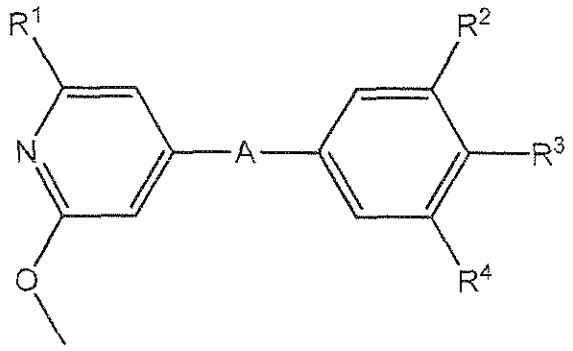
even years after transplantation. Combinations of up to three or four medications are commonly used to give maximum protection against rejection while minimizing side effects. Current standard drugs used to treat the rejection of transplanted organs interfere with discrete intracellular pathways in the activation of T-type or B-type white blood cells. Examples of such drugs are cyclosporin, daclizumab, basiliximab, everolimus, or FK506, which interfere with cytokine release or signaling; azathioprine or leflunomide, which inhibit nucleotide synthesis; or 15-deoxyspergualin, an inhibitor of leukocyte differentiation.

The beneficial effects of broad immunosuppressive therapies relate to their effects; however, the generalized immunosuppression which these drugs produce diminishes the immune system's defense against infection and malignancies. Furthermore, standard immunosuppressive drugs are often used at high dosages and can cause or accelerate organ damage.

Summary

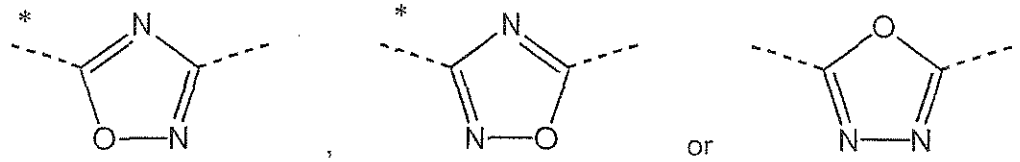
In one aspect of the invention, there is provided a compound of the Formula (I),



Formula (I)

wherein

A represents



wherein the asterisks indicate the bond that is linked to the pyridine group of Formula (I);

R^1 represents cyclopentyl;

R^2 represents methyl, and R^4 represents ethyl or chloro; or

R^2 represents methoxy, and R^4 represents chloro;

R^3 represents $-OCH_2COOH$, $-OCH_2CH_2CH_2COOH$, $-OCH_2CONHCH_2CH_2OH$, $-OCH_2CH_2CH_2CONHCH_2CH_2OH$, $-OCH_2-(CH_2)_n-NH-(CH_2)_m-COOH$, $-OCH_2-(CH_2)_n-N(CH_3)-(CH_2)_m-COOH$, 2-[(azetidine-3-carboxylic acid)-1-yl]-ethoxy, 2-[(pyrrolidin-3-carboxylic acid)-1-yl]-ethoxy, 3-[(azetidine-3-carboxylic acid)-1-yl]-propoxy, 3-[(pyrrolidin-3-carboxylic acid)-1-yl]-propoxy, $-OCH_2CH(OH)-CH_2NH-CH_2COOH$, $-OCH_2CH(OH)-CH_2NH-CH_2CH_2COOH$, $-OCH_2CH(OH)-CH_2N(CH_3)-CH_2COOH$, $-OCH_2CH(OH)-CH_2N(CH_3)-CH_2CH_2COOH$, 3-[(azetidine-3-carboxylic acid)-1-yl]-2-hydroxy-propoxy, 2-hydroxy-3-[(pyrrolidin-3-carboxylic acid)-1-yl]-propoxy, $-OCH_2-(CH_2)_n-NH-CH_2CH_2OH$, $-OCH_2-(CH_2)_n-NH-CH(CH_2OH)_2$, $-OCH_2-(CH_2)_n-NH-CH_2CH(OH)-CH_2OH$, $-OCH_2CH(OH)-CH_2NH-CH_2CH_2OH$, $-OCH_2CH(OH)-CH_2NH-CH(CH_2OH)_2$, $-OCH_2-(CH_2)_k-NH-CO-CH_2OH$, $-OCH_2-$

$(CH_2)_n$-NH-CO-CH_2COOH, -OCH_2-$(CH_2)_n$-NH-CO-CH_2CH_2COOH, -OCH_2CH(OH)-CH_2NH-CO-$(CH_2)_n$COOH, -OCH_2-$(CH_2)_n$-N(CH_3)-CO-CH_2OH, -OCH_2-$(CH_2)_n$-N(CH_3)-CO-CH_2COOH, or -OCH_2-$(CH_2)_n$-N(CH_3)-CO-CH_2CH_2COOH;

n independently represents 1 or 2;
m independently represents 1, 2, or 3; and
k represents 1 or 2;

or a salt thereof.

In another aspect of the invention, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect of the invention, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use as a medicament.

In another aspect of the invention, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of diseases or disorders selected from the group consisting of rejection of transplanted organs such as kidney, liver, heart, lung, pancreas, cornea, and skin; graft-versus-host diseases brought about by stem cell transplantation; autoimmune syndromes including rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, psoriatic arthritis, thyroiditis such as Hashimoto's thyroiditis, uveo-retinitis; atopic diseases such as rhinitis, conjunctivitis, dermatitis; asthma; type I diabetes; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; solid cancers and tumor metastasis.

In another aspect of the invention, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the prevention or treatment of diseases or disorders associated with an activated immune system.

Description of the invention

The present invention provides novel compounds of Formula (I) that are agonists for the G protein-coupled receptor S1P1/EDG1 and have a powerful and long-lasting immunomodulating effect which is achieved by reducing the number of circulating and infiltrating T- and B-lymphocytes, without affecting their maturation, memory, or expansion. The reduction of circulating T- / B-lymphocytes as a result of S1P1/EDG1 agonism, possibly in combination with the observed improvement of endothelial cell layer function associated with S1P1/EDG1 activation, makes such compounds useful to treat uncontrolled inflammatory diseases and to improve vascular functionality. Prior art document WO 2008/029371 (document **D1**) discloses compounds that act as S1P1/EDG1 receptor agonists and show an immunomodulating effect as described above. Unexpectedly, it has been found that the compounds of the present invention have a reduced potential to constrict airway tissue/vessels when compared to the corresponding analogs generically claimed in the prior art document **D1**. The compounds of the present invention therefore demonstrate superiority with respect to their safety profile, e.g. a lower risk of bronchoconstriction.

Compounds generically claimed in **D1** (Compounds **1-4**, **7**, and **10**) and Compounds **5**, **6**, **8**, **9**, and **11**, which can be considered close analogs of Examples 1-4, 7, 45, 5, 6, 35, 41, and 50, respectively, are shown in Figure 1.