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**Declarations under Rule 4.17**:

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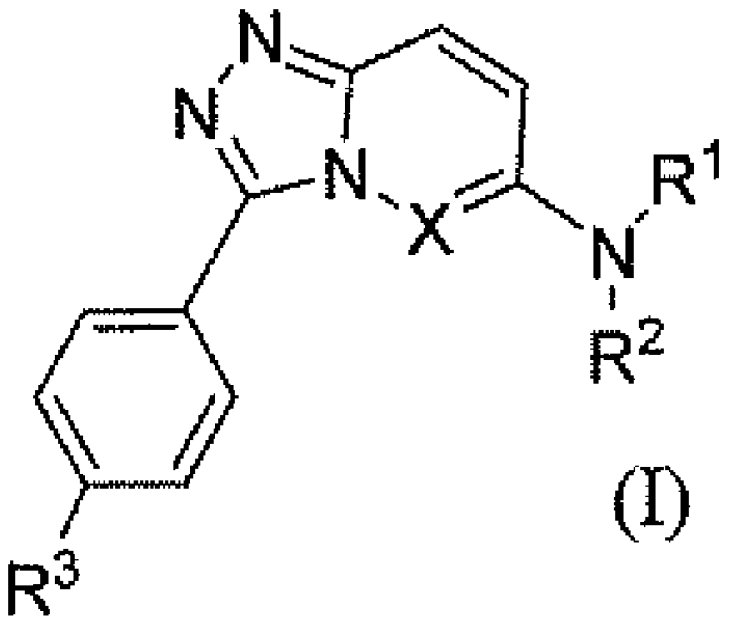
*[Continued on next page]*

(54) Title: TrkA KINASE INHIBITORS, COMPOSITIONS AND METHODS THEREOF




(I)

(57) Abstract: The present invention is directed to pyridotriazole and benztriazole compounds of formula (I) (I) which are tropomyosin-related kinase (Trk) family protein kinase inhibitors, and hence are useful in the treatment of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.

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TITLE OF THE INVENTION

TrkA KINASE INHIBITORS, COMPOSITIONS AND METHODS THEREOF

FIELD OF THE INVENTION

The invention is directed to a class of substituted pyridotriazole and benztriazole compounds, their salts, pharmaceutical compositions comprising them and their use in therapy of the human body. In particular, the invention is directed to a class of substituted pyridotriazole and benztriazole compounds, which are tropomyosin-related kinase (Trk) family protein kinase inhibitors, and hence are useful in the treatment of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.

BACKGROUND OF THE INVENTION

Trks are high affinity binding protein kinase receptors that are activated by Neurotrophins (NT), a group of soluble growth factors Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF) and Neurotrophin 3-5 (NT 3-5). The Trk's are made up of three family members TrkA, TrkB and TrkC that bind to and mediate the the signal transduction derived from the Neurotrophins. NGF activates TrkA, BDNF and NT-4/5 activate TrkB and NT3 activates TrkC.

Inhibitors of the Trk/neutrophin pathway have been demonstrated to be highly effective in numerous pre-clinical animal models of pain. Antagonistic NGF and TrkA antibodies have been shown to be efficacious in inflammatory and neuropathic pain animal models and in human clinical trials. See Woolf, C.J. et al. (1994) *Neuroscience* 62, 327-331; Zahn, P.K. et al. (2004) *J. Pain* 5, 157-163; McMahon, S. B. et al., (1995) *Nat. Med.* 1, 774-780; Ma, Q.P. and Woolf, C. J. (1997) *Neuroreport* 8, 807-810; Shelton, D. L. et al. (2005) *Pain* 116, 8-16; Delafoy, L. et al. (2003) *Pain* 105, 489-497; Lamb, K. et al. (2003) *Neurogastroenterol. Motil.* 15, 355-361; and Jaggar, S. I. et al. (199) *Br. J. Anaesth.* 83, 442-448. Through gene disruption studies in mice the Trka-NGF interaction was found to be required for the survival of certain peripheral neuron populations involved in mediating pain signaling in the case of pancreatic cancer - an increase in the expression of TrkA was shown to correlate with an increase level of pain signaling (Zhu et al., *Journal of Clinical oncology*, 17:2419-2428 (1999)). Increased expression of NGF and TrkA was also observed in human osteoarthritis chondrocytes (Iannone et al, *Rheumatology* 41:1413-1418 (2002)). In particular, anti-TrkA antibodies and anti-NGF antibodies have been demonstrated to be effective analgesics in in vivo models of inflammatory and neuropathic pain. See WO2006/131952, WO2005/061540, EP1181318 and WO01/78698, WO2004/058184 and

WO2005/019266, respectively. See also WO2004/096122 and WO2006/137106 which describe the use of an anti-TrkA antibody in combination with an opioid analgesic for the treatment or prevention of pain.

