

TRIAZOLOPYRIDINE COMPOUNDS AS PIM KINASE INHIBITORS

BACKGROUND OF THE INVENTION

[0001] The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to a process for making the compounds and to the use of the compounds in therapy. More particularly, it relates to certain triazolopyridine compounds useful in the treatment and prevention of diseases which can be treated with a PIM kinase inhibitor, including diseases mediated by PIM kinases. Particular compounds of this invention have been found to be inhibitors of PIM-1 and/or PIM-2 and/or PIM-3.

[0002] Protein kinases constitute a family of structurally related enzymes that are responsible for the control of a vast array of cellular processes.

[0003] The PIM kinase sub-family consists of three distinct serine/threonine protein kinase isoforms (PIM-1, -2 and -3) belonging to the calmodulin-dependent protein kinase-related (CAMK) group. PIM-2 and PIM-3 are respectively 58% and 69% identical to PIM-1 at the amino acid level.

[0004] The over-expression of PIM-1 has been reported in various human lymphomas and acute leukemias (Amson, R. et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86: 8857-8861). PIM-1 has been shown to synergize with c-Myc to drive lymphomagenesis (Breuer M., et al., *Nature*, 1989, 340: 61-63), and plays an important role in cytokine signaling in T-cell development (Schmidt, T., et al., *EMBO J*, 1998, 17:5349-5359). In addition, there is evidence that PIM-1 is over-expressed in prostatic neoplasia and human prostate cancer (Valdman, A. et al., *The Prostate*, 2004, 60: 367-371; Cibull, T.L. et al., *J. Clin. Pathol.*, 2006, 59: 285-288) and may serve as a useful biomarker in identification of prostate cancer (Dhanasekaran, S.M. et al., *Nature*, 2001, 412(13): 822-826). PIM-1 has been shown to be critical for IL-6 mediated proliferation of hematopoietic cells (Hirano, T., et al., *Oncogene* 2000, 19:2548-2556), as well as STAT3 mediated cell cycle progression (Shirogane, T., et al., *Immunity* 1999, 11:709).

[0005] Recently, it has been discovered that PIM-1 is up-regulated by Flt-3 and may play an important role in Flt-3 mediated cell survival (Kim, K.T. et al *Neoplasia*, 2005, 105(4): 1759-1767). Since Flt-3 itself is implicated in leukemias like AML, additional knockdown of PIM-1 may be a useful approach to treating leukemias driven by Flt-3 or various mutations. Accordingly, PIM-1 inhibitors may be useful as therapeutic agents for a variety of cancers such as hematological cancers.

[0006] PIM-2 is a highly conserved serine/threonine kinase involved in cell proliferation and the prevention of apoptosis (Baytel et al., *Biochim. Biophys. Acta Gene*

Struct. Expr. 1442: 274 (1998)). PIM-2 is upregulated in AML, CLL, and possibly in prostate cancer.

[0007] PIM-3 is a proto-oncogene identified in pancreatic liver and colon cancers, and is an apoptotic regulator (Popivanova, B., et al., Cancer Sci., 98(3): 321 (2007)).

[0008] Based upon the direct involvement of the PIM kinases in a wide variety of cancers downstream of STAT3/5 activation, it is expected that inhibition of the PIM kinases will result in inhibition of proliferation and survival of multiple cancer cell types. This would then be expected to provide a therapeutic benefit to cancer patients with a variety of cancers (both solid tumor and hematologic settings), as well as other conditions that are mediated by PIM kinase signaling.

[0009] In addition to the malignant cells detailed above, PIM kinases are also expressed in hematopoietically-derived cell lines and hematopoietically-derived primary cells including cells of the immune system such as B cells, T cells, monocytes, macrophages, eosinophils, basophils, and dendritic cells. Expression of PIM kinases can be induced, for example, by cytokines which utilize Jak/Stat signaling, such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-15, GM-CSF, IFN α , IFN γ , erythropoietin, thrombopoietin, and prolactin, and the generation, differentiation, maintenance and activation of hematopoietically-derived cells is dependent on these cytokines. Moreover, PIM proteins have been shown to be required for the efficient proliferation of peripheral T cells mediated by T-cell receptor and IL-2 signaling (Mlikkers, et al., Mol. Cell Biol., 2004, 6104). Although the exact mechanism of action of PIM kinases in an immunological setting has yet to be fully defined, they have been reported to phosphorylate a number of substrates involved in cellular proliferation, differentiation, and survival (Bullock et al., J. Biol. Chem., 2005 280:41675; Chen et al., PNAS 2002 99:2175; Dautry et al. J. Biol. Chem. 1998 263:17615).

