

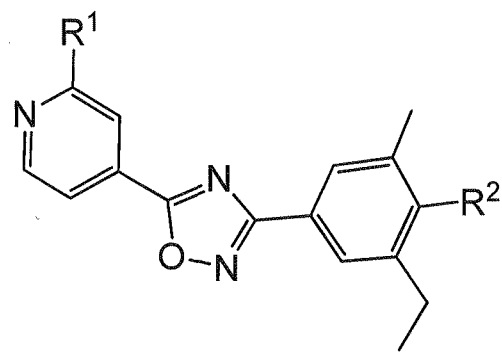
even years after transplantation. Combinations of up to three or four medications are commonly used to give maximum protection against rejection while minimizing side effects. Current standard drugs used to treat the rejection of transplanted organs interfere with discrete intracellular pathways in the activation of T-type or B-type white blood cells.

- 5 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

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



Formula (I)

20 wherein

R<sup>1</sup> represents C<sub>2-6</sub>-alkyl or cyclopentyl; and

R<sup>2</sup> represents -OCH<sub>2</sub>-CH(OH)-CH<sub>2</sub>-NHCO-CH<sub>2</sub>OH;

25 or a salt thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5 In yet another aspect, there is provided the use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of diseases or disorders associated with an activated immune system.

10 In another aspect, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, for use as a medicament.

15 In another aspect, there is provided the use of a compound described 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  
20 such as Crohn's disease and ulcerative colitis, psoriasis, psoriatic arthritis, thyroiditis such as Hashimoto's thyroiditis, and uveo-retinitis; atopic diseases such as rhinitis, conjunctivitis, and atopic dermatitis; asthma; type I diabetes; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; and solid cancers and tumor metastasis.

25 In yet another aspect, there is provided the use of a compound described 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 selected from kidney, liver, heart and lung; graft-versus-  
30 host diseases brought about by stem cell transplantation; autoimmune syndromes selected from rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, Crohn's disease, and Hashimoto's thyroiditis; and atopic dermatitis.

### **Detailed Description of the Invention**

The present invention provides novel compounds of Formula (I) that are agonists for the G protein-coupled receptor S1P<sub>1</sub>/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.

- 5 The reduction of circulating T- / B-lymphocytes as a result of S1P<sub>1</sub>/EDG1 receptor agonism, possibly in combination with the observed improvement of endothelial cell layer function associated with S1P<sub>1</sub>/EDG1 receptor 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 S1P<sub>1</sub>/EDG1
- 10 receptor agonists and show an immunomodulating effect as described above. On the other hand, several reports suggest that activation of the S1P<sub>3</sub> receptor is associated with vaso- and bronchoconstriction (e.g. Salomone et al. *Brit. J. Pharmacol.* **153** (2008) 140-147; Murakami et al. *Mol. Pharmacol.* **77** (2010) 704-713; Lucke et al. *Cellular Physiology and Biochemistry* **26** (2010) 87-96), blood pressure increase (e.g. Fryer et al. *PLOS One* **7**
- 15 (2012) e52985), heart rate reduction (e.g. Hamada et al. *J. Med. Chem.* **53** (2010) 3154-3168) and pulmonary epithelial leakage (e.g. Gon et al. *PNAS* **102** (2005) 9270-9275). Selectivity against the S1P<sub>3</sub> receptor is therefore deemed an advantage of a given S1P<sub>1</sub> receptor agonist (e.g. Hale et al. *Bioorg. Med. Chem. Lett.* **14** (2004) 3501-3505).
- 20 Unexpectedly, it has been found that the compounds of the present invention have a reduced activity on the S1P<sub>3</sub> receptor when compared to closest analogs disclosed in

- (S)-N-(3-(2-ethyl-4-(5-(2-isopropylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide;
- (S)-N-(3-(2-ethyl-4-(5-(2-butylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide;
- 5 (S)-N-(3-(2-ethyl-4-(5-(2-isobutylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide;
- (S)-N-(3-(2-ethyl-4-(5-(2-isopentylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide;
- (S)-N-(3-(2-ethyl-4-(5-(2-(pentan-3-yl)-pyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide; and
- 10 (S)-N-(3-(2-ethyl-4-(5-(2-cyclopentylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide;
- or a salt of such compounds.
- 15 7. A compound according to claim 1 which is (S)-N-(3-(2-ethyl-4-(5-(2-cyclopentylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide or a salt thereof.
- 20 8. A compound according to claim 1 which is (S)-N-(3-(2-ethyl-4-(5-(2-ethylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-6-methyl-phenoxy)-2-hydroxypropyl)-2-hydroxyacetamide or a salt thereof.
89. A pharmaceutical composition comprising a compound according to any one of claims 1 to 78, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
- 25 910. A compound according to any one of claims 1 to 78, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 89, for use as a medicament.
- 30 1011. A-Use of a compound according to any one of claims 1 to 78, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the prevention or treatment of diseases or disorders associated with an activated immune system.
- 35 1112. A-Use of a compound according to any one of claims 1 to 78, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in 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, and uveo-retinitis; atopic diseases such as rhinitis, conjunctivitis, and atopic dermatitis; asthma; type I diabetes; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; and solid cancers and tumor metastasis.

5

1213. A-Use of a compound according to any one of claims 1 to 78, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the prevention or treatment of diseases or disorders selected from the group consisting of rejection of transplanted organs selected from kidney, liver, heart and lung; graft-versus-host diseases brought about by stem cell transplantation; autoimmune syndromes selected from rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, Crohn's disease, and Hashimoto's thyroiditis; and atopic dermatitis.

10

15

~~13. Use of a compound according to any one of claims 1 to 7, 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.~~