyl-2-pyridyl)piperazin-1-ylcarbonyloxy)phenylalanine

and pharmaceutically acceptable salts thereof.

24. The use according to any one of claims 5, 14, and 16, wherein the mammal is a human.

25. The use according to any one of claims 5, 14, and 16, wherein the compound is administered parenterally.

26. The use according to any one of claims 5, 14, and 16, wherein the compound is administered chronically to the mammal in need thereof.

27. The use according to claim 26, wherein the chronic administration of the compound is weekly or monthly over a period of at least one year.

28. The use according to any one of claims 5, 14, and 16, wherein the compound is administered intravenously or subcutaneously.

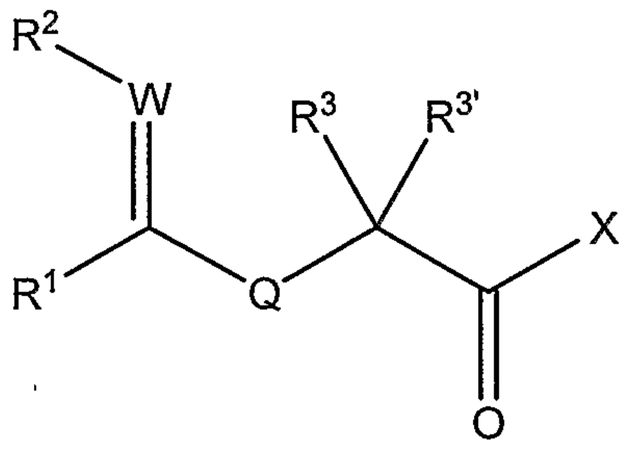
29. The use according to claim 28, wherein the compound is administered intravenously to a mammal, and wherein the administration results in an effective blood level of the compound in the mammal of $\geq$ 10 ng/ml.

30. The use according to claim 28, wherein the compound is administered intravenously in an amount of 20 μg to about 500 μg per kilogram body weight of the mammal.

31. The use according to claim 28, wherein the compound is administered in series of doses separated by intervals of days or weeks.

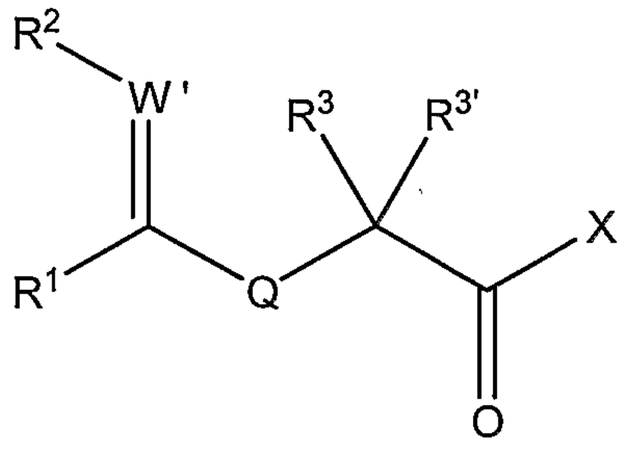
32. The use of any one of claims 5, 14, or 16, wherein the methotrexate is administered in a dose of approximately 2 mg to 20 mg.

33. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula IIIa and/or IIIb below:



IIIa

and



IIIb

wherein, in Formula IIIa, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form an aryl, cycloalkenyl, heteroaryl or heterocyclic group having at least five atoms in the aryl, cycloalkenyl, heteroaryl or heterocyclic group and optionally containing or additionally containing in the case of heteroaryl and heterocyclic groups 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heteroaryl or heterocyclic group is mono-cyclic;

in Formula IIIb, $R^1$ and $R^2$, together with the carbon atom and W' to which they are bound respectively, are joined to form a cycloalkyl, cycloalkenyl or heterocyclic group having at least five atoms in the cycloalkyl, cycloalkenyl or heterocyclic group and optionally containing or additionally containing in the case of the heterocyclic group 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heterocyclic group is mono-cyclic;

and further wherein said aryl, cycloalkyl, cycloalkenyl, heteroaryl or heterocyclic group of Formula IIIa or IIIb is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-N[S(O)_2-R']_2$ and $-N[S(O)_2-NR']_2$ where each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^3$ and $R^{3'}$ are independently selected from the group consisting of hydrogen, isopropyl, $-CH_2Z$ where Z is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-

substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and

where $R^3$ and $R^{3'}$ are joined to form a substituent selected from the group consisting of =CHZ where Z is defined above provided that Z is not hydroxyl or thiol, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic and substituted heterocyclic;

Q is selected from the group consisting of -O-, -S-, -S(O)-, $-S(O)_2$, and $-NR^4$-;

$R^4$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic or, optionally, $R^4$ and $R^1$ or $R^4$ and $R^2$, together with the atoms to which they are bound, are joined to form a heteroaryl, a substituted heteroaryl, a heterocyclic or a substituted heterocyclic group;

W is selected from the group consisting of nitrogen and carbon; and

W' is selected from the group consisting of nitrogen, carbon, oxygen, sulfur, S(O), and $S(O)_2$;

X is selected from the group consisting of hydroxyl, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, cycloalkoxy, substituted cycloalkoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy and -NR″R″ where each R″ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

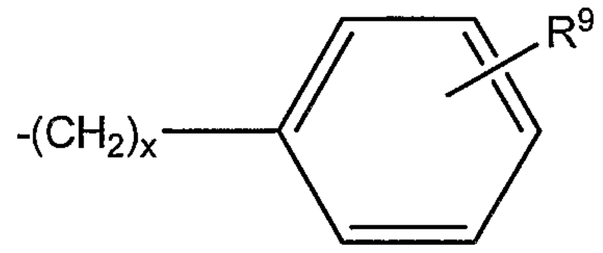
and enantiomers, diastereomers and pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula IIIa and/or IIIb has a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15μM or less.

34. The use according to claim 33, wherein $R^3$ is $-(CH_2)_x$-Ar-$R^9$, where Ar is aryl, substituted aryl, heteroaryl and substituted heteroaryl; $R^9$ is selected from the group consisting acyl, acylamino, acyloxy, aminoacyl, aminocarbonylamino,

aminothiocarbonylamino, aminocarbonyloxy, oxycarbonylamino, oxythiocarbonylamino, thioamidino, thiocarbonylamino, aminosulfonylamino, aminosulfonyloxy, aminosulfonyl, oxysulfonylamino and oxysulfonyl; and *x* is an integer from 0 to 4; and $R^{3'}$ is hydrogen.

35. The use according to claim 34, wherein $R^3$ is a group of the formula:

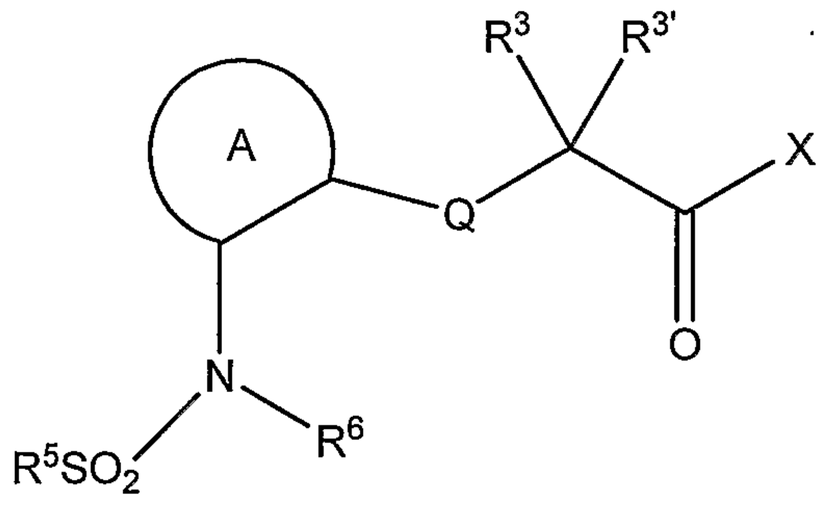



wherein $R^9$ and *x* are as defined in claim 34.

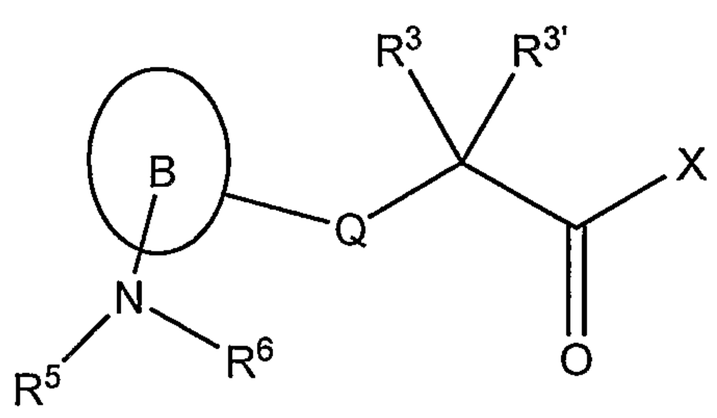
36. The use according to claim 35, wherein Z is -C(O)-.

37. The use according to claim 35, wherein Q is $-NR^4-$.

38. The use according to claim 33, wherein the compound has Formula IVa or IVb:




IVa




IVb

wherein

ring A and ring B independently form a heteroaryl or substituted heteroaryl group having two nitrogen atoms in the heteroaryl ring;

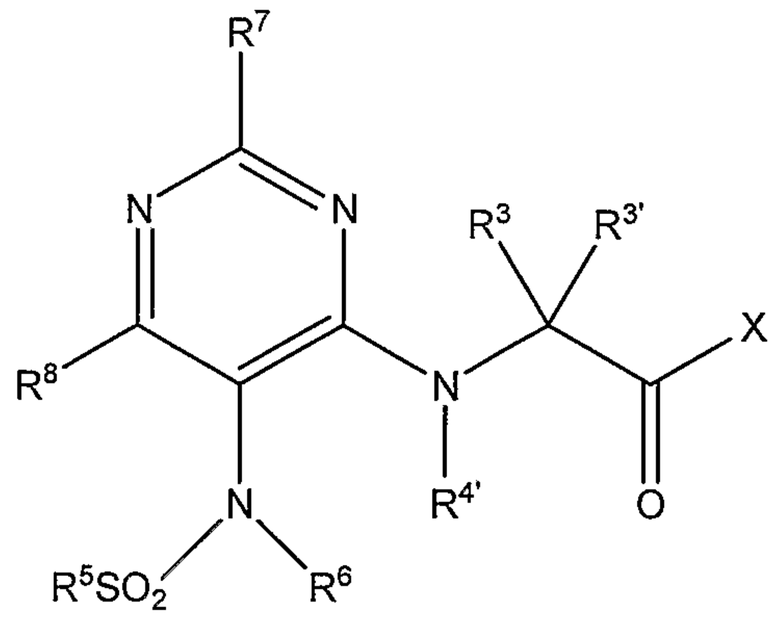
$R^5$ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^6$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-SO_2R^{10}$ where $R^{10}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

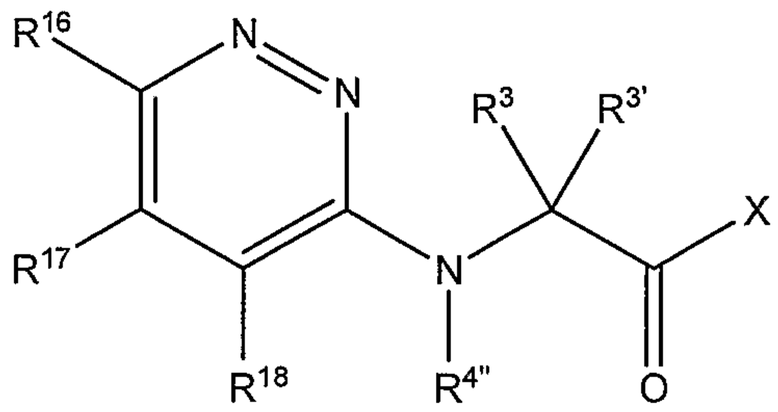
or optionally, one of, $R^4$ and ring A, $R^4$ and $R^5$, $R^4$ and $R^6$, or $R^5$ and $R^6$, together with the atoms to which they are bound, can be joined to form a heterocyclic or substituted heterocyclic ring;

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof.

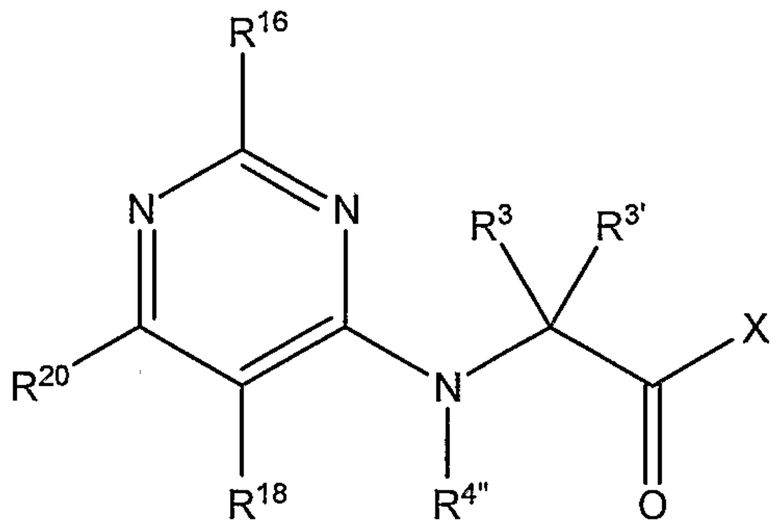
39. The use according to claim 33, wherein the compound has Formula Va, Vb, Vc, Vd or Ve:



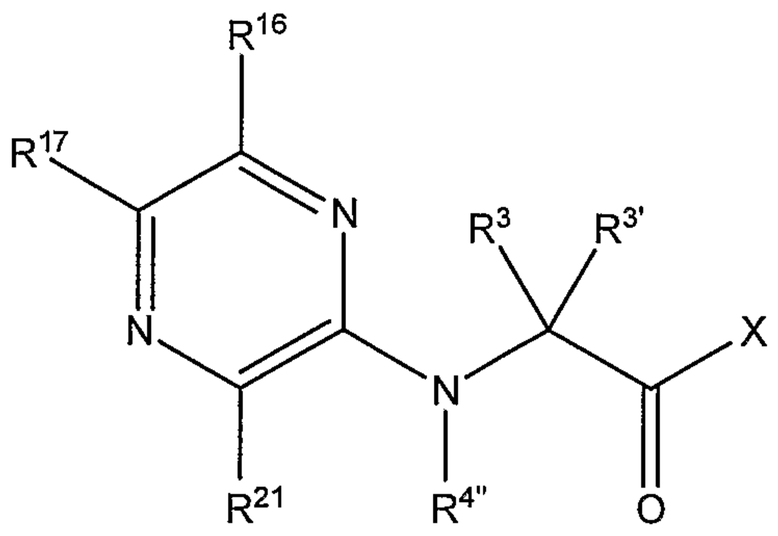
Va



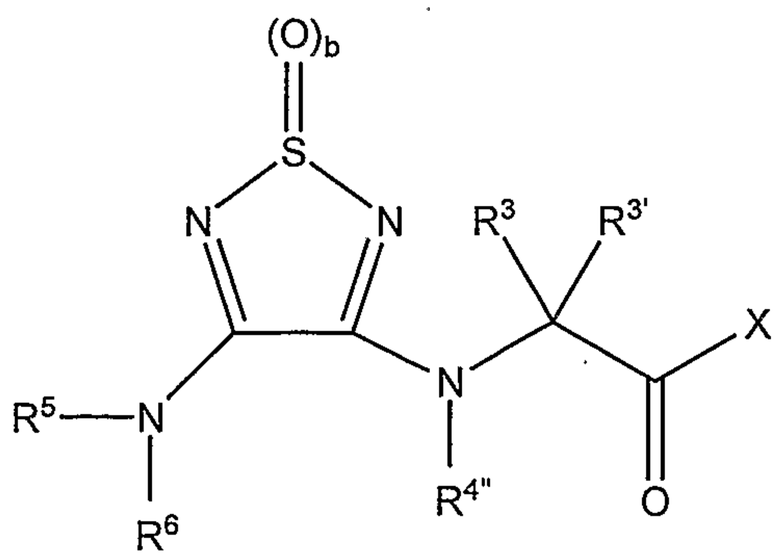
Vb



Vc



Vd



Ve

wherein

$R^{4'}$ is selected from the group consisting of hydrogen and alkyl or, optionally, one of, $R^{4'}$ and $R^5$, $R^{4'}$ and $R^6$, $R^5$ and $R^6$, $R^5$ and $R^8$, or $R^6$ and $R^8$, together with the atoms to which they are bound, are joined to form a heterocyclic, a substituted heterocyclic, a heteroaryl or substituted heteroaryl group optionally containing from 1 to 3 additional hetero ring atoms selected from the group consisting of oxygen, nitrogen and sulfur;

$R^{4''}$ is selected from the group consisting of hydrogen and alkyl;

$R^5$ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

$R^6$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-SO_2R^{10}$ where $R^{10}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, amino, substituted amino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{16}$ and $R^{17}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

$R^{18}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{20}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

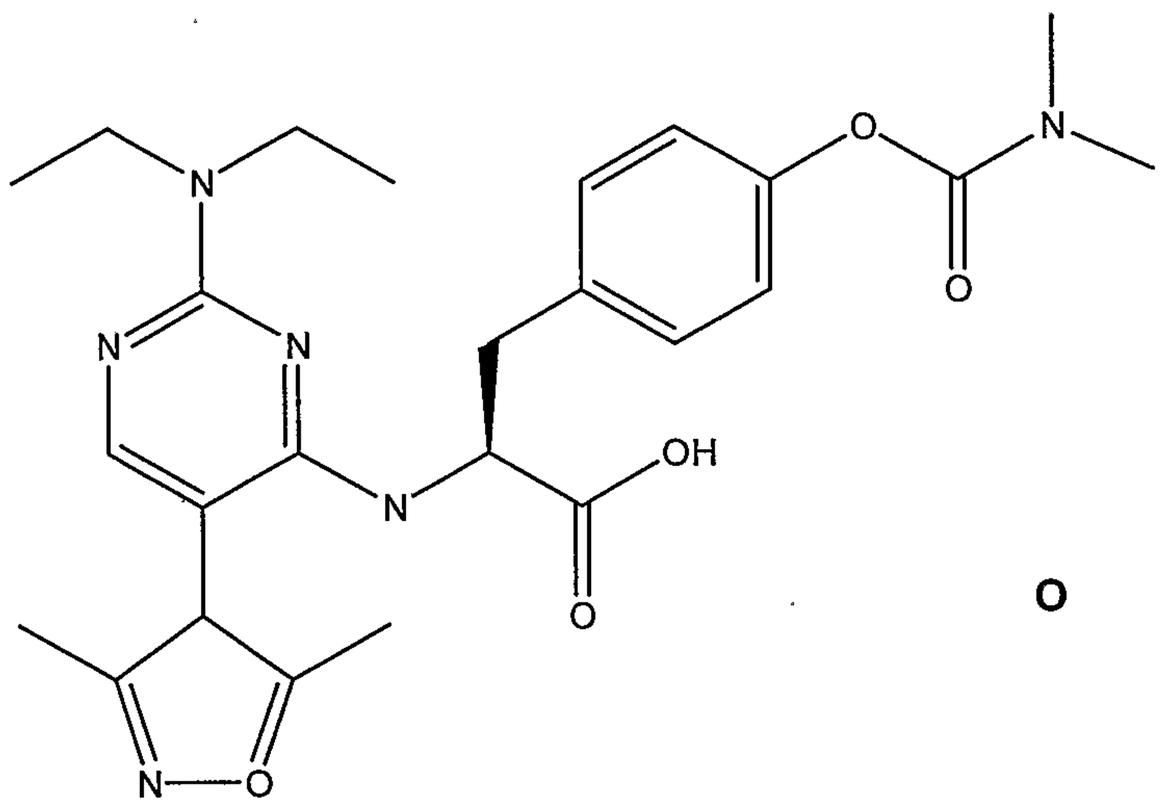
$R^{21}$ is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

*b* is 1 or 2;

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof.

40. The use according to claim 39, wherein the compound is selected from Formula Va, Vc, or Vd.

41. The use according to claim 39, wherein the compound is the compound of Formula O below:



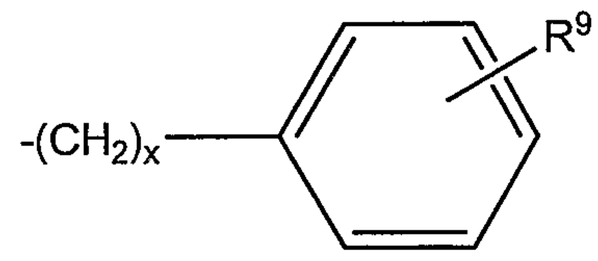

O

42. The use according to claim 39, wherein:

$R^5$, $R^{18}$, and $R^{21}$ are independently selected from the group consisting of heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

$R^7$ and $R^{16}$ are independently amino or substituted amino;

$R^3$ is a group of the formula:




wherein $R^9$ is selected from the group consisting acyl, acylamino, acyloxy, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, oxycarbonylamino, oxythiocarbonylamino, thioamidino, thiocarbonylamino, aminosulfonylamino,

aminosulfonyloxy, aminosulfonyl, oxysulfonylamino and oxysulfonyl; and *x* is an integer from 0 to 4; and

$R^{3'}$ is hydrogen.

43. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound selected from the group consisting of:

*N*-(2-chloro-5-nitropyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

*N*-[5-(*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

*N*-[5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*,*N*-di-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-[*N*-(1-*N'*-methylpyrazol-4-ylsulfonyl)-*N*-methylamino]pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-[5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-[5-(*N*-methyl-*N*-3-pyridylsulfonylamino)pyrimidin-4-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

*N*-(5-(*N*-methyl-*N*-(1-butylpyrazol-4-yl)sulfonylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,4-dimethoxypyrimidin-5-yl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,6-difluorophenyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-hydroxymethylphenyl)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-cyclohexylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)amino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-ethyl-*N*-isopropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,4-6-trimethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-isopropylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-butylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-ethyl-*N*-propylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-diethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-ethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-benzyloxypyrimidin-4-yl)-L-phenylalanine,

*N*-(5-benzyloxypyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl)-L-phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-phenylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(3-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrazin-2-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine isopropyl ester,

*N*-(5-benzylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine tert-butyl ester,

*N*-(5-(2-trifluoromethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-*N,N*-dimethylcarbamylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(*N*-methyl-*N*-3-(1-methylpyrazole)sulfonylamino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-(6-phenylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(6-(2-trifluoromethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(6-(2-hydroxymethylphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-cyclohexylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-furanmethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-4-chlorophenylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(3-thienyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-thienyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-hydroxyethylamino)-5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(piperidin-1-yl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(1-propylbutyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclobutylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclobutylamino)-5-ethylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-bis-(2-hydroxyethyl)amino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-bis-(2-hydroxyethyl)amino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-phenylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(isopropoxy)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(N-methyl-N-3-methylbutylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(2-tolyl)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-hydroxyethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-2-methylpropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-propylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N,N*-dimethylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-pyridyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenyl-2,2-difluoroethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenyl-2,2-difluoroethyl)-6-chloropyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-propylpyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-methoxyphenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-Methyl-*N*-isopropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-isopropylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-(3-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrazin-2-yl)-L-phenylalanine isopropyl ester,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-phenylalanine isopropyl ester,

*N*-(5-(*N*-methyl-*N*-3-pyridinesulfonylamino)pyrimidin-4-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine isopropyl ester,

*N*-(5-(3-nitrophenyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(3-pyridyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(2-phenylethyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-*N,N*-dimethylamino-5-(*N*-methyl-*N*-4-toluenesulfonylamino)pyrimidin-4-yl)-L-phenylalanine,

N-(5-(2-tolyl)pyrimidin-4-yl)-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-methoxyphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-isopropylamino)-5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-isopropylamino)-5-(2-phenyl)pyrimidin-4-yl)-L-4-(2-methoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2,6-difluorophenyl)pyrimidin-4-yl)-L-4-(2,6-difluorophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-hydroxymethylphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N,N*-bis-(2-hydroxyethyl)amino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-trifluoromethylphenyl)pyrimidin-4-yl)-L-4-(2-cyanophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-thienyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2-thienyl)pyrimidin-4-yl)-L-4-(4-trifluoromethylphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-pyridyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(3-nitrophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2,6-dichlorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(4-pyridyl)pyrimidin-4-yl)-L-4-(3-hydroxymethylphenyl)phenylalanine,

*N*-(2-(*N*-ethyl-N-isopropylamino)-5-(2,6-dimethoxyphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-(2,3-dichlorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-ethylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2-cyanophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-isopropylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(3-pyridyl)phenylalanine,

*N*-(2-(*N*,*N*-bis-(2-hydroxyethyl)amino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2-cyanophenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)amino)-5-(2-cyanophenyl)pyrimidin-4-yl)-L-4-(2,6-difluorophenyl)phenylalanine,

*N*-(2-(*N*-ethyl-N-isopropylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(o-tolyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-4-chlorophenylamino)-5-(2,4,6-trimethylphenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(*N*-methyl-N-2-(phenyl)ethylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-hexylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-*tert*-butylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-ethyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-2-(4-pyridyl)ethyl-pyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

*N*-(5-(N-methyl-N-2-(phenyl)ethylamino)pyrimidin-4-yl)-L-4-(-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-hexylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-*tert*-butylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-ethyl-N-isopropylamino)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(N-methyl-N-2-(4-pyridyl)ethyl-pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(*N*-methyl-*N*-cyclohexylamino)-5-ethylpyrimidin-4-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

N-(4-(N,N-di-*n*-hexylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl)-L-tyrosine,

N-(4-(N,N-di-*n*-hexylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine,

N-(4-(N,N-dimethylamino)-1-oxo-1,2,5-thiadiazol-3-yl)-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester,

N-[4-(2-(3-methylphenylaminocarbonylamino)eth-1-ylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl]-L-4-(*N*,*N*-dimethylcarbamyloxy)phenylalanine

N-(4-(N,N-di-*n*-hexylamino)-1,1-dioxo-1,2,5-thiadiazol-3-yl)-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

*N*-(5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

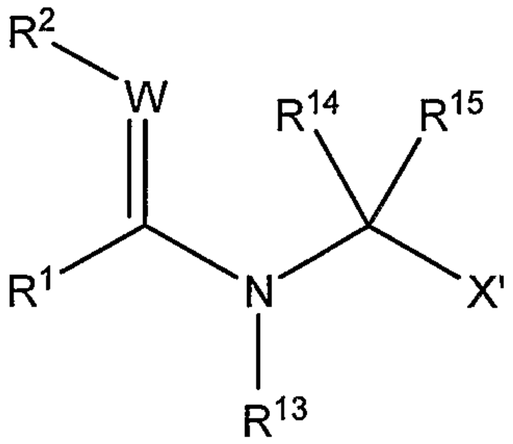
*N*-(2-(N-cyclohexyl-N-methyl)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(5-(2-fluorophenyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

*N*-(2-(N-methyl-N-propyl)-5-(2-tolyl)pyrimidin-4-yl)-L-4-(2,6-dimethoxyphenyl)phenylalanine,

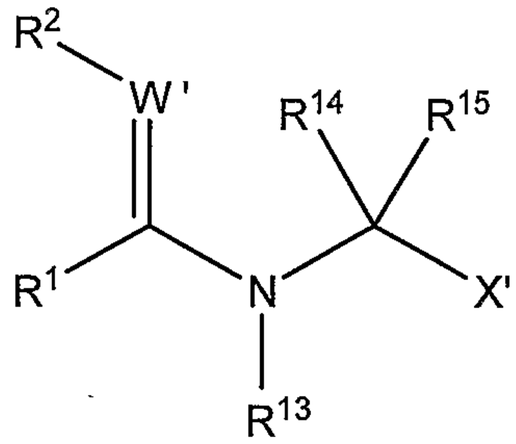
and pharmaceutically acceptable salts thereof.

44. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula VIa and/or VIb below:



VIa

and



VIb

wherein, in Formula VIa, $R^1$ and $R^2$, together with the carbon atom and W to which they are bound respectively, are joined to form an aryl, cycloalkenyl, heteroaryl or heterocyclic group having at least five atoms in the aryl, cycloalkenyl, heteroaryl or heterocyclic group and optionally containing or additionally containing in the case of heteroaryl and heterocyclic groups 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heteroaryl or heterocyclic group is mono-cyclic;

in Formula VIb, $R^1$ and $R^2$, together with the carbon atom and W' to which they are bound respectively, are joined to form a cycloalkyl, cycloalkenyl or heterocyclic group having at least five atoms in the cycloalkyl, cycloalkenyl or heterocyclic group and optionally containing or additionally containing in the case the heterocyclic group 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, and wherein the heterocyclic group is mono-cyclic; and

further wherein said aryl, cycloalkyl, cycloalkenyl, heteroaryl or heterocyclic group of Formula VIa or VIb is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted

thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-N[S(O)_2-R']_2$ and $-N[S(O)_2-NR']_2$ where each R′ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{13}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, Cy, and Cy-$C_{1-10}$ alkyl, wherein alkyl is optionally substituted with one to four substituents independently selected from $R^a$; and Cy is optionally substituted with one to four substituents independently selected from $R^b$;

$R^{14}$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, Cy, Cy-$C_{1-10}$ alkyl, Cy-$C_{2-10}$ alkenyl and Cy-$C_{2-10}$ alkynyl, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents selected from phenyl and $R^X$, and Cy is optionally substituted with one to four substituents independently selected from $R^y$;

or $R^{13}$, $R^{14}$ and the atoms to which they are attached together form a mono- or bicyclic ring containing 0-2 additional heteratoms selected from N, O and S;

$R^{15}$ is selected from the group consisting of $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl, aryl-$C_{1-10}$ alkyl, heteroaryl, heteroaryl-$C_{1-10}$ alkyl, wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from $R^x$, and aryl and heteroaryl are optionally substituted with one to four substituents independently selected from $R^y$;

or $R^{14}$, $R^{15}$ and the carbon to which they are attached form a 3-7 membered mono- or bicyclic ring containing 0-2 heteroatoms selected from N, O and S;

$R^a$ is selected from the group consisting of Cy and a group selected from $R^x$, wherein Cy is optionally substituted with one to four substituents independently selected from $R^c$;

$R^b$ is selected from the group consisting of $R^a$, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl $C_{1-10}$alkyl, heteroaryl $C_{1-10}$ alkyl, wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from $R^c$;

$R^c$ is selected from the group consisting of halogen, $NO_2$, $C(O)OR^f$, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, aryl, aryl $C_{1-4}$ alkyl, aryloxy, heteroaryl, $NR^fR^g$, $R^fC(O)R^g$, $NR^fC(O)NR^fR^g$, and CN;

$R^d$ and $R^e$ are independently selected from hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, Cy and Cy $C_{1-10}$alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from $R^c$;

or $R^d$ and $R^e$ together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

$R^f$ and $R^g$ are independently selected from hydrogen, $C_{1-10}$ alkyl, Cy and Cy-$C_{1-10}$ alkyl wherein Cy is optionally substituted with $C_{1-10}$ alkyl; or $R^f$ and $R^g$ together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

$R^h$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, cyano, aryl, aryl $C_{1-10}$ alkyl, heteroaryl, heteroaryl $C_{1-10}$ alkyl, and $-SO_2R^i$; wherein alkyl, alkenyl, and alkynl are optionally substituted with one to four substitutents independently selected from $R^a$; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from $R^b$;

$R^i$ is selected from the group consisting of $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, and aryl; wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from $R^c$;

$R^x$ is selected from the group consisting of $-OR^d$, $-NO_2$, halogen, $-S(O)_mR^d$, $-SR^d$, $-S(O)_2OR^d$, $-S(O)_mNR^dR^e$, $-NR^dR^e$, $-O(CR^fR^g)_nNR^dR^e$, $-C(O)R^d$, $-CO_2R^d$, $-CO_2(CR^fR^g)_nCONR^dR^e$, $-OC(O)R^d$, -CN, $-C(O)NR^dR^e$, $-NR^dC(O)R^e$, $-OC(O)NR^dR^e$, $-NR^dC(O)OR^e$, $-NR^dC(O)NR^dR^e$, $-CR^d(N-OR^e)$, $CF_3$, oxo, $NR^dC(O)NR^dSO_2R^i$, $NR^dS(O)_mR^e$, $-OS(O)_2OR^d$, and $-OP(O)(OR^d)_2$;

$R^y$ is selected from the group consisting of $R^x$, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl $C_{1-10}$alkyl, heteroaryl $C_{1-10}$ alkyl, cycloalkyl, heterocyclyl; wherein alkyl, alkenyl,

alkynyl and aryl are each optionally substituted with one to four substitutents independently selected from $R^x$;

Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

*m* is an integer from 1 to 2;

*n* is an integer from 1 to 10;

W is selected from the group consisting of carbon and nitrogen;

W' is selected from the group consisting of carbon, nitrogen, oxygen, sulfur, S(O) and $S(O)_2$;

X' is selected from the group consisting of $-C(O)OR^d$, $-P(O)(OR^d)(OR^e)$, $-P(O)(R^d)(OR^e)$, $-S(O)_mOR^d$, $-C(O)NR^dR^h$, and -5-tetrazolyl; and

enantiomers, diastereomers and pharmaceutically acceptable salts thereof; and

further wherein the compound of Formula VIa and/or VIb has a binding affinity to VLA-4 as expressed by an $IC_{50}$ of about 15μM or less.

45. The use according to any one of claims 33 or 39, wherein the mammal is a human.

46. The use according to any one of claims 33 or 39, wherein the compound is administered parenterally.

47. The use according to any one of claims 33 or 39, wherein the compound is administered chronically to the mammal in need thereof.

48. The use according to claim 47, wherein the chronic administration of the compound is weekly or monthly over a period of at least one year.

49. The use according to any one of claims 33 or 39, wherein the compound is administered intravenously or subcutaneously.

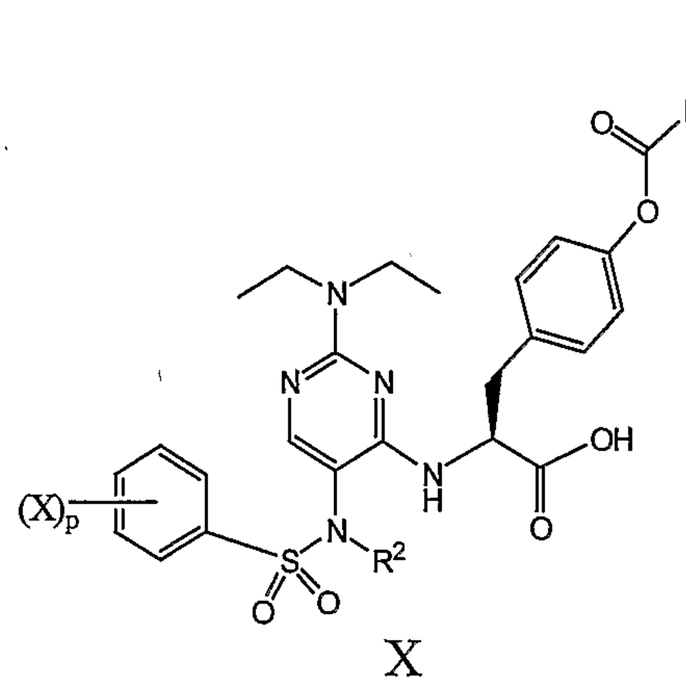
50. The use according to claim 49, wherein the compound is administered intravenously to a mammal, and wherein the administration results in an effective blood level of the compound in the mammal of $\geq$ 10 ng/ml.

51. The use according to claim 49, wherein the compound is administered intravenously in an amount of 20 μg to about 500 μg per kilogram body weight of the mammal.

52. The use according to claim 49, wherein the compound is administered in series of doses separated by intervals of days or weeks.

53. The use of any one of claims 33 or 39, wherein the methotrexate is administered in a dose of approximately 2 mg to 20 mg.

54. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula X below:



X

wherein each X is independently fluoro, chloro or bromo;

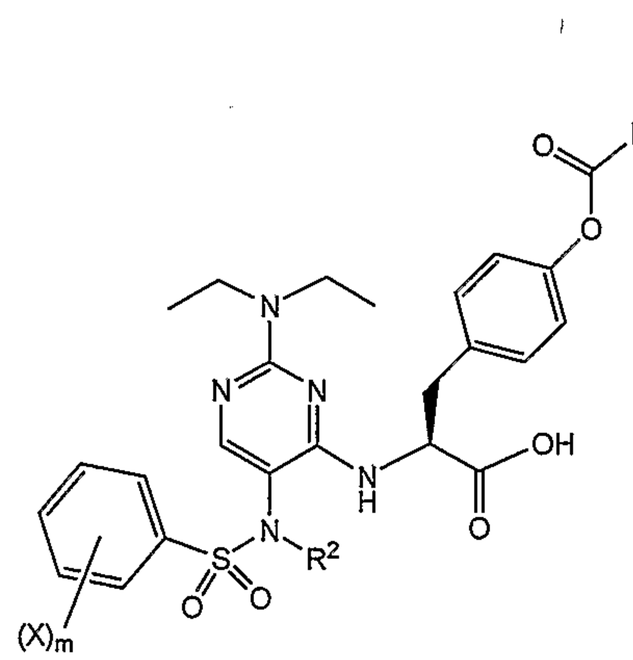
p is an integer from 0 to 3;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, pyrrolyl, 2,5-dihydopyrrol-1-yl, piperidinyl, or 1,2,3,6-tetrahydro-pyridin-1-yl;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

55. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XI below:



XI

wherein each X is independently selected from the group consisting of fluoro and chloro;

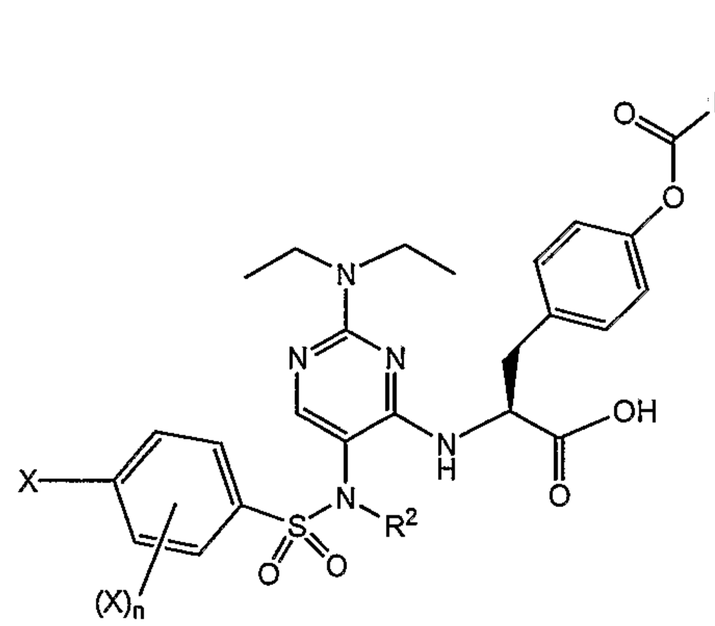
*m* is an integer equal to 1 or 2;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

56. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XII below:



XII

wherein each X is independently fluoro or chloro;

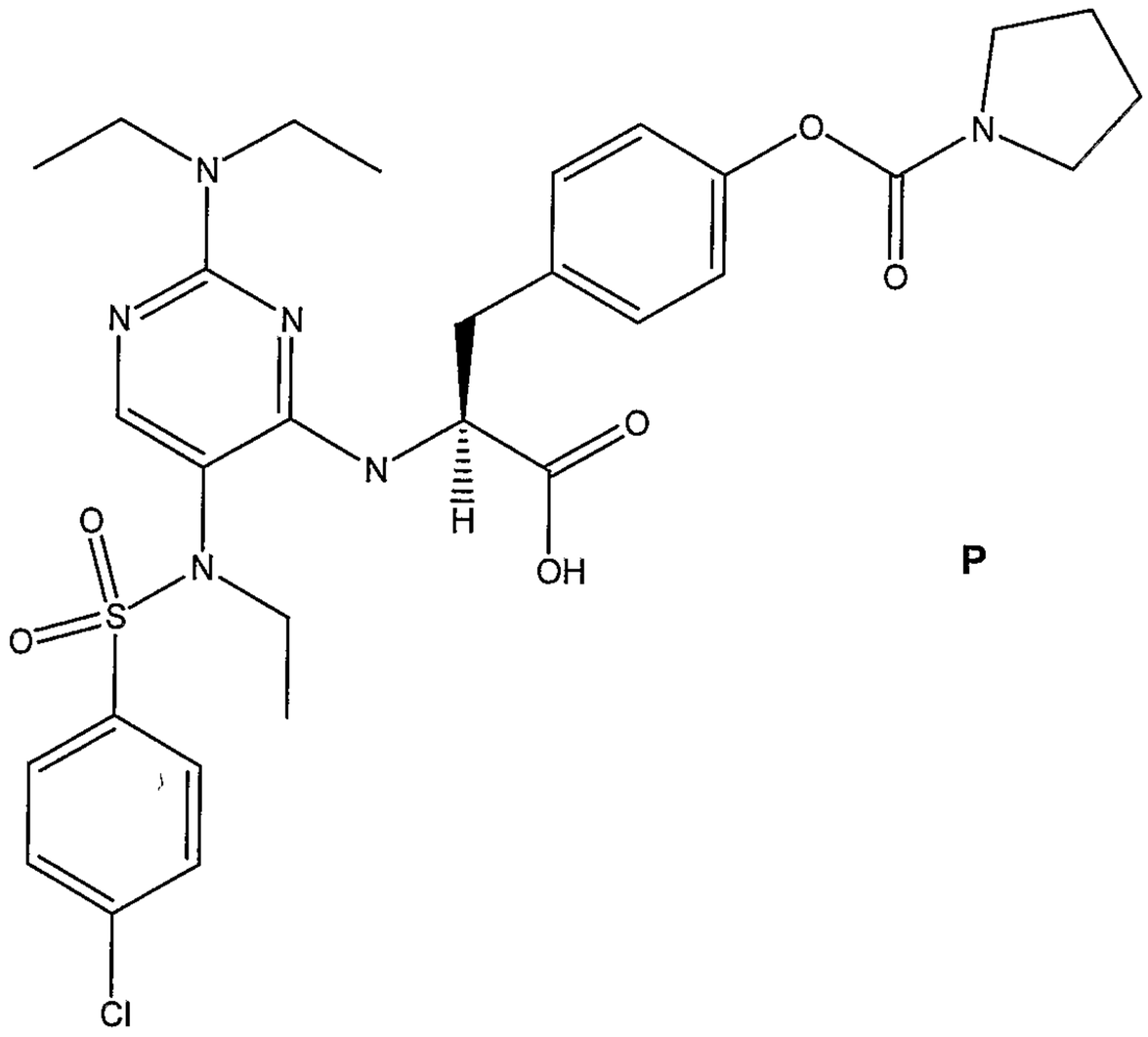
*n* is zero or one;

$R^2$ is -$CH_2$-R' where R' is selected from the group consisting of hydrogen, methyl or -CH=$CH_2$;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

57. The use according to claim 56, wherein the compound of Formula XII is the compound of Formula P below:



P

58. The use according to claim 54, wherein $R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group.

59. The use according to any one of claims 54, 55, or 56, wherein $R^2$ is $CH_3$.

60. The use according to claim 56, wherein X is F or Cl and n is 0.

61. The use according to claim 54, wherein the compound of Formula X is selected from the group consisting of:

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine ELN;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(pyrrolidin -1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(piperidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(piperidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

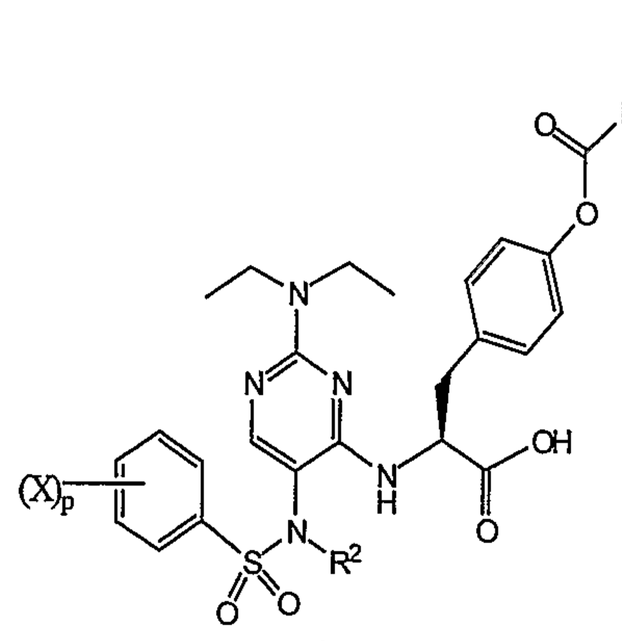
N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-methylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-ethylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine; and

pharmaceutically acceptable salts thereof.

62. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XIII below:



XIII

wherein each X is independently fluoro, chloro or bromo;

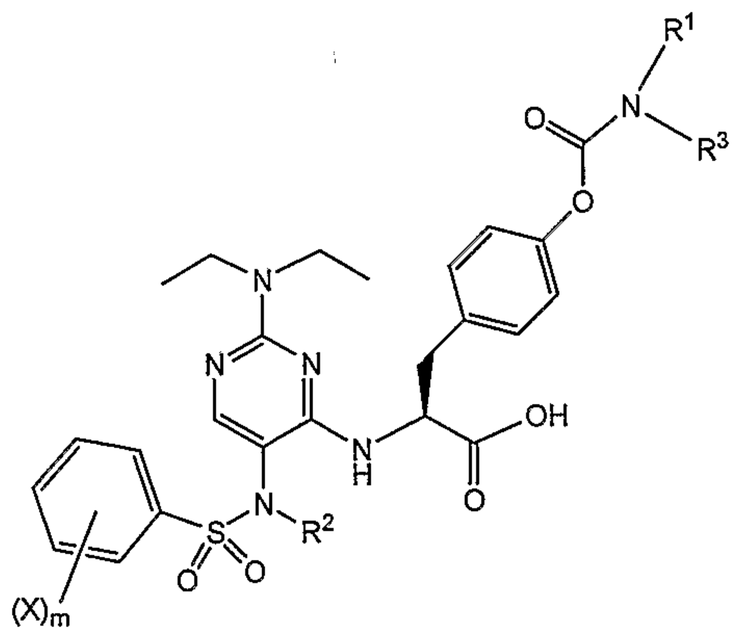
p is an integer from 0 to 3;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, pyrrolyl, 2,5-dihydopyrrol-1-yl, piperidinyl, or 1,2,3,6-tetrahydropyridin-1-yl;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

63. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XIV below:



XIV

wherein each X is independently selected from the group consisting of fluoro and chloro;

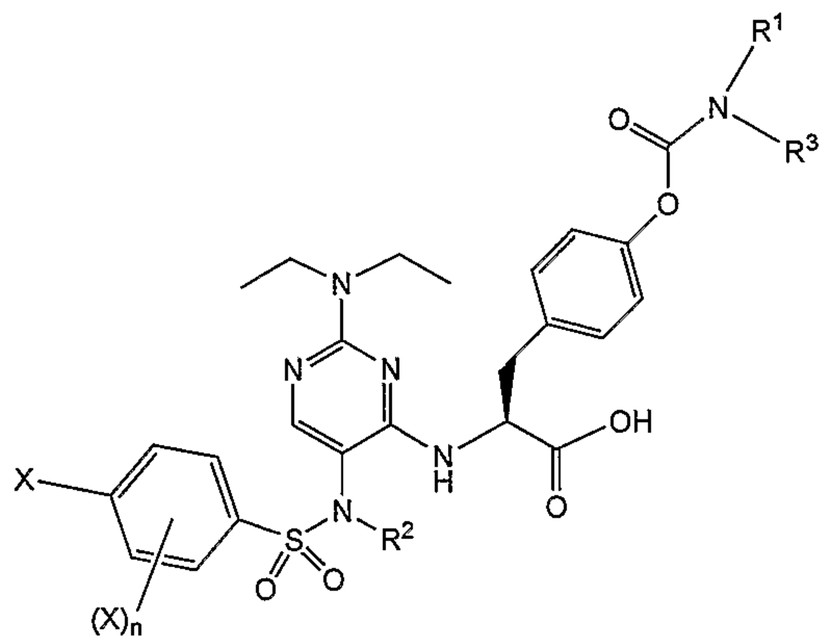
*m* is an integer equal to 1 or 2;

$R^2$ is lower alkynyl;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

64. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XV below:



XV

wherein each X is independently fluoro or chloro;

*n* is zero or one;

$R^2$ is lower alkynyl;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

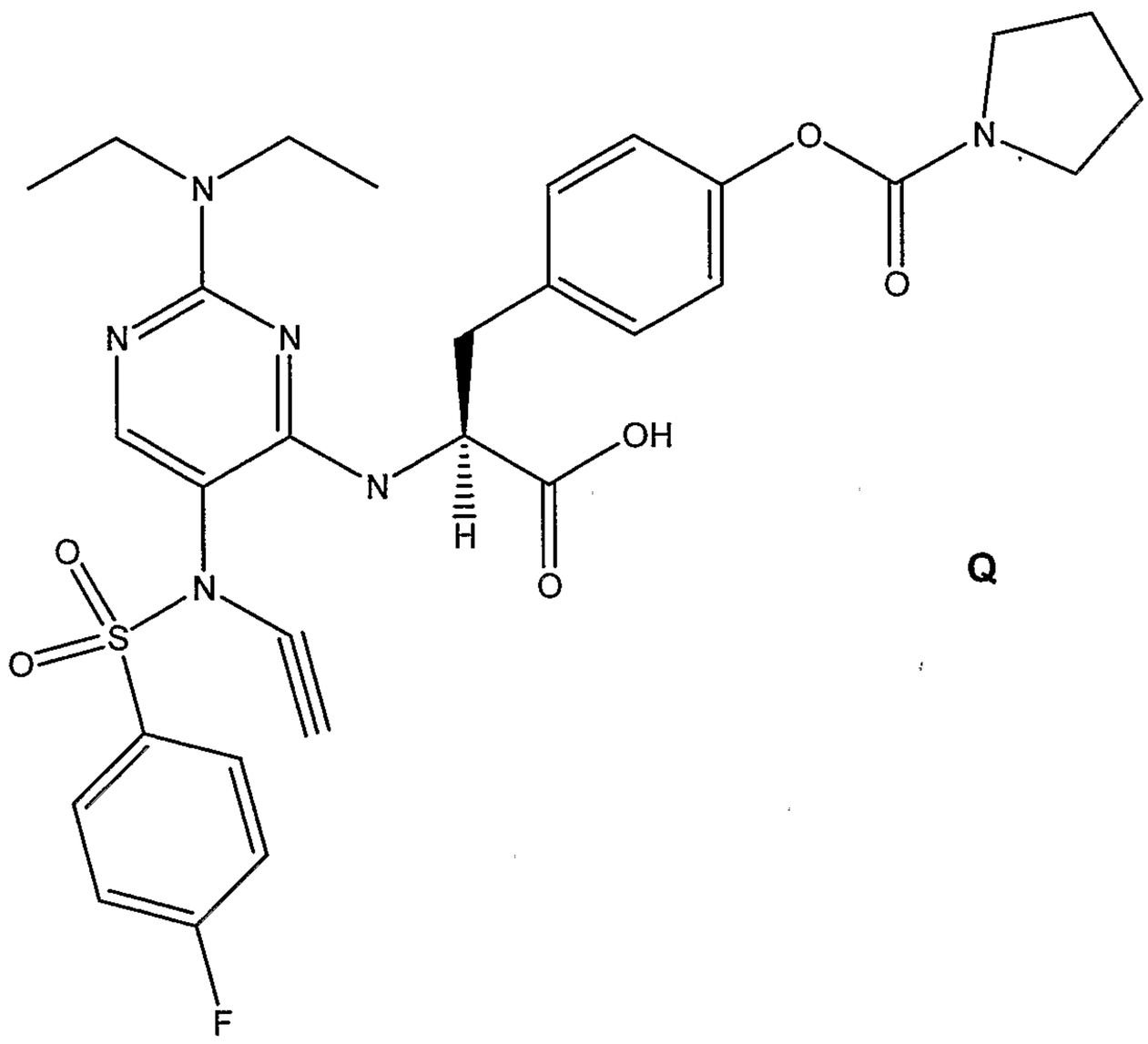
and pharmaceutically acceptable salts thereof.