[0010] Chronic and acute inflammatory and autoimmune diseases are associated with the overproduction of pro-inflammatory cytokines and activation of immune cells against the body's own tissues. However, many of these diseases are not adequately treated by current therapies and/or these therapies have significant side effects/risks.

[0011] A particular example of an autoimmune disease is multiple sclerosis (MS). MS is a progressive central nervous system (CNS) inflammatory autoimmune disease wherein the immune system mounts responses against CNS components. The resulting damage to axons and nerves leads to progressive neurological impairment and significant disability. MS affects over 2.5 million people worldwide (www.nationalmssociety.org);

however many current therapies are only moderately effective and have questionable risk factors

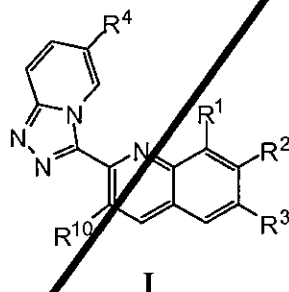
[0012] A need therefore remains for compounds and methods for treating autoimmune and inflammatory diseases.

[0013] International patent application, publication number WO 2004/058769 discloses, *inter alia*, certain 3-aryl and 3-N-aryl-amino-substituted [1,2,4]triazolo[4,3-b]pyridazines purported to inhibit several protein kinases, including PIM-1.

SUMMARY OF THE INVENTION

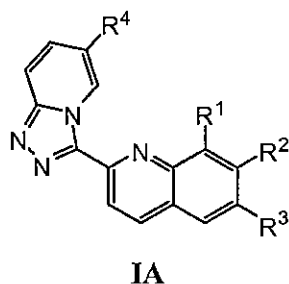
[0014] It has now been found that [1,2,4]triazolo[4,3-a]pyridine compounds bearing a quinolinyl group at the 3 position of the triazolopyridine ring are inhibitors of PIM kinases, in particular PIM-1 and/or PIM-2 and/or PIM-3 kinases, which are useful for treating diseases such as cancers and inflammatory diseases.

[0015] More specifically, one aspect of the present invention provides compounds of Formula I:



[0016] and stereoisomers, pharmaceutically acceptable salts and solvates thereof, wherein R¹, R², R³, R⁴ and R¹⁰ are as defined herein.

[0017] Another aspect of the present invention provides compounds of Formula I having the Formula IA:



[0018] and stereoisomers, pharmaceutically acceptable salts and solvates thereof, wherein R¹, R², R³, and R⁴ are as defined herein.

[0019] Another aspect of the present invention provides methods of preventing or treating a disease or disorder modulated by PIM-1 and/or PIM-2 and/or PIM-3, comprising administering to a mammal in need of such treatment an effective amount of a compound of

32. A compound according to any of claims 1 or 3-30, wherein R¹⁰ is fluoro.

33. A compound of claim 1, selected from any one of Examples 1-328.

34. A composition comprising a compound according to any of claims 1-33 or
5 a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

35. A compound of Formula I as defined in any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory or autoimmune disease.

36. A compound as defined in claim 35, wherein the inflammatory or
10 autoimmune disease is multiple sclerosis, lupus, inflammatory bowel disease or rheumatoid arthritis.

37. A compound of Formula I as defined in any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

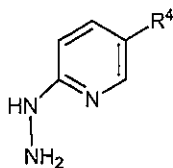
38. A method of treating a PIM-1 and/or PIM-2 and/or PIM-3 kinase-mediated
15 condition in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof.

39. A method of treating an inflammatory or autoimmune disorder in a mammal, which comprises administering to said mammal a therapeutically effective
20 amount of a compound of Formula I as defined in any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof.

40. The method as defined in claim 39 wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus, inflammatory bowel disease or rheumatoid arthritis.

25 41. A method of treating cancer in a patient in need thereof, comprising administering to said patient a compound as defined in any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof.

42. A process for the preparation a compound of claim 1, which comprises:
(a) reacting a corresponding compound of formula II or a protected
30 derivative thereof



II

TRIAZOLOPYRIDINE COMPOUNDS AS PIM KINASE INHIBITORS

BACKGROUND OF THE INVENTION

[0001] The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to a process for making the compounds and to the use of the compounds in therapy. More particularly, it relates to certain triazolopyridine compounds useful in the treatment and prevention of diseases which can be treated with a PIM kinase inhibitor, including diseases mediated by PIM kinases. Particular compounds of this invention have been found to be inhibitors of PIM-1 and/or PIM-2 and/or PIM-3.