Trk inhibitors that can induce apotosis of proliferating osteoblast may be useful in treating diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis and bone metastases. The expression of TrKa and TrkC receptors in the bone forming area in mouse models of bone facture and localization of NGF in almost all bone forming cells have been observed (K. Asaumi, et al., Bone (2000) 26(6) 625-633). See also Exper Opin. Ther. Patents (2009) 19(3)), WO2006/115452 and WO2006/087538, WO6123113, WO10033941, WO10077680, WO2005110994, *Investigational New Drugs* (2004), 22, 449-458 and R. Tripathy, et al., Bioorganic & Medicinal Chem Ltrs., 2008, 18, 3551-3555. The association between overexpression, activation, amplification and/or mutation of Trks and several cancers as seen with studies conduct on neuroblastoma (Brodeur, G. M., Nat. Rev. Cancer 2003, 3, 203-216), ovarian cancer (Kruettgen et al., *Brain Pathology* 2006, 16: 304-310), prostate cancer (Dionne et al., Clin. Cancer Res. 1998, 4(8): 1887-1898), pancreatic cancer (Dang et al., *J of Gastroenterology and Hepatology* 2006, 21(5): 850-858), large cell neuroendocrine tumors (Marchetti et al., *Human Mutation* 2008, 29(5), 609-616, and colorectal cancer (Bardelli, A., *Science* 2003, 300, 949) support the reasoning that therapeutic implications of an effective Trk inhibitor may extend far beyond pain therapy. See also WO07013673, WO07025540 and WO08052734.

Also promising is the utility of Trk inhibitors in the treatment of inflammatory lung diseases such as asthma (Freund-Michel, V; et al., *Pharmacology & Therapeutics* (2008), 117(1), 52-76), interstitial cystitis (Hu Vivian Y; et . al., *J of Urology* (2005, 173(3), 1016-21), inflammatory bowel disease including ulcerative colitis and Chron's disease (Di Mola, F. F., et al., *Gut* (2000), 46(5), 670-678 and inflammatory skin diseases such as atopic dermatitis (Dou, Y.C., et. Al., *Archives of Dermatological Research* (2006), 298(1), 31-37, eczema and psoriasis (Raychaudhuri, S. P. et. al., *J of Investigative Dermatology* (2004), 122(3), 812-819).

Modulation of the neutrophin/Trk pathway also has been shown to have an effect in the etiology of neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's disease (Sohrabji, et. al., Neuroendocrinology (2006), 27(4), 404-414).

Thus, the compounds of the invention, which are Trk inhibitors, are believed to be useful in the treatment of multiple types of acute and chronic pain including but not limited to inflammatory pain, neuropathic pain, and pain associated with cancer, surgery and bone fracture. The compounds may also useful in the treatment of cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

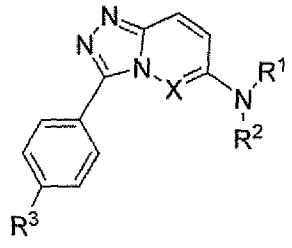
## SUMMARY OF THE INVENTION

The present invention is directed to compounds of generic formula (I) below or pharmaceutically acceptable salts thereof that are useful as a Trk kinase mediator of NGF driven biological responses, an inhibitor of TrkA and other Trk kinases.

The invention is further directed to methods of treating a patient (preferably a human) for diseases or disorders in which the NGF receptor Trk kinases are involved, in particular TrkA. The invention further involves use of the compounds as NGF receptor TrkA inhibitor and/or antagonist for the preparation of a medicament for the treatment and/or prevention of diseases associated with inhibiting TrKA, which includes pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder, or injury relating to dysmyelination or demyelination. The invention is also directed to pharmaceutical compositions which include an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and the use of the compounds and pharmaceutical compositions of the invention in the treatment of such diseases.

## DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention is directed to compounds of general formula (I)



(I)

and pharmaceutically acceptable salts thereof, wherein

X is –N or –CH;

R represents hydrogen or -$C_{1-6}$alkyl;

$R^1$, $R^2$, $R^{1'}$, and $R^{2'}$ are independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, –S-$C_{1-6}$ alkyl, –C(=O)-$(O)_n$-R, OR; $(CHR)_nC_{3-10}$ cycloalkyl, $(CHR)_nC_{6-10}$ aryl, $(CHR)_nC_{5-10}$ heterocycle, said alkyl, cycloalkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$;

or $R^1$ and $R^2$, or $R^{1'}$and $R^{2'}$ together with the nitrogen atom to which they are attached can combine to form a 3 to 6 membered cyclic group which is optionally substituted with $R^4$;

$R^3$ represents -$C_{1-6}$ alkyl, -$NR^1'R^2'$, –$NRCOR^1$, -$NRCO_2R^1$, -$NRSO_2R^1$, –$NRCONR^1R^2$, $(CHR)_nC_{5-10}$ heterocycle, said alkyl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$;

$R^4$ is $R^1$;

$R^a$ represents –CN, $NO_2$, -$C_{1-4}$haloalkyl, -$OC_{1-4}$haloalkyl, -$C_{1-6}$alkyl, -$C_{1-6}$alkenyl, -$C_{1-6}$alkynyl, -$(CHR)_nC_{6-10}$ aryl, -$(CHR)_nC_{5-10}$ heterocycle, -O-$C_{6-10}$ aryl, -O-$C_{5-10}$ heterocycle, -O-, -$C(O)CF_3$, -$(CH_2)_n$halo, –OR, –$NRR^1$,–$NRCOR^1$, -$NRCO_2R^1$, -$NRSO_2R^1$, –$NRCONR^1R^2$, -$COR^1$, -$CO_2R^1$, or –$CONR^1R^2$, said aryl and heterocycle optionally substituted with 1 to 3 groups of $R^b$;

$R^b$ represents, -$C_{1-6}$alkyl,halo, $SO_2R^3$, $NRSO_2R^3$, and

n represents 0-6.