65. The use according to claim 62, wherein $R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group.

66. The use according to any one of claims 62, 63, or 64, wherein $R^2$ is propargyl.

67. The use according to claim 65, wherein X is F or Cl and n is 0.

68. The use according to claim 65, wherein the compound of Formula XIII is the compound of Formula Q below:



Q

69. The use according to claim 62, wherein the compound of Formula XIII is selected from the group consisting of:

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine;

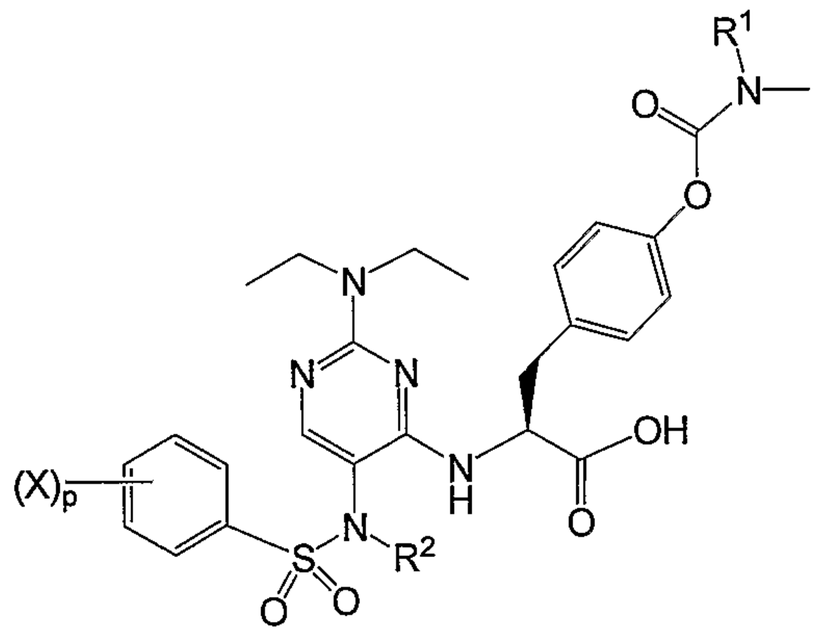
N-(2-[N',N'-diethylamino]-5-[N"-(2,4-difluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-fluorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(azetidin-1-ylcarbonyloxy)-L-phenylalanine;

N-(2-[N',N'-diethylamino]-5-[N"-(4-chlorophenylsulfonyl)-N"-propargylamino]pyrimidin-4-yl)-4'-(pyrrolidin-1-ylcarbonyloxy)-L-phenylalanine; and

pharmaceutically acceptable salts thereof.

70. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XVI below:



XVI

wherein each X is independently fluoro, chloro or bromo;

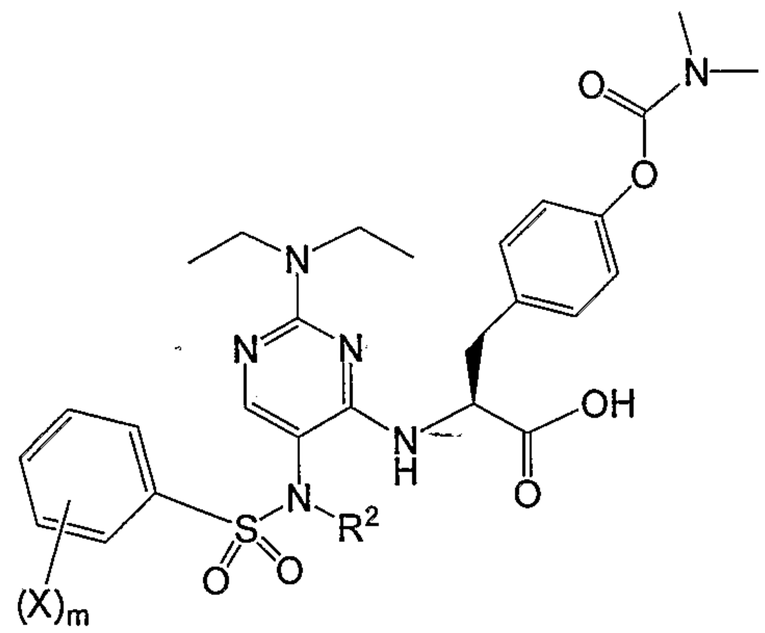
p is 0 or an integer from 1 - 3;

$R^1$ is selected from the group consisting of methyl and ethyl;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

71. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XVII below:



XVII

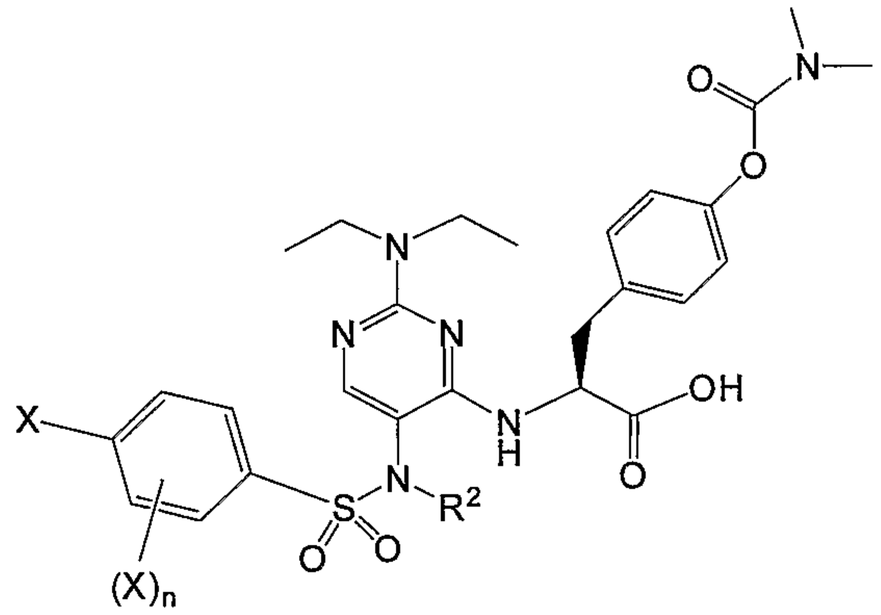
wherein each X is independently selected from the group consisting of fluoro and chloro,

*m* is an integer equal to 1 or 2;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

72. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XVIII below:



XVIII

wherein each X is independently fluoro or chloro;

*n* is zero or one;

$R^2$ is -$CH_2$-R' where R' is selected from the group consisting of hydrogen, methyl or -CH=$CH_2$;

and pharmaceutically acceptable salts thereof.

73. The use according to any one of claims 70, 71 or 72, wherein $R^2$ is $CH_3$.

74. The use according to claim 72, wherein X is F or Cl, and n is 0.

75. The use according to claim 70, wherein the compound of Formula XVI is selected from the group consisting of:

2-{2-diethylamino-5-[(4-chlorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-dichlorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(benzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2-fluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3-fluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)isopropylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-difluorobenzenesulfonyl)isopropylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-chlorobenzenesulfonyl)isopropylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,4-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-chlorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)cylclopropylmethyl-amino]pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid

2-{2-diethylamino-5-[(3,5-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,4-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,4-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-dichlorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(3,5-dichlorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)-n-propylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)allylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)isobotylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid

2-{2-diethylamino-5-[(4-fluorobenzenesulfonyl)-n-butylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

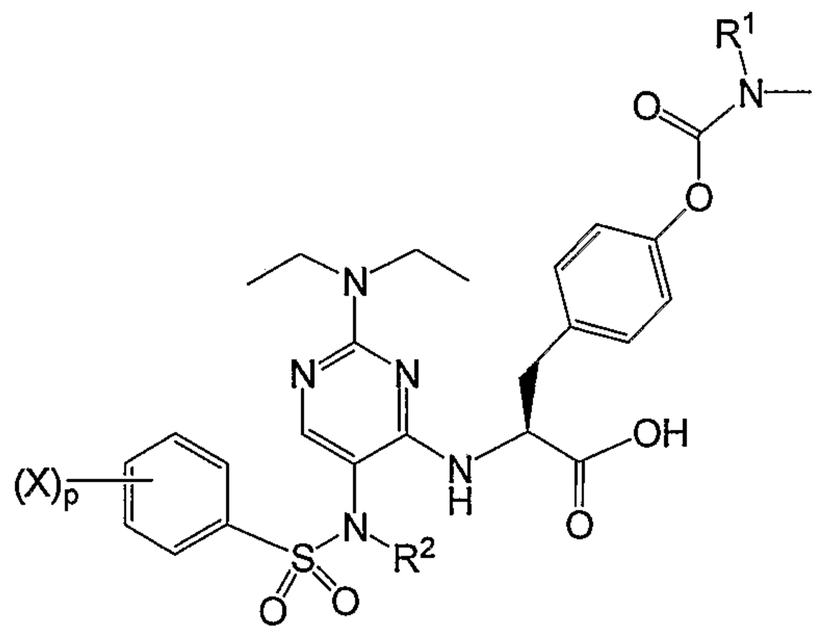
2-{2-diethylamino-5-[(2,5-difluorobenzenesulfonyl)methylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-diethylamino-5-[(2,3-difluorobenzenesulfonyl)ethylamino]-pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid;

2-{2-Diethylamino-5-[(4-fluorobenzenesulfonyl)-(2-trisfluoroethyl)-amino]pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid; and

pharmaceutically acceptable salts thereof.

76. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XIX below:



XIX

wherein each X is independently fluoro, chloro or bromo;

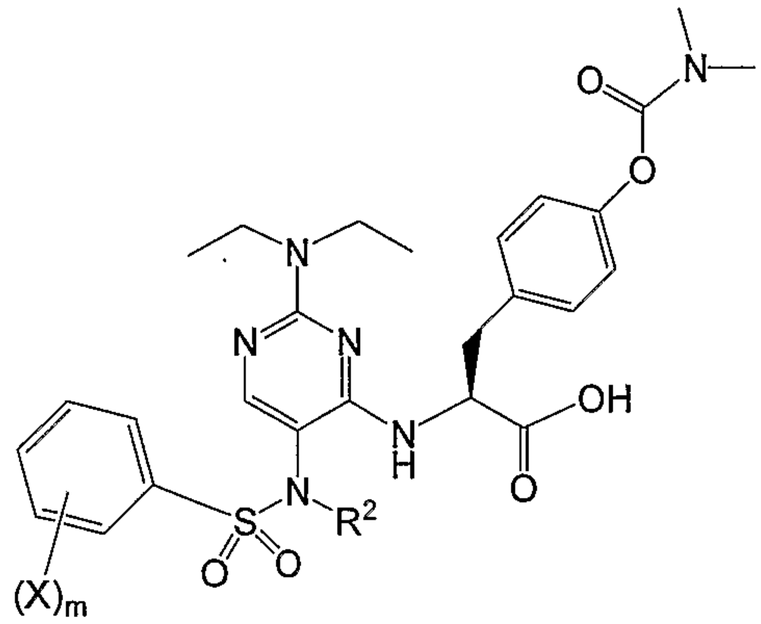
p is 0 or an integer from 1 - 3;

$R^1$ is selected from the group consisting of methyl and ethyl;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

77. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XX below:



XX

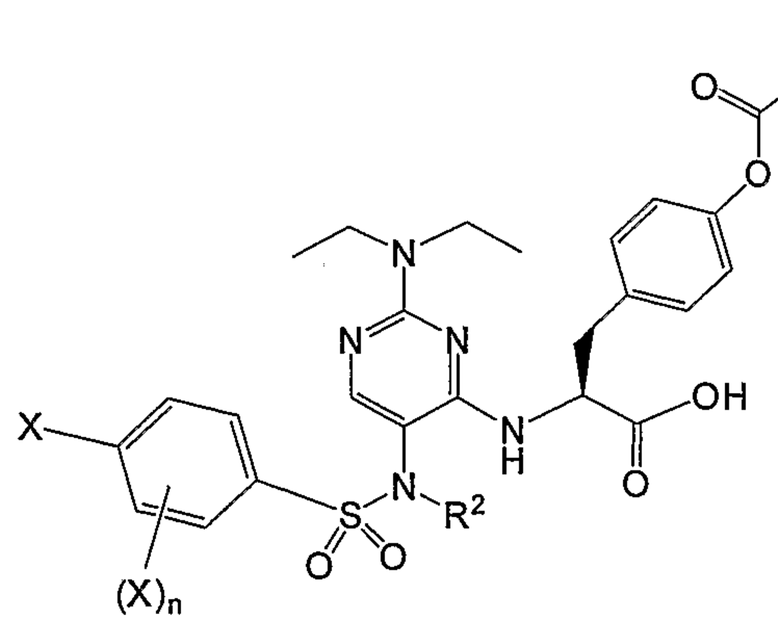
wherein each X is independently selected from the group consisting of fluoro and chloro,

*m* is an integer equal to 1 or 2;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

78. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXI below:



XXI

wherein each X is independently fluoro or chloro;

*n* is zero or one;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

79. The use according to any one of claims 76, 77 or 78, wherein $R^2$ is propargyl.

80. The use according to claim 78, wherein X is F or Cl, and n is 0.

81. The use according to claim 76, wherein the compound of Formula XIX is selected from the group consisting of:

2-{2-Diethylamino-5-[(4-fluorobenzenesulfonyl)propargylamino] pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid,

2-{2-Diethylamino-5-[(2,4-difluorobenzenesulfonyl)propargylamino] pyrimidin-4-ylamino}-3-(4-dimethylcarbamoyloxyphenyl)propionic acid; and

pharmaceutically acceptable salts thereof.

82. The use according to any one of claims 54, 55, 56, 62, 63, 64, 70, 71, 72, 76, 77 or 78, wherein the mammal is a human.

83. The use according to any one of claims 54, 55, 56, 62, 63, 64, 70, 71, 72, 76, 77 or 78, wherein the compound is administered parenterally.

84. The use according to any one of claims 54, 55, 56, 62, 63, 64, 70, 71, 72, 76, 77 or 78, wherein the compound is administered chronically to the mammal in need thereof.

85. The use according to claim 79, wherein the chronic administration of the compound is weekly or monthly over a period of at least one year.

86. The use according to any one of claims 54, 55, 56, 62, 63, 64, 70, 71, 72, 76, 77 or 78, wherein the compound is administered intravenously or subcutaneously.

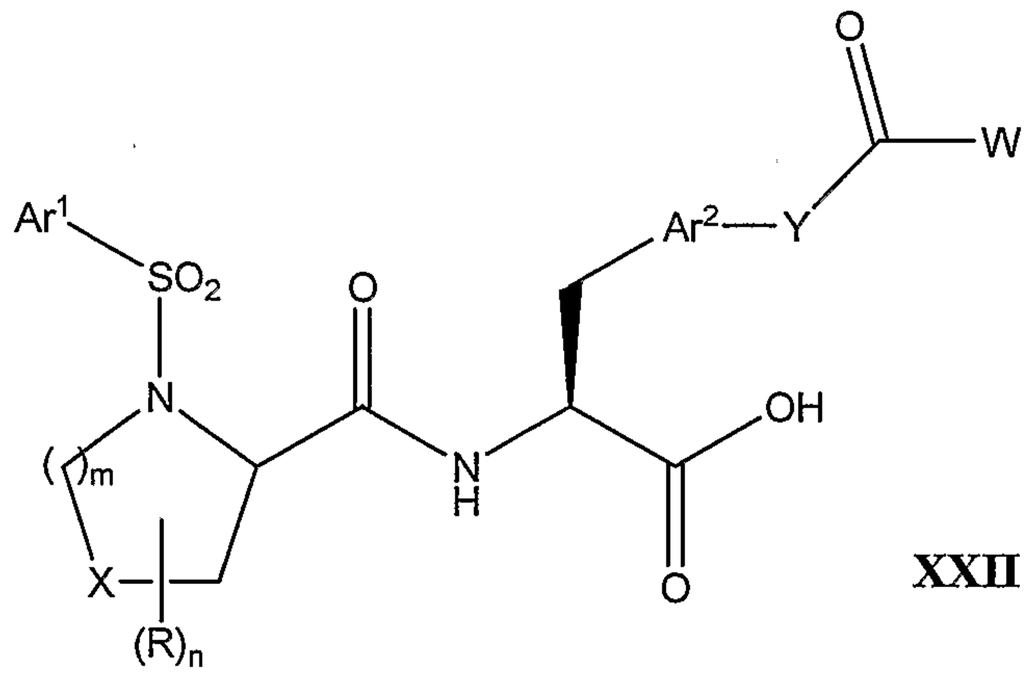
87. The use according to claim 81, wherein the compound is administered intravenously to a mammal, and wherein the administration results in an effective blood level of the compound in the mammal of $\geq$ 10 ng/ml.

88. The use according to claim 81, wherein the compound is administered intravenously in an amount of 20 μg to about 500 μg per kilogram body weight of the mammal.

89. The use according to claim 81, wherein the compound is administered in series of doses separated by intervals of days or weeks.

90. The use of any one of claims 54, 55, 56, 62, 63, 64, 70, 71, 72, 76, 77 or 78, wherein the methotrexate is administered in a dose of approximately 2 mg to 20 mg.

91. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXII below:



**XXII**

wherein

R is selected from the group consisting of a PEG moiety, alkyl and substituted alkyl wherein each of alkyl and substituted alkyl is optionally substituted with a PEG moiety wherein, in each case, the PEG moiety optionally comprises a linker which covalently links the PEG moiety;

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted

heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

$Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

X is selected from the group consisting of -S-, -SO-, $-SO_2$ and optionally substituted -$CH_2$-;

Y is selected from the group consisting of -O- and $-NR^1$- wherein $R^1$ is selected from the group consisting of hydrogen and alkyl;

W is selected from the group consisting of a PEG moiety which optionally comprises a linker and $-NR^2R^3$ wherein $R^2$ and $R^3$ are independently selected from the group consisting of alkyl, substituted alkyl, and where $R^2$ and $R^3$, together with the nitrogen atom bound thereto, form a heterocyclic ring or a substituted heterocyclic ring wherein each of alkyl, substituted alkyl, heterocyclic and substituted heterocyclic is optionally substituted with a PEG moiety which further optionally comprises a linker;

*m* is an integer equal to 0, 1 or 2;

*n* is an integer equal to 0 to 2; and

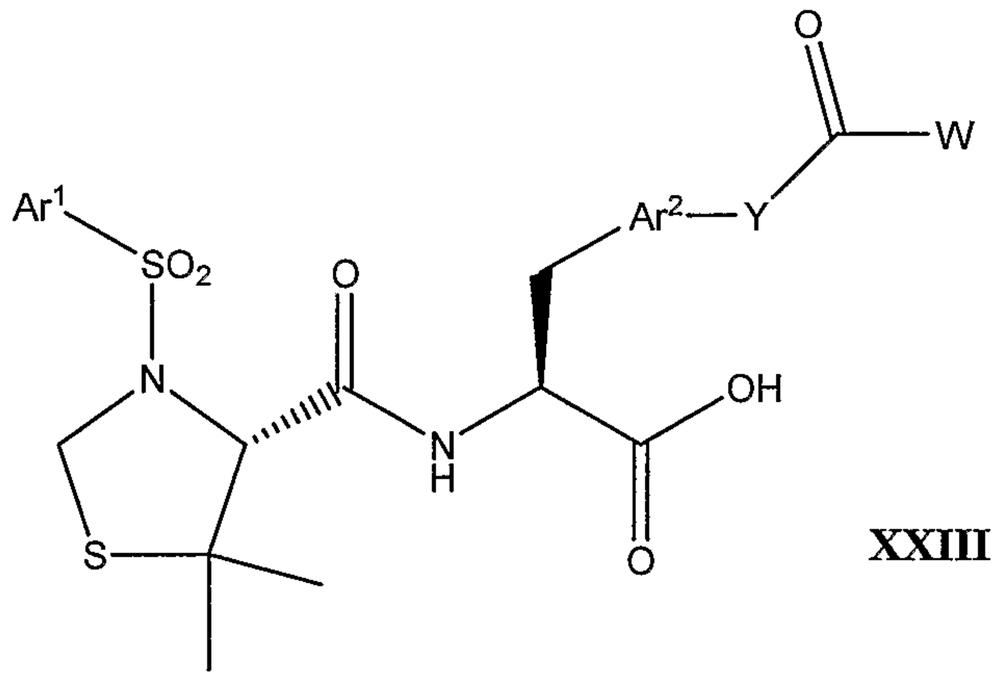
pharmaceutically acceptable salts thereof;

provided that at least one of R, $Ar^1$, $Ar^2$, W and $-NR^2R^3$ contains a PEG moiety;

further provided that when R is a PEG moiety, *n* is one and X is not -S-;

and still further provided that the compound of Formula XXII has a molecular weight of no more than 100,000.

92. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXIII below:



XXIII

wherein:

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

$Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

Y is selected from the group consisting of -O- and $-NR^1-$ wherein $R^1$ is selected from the group consisting of hydrogen and alkyl;

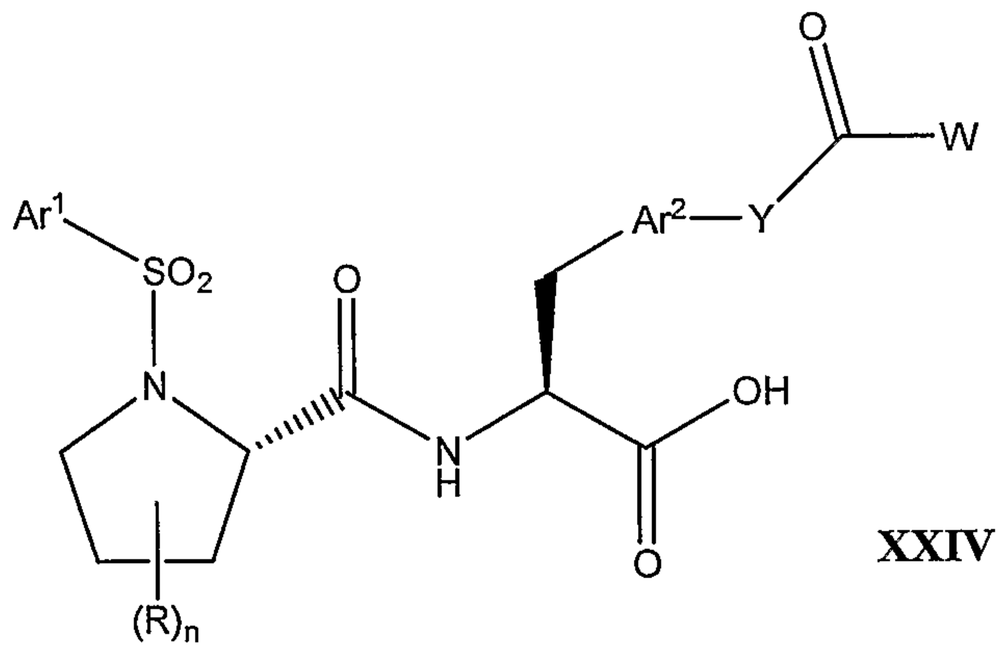
W is selected from the group consisting of a PEG moiety which optionally comprises a linker and $-NR^2R^3$ wherein $R^2$ and $R^3$ are independently selected from the group consisting of alkyl, substituted alkyl, and where $R^2$ and $R^3$, together with the nitrogen atom bound thereto, form a heterocyclic ring or a substituted heterocyclic ring wherein each of alkyl, substituted alkyl, heterocyclic and substituted heterocyclic is optionally substituted with a PEG moiety which further optionally comprises a linker;

pharmaceutically acceptable salts thereof;

provided that at least one of $Ar^1$, $Ar^2$, W and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of Formula XXIII has a molecular weight of no more than 100,000.

93. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXIV below:



**XXIV**

wherein:

R is selected from the group consisting of a PEG moiety, alkyl and substituted alkyl wherein each of alkyl and substituted alkyl is optionally substituted with a PEG moiety wherein, in each case, the PEG moiety optionally comprises a linker which covalently links the PEG moiety;

*n* is an integer of from 0 to 2;

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

$Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl wherein each of aryl, substituted aryl, heteroaryl and substituted heteroaryl is optionally substituted with a PEG moiety wherein the PEG moiety optionally comprises a linker which covalently links the PEG moiety to $Ar^1$;

Y is selected from the group consisting of -O- and $-NR^1-$ wherein $R^1$ is selected from the group consisting of hydrogen and alkyl;

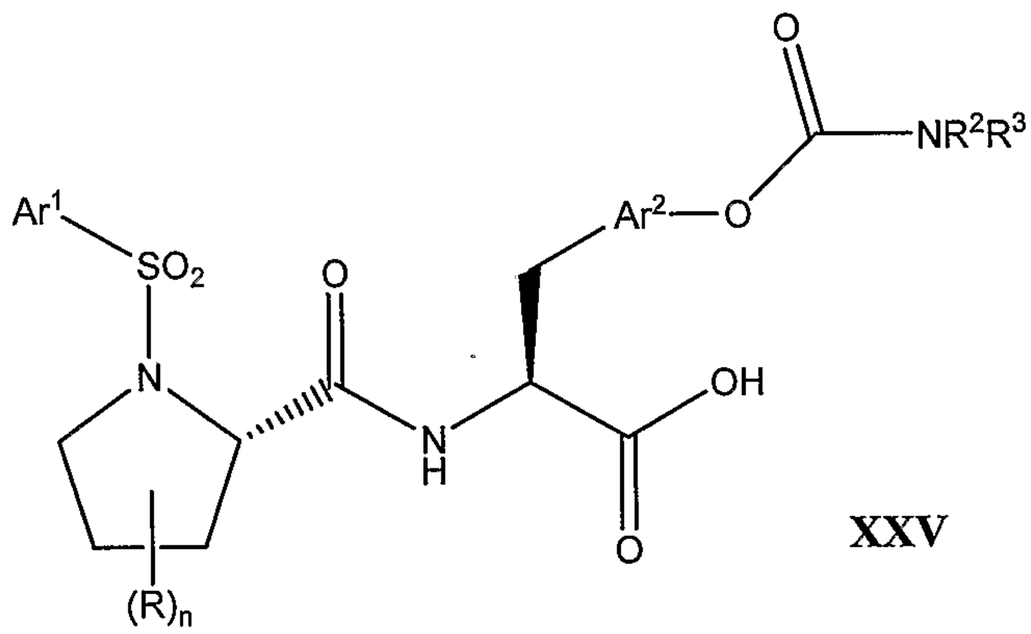
W is selected from the group consisting of a PEG moiety which optionally comprises a linker and $-NR^2R^3$ wherein $R^2$ and $R^3$ are independently selected from the group consisting of alkyl, substituted alkyl, and where $R^2$ and $R^3$, together with the nitrogen atom bound thereto, form a heterocyclic ring or a substituted heterocyclic ring wherein each of alkyl, substituted alkyl, heterocyclic and substituted heterocyclic is optionally substituted with a PEG moiety which further optionally comprises a linker;

pharmaceutically acceptable salts thereof;

provided that at least one of R, $Ar^1$, $Ar^2$, W and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of Formula XXIV has a molecular weight of no more than 100,000.

94. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXV below:



**XXV**

wherein

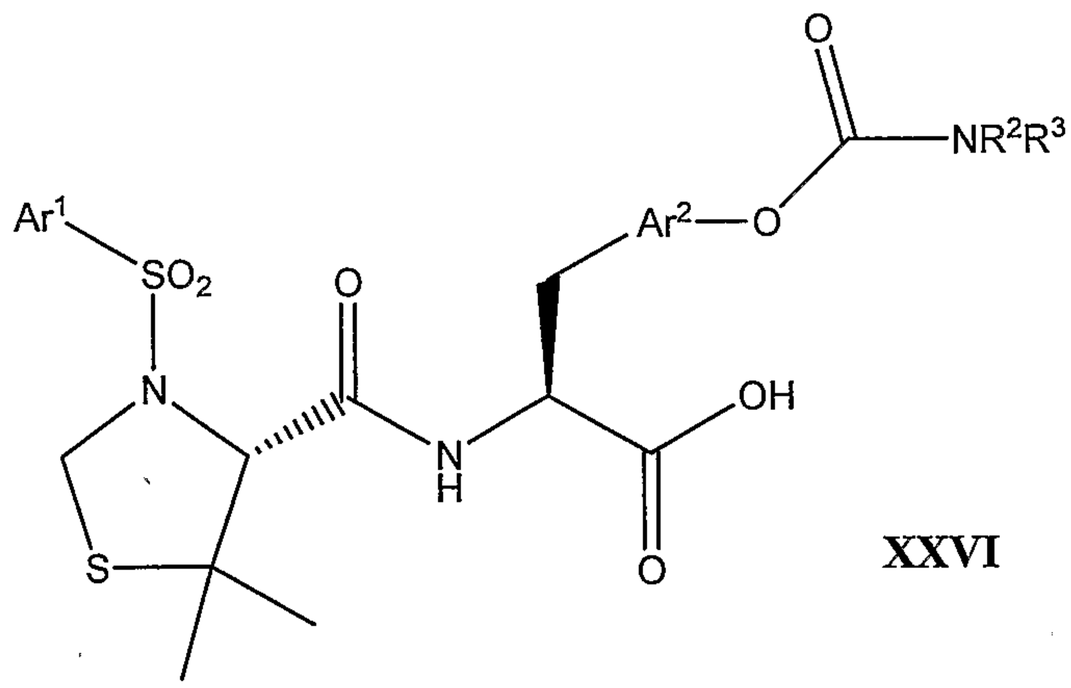
R, $R^2$, $R^3$, $Ar^1$, $Ar^2$ and *n* are as defined in claim 1; and

pharmaceutically acceptable salts thereof;

provided that at least one of R, $Ar^1$, $Ar^2$, and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of Formula XXV has a molecular weight of no more than 100,000.

95. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXVI below:



XXVI

wherein

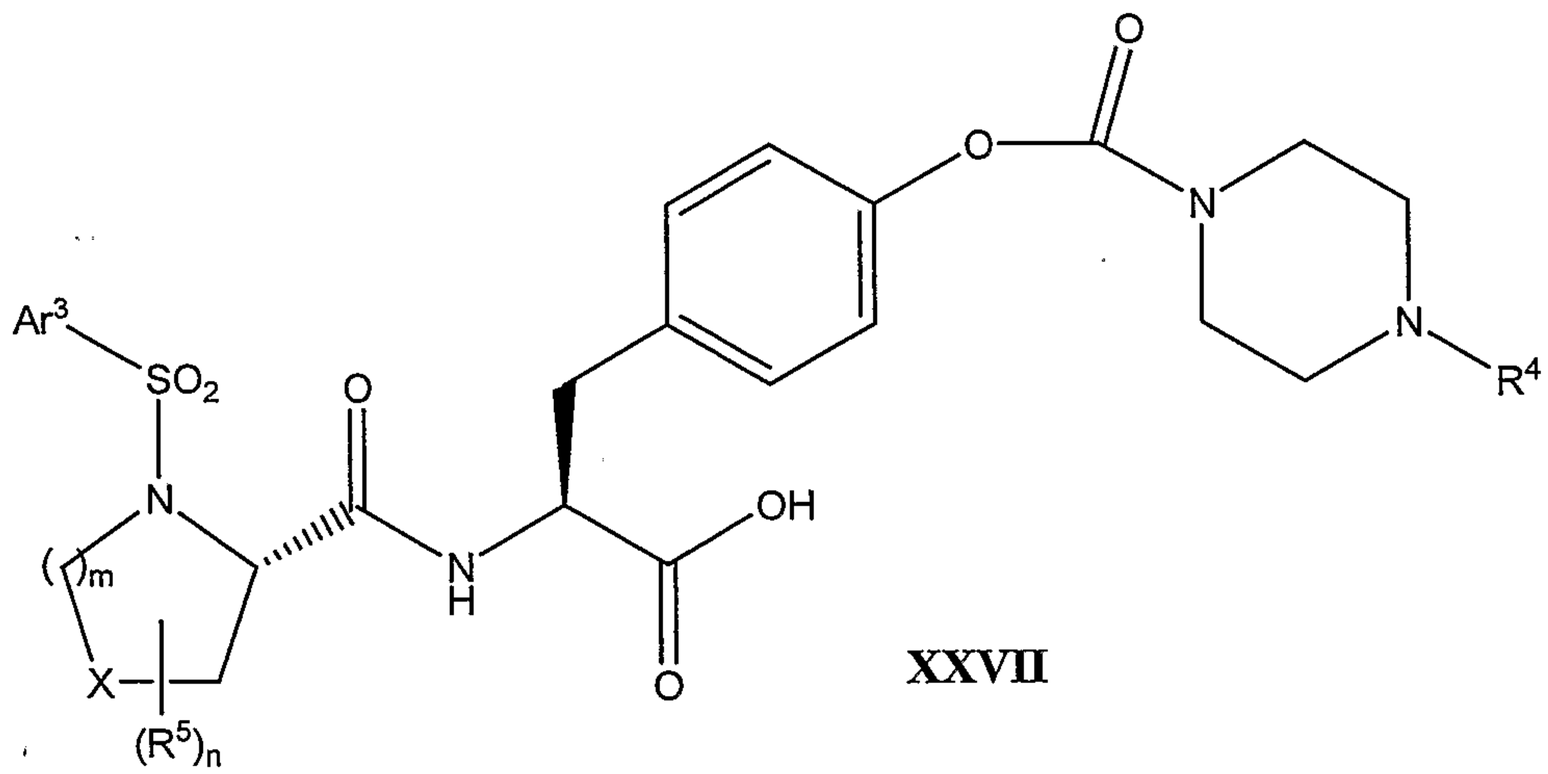
$R^2$, $R^3$, $Ar^1$, and $Ar^2$ are as defined in claim 1; and

pharmaceutically acceptable salts thereof;

provided that at least one of $Ar^1$, $Ar^2$ and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of Formula XXVI has a molecular weight of no more than 100,000.

96. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXVII:



XXVII

wherein

$R^4$ is a PEG moiety which optionally comprises a linker;

$R^5$ is selected from the group consisting of alkyl and substituted alkyl;

$Ar^3$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

X is selected from the group consisting of -S- or optionally substituted -$CH_2$-;

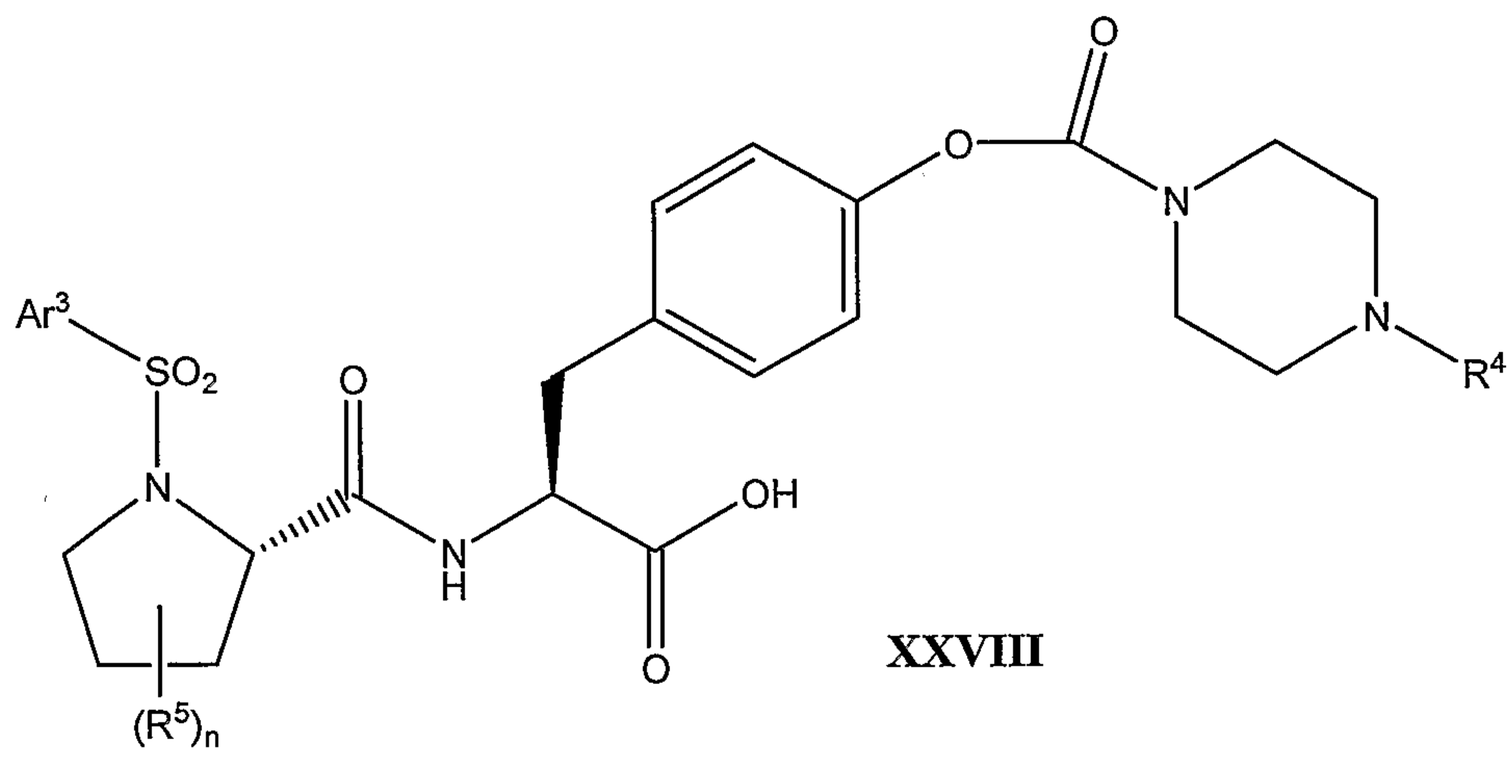
*m* is an integer equal to 0, 1 or 2;

*n* is an integer equal to 0 to 2; and

pharmaceutically acceptable salts thereof;

provided that the compound of Formula XXVII has a molecular weight of no more than 100,000.

97. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXVIII:



**XXVIII**

wherein

$R^4$ is a PEG moiety which optionally comprises a linker;

$R^5$ is selected from the group consisting of alkyl and substituted alkyl;

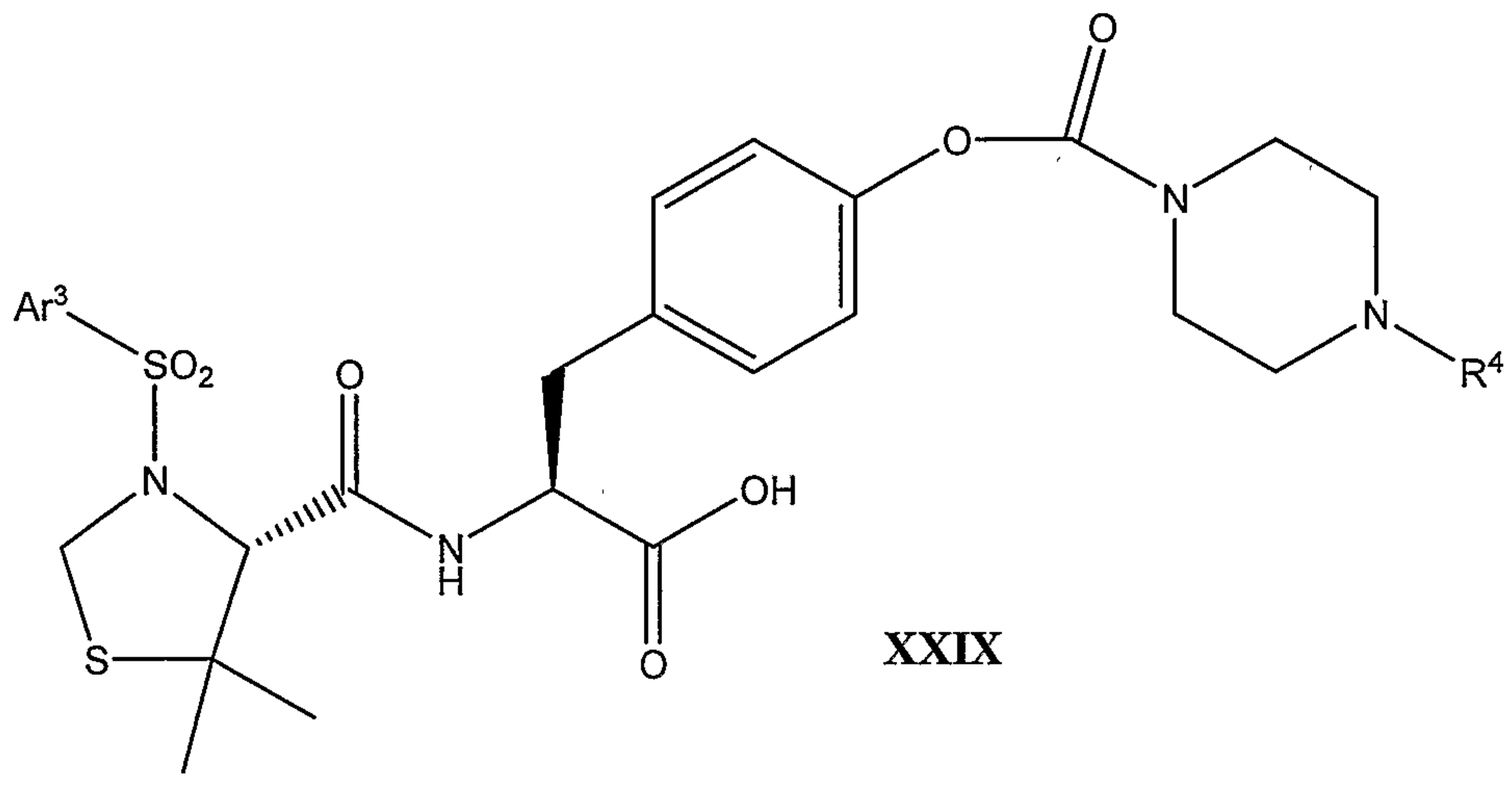
$Ar^3$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

*n* is an integer equal to 0 to 2; and

pharmaceutically acceptable salts thereof;

provided that the compound of Formula XXVIII has a molecular weight of no more than 100,000.

98. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound of Formula XXIX:



**XXIX**

wherein

$R^4$ is a PEG moiety which optionally comprises a linker;

$Ar^3$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

*n* is an integer equal to 0 to 2; and

pharmaceutically acceptable salts thereof;

provided that the compound of Formula XXIX has a molecular weight of no more than 100,000.

99. The use according to any one of claims 91 – 98 wherein, when $Ar^1$ does not contain a PEG moiety, $Ar^1$ in Formulae XXII-XXVI and $Ar^3$ in Formulae XXVII-XXIX is selected from the group consisting of:

phenyl,

4-methylphenyl,

4-*t*-butylphenyl,

2,4,6-trimethylphenyl,

2-fluorophenyl,

3-fluorophenyl,

4-fluorophenyl,

2,4-difluorophenyl,

3,4-difluorophenyl,
3,5-difluorophenyl,
2-chlorophenyl,
3-chlorophenyl,
4-chlorophenyl,
3,4-dichlorophenyl,
3,5-dichlorophenyl,
3-chloro-4-fluorophenyl,
4-bromophenyl,
2-methoxyphenyl,
3-methoxyphenyl,
4-methoxyphenyl,
3,4-dimethoxyphenyl,
4-*t*-butoxyphenyl,
4-(3'-dimethylamino-*n*-propoxy)-phenyl,
2-carboxyphenyl,
2-(methoxycarbonyl)phenyl,
4-($H_2NC(O)$-)phenyl,
4-($H_2NC(S)$-)phenyl,
4-cyanophenyl,
4-trifluoromethylphenyl,
4-trifluoromethoxyphenyl,
3,5-di-(trifluoromethyl)phenyl,
4-nitrophenyl,
4-aminophenyl,
4-($CH_3C(O)NH$-)phenyl,
4-(PhNHC(O)NH-)phenyl,
4-amidinophenyl,
4-methylamidinophenyl,
4-[$CH_3SC(=NH)$-]phenyl,
4-chloro-3-[$H_2NS(O)_2$-]phenyl,
1-naphthyl,
2-naphthyl,

pyridin-2-yl,
pyridin-3-yl,
pyridine-4-yl,
pyrimidin-2-yl,
quinolin-8-yl,
2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl,
2-thienyl,
5-chloro-2-thienyl,
2,5-dichloro-4-thienyl,
1-*N*-methylimidazol-4-yl,
1-*N*-methylpyrazol-3-yl,
1-*N*-methylpyrazol-4-yl,
1-*N*-butylpyrazol-4-yl,
1-*N*-methyl-3-methyl-5-chloropyrazol-4-yl,
1-*N*-methyl-5-methyl-3-chloropyrazol-4-yl,
2-thiazolyl and
5-methyl-1,3,4-thiadiazol-2-yl.

100. The use according to any one of claims 91-95, wherein when $Ar^1$ contains a PEG group, $Ar^1$ is of the formula:

$$-Ar^1-Z-(CH_2CHR^7O)_pR^8$$

wherein

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

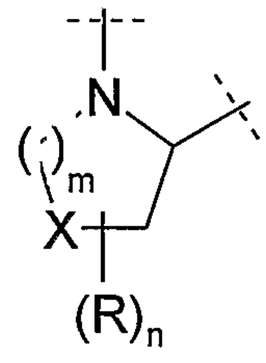
Z is selected from the group consisting of a covalent bond, a linking group of from 1 to 40 atoms, -O-, $-NR^9-$, $-NR^9C(O)O-$, $-OC(O)NR^9-$, $-NR^9C(O)-$, and $-C(O)NR^9-$, where $R^9$ is selected from the group consisting of hydrogen and alkyl,

$R^7$ is selected from the group consisting of hydrogen and methyl;

$R^8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and $-CH_2CHR^7NR^{10}R^{11}$ where $R^7$ is as defined above and $R^{10}$ and $R^{11}$ are independently selected from the group consisting of hydrogen and alkyl; and

*p* is an integer such that the molecular weight of the PEG moiety ranges from 100 to 100,000.

101. The use according to claims 91 or 96, wherein, when R does not contain a PEG moiety, the substituent of the formula:



is selected from the group consisting of azetidinyl, thiazolidinyl, piperidinyl, piperazinyl, thiomorpholinyl, pyrrolidinyl, 4-hydroxypyrrolidinyl, 4-oxopyrrolidinyl, 4-fluoropyrrolidinyl, 4,4-difluoropyrrolidinyl, 4-(thiomorpholin-4-ylC(O)O-)pyrrolidinyl, 4-[$CH_3S(O)_2O$-]pyrrolidinyl, 3-phenylpyrrolidinyl, 3-thiophenylpyrrolidinyl, 4-aminopyrrolidinyl, 3-methoxypyrrolidinyl, 4,4-dimethylpyrrolidinyl, 4-*N*-Cbz-piperazinyl, 4-[$CH_3S(O)_2$-]piperazinyl, 5,5-dimethylthiazolindin-4-yl, 1,1-dioxo-thiazolidinyl, 1,1-dioxo-5,5-dimethylthiazolidin-2-yl and 1,1-dioxothiomorpholinyl.

102. The use according to any one of claims 91-95, wherein, when $Ar^2$ does not contain a PEG moiety, $Ar^2$ is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and 4-pyrid-2-onyl.