[0002] Protein kinases constitute a family of structurally related enzymes that are responsible for the control of a vast array of cellular processes.

[0003] The PIM kinase sub-family consists of three distinct serine/threonine protein kinase isoforms (PIM-1, -2 and -3) belonging to the calmodulin-dependent protein kinase-related (CAMK) group. PIM-2 and PIM-3 are respectively 58% and 69% identical to PIM-1 at the amino acid level.

[0004] The over-expression of PIM-1 has been reported in various human lymphomas and acute leukemias (Amson, R. et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86: 8857-8861). PIM-1 has been shown to synergize with c-Myc to drive lymphomagenesis (Breuer M., et al., *Nature*, 1989, 340; 61-63), and plays an important role in cytokine signaling in T-cell development (Schmidt, T., et al., *EMBO J*, 1998, 17:5349-5359). In addition, there is evidence that PIM-1 is over-expressed in prostatic neoplasia and human prostate cancer (Valdman, A. et al., *The Prostate*, 2004, 60: 367-371; Cibull, T.L. et al., *J. Clin. Pathol.*, 2006, 59: 285-288) and may serve as a useful biomarker in identification of prostate cancer (Dhanasekaran, S.M. et al., *Nature*, 2001, 412(13): 822-826). PIM-1 has been shown to be critical for IL-6 mediated proliferation of hematopoietic cells (Hirano, T., et al., *Oncogene* 2000, 19:2548-2556), as well as STAT3 mediated cell cycle progression (Shirogane, T., et al., *Immunity* 1999, 11:709. WO 2010/022081 discloses PIM kinase inhibitors based on [1,2,4]-triazolo[4,3-a]pyridines substituted at the 7-position by quinolin-2-yl. The quinoline is substituted at the position piperidin-1-yl or piperazin-1-yl. WO 2010/022076 discloses PIM kinase inhibitors based on [1,2,4]-triazolo[4,3-a] pyridines substituted at the 7-position by quinolin-2-yl.

[0005] Recently, it has been discovered that PIM-1 is up-regulated by Flt-3 and may play an important role in Flt-3 mediated cell survival (Kim, K.T. et al *Neoplasia*, 2005, 105(4): 1759-1767). Since Flt-3 itself is implicated in leukemias like AML, additional knockdown of PIM-1 may be a useful approach to treating leukemias driven by Flt-3 or various mutations. Accordingly, PIM-1 inhibitors may be useful as therapeutic agents for a variety of cancers such as hematological cancers.

[0006] PIM-2 is a highly conserved serine/threonine kinase involved in cell proliferation and the prevention of apoptosis (Baytel et al., *Biochim. Biophys. Acta Gene Struct. Expr.* 1442: 274 (1998)). PIM-2 is upregulated in AML, CLL, and possibly in prostate cancer.

[0007] PIM-3 is a proto-oncogene identified in pancreatic liver and colon cancers, and is an apoptotic regulator (Popivanova, B., et al., Cancer Sci., 98(3): 321 (2007)).

[0008] Based upon the direct involvement of the PIM kinases in a wide variety of cancers downstream of STAT3/5 activation, it is expected that inhibition of the PIM kinases will result in inhibition of proliferation and survival of multiple cancer cell types. This would then be expected to provide a therapeutic benefit to cancer patients with a variety of cancers (both solid tumor and hematologic settings), as well as other conditions that are mediated by PIM kinase signaling.

[0009] In addition to the malignant cells detailed above, PIM kinases are also expressed in hematopoietically-derived cell lines and hematopoietically-derived primary cells including cells of the immune system such as B cells, T cells, monocytes, macrophages, eosinophils, basophils, and dendritic cells. Expression of PIM kinases can be induced, for example, by cytokines which utilize Jak/Stat signaling, such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, GM-CSF, IFN α , IFN γ , erythropoietin, thrombopoietin, and prolactin, and the generation, differentiation, maintenance and activation of hematopoietically-derived cells is dependent on these cytokines. Moreover, PIM proteins have been shown to be required for the efficient proliferation of peripheral T cells mediated by T-cell receptor and IL-2 signaling (Mikkers, et al., Mol. Cell Biol., 2004, 6104). Although the exact mechanism of action of PIM kinases in an immunological setting has yet to be fully defined, they have been reported to phosphorylate a number of substrates involved in cellular proliferation, differentiation, and survival (Bullock et al., J. Biol. Chem., 2005 280:41675; Chen et al., PNAS 2002 99:2175; Dautry et al. J. Biol. Chem. 1998 263:17615).