In certain embodiments of this invention X is –N-.

In another embodimetn X is –CH.

In certain embodiments, $R^1$ is hydrogen, $C_{1-6}$ alkyl, $(CHR)_nC_{6-10}$ aryl, or $(CHR)_nC_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$; and all other variables are as originally described. In a subembodiment of this invention $R^1$ is hydrogen and all other variables are as originally described. In another subembodiment of this invention $R^1$ is $C_{1-6}$ alkyl, and all other variables are as originally described. Still in another subembodiment of this invention $R^1$ is $(CHR)_nC_{6-10}$ aryl, and all other variables are as originally described. Yet in another subembodiment of this invention $R^1$ is $(CHR)_nC_{5-10}$ heterocycle, and all other variables are as originally described.

In certain embodiments, $R^2$ is hydrogen, $C_{1-6}$ alkyl, $(CHR)_nC_{6-10}$ aryl, or $(CHR)_nC_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$; and all other variables are as originally described. In a subembodiment of this invention $R^2$ is hydrogen and all other variables are as originally described. In another subembodiment of this invention $R^2$ is $C_{1-6}$ alkyl, and all other variables are as originally described. Still in another subembodiment of this invention $R^2$ is $(CHR)_nC_{6-10}$ aryl, and all other variables are as originally described. Yet in another subembodiment of this invention $R^2$ is $(CHR)_nC_{5-10}$ heterocycle, and all other variables are as originally described.

In another embodiment $R^1$ and $R^2$ are not the same. In a subembodiment of this aspect of the invention one of $R^1$ and $R^2$ is hydrogen or methyl and the other is not.

Still in another embodiment, $R^1$ and $R^2$ combine with the nitrogen to which they are attached to form a 3 to 6 membered cyclic ring and all other variables are as originally described.

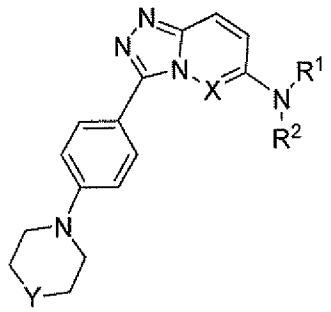
In a subembodiment of this invention $R^1$ and $R^2$ together with the nitrogen to which they are attached combine to form an pyrrolidinyl optionally substituted with 1 to 3 groups of $R^4$. Still in another subembodiment of this aspect of the invention the pyrrolidinly is substituted with phenyl, said phenyl being optionally substituted with 1 to 3 groups of $R^a$. In another subembodiment of this aspect of the invention $R^1$ and $R^2$ combine to form a pyrrolidinly substituted with an optionally substituted phenyl and X is -N. In yet another subembodiment of this aspect of the invention $R^1$ and $R^2$ combine to form a substituted pyrrolidinly substituted with an optionally substituted $(CH_2)_n$phenyl and X is –CH.

In yet another embodiment $R^3$ is $NR^{1'}R^{2'}$. A subembodiment of this aspect of the invention is realized when $R^{1'}$ and $R^{2'}$ are not the same. Another subembodiment of this aspect of the invention is realized when $R^{1'}$ and $R^{2'}$ combine with the nitrogen they are attached to form a 3 to 6 membered cyclic ring which is optionally substituted.

In another embodiment $R^3$ is $(CHR)_nC_{5-10}$ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of $R^a$, all other variables are as originally described. Another subembodiment of this aspect of the invention is realized when n is 0. Still another subembodiment of this aspect of the invention is realized when the heterocycle is morpholinyl or a piperazinyl optionally substutted with 1 to 3 gorups of $R^a$.

In another embodiment n is 0 to 4, preferably 0 to 3 and more preferably 0 to 2.

Still in another embodiment the compounds of formula I are represented by structural formula II:



II

and pharmaceutically acceptable salts thereof, wherein

Y is –NR, or –O-, and X, R $R^1$ and $R^2$ are as originally described.

An embodiment of formula II is realized when Y is –NR.

Another embodiment of formula II is realized when Y is –O-.

Another embodiment of formula II is realized when Y is –NR and X is –N or –CH.

Another embodiment of formula II is realized when Y is –O- and X is –N or –CH.

Still another embodiment of formula II is realized when Y is –NR, R is $CH_3$, and X is -N; or Y is –NR, R is $CH_3$ and X is –CH.

Yet another embodiment of formula II is realized when Y is –O-and X is -N; or Y is –O-, and X is –CH.

Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is $C_{1-6}$ alkyl, $(CHR)_nC_{6-10}$ aryl, $(CHR)_nC_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$.

Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is optionally substituted $C_{1-6}$ alkyl, $(CHR)_n$phenyl, or $(CHR)_n$pyridyl.

Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is optionally substituted $C_{1-6}$ alkyl, $(CHR)_n$phenyl, or $(CHR)_n$pyridyl, Y is –NR, or –O-, X is –N or –CH, and R is hydrogen or -$C_{1-6}$alkyl.

Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is optionally substituted $C_{1-6}$ alkyl, $(CHR)_n$phenyl, or $(CHR)_n$pyridyl, Y is –NR, X is –N or –CH, and R is hydrogen or -$C_{1-6}$alkyl.

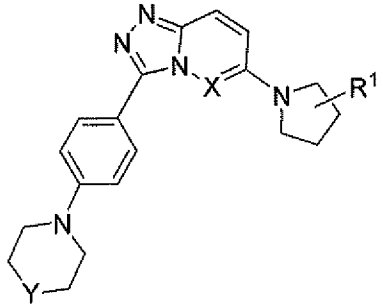
Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is optionally substituted $C_{1-6}$ alkyl, $(CHR)_n$phenyl, or $(CHR)_n$pyridyl, Y is–O-, and X is –N or –CH.

Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is optionally substituted $C_{1-6}$ alkyl, $(CHR)_n$phenyl, or $(CHR)_n$pyridyl, Y is –NR, or –O-, X is –N and R is hydrogen or -$C_{1-6}$alkyl.

Another embodiment of formula II is realized when one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is optionally substituted $C_{1-6}$ alkyl, $(CHR)_n$phenyl, or $(CHR)_n$pyridyl, Y is –NR, or –O-, X is–CH, and R is hydrogen or -$C_{1-6}$alkyl.

In another embodiment of formula II $R^1$ and $R^2$ combine with the nitrogen to which they are attached to form a 3 to 6 membered cyclic ring optionally substituted with 1 to 3 groups of $R^4$.

Another embodiment of formula II is represented by structural formula IIa



IIa

wherein Y, X and $R^1$ are as originally described.

Another embodiment of formula IIa is realized when Y is –NR.

Another embodiment of formula IIa is realized when Y is –O-.

Anothr embodiment of formula IIa is realized when $R^1$ is $(CHR)_nC_{6-10}$ aryl, or $(CHR)_nC_{5-10}$ heterocycle, said aryl and heterocycle optionally substituted with 1 to 3 groups of $R^a$.

Another embodiment of formula IIa is realized when Y is –NR, R is $CH_3$, X is –N or –CH and $R^1$ is $(CHR)_nC_{6-10}$ aryl, said aryl, optionally substituted with 1 to 3 groups of $R^a$.

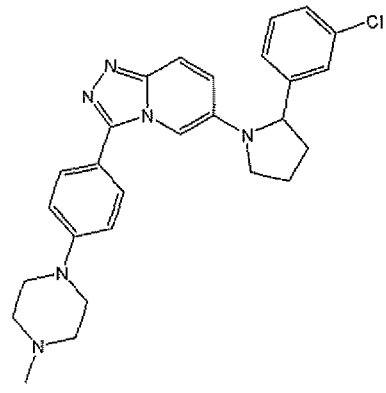
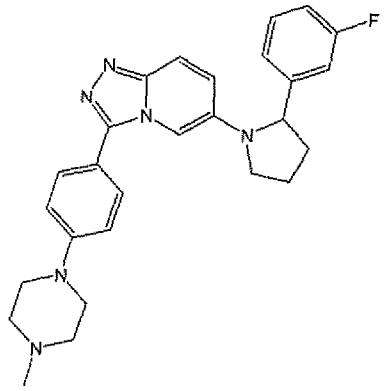
Another embodiment of formula IIa is realized when Y is –O- and X is –N or –CH and $R^1$ is $(CHR)_nC_{6-10}$ aryl, said aryl, optionally substituted with 1 to 3 groups of $R^a$.