103. The use according to any one of claims 91-93, wherein -YC(O)W is -$OC(O)NR^2R^3$.

104. The use according to claim 103, wherein the -YC(O)W substituent is selected from the group consisting of:

-$OC(O)NH(CH_2CH_2O)_pCH_2CH_2NH_2$;

-$OC(O)NH(CH_2CH(CH_3)O)_pCH_2CH(CH_3)NH_2$;

-$NHC(O)O(CH_2CH_2O)_pH$;

-$NHC(O)O(CH_2CH(CH_3)O)_pH$;

-$NHC(O)O(CH_2CH_2O)_pCH_3$;

-NHC(O)O($CH_2CH(CH_3)O)_pCH_3$;

-NHC(O)O($CH_2CH_2O)_p$-φ;

-NHC(O)O($CH_2CH(CH_3)O)_p$-φ;

-NHC(O)NH($CH_2CH_2O)_pCH_2CH_2NH_2$;

-NHC(O)NH($CH_2CH(CH_3)O)_pCH_2CH(CH_3)NH_2$;

-OC(O)NH-(1,4)-φ-O-($CH_2CH_2O)_pH$;

-OC(O)NH-(1,4)-φ-O-($CH_2CH(CH_3)O)_pH$;

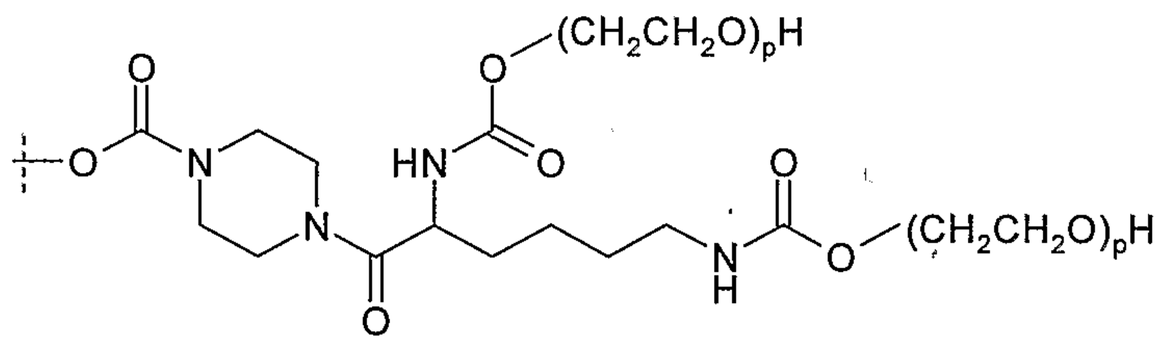
-OC(O)NH($CH_2CH(CH_3)O)_pCH_2CH(CH_3)NH_2$;

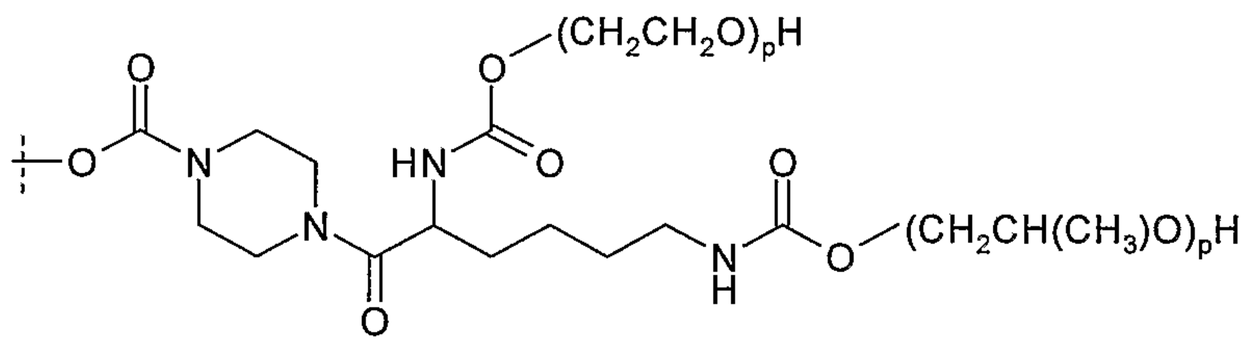
-NHC(O)O($CH_2CH_2O)_pH$;

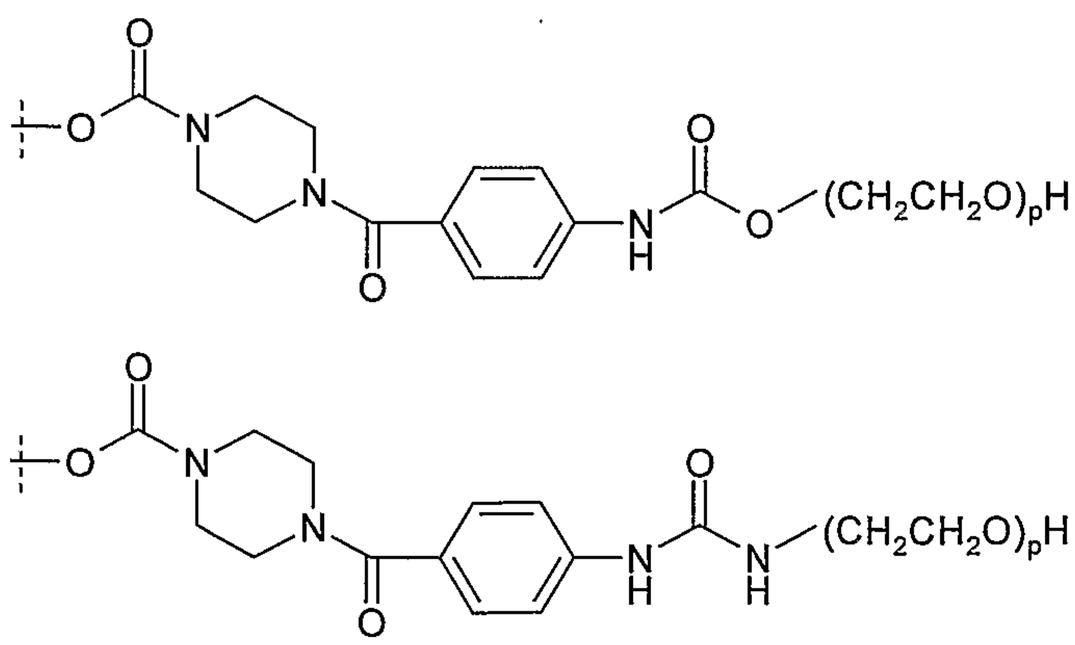
-NHC(O)O($CH_2CH(CH_3)O)_pH$;

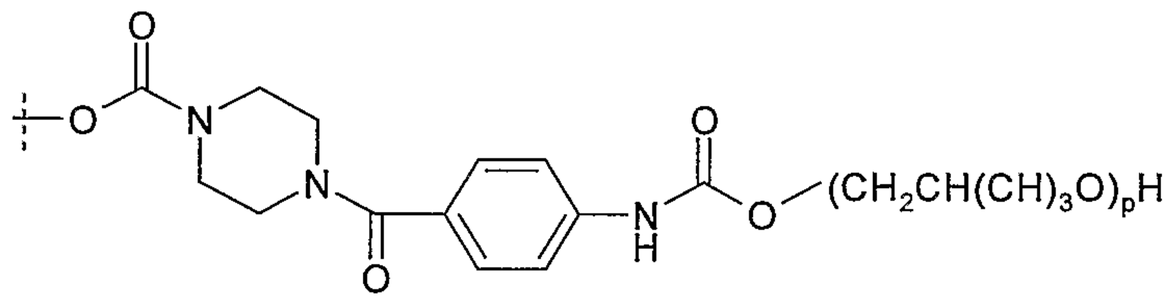
-NHC(O)NH($CH_2CH_2O)_pCH_2CH_2NH_2$;

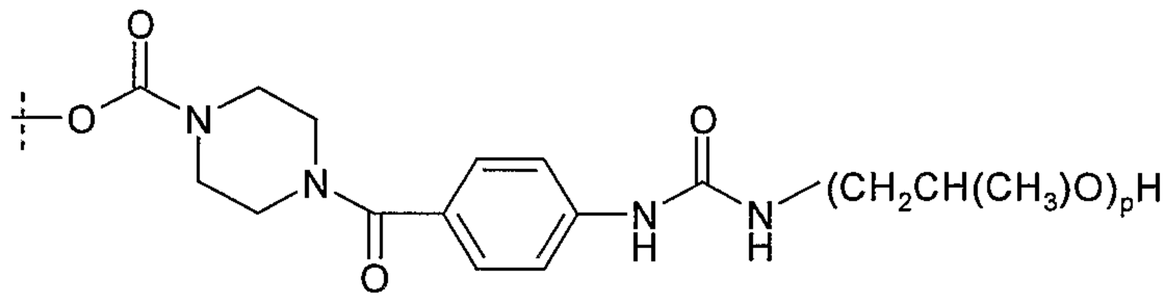
-NHC(O)NH($CH_2CH(CH_3)O)_pCH_2CH(CH_3)NH_2$;