[0010] Chronic and acute inflammatory and autoimmune diseases are associated with the overproduction of pro-inflammatory cytokines and activation of immune cells against the body's own tissues. However, many of these diseases are not adequately treated by current therapies and/or these therapies have significant side effects/risks.

[0011] A particular example of an autoimmune disease is multiple sclerosis (MS). MS is a progressive central nervous system (CNS) inflammatory autoimmune disease wherein the immune system mounts responses against CNS components. The resulting damage to axons and nerves leads to progressive neurological impairment and significant disability. MS affects over 2.5 million people worldwide (www.nationalmssociety.org); however many current therapies are only moderately effective and have questionable risk factors.

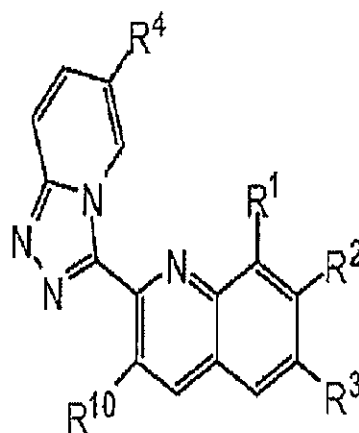
[0012] A need therefore remains for compounds and methods for treating autoimmune and inflammatory diseases.

[0013] International patent application, publication number WO 2004/058769 discloses, *inter alia*, certain 3-aryl and 3-N-arylamino-substituted [1,2,4] triazolo [4,3-b] pyridazines purported to inhibit several protein kinases, including PIM-1.

SUMMARY OF THE INVENTION

[0014] It has now been found that [1,2,4] triazolo[4,3-a] pyridine compounds bearing a quinolinyl group at the 3 position of the triazolopyridine ring are inhibitors of PIM kinases, in particular PIM-1 and/or PIM-2 and/or PIM-3 kinases, which are useful for treating diseases such as cancers and inflammatory diseases.

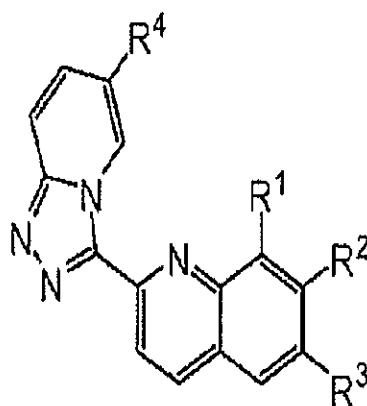
[0015] More specifically, one aspect of the present invention provides compounds of Formula I:



I

[0016] and stereoisomers, pharmaceutically acceptable salts and solvates thereof, wherein R¹, R², R³, R⁴ and R¹⁰ are as defined herein.

[0017] Another aspect of the present invention provides compounds of Formula I having the Formula IA:



IA

[0018] and stereoisomers, pharmaceutically acceptable salts and solvates thereof, wherein R¹, R², R³ and R⁴ are as defined herein.

[0019] Another aspect of the present invention provides methods of preventing or treating a disease or disorder modulated by PIM-1 and/or PIM-2 and/or PIM-3, comprising administering to a mammal in need of such treatment an effective amount of a compound of

32. A compound according to any of claims 1 or 3-30, wherein R¹⁰ is fluoro.
33. A compound of claim 1, selected from anyone of Examples 1-328.
34. A composition comprising a compound according to any of claims 1-33 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.
35. A compound of Formula I as defined in anyone of claims 1 to 33, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory or autoimmune disease.
36. A compound as defined in claim 35, wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus, inflammatory bowel disease or rheumatoid arthritis.
37. A compound of Formula I as defined in anyone of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.
38. A compound of Formula I as defined in anyone of claims 1 to 33, or a pharmaceutically acceptable salt thereof for use in the treatment of PIM-1 and/or PIM-2 and/or PIM-3 kinase-mediated condition.
39. A compound of Formula I as defined in anyone of claims 1 to 33, or a pharmaceutically acceptable salt thereof for use in the treatment of an inflammatory or autoimmune disorder.
40. The compound as defined in claim 39 wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus, inflammatory bowel disease or rheumatoid arthritis.
41. A compound as defined in anyone of claims 1 to 33, or a pharmaceutically acceptable salt thereof for use in the treatment of cancer.
42. A process for the preparation a compound of claim 1, which comprises:
(a) reacting a corresponding compound of formula II or a protected derivative thereof