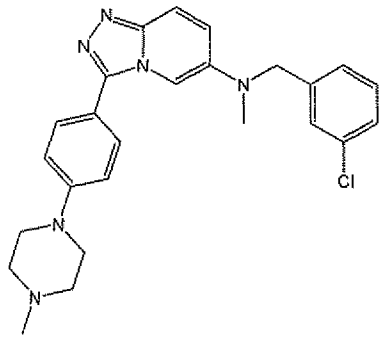
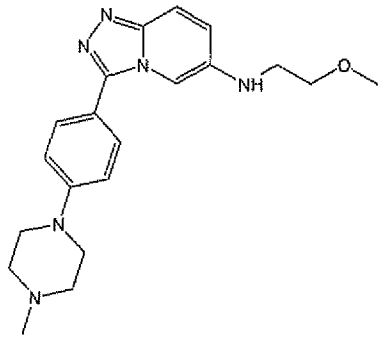
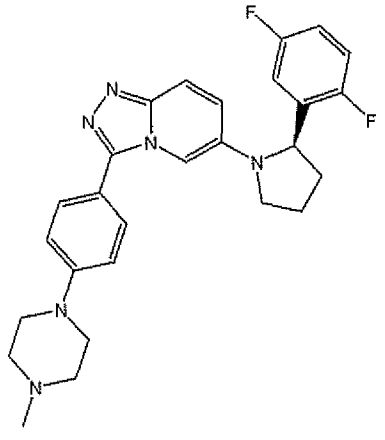
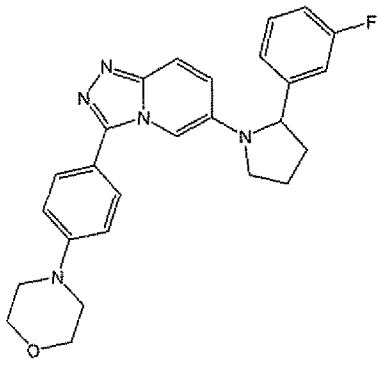
Still another embodiment of formula IIa is realized when Y is –NR, R is $CH_3$, the aryl of $R^1$ is an optionally substituted phenyl and X is -N; or Y is –NR, R is $CH_3$, the aryl of $R^1$ is an optionally substituted phenyl, and X is –CH.

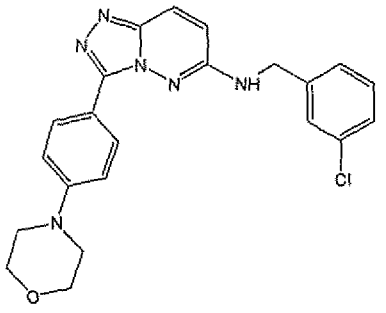
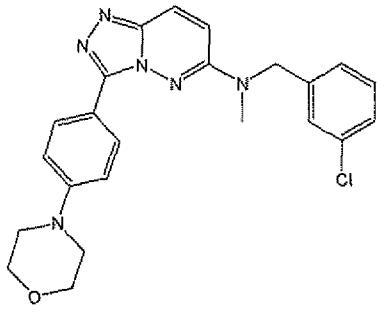
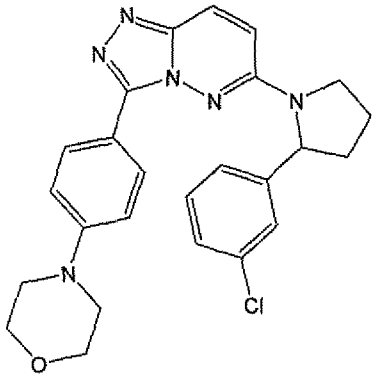
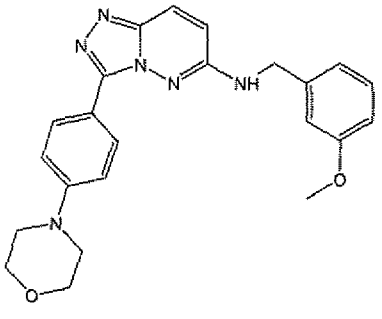
Yet another embodiment of formula IIa is realized when Y is –O-, X is –N and the aryl of $R^1$ is optionally substituted phenyl, or Y is –O-, X is –CH and the aryl of $R^1$ is optionally substituted phenyl.

Examples of compounds of this invention include those in Table 1:

Table 1

| Cpd. | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| 1 |  | 6-[2-(3-chlorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine | 473.2217 |
| 2 |  | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine | 457.2515 |

| | | | |
|---|---|---|---|
| 3 |  | N-(3-chlorobenzyl)-N-methyl-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridin-6-amine | 447.2065 |
| 4 |  | N-(2-methoxyethyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridin-6-amine | 367.2247 |
| 5 |  | 6-[(2R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine | 475.242 |
| 6 |  | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine | 444.2193 |

| | | | |
|---|---|---|---|
| 7 |  | N-(3-chlorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 421.1527 |
| 8 |  | N-(3-chlorobenzyl)-N-methyl-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 435.17 |
| 9 |  | 6-[2-(3-chlorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine | 461.1856 |
| 10 |  | N-(3-methoxybenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 417.2039 |