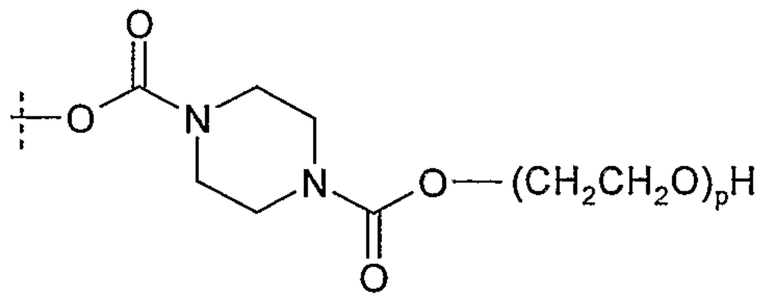


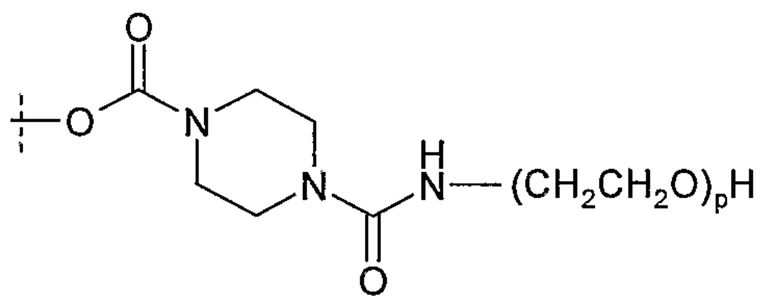



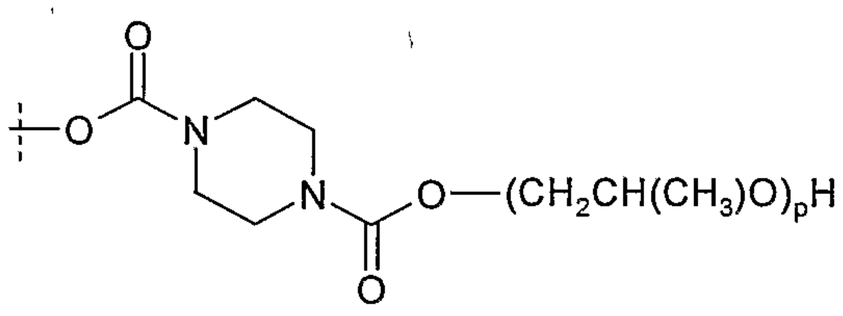



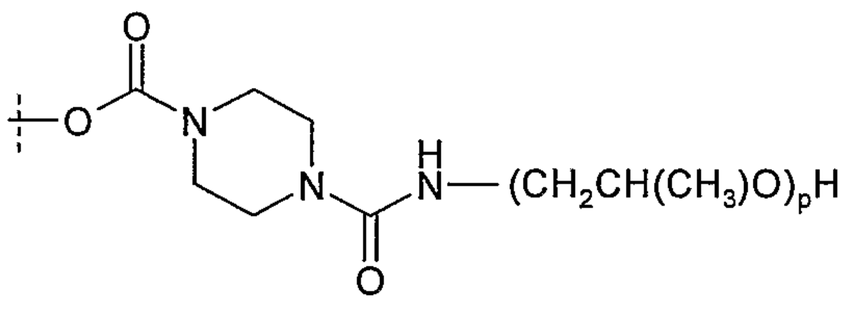


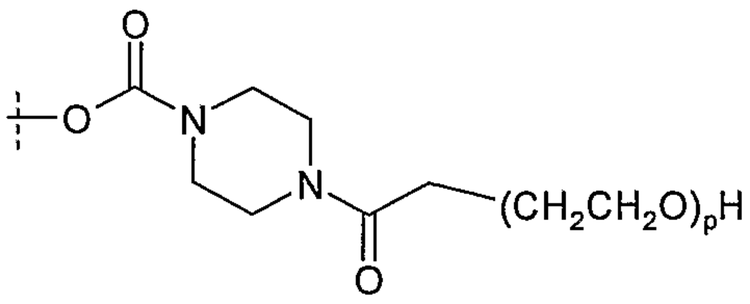


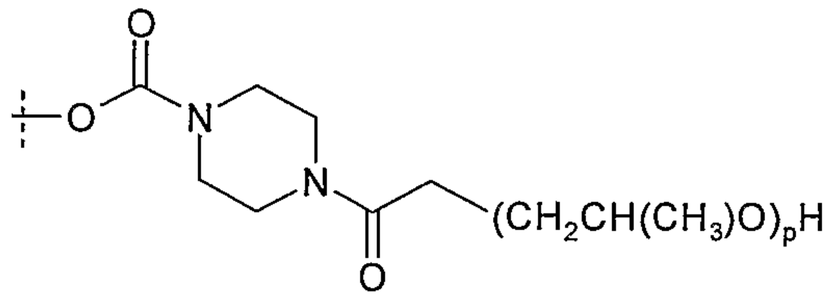


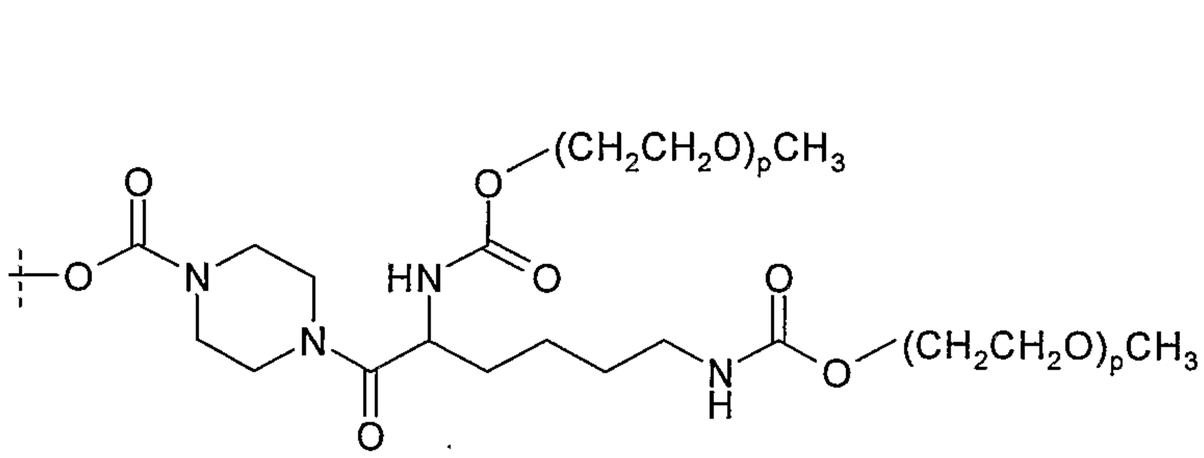


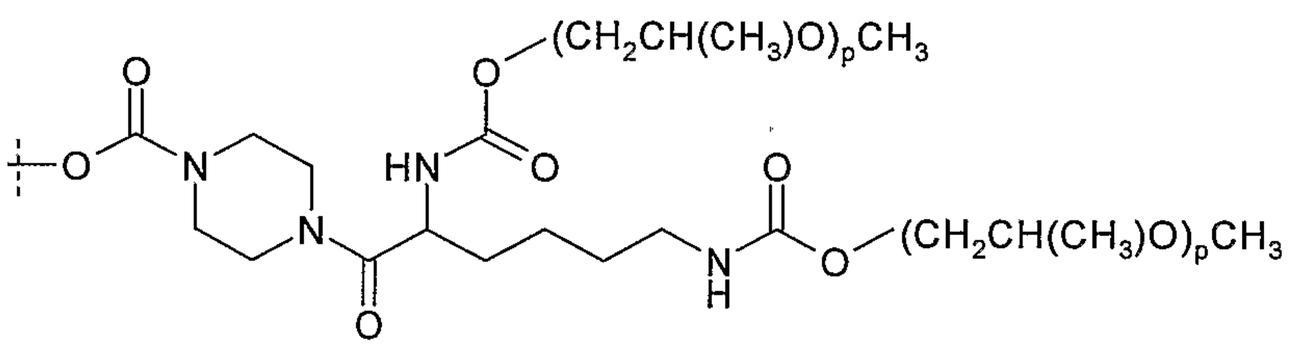


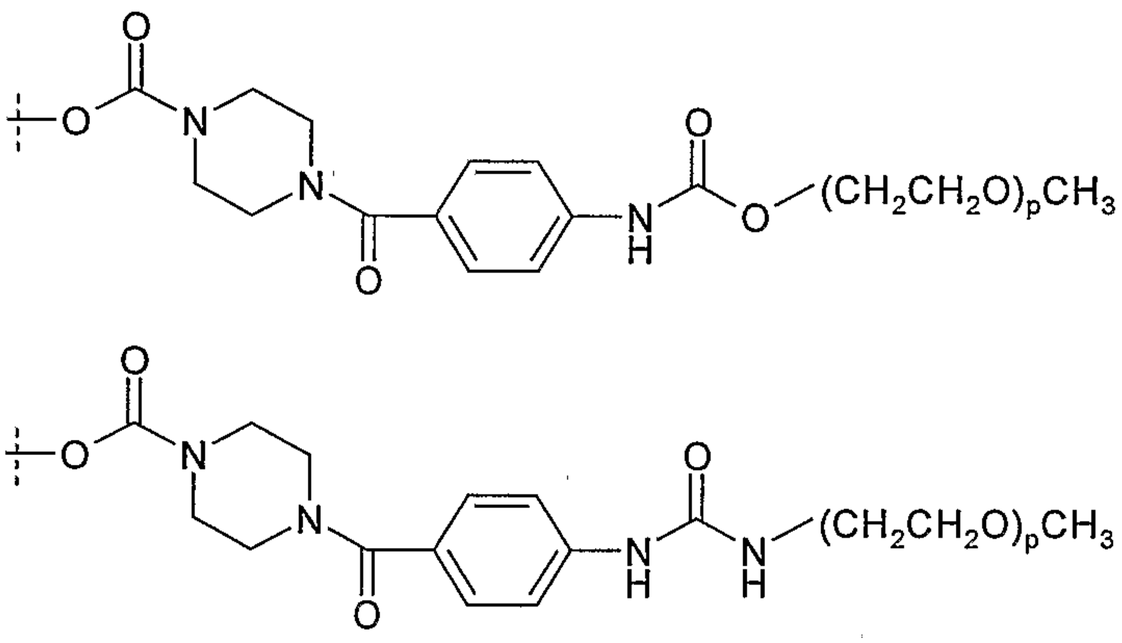




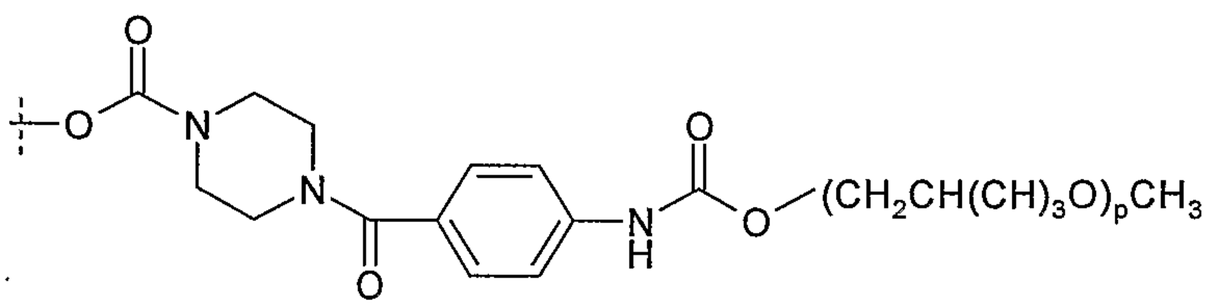


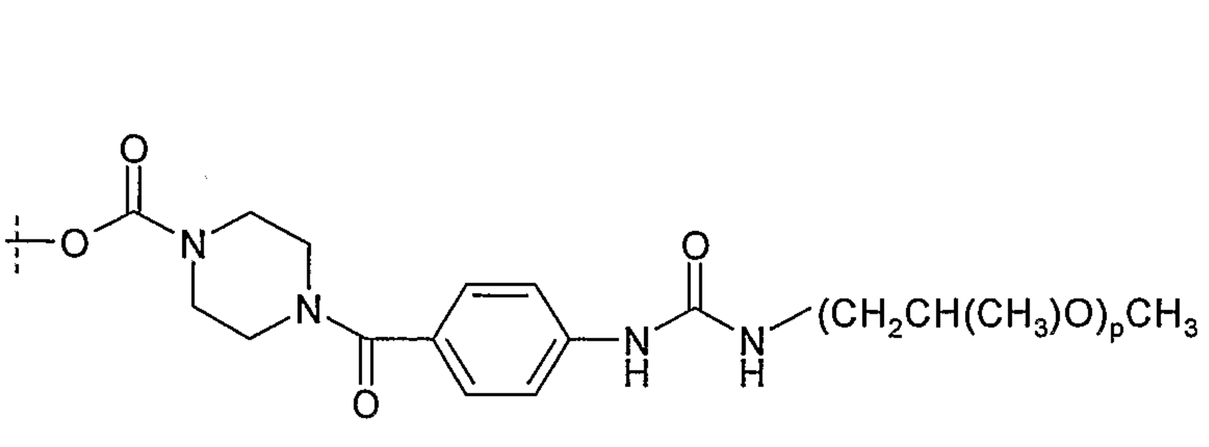


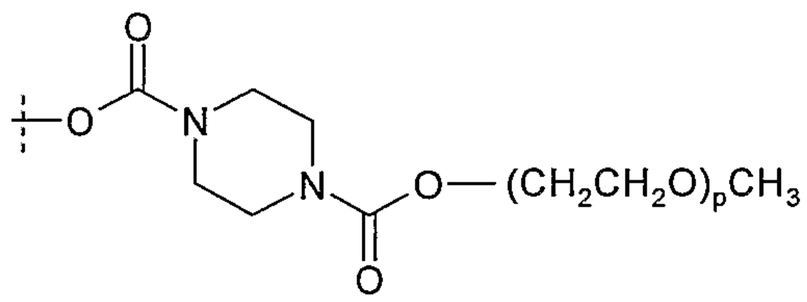


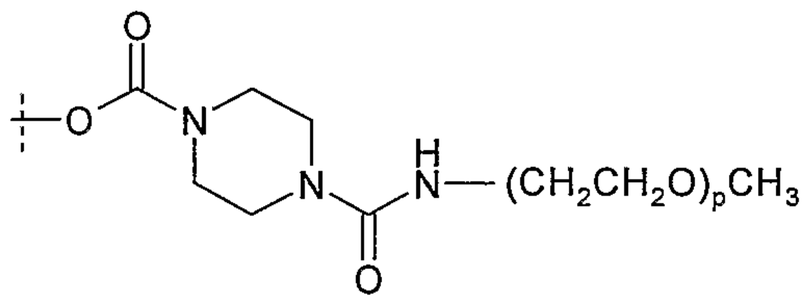


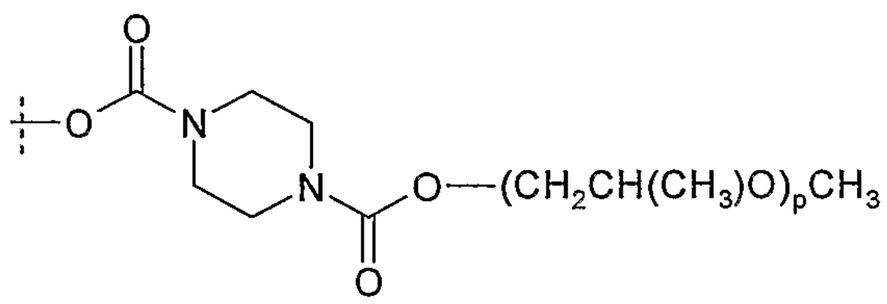


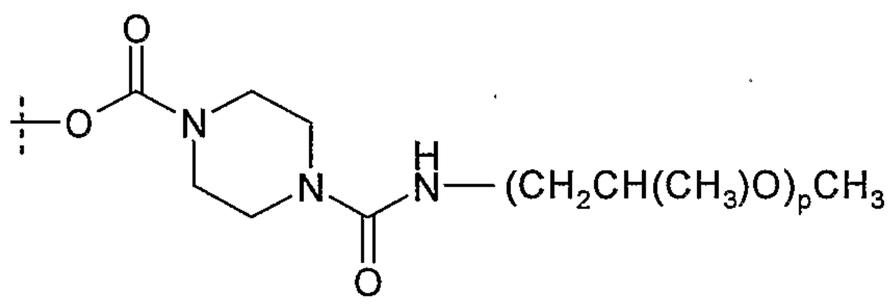


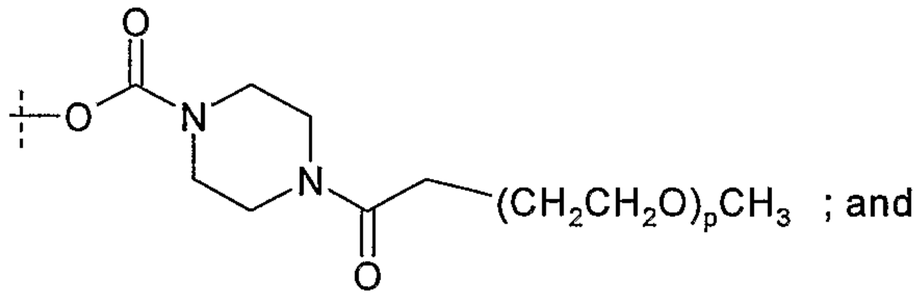




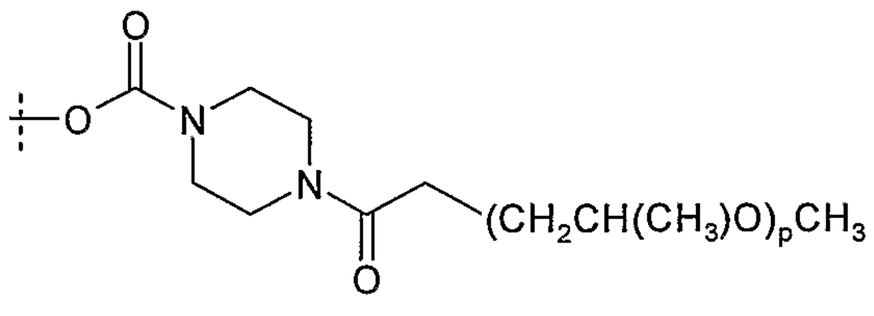






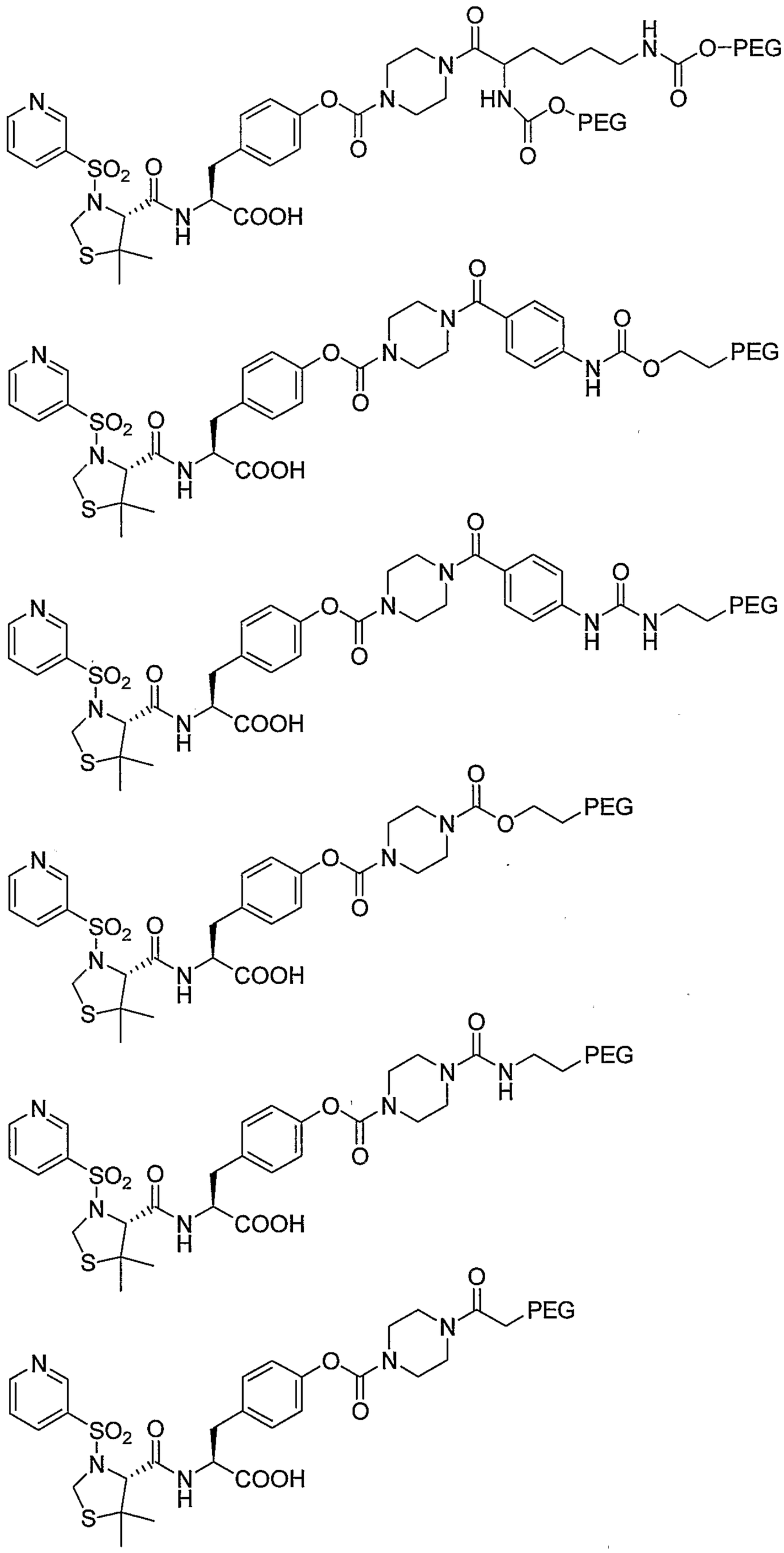


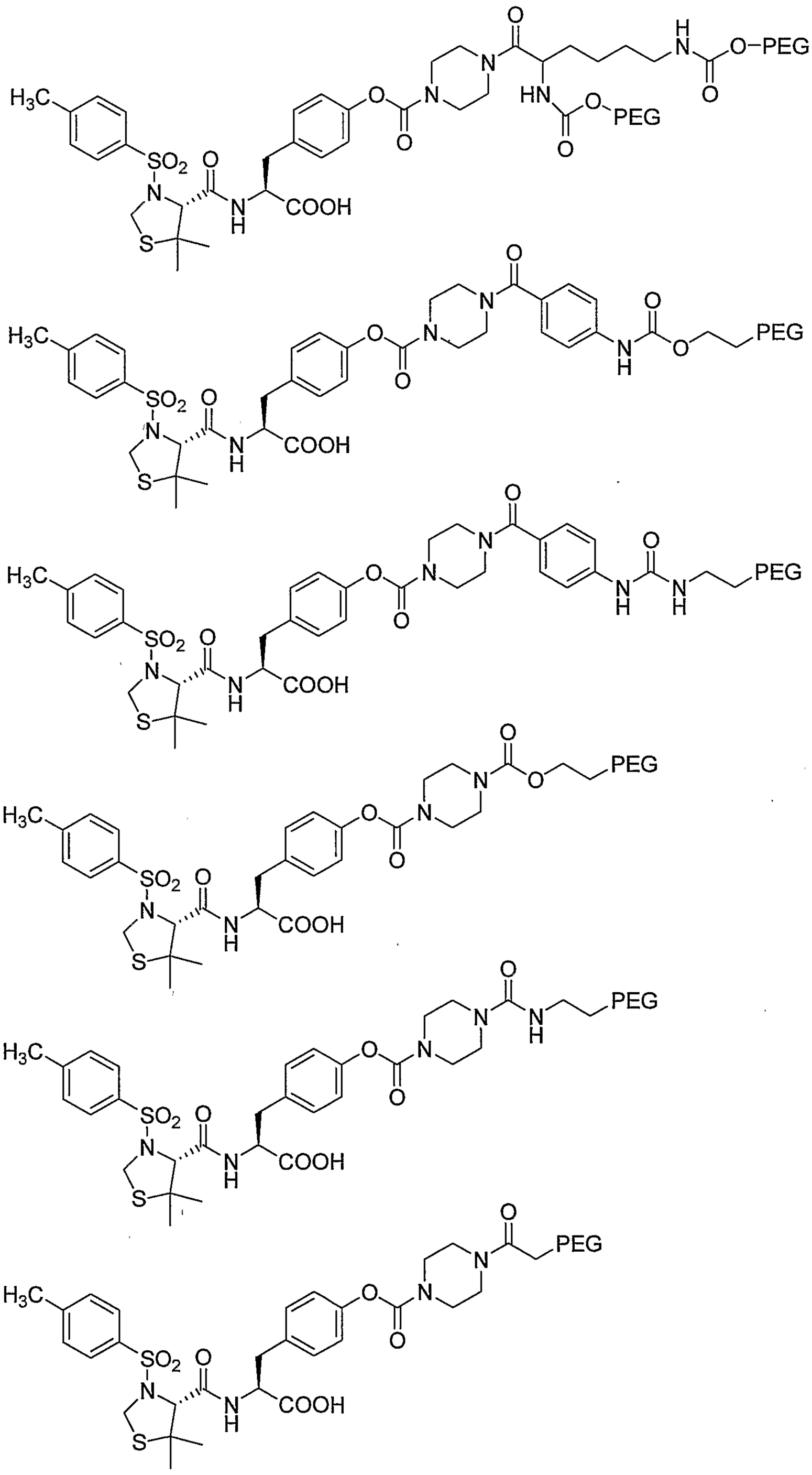
; and



where φ, when monovalent, is phenyl and, when divalent, is phenylene and *p* is an integer such that the molecular weight of the PEG moiety ranges from about 100 to 100,000.

105. Use of a combination therapy for the preparation of a medicament for the treatment of rheumatoid arthritis, wherein the combination therapy comprises therapeutically effective amounts of methotrexate and a compound selected from the group consisting of:





and pharmaceutically acceptable salts thereof;

where, in each case, PEG is a methyl capped polyoxyethylene group having a molecular weight of approximately 20,000.

106. The use according to any one of claims 91-98 or 105, wherein the mammal is a human.

107. The use according to any one of claims 91-98 or 105, wherein the compound is administered parenterally.

108. The use according to any one of claims 91-98 or 105, wherein the compound is administered chronically to the mammal in need thereof.

109. The use according to claim 108, wherein the chronic administration of the compound is weekly or monthly over a period of at least one year.

110. The use according to any one of claims 91-98 or 105, wherein the compound is administered intravenously or subcutaneously.

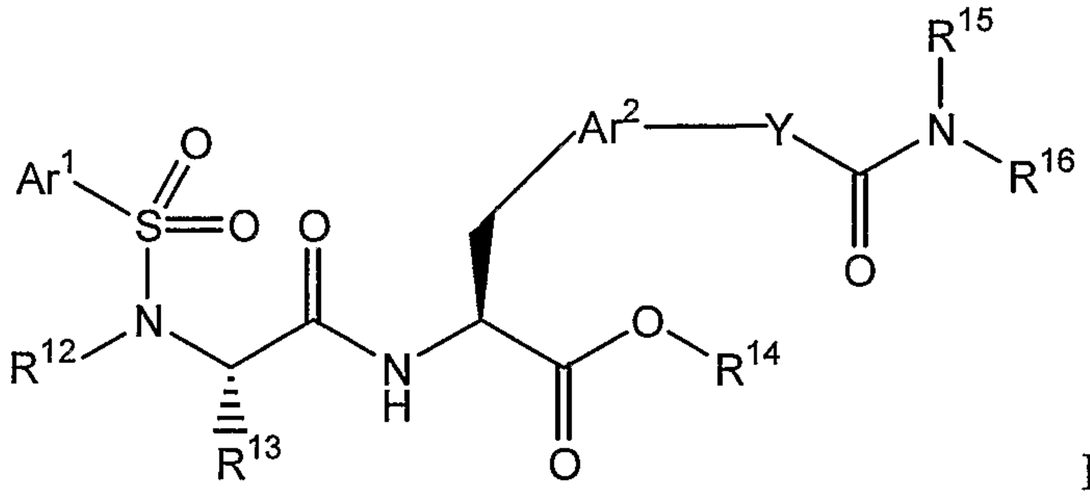
111. The use according to claim 110, wherein the compound is administered intravenously to a mammal, and wherein the administration results in an effective blood level of the compound in the mammal of $\geq$ 10 ng/ml.

112. The use according to claim 110, wherein the compound is administered intravenously in an amount of 20 μg to about 500 μg per kilogram body weight of the mammal.

113. The use according to claim 110, wherein the compound is administered in series of doses separated by intervals of days or weeks.

114. The use of any one of claims 91-98 or 105, wherein the methotrexate is administered in a dose of approximately 2 mg to 20 mg.

115. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula IB, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula IB is as below:



IB

and wherein:

$Ar^1$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

$Ar^2$ is selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R^{12}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl or $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic group;

$R^{13}$ is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or $R^{12}$ and $R^{13}$ together with the nitrogen atom bound to $R^{12}$ and the carbon atom bound to $R^{13}$ form a heterocyclic or substituted heterocyclic group;

$R^{14}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl;

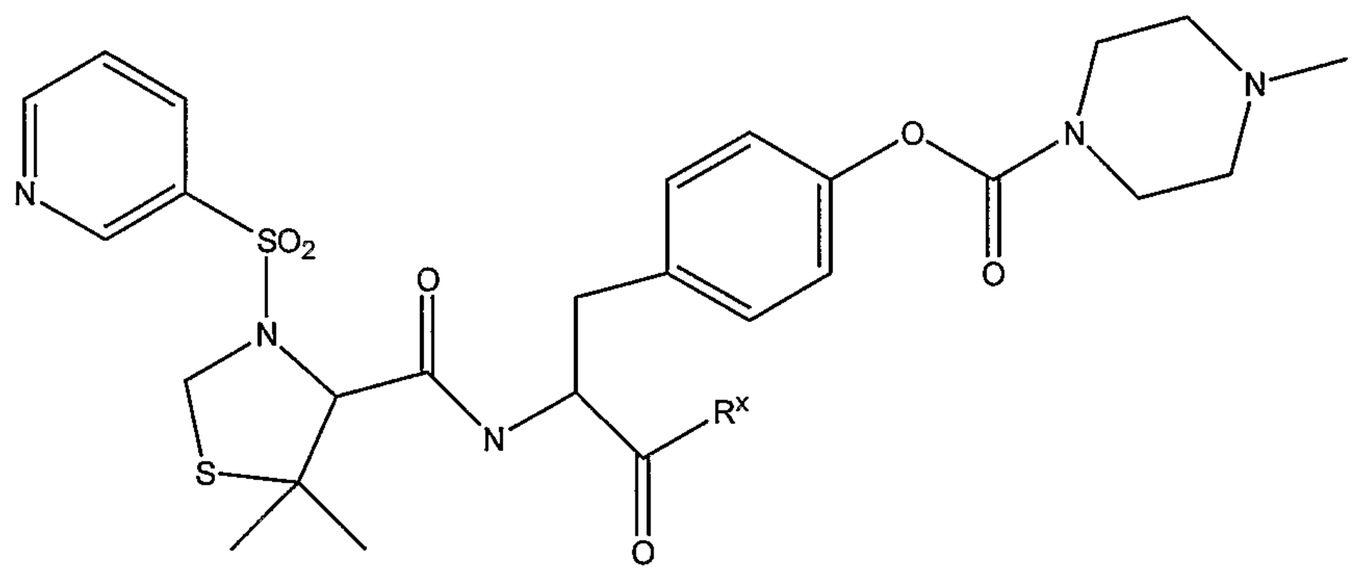
$R^{15}$ is selected from the group consisting of alkyl, and substituted alkyl, or $R^{15}$ and $R^{16}$ together with the nitrogen atom to which they are bound form a heterocyclic or substituted heterocyclic group;

$R^{16}$ is selected from the group consisting of alkyl and substituted alkyl or $R^{15}$ and $R^{16}$ together with the nitrogen atom to which they are bound form a heterocyclic or substituted heterocyclic group; and

Y is selected from the group consisting of -O-, -$NR^{100}$-, and -$CH_2$- wherein $R^{100}$ is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof.

116. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula IC, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula IC is as below:



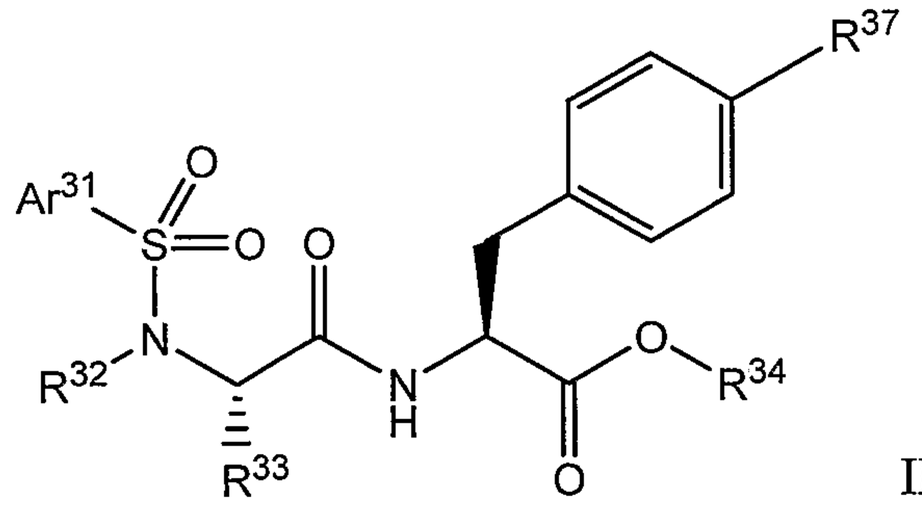
IC

wherein

$R^x$ is hydroxy or $C_{1-5}$ alkoxy; and

pharmaceutically acceptable salts thereof.

117. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula IIB, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula IIB is as below:



IIB

wherein:

$Ar^{31}$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

$R^{32}$ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group;

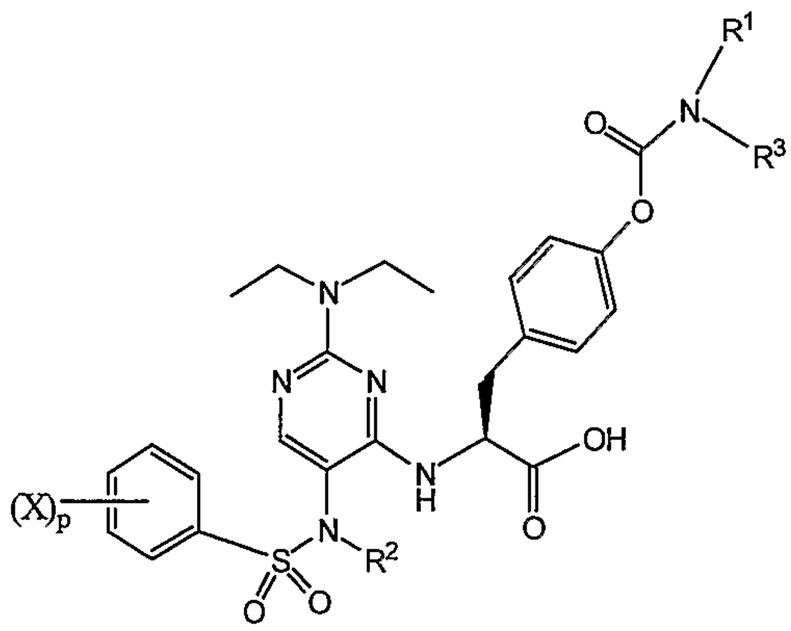
$R^{33}$ is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or $R^{32}$ and $R^{33}$ together with the nitrogen atom bound to $R^{32}$ and the carbon atom bound to $R^{33}$ form a heterocyclic or substituted heterocyclic group;

$R^{34}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl; and

$R^{37}$ is aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy;

and pharmaceutically acceptable salts thereof.

118. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula X, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula X is as below:



X

wherein each X is independently fluoro, chloro or bromo;

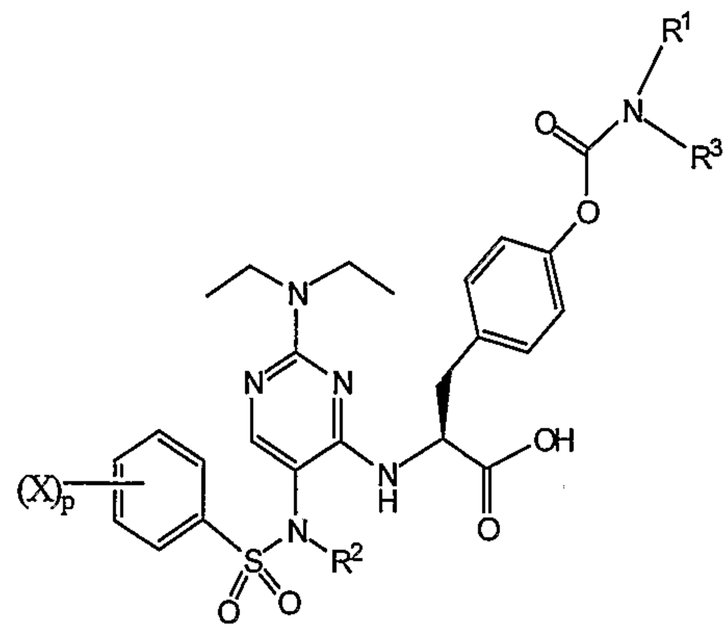
p is an integer from 0 to 3;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, pyrrolyl, 2,5-dihydopyrrol-1-yl, piperidinyl, or 1,2,3,6-tetrahydro-pyridin-1-yl;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

119. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula XIII, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula XIII is as below:



XIII

wherein each X is independently fluoro, chloro or bromo;

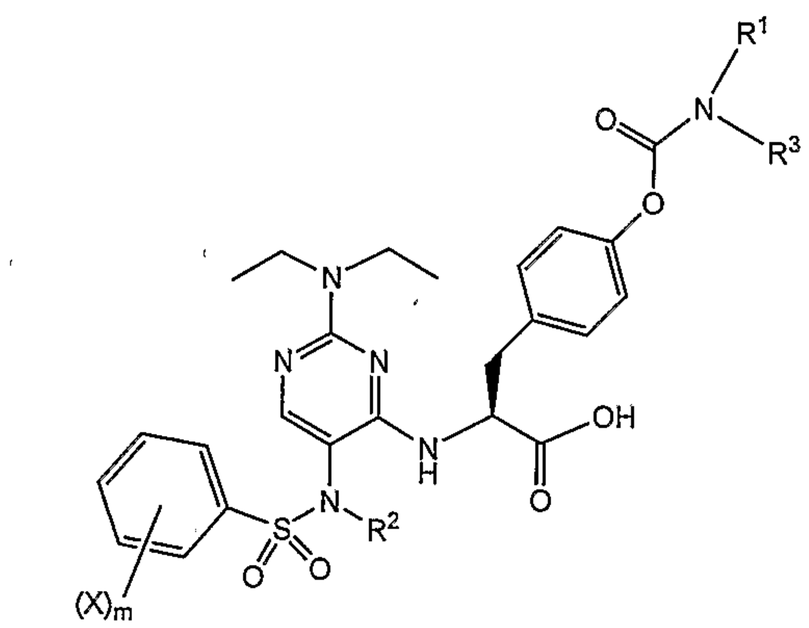
p is an integer from 0 to 3;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, pyrrolyl, 2,5-dihydopyrrol-1-yl, piperidinyl, or 1,2,3,6-tetrahydropyridin-1-yl;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

120. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula XIV, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula XIV is as below:



XIV

wherein each X is independently selected from the group consisting of fluoro and chloro;

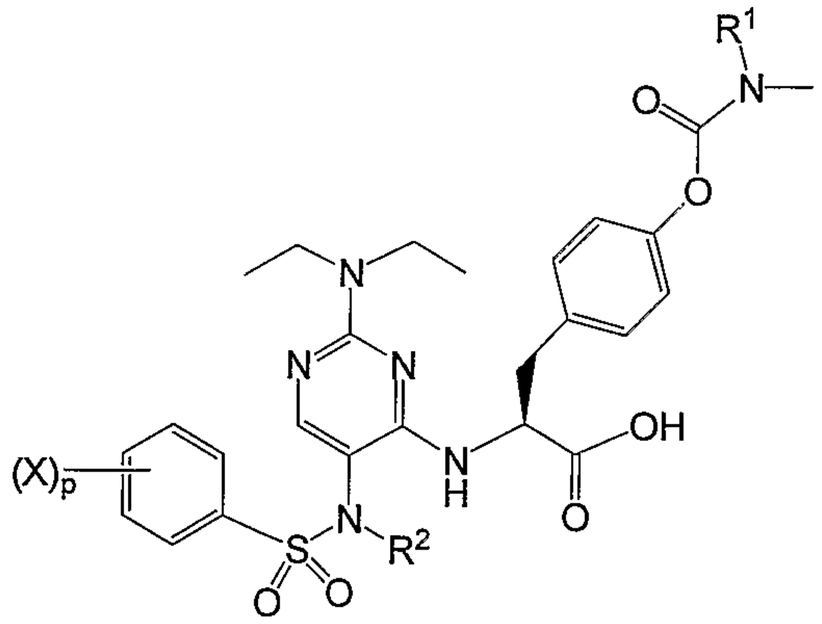
*m* is an integer equal to 1 or 2;

$R^2$ is lower alkynyl;

$R^1$ and $R^3$ together with the nitrogen atom to which they are bound form an azetidinyl, pyrrolidinyl, or piperidinyl group;

and pharmaceutically acceptable salts thereof.

121. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula XVI, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula XVI is as below:



XVI

wherein each X is independently fluoro, chloro or bromo;

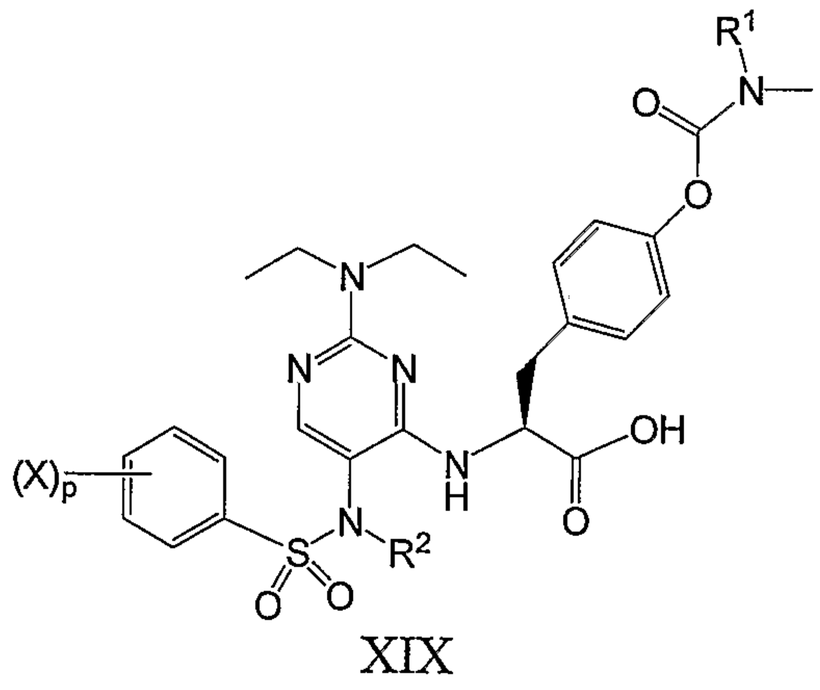
p is 0 or an integer from 1 - 3;

$R^1$ is selected from the group consisting of methyl and ethyl;

$R^2$ is selected from the group consisting of lower alkyl, lower alkenyl, and lower alkylenecycloalkyl;

and pharmaceutically acceptable salts thereof.

122. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula XIX, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula XIX is as below:



XIX

wherein each X is independently fluoro, chloro or bromo;

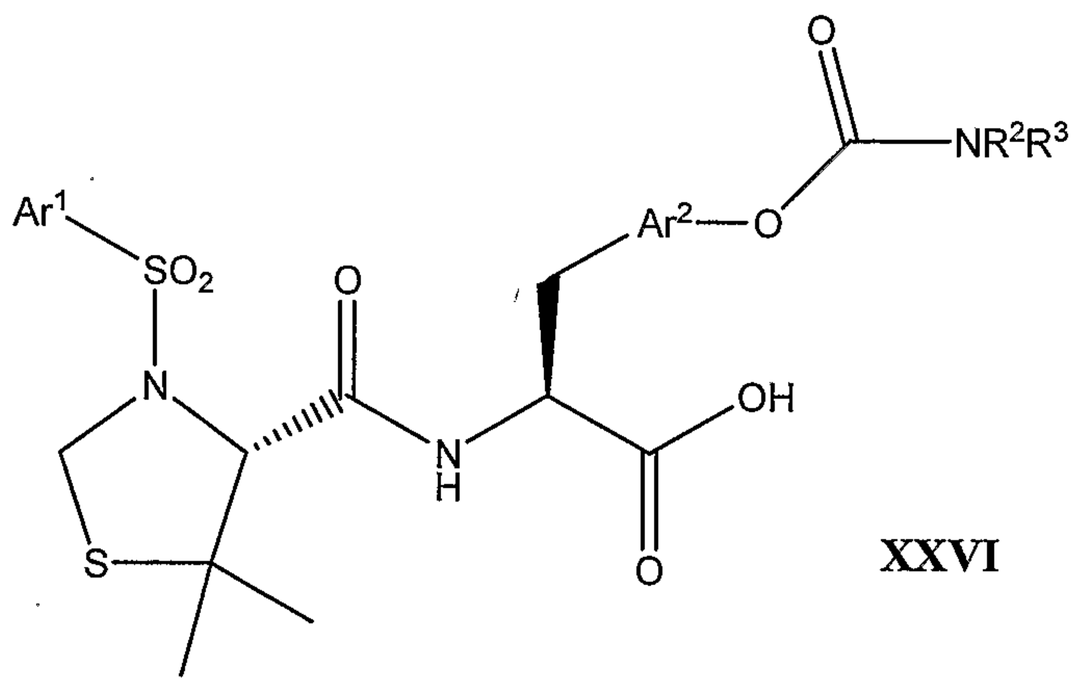
p is 0 or an integer from 1 - 3;

$R^1$ is selected from the group consisting of methyl and ethyl;

$R^2$ is lower alkynyl;

and pharmaceutically acceptable salts thereof.

123. A regimen for the treatment of rheumatoid arthritis which comprises administering to a subject in need thereof about 2 mg to about 20 mg of methotrexate and about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a compound of formula XXVI, wherein the amount of methotrexate administered per week does not exceed 20 mg, wherein the compound of formula XXVI is as below:




**XXVI**

wherein

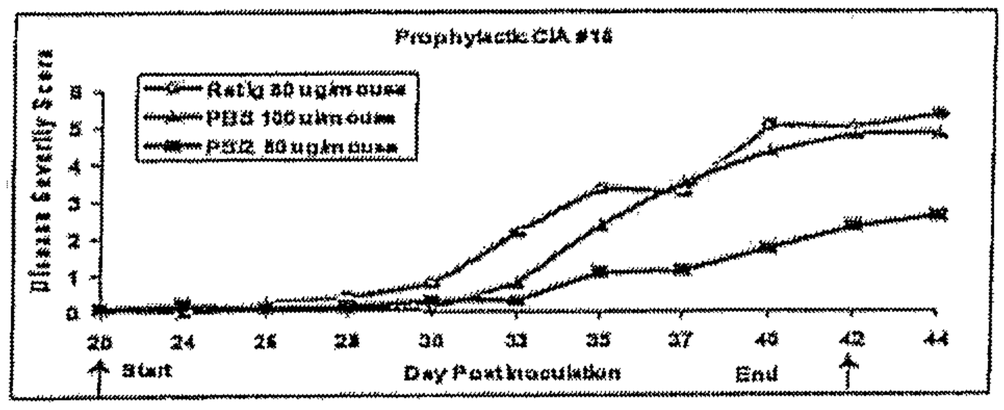
$R^2$, $R^3$, $Ar^1$, and $Ar^2$ are as defined in claim 1; and

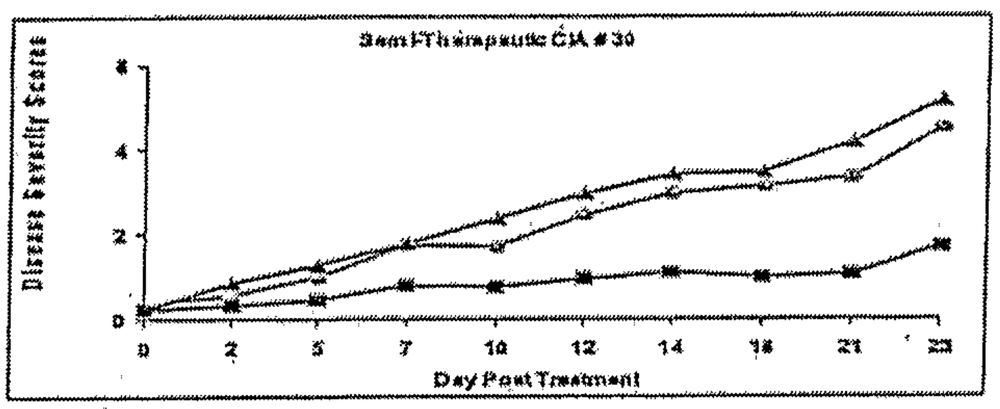
pharmaceutically acceptable salts thereof;

provided that at least one of $Ar^1$, $Ar^2$ and $-NR^2R^3$ contains a PEG moiety which optionally comprises a linker;

and further provided that the compound of Formula XXVI has a molecular weight of no more than 100,000.

FIGURE 1


Prophylactic CIA #16
Rat Ig 50 ug/mouse
PBS 100 ul/mouse
PS12 50 ug/mouse
Disease Severity Score
0
1
2
3
4
5
6
20
24
26
28
30
33
35
37
40
42
44
Start
Day Post Inoculation
End


Semi-Therapeutic CIA #30
Disease Severity Scores
0
2
4
6
0
2
5
7
10
12
14
16
21
23
Day Post Treatment

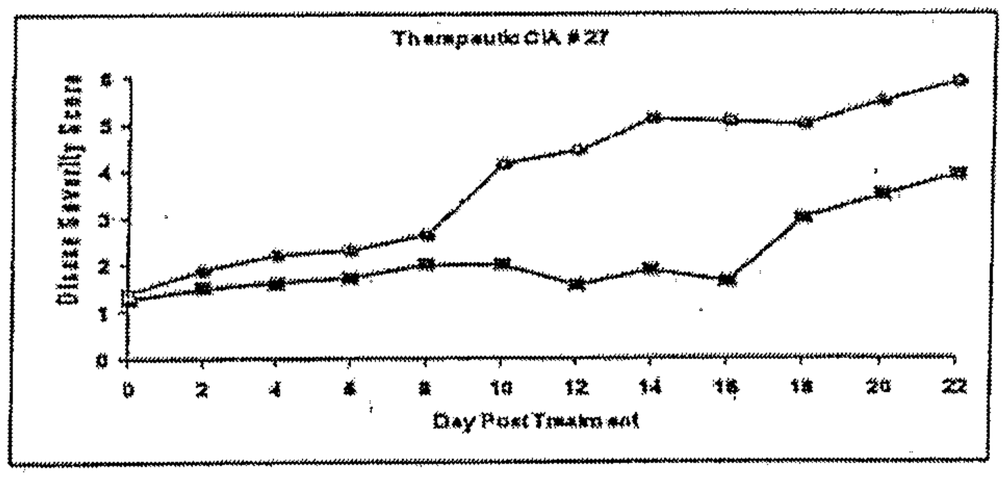
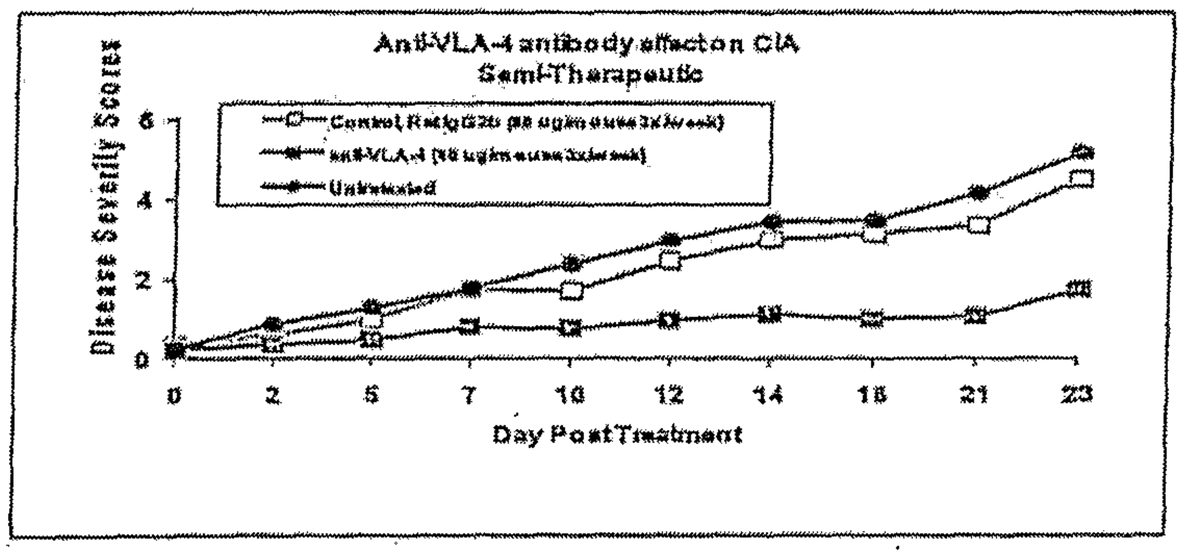
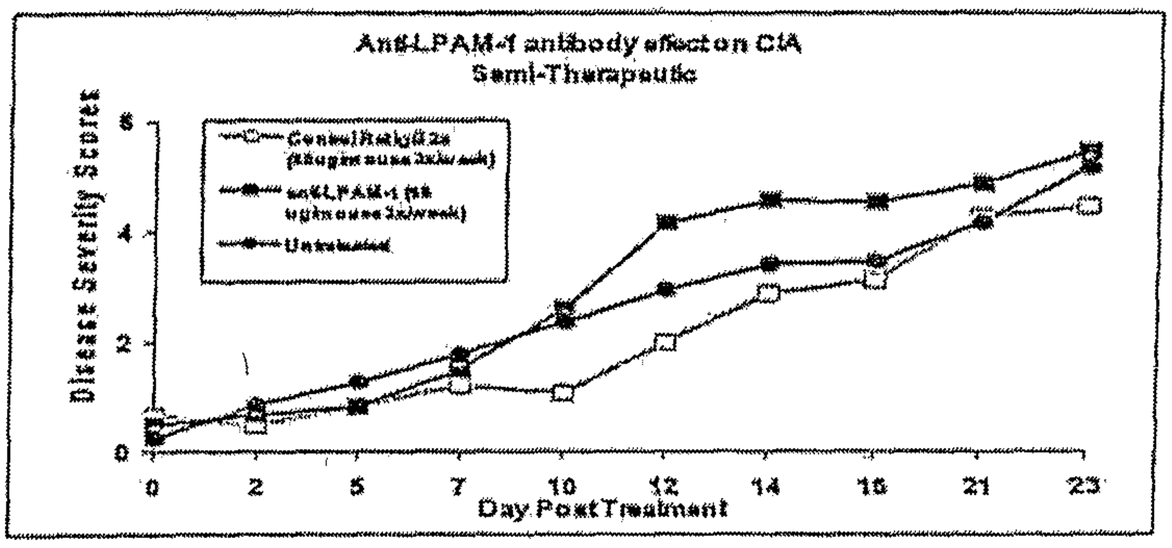

Therapeutic CIA #27
Disease Severity Scores
0
1
2
3
4
5
6
0
2
4
6
8
10
12
14
16
18
20
22
Day Post Treatment

FIGURE 2


Anti-VLA-4 antibody effect on CIA
Semi-Therapeutic
Disease Severity Scores
Day Post Treatment
Control Rat IgG2a
Untreated
0
2
4
6
0
2
5
7
10
12
14
16
21
23


Anti-LPAM-1 antibody effect on CIA
Semi-Therapeutic
Disease Severity Scores
Day Post Treatment
Untreated
0
2
4
6
0
2
5
7
10
12
14
16
21
23

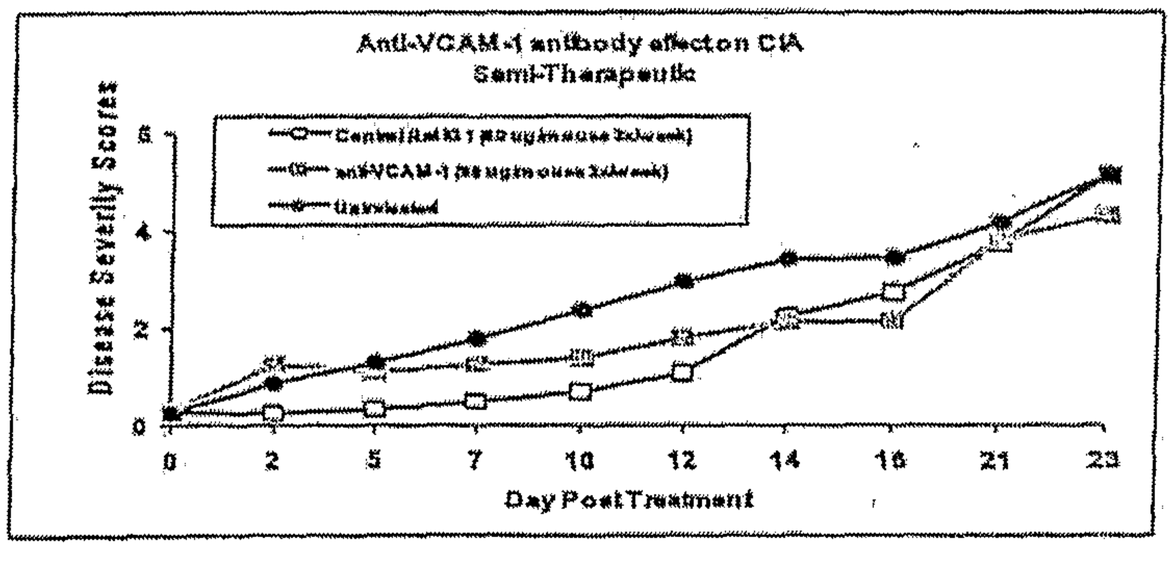

Anti-VCAM-1 antibody effect on CIA
Semi-Therapeutic
Disease Severity Scores
Day Post Treatment
Untreated
0
2
4
6
0
2
5
7
10
12
14
16
21
23

FIGURE 3

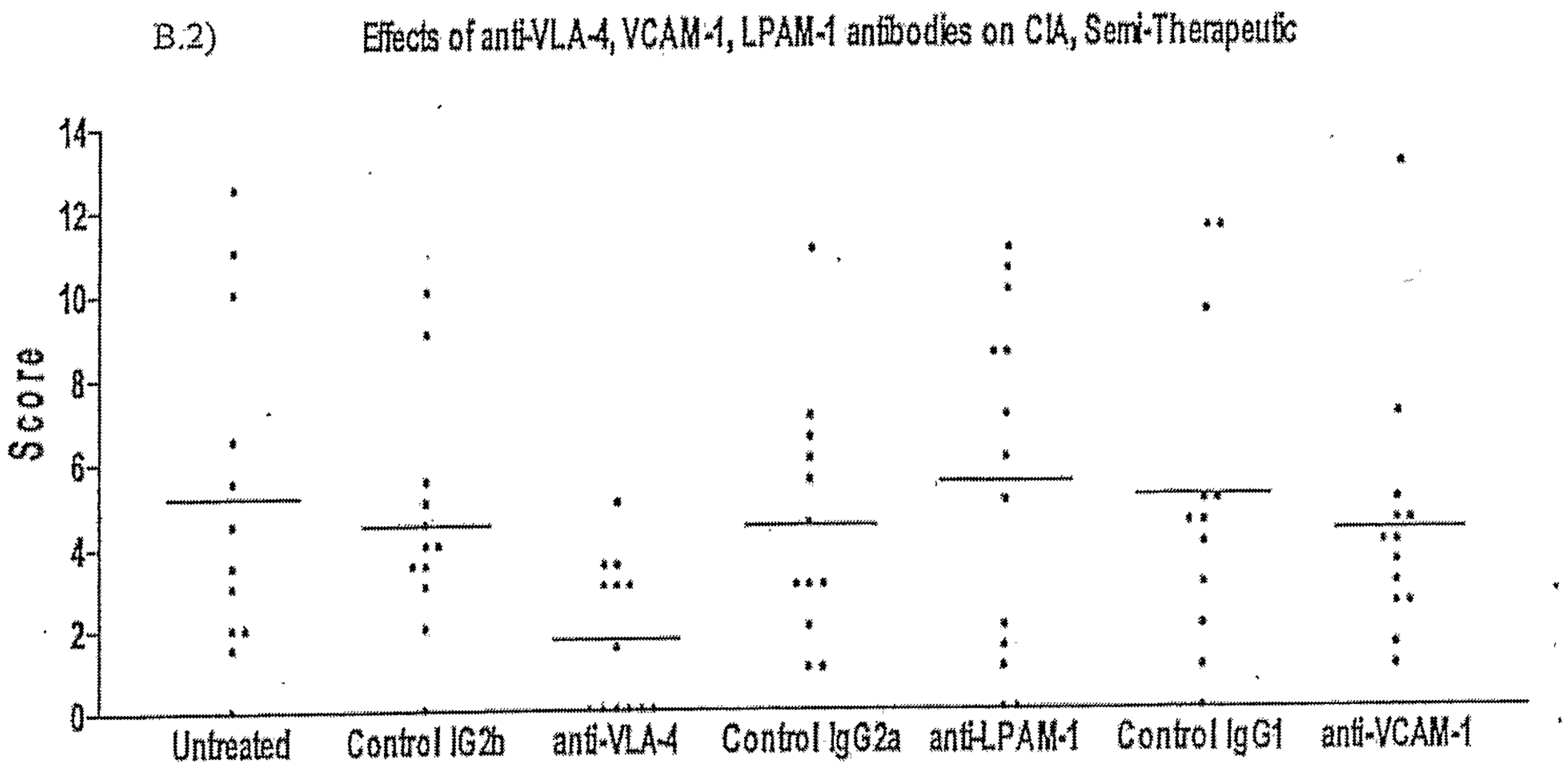

B.2) Effects of anti-VLA-4, VCAM-1, LPAM-1 antibodies on CIA, Semi-Therapeutic
Score
14
12
10
8
6
4
2
0
Untreated
Control IG2b
anti-VLA-4
Control IgG2a
anti-LPAM-1
Control IgG1
anti-VCAM-1

FIGURE 4

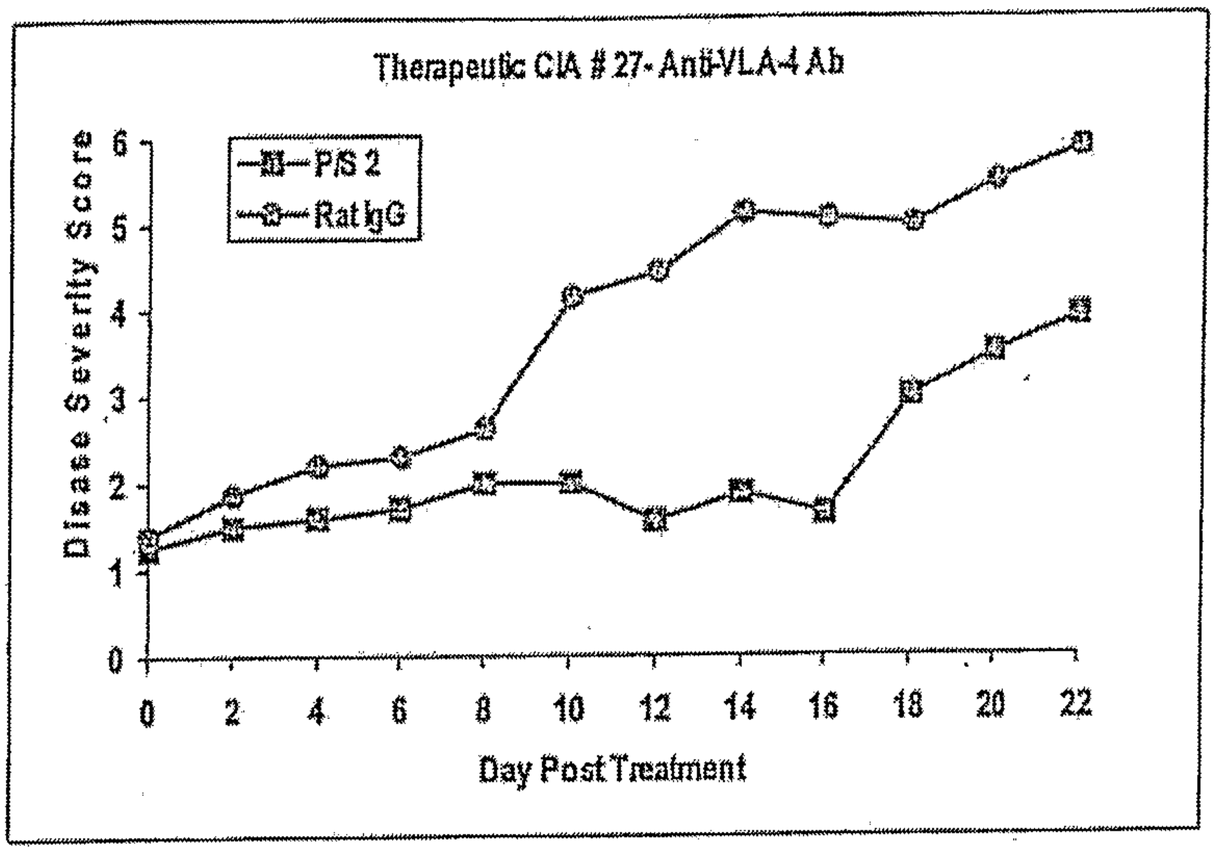

Therapeutic CIA # 27- Anti-VLA-4 Ab
Disease Severity Score
PIS 2
Rat IgG
Day Post Treatment
Therapeutic CIA #27- Courtesy of Formula T
Disease Severity Score
untreated
Courtesy of Formula T
vehicle
Day Post Treatment