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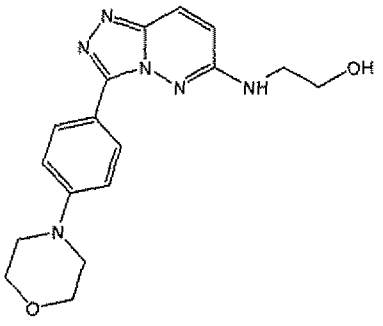
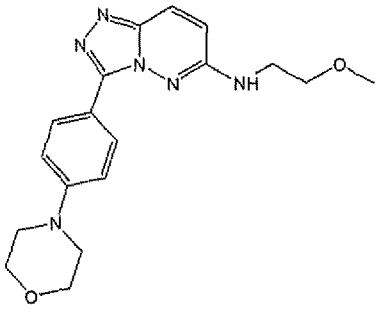
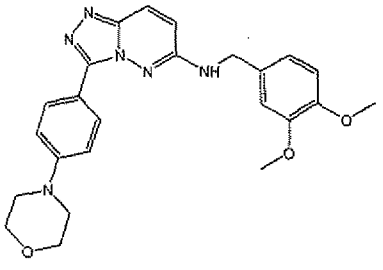
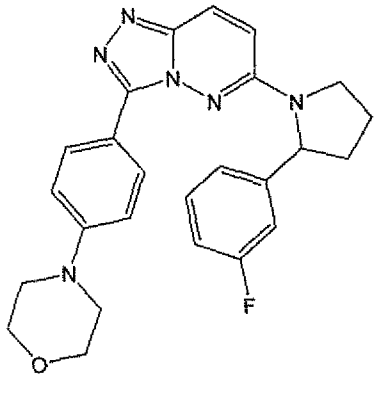
|---|---|---|---|
| 11 |  | 2-({3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)ethanol | 341.1724 |
| 12 |  | N-(2-methoxyethyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 355.1880 |
| 13 |  | N-(3,4-dimethoxybenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 447.2147 |
| 14 |  | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine | 445.2154 |

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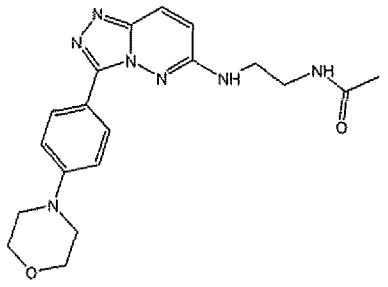
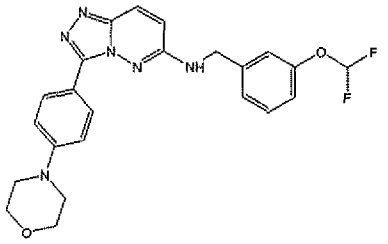
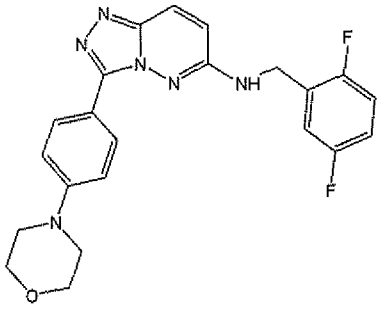
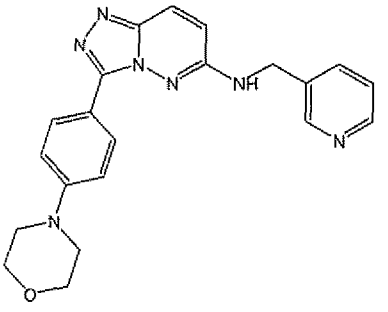
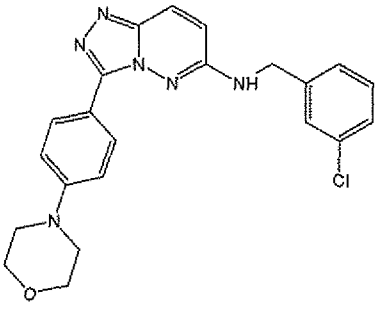
|---|---|---|---|
| 15 |  | N-[2-({3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)ethyl]acetamide | 382.1989 |
| 16 |  | N-[3-(difluoromethoxy)benzyl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 453.1847 |
| 17 |  | N-(2,5-difluorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 423.1743 |
| 18 |  | 3-[4-(morpholin-4-yl)phenyl]-N-(pyridin-3-ylmethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-amine | 388.1886 |
| 19 |  | N-(3-chlorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 421.1547 |

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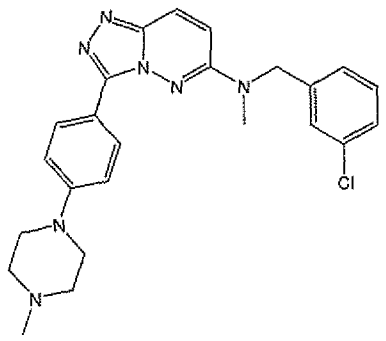
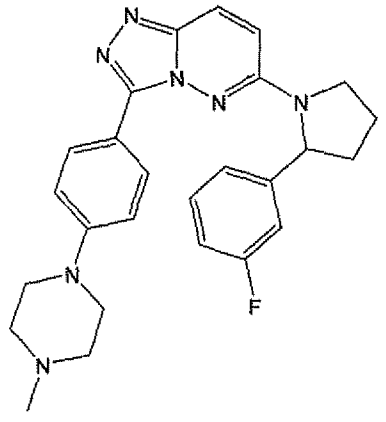
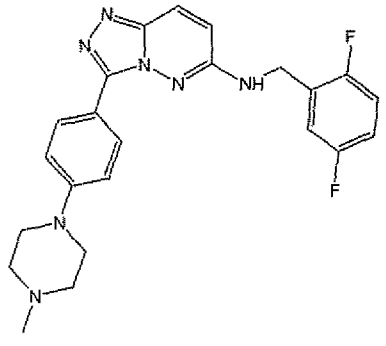
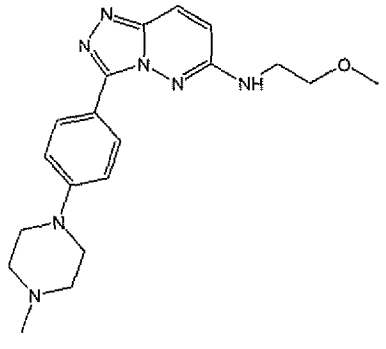
|---|---|---|---|
| 20 |  | N-(3-chlorobenzyl)-N-methyl-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 448.202 |
| 21 |  | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine | 458.2369 |
| 22 |  | N-(2,5-difluorobenzyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 436.2063 |
| 23 |  | N-(2-methoxyethyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine | 368.22 |

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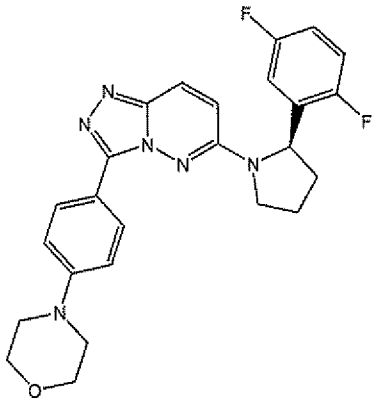
|---|---|---|---|
| 24 |  | 6-[(2R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine | 463.2056 |

and pharmaceutically acceptable salts thereof.

The invention is also directed to methods of treating a patient (preferably a human) for diseases or disorders in which the TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA, by administering to the patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention is also directed to the use of a compound of the invention for treating a disease or disorder in which the TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA, by administering to the patient a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention is also directed to medicaments or pharmaceutical compositions for the treatment of diseases or disorders in a patient (preferably a human) in which the TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA, which comprise a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to a method for the manufacture of a medicament or a pharmaceutical composition for treating diseases in which TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA comprising

combining a compound of the inventionor a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

Where a variable occurs more than once in any formula of the invention, or in a substituent thereof, the individual occurrences of that variable are independent of each other, unless otherwise specified. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, the term "alkyl," by itself or as part of another substituent, means a saturated straight or branched chain hydrocarbon radical having the number of carbon atoms designated (*e.g.*, $C_{1-10}$ alkyl means an alkyl group having from one to ten carbon atoms). Preferred alkyl groups for use in the invention are $C_{1-6}$ alkyl groups, having from one to six atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, and the like. $C_0$ alkyl means a bond.

As used herein, the term "alkenyl," by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical having a single carbon-carbon double bond and the number of carbon atoms designated (*e.g.*, $C_{2-10}$ alkenyl means an alkenyl group having from two to ten carbon atoms). Preferred alkenyl groups for use in the invention are $C_{2-6}$ alkenyl groups, having from two to six carbon atoms. Exemplary alkenyl groups include ethenyl and propenyl.

As used herein, the term "cycloalkyl," by itself or as part of another substituent, means a saturated cyclic hydrocarbon radical having the number of carbon atoms designated (*e.g.*, $C_{3-12}$ cycloalkyl means a cycloalkyl group having from three to twelve carbon atoms). The term cycloalkyl as used herein includes mono-, bi- and tricyclic saturated carbocycles, spirocycles, and bridged and fused ring carbocycles.

Preferred cycloalkyl groups for use in the invention are monocyclic $C_{3-8}$ cycloalkyl groups, having from three to eight carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Exemplary bridged cycloalkyl groups include adamantyl and norbornyl. Exemplary fused cycloalkyl groups include decahydronaphthalene.

As used herein, the term "aryl," by itself or as part of another substituent, means an aromatic cyclic hydrocarbon radical. Preferred aryl groups have from six to ten carbons atoms. The term "aryl" includes multiple ring systems as well as single ring systems. Preferred aryl groups for use in the invention include phenyl and naphthyl.

The term "aryl" also includes fused cyclic hydrocarbon rings which are partially aromatic (i.e., one of the fused rings is aromatic and the other is non-aromatic). An exemplary aryl group which is partially aromatic is indanyl.

The term heterocyclyl, heterocycle or heterocyclic, as used herein, represents

a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocyclyl, heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzodioxolyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzotriazolyly, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and triazolyl.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

When a heterocyclyl group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heteroaryl group, or on a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the substituent is bonded to a ring carbon atom. Similarly, when a heteroaryl group is defined as a substituent herein, the

point of attachment may be at a ring carbon atom of the heteroaryl group, or on a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits attachment. Preferably, the attachment is at a ring carbon atom.

As used herein, the term "halo" or "halogen" includes fluoro, chloro, bromo and iodo.