FIGURE 5

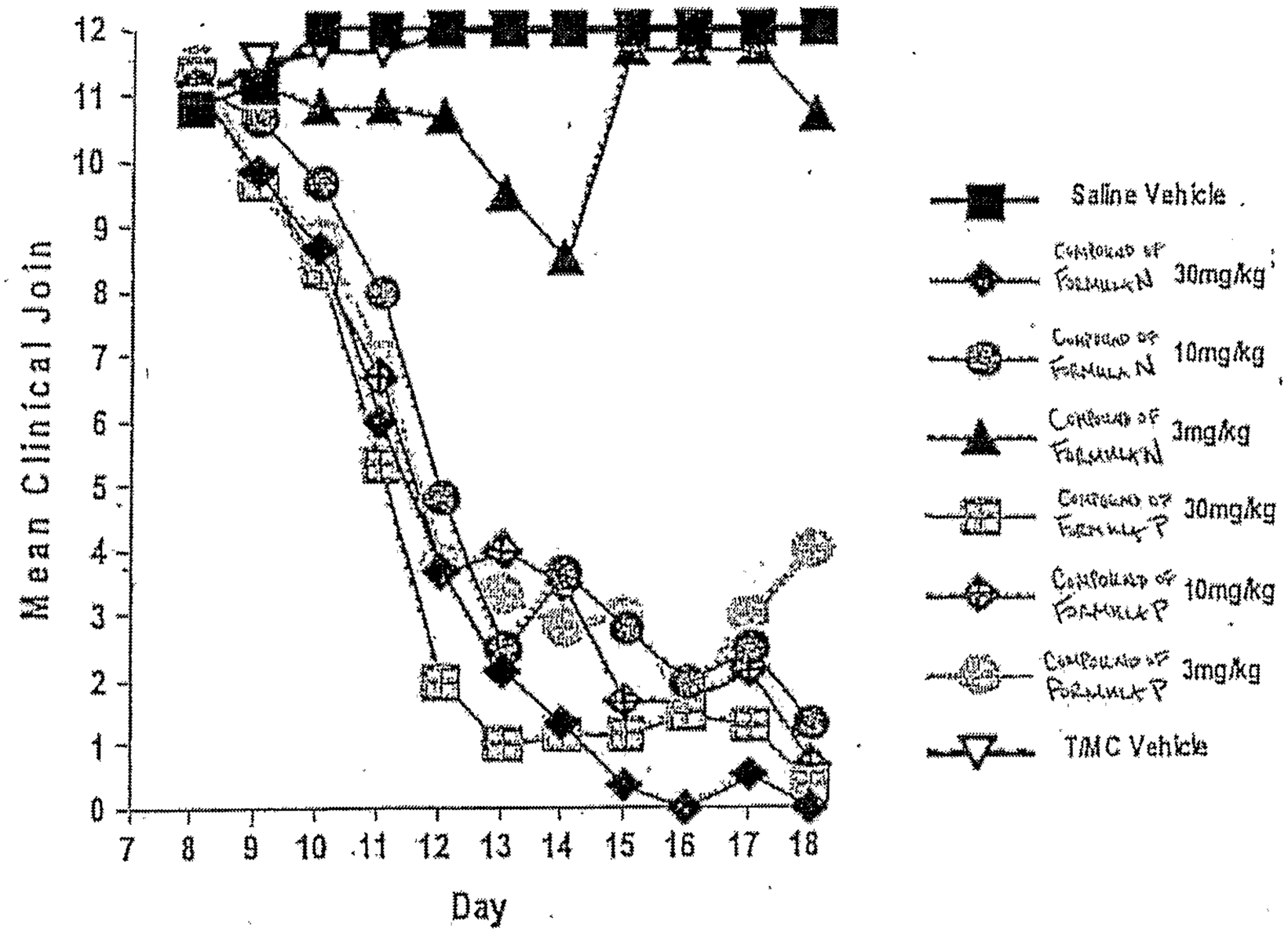

Mean Clinical Join
0
1
2
3
4
5
6
7
8
9
10
11
12
7 8 9 10 11 12 13 14 15 16 17 18
Day
Saline Vehicle
Compound of Formula N 30mg/kg
Compound of Formula N 10mg/kg
Compound of Formula N 3mg/kg
Compound of Formula P 30mg/kg
Compound of Formula P 10mg/kg
Compound of Formula P 3mg/kg
T/M/C Vehicle

FIGURE 6

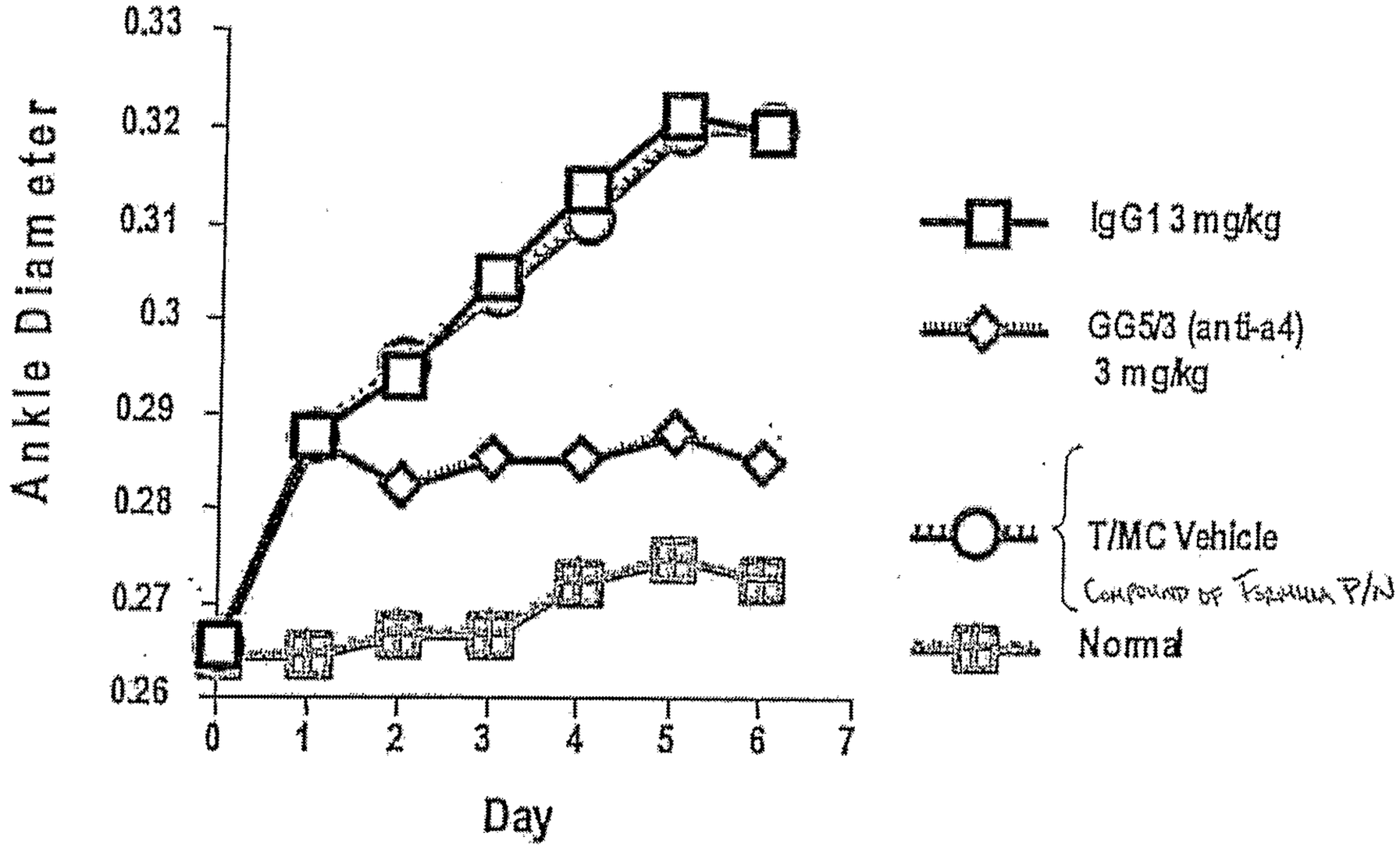

Ankle Diameter
0.33
0.32
0.31
0.3
0.29
0.28
0.27
0.26
0
1
2
3
4
5
6
7
Day
IgG1 3 mg/kg
GG5/3 (anti-a4)
3 mg/kg
T/MC Vehicle
Normal

FIGURE 7

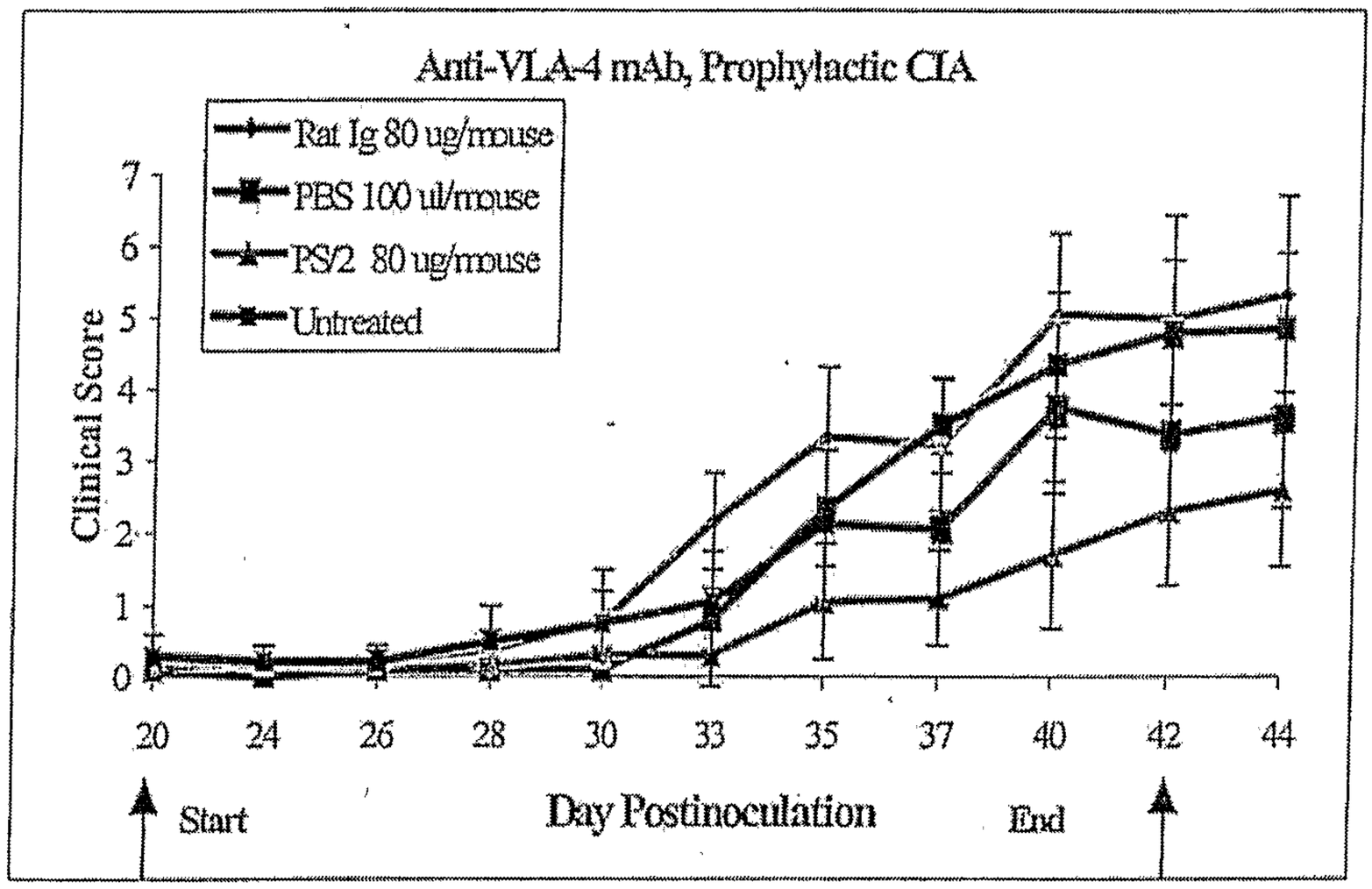

Anti-VLA-4 mAb, Prophylactic CIA
Rat Ig 80 ug/mouse
PBS 100 ul/mouse
PS/2 80 ug/mouse
Untreated
Clinical Score
0
1
2
3
4
5
6
7
20
24
26
28
30
33
35
37
40
42
44
Start
Day Postinoculation
End

FIGURE 8

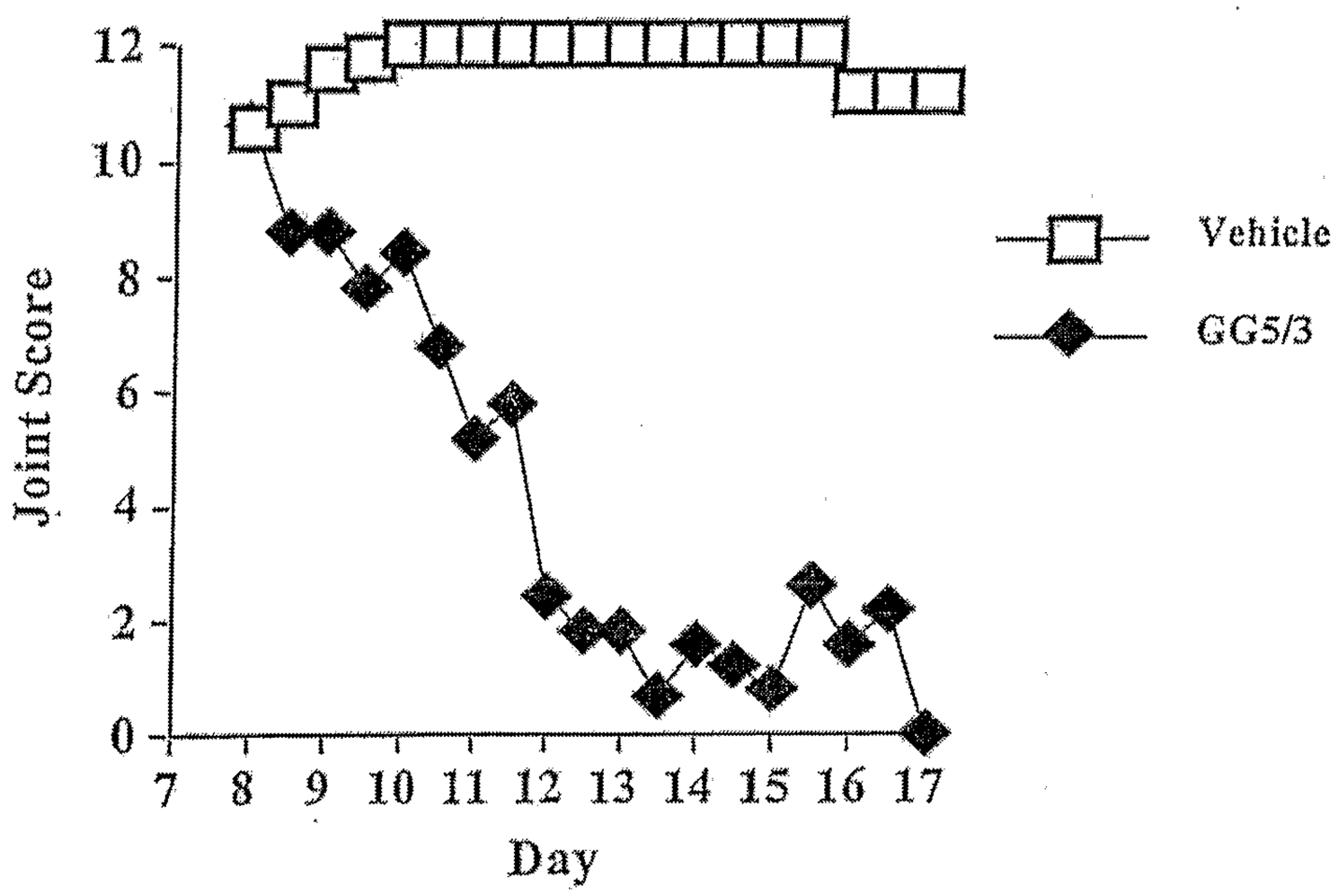

12
10
8
6
4
2
0
Joint Score
7 8 9 10 11 12 13 14 15 16 17
Day
Vehicle
GG5/3

FIGURE 9

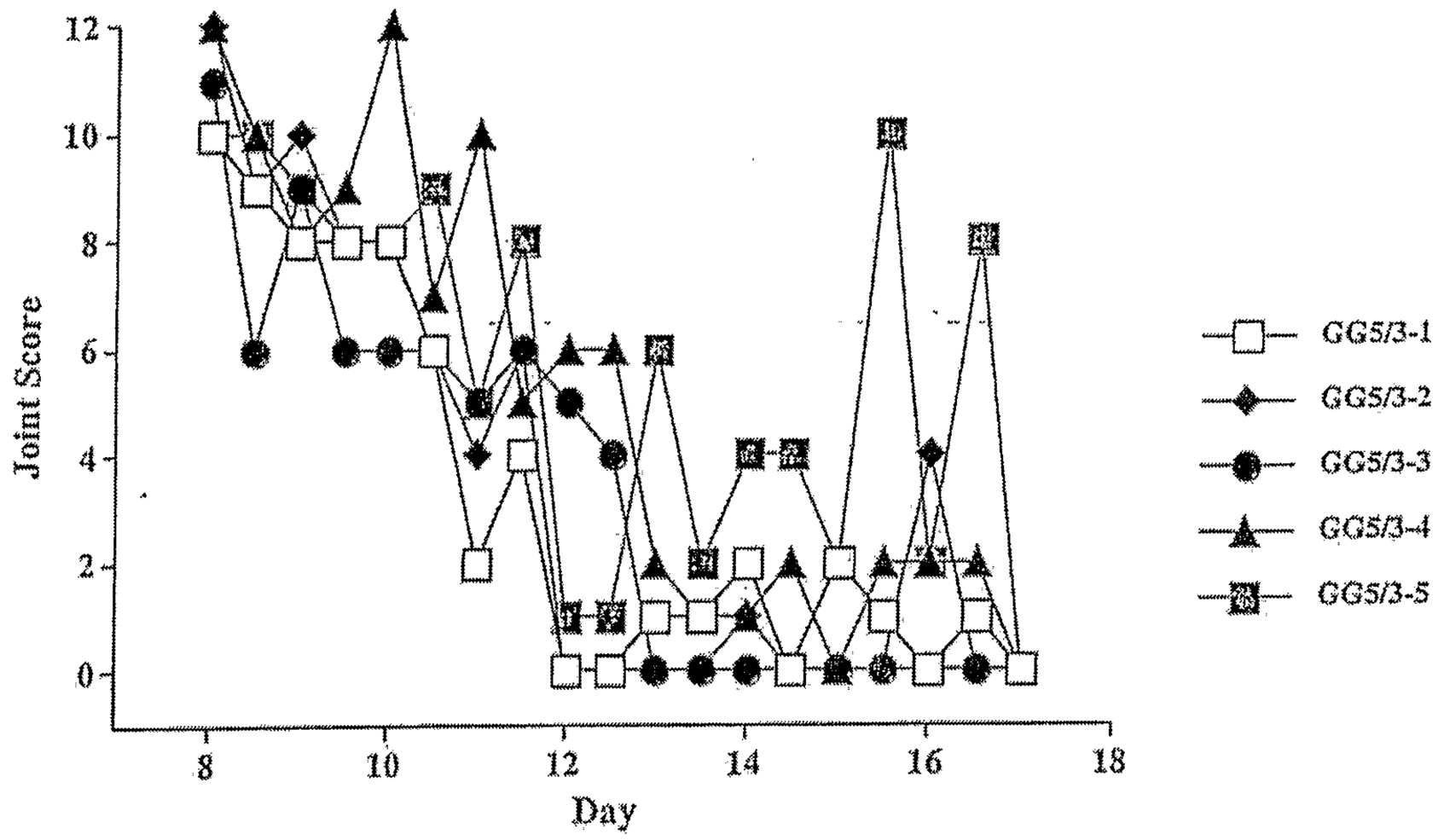


FIGURE 10

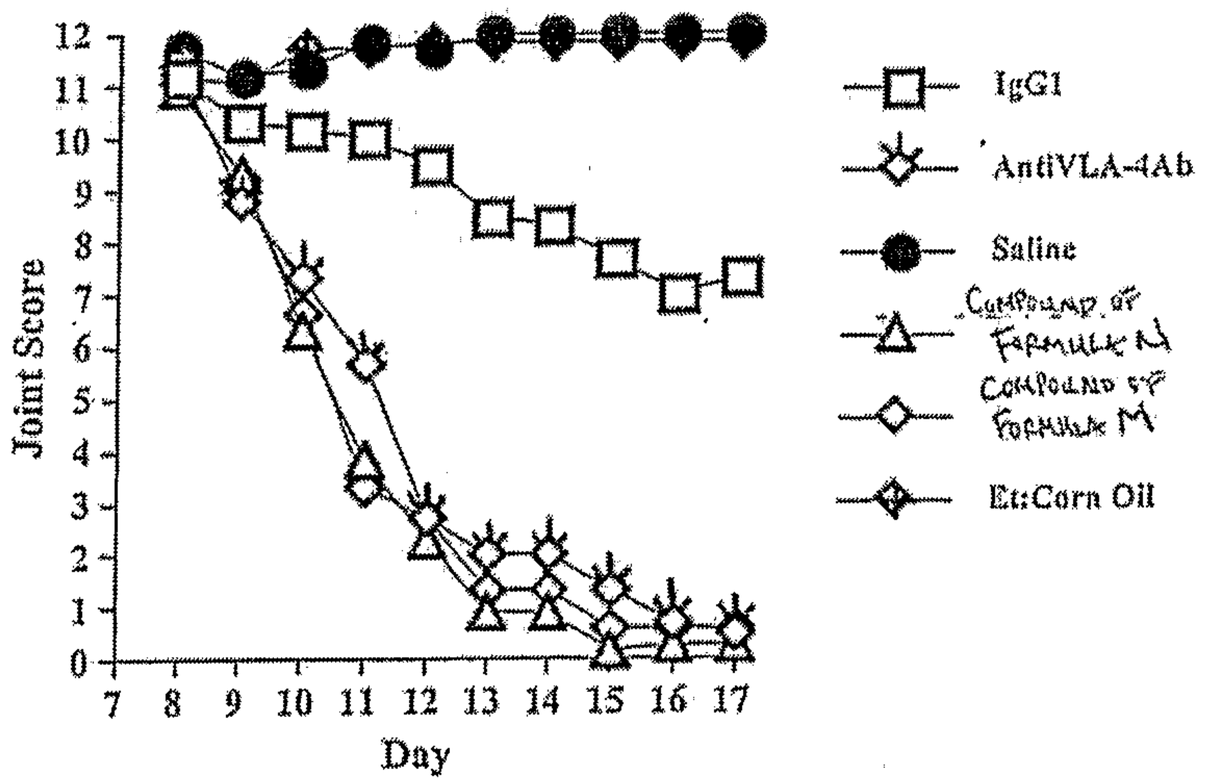
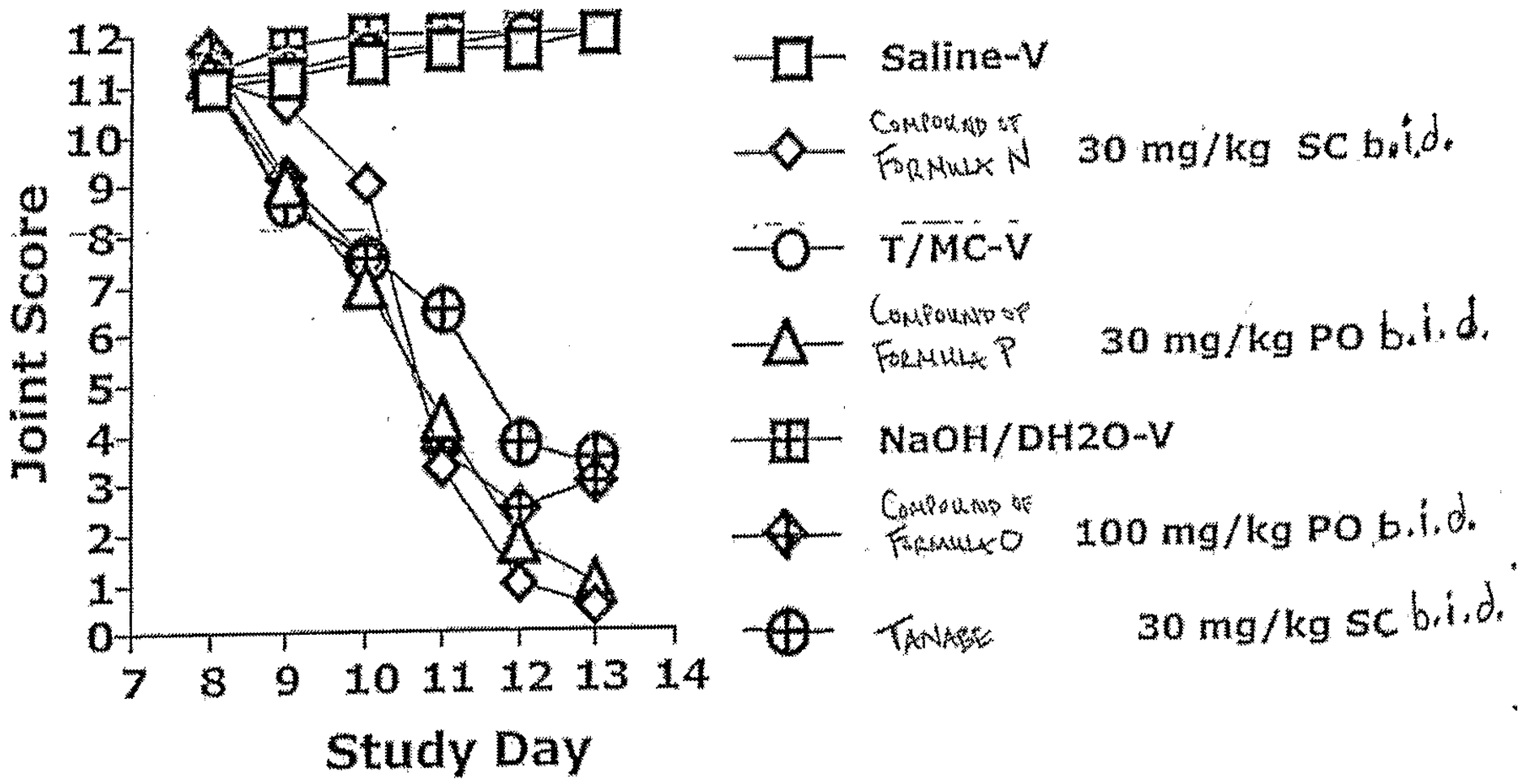

Joint Score
Day
0
1
2
3
4
5
6
7
8
9
10
11
12
7
8
9
10
11
12
13
14
15
16
17
IgG1
AntiVLA-4Ab
Saline
Compound of Formula N
Compound of Formula M
Et:Corn Oil

FIGURE 11


IA
Joint Score
0
1
2
3
4
5
6
7
8
9
10
11
12
7
8
9
10
11
12
13
14
Study Day
Saline-V
Compound of Formula N
30 mg/kg SC b.i.d.
T/MC-V
Compound of Formula P
30 mg/kg PO b.i.d.
NaOH/DH2O-V
Compound of Formula O
100 mg/kg PO b.i.d.
Tanabe
30 mg/kg SC b.i.d.