As used herein, unless otherwise specifically defined, substituted alkyl, substituted cycloalkyl, substituted aryl, substituted heteroaryl, and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, such substituents are selected from the group which includes but is not limited to F, Cl, Br, $CF_3$, $NH_2$, $N(C_1\text{-}C_6$ alkyl$)_2$, $NO_2$, CN, $(C_1\text{-}C_6$ alkyl$)O$-, (aryl)O-, -OH, $(C_1\text{-}C_6$ alkyl$)S(O)_m$-, $(C_1\text{-}C_6$ alkyl$)C(O)NH$-, $H_2N\text{-}C(NH)$-, $(C_1\text{-}C_6$ alkyl$)C(O)$-, $(C_1\text{-}C_6$ alkyl$)OC(O)$-, $(C_1\text{-}C_6$ alkyl$)OC(O)NH$-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and $C_1\text{-}C_{20}$ alkyl.

The compounds of the invention may have one or more asymmetric centers. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all such isomeric forms of the compounds of the invention. The present invention includes all stereoisomers of formulae (I) and pharmaceutically acceptable salts thereof.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers or diastereomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer or diastereomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

In the compounds of the invention the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic formulae (I). For example, different isotopic forms of hydrogen (H) include protium ($^{1}H$) and deuterium ($^{2}H$). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic formulae (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The term "substantially pure" means that the isolated material is at least 90% pure, and preferably 95% pure, and even more preferably 99% pure as assayed by analytical techniques known in the art.

As used herein, the term "TrkA" refers to one of Trk's high affinity binding protein kinase receptors that are activated by Neurotrophins (NT), a group of soluble growth factors Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF) and Neurotrophin 3-5 (NT 3-5). The Trk's are made up of three family members TrkA, TrkB and TrkC that bind to and mediate the the signal transduction derived from the Neurotrophins. Inhibitors of the Trk/neutrophin pathway have been demonstrated to be highly effective in numerous pre-clinical animal models of pain. The compounds of the invention are modulators of the Trk receptors, particularly TrkA.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. The compounds of the invention may be mono, di or tris salts, depending on the number of acid functionalities present in the free base form of the compound. Free bases and salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally

occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, trifluoroacetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *para*-toluenesulfonic acid, and the like.

The present invention is directed to the use of the compounds of formula (I) disclosed herein as TrkA inhibitors in a patient or subject such as a mammal in need of such activity, comprising the administration of an effective amount of the compound. In addition to humans, a variety of other mammals can be treated according to the method of the present invention.

The compounds of the present invention have utility in treating or ameliorating pain disorders (including pain associated with cancer, surgery, and bone fracture, acute pain, inflammatory pain and neuropathic pain). The compounds of formula I are also useful for treating cancers including neuroblastoma, ovarian, pancreatic and colorectal cancer. Other conditions that may be treated by the compounds of the invention include inflammation and certain infectious diseases, interstitial cystitis, painful bladder syndrome, urinary incontinence, asthma, anorexia, atopic dermatitis, and psoriasis. Treament of demyelination and dysmyelination, by promoting myelination, neuronal survival, and oligodendrocyte differentiation via blocking Sp35-TrkA interaction may also be possible with the compounds of the present invention.

The compounds of formula I may also be useful in the treatment of bone-related diseases (e.g., those involved in bone resorption). Examples of bone-related diseases include metastatic bone disease, treatment-induce bone loss, osteoporosis, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and periodontal disease. Another bone disorder or disease that can be treated with the compounds of the claimed invention is metastatic tumor-induced osteolysis. Cancers known to cause tumor induced osteolysis are hematological malignancies such as myeloma and lymphoma and solid tumors such as breast, prostate, lung, renal and thyroid.

Pain disorders for which the compounds of the invention may be useful include neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodynia, phantom limb pain, root avulsions, painful diabetic neuropathy, painful traumatic mononeuropathy, painful polyneuropathy); central pain syndromes (potentially caused by

virtually any lesion at any level of the nervous system); postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, stump pain); bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia); perioperative pain (general surgery, gynecological), chronic pain, dysmennorhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno- synovitis and gout), headache, migraine and cluster headache, headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization.

Compounds of the invention may also be used to treat or prevent dyskinesias. Furthermore, compounds of the invention may be used to decrease tolerance and/or dependence to opioid treatment of pain, and for treatment of withdrawal syndrome of e.g., alcohol, opioids, and cocaine.

The subject or patient to whom the compounds of the present invention is administered is generally mammals such a human being, male or female, in whom Trk-A and/or Trk-B modulation is desired. Thus, an aspect of the present invention is a method of treating diseases with an inhibitor of Trk-A and/or Trk-B comprising administering to said mammal one or more compounds of formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat or prevent said disorder. In a particular aspect of the invention is directed to a method of treating pain, cancer, inflammation, neurodegenerative disease or Typanosoma cruzi infection by administering to said mammal a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. Still another aspect of the present invention is directed to a method of treating osteolytic disease in a mammal by administering a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. For purposes of this invention mammals include dogs, cats, mice, rats, cattle, horses, sheep, rabbits, monkeys, chimpanzees or other apes or primates, for which treatment of the above noted disorders is desired.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the compounds of the present invention have utility, where the combination of the drugs together are safer or more effective than either drug alone. Additionally, the compounds of the present invention may be used in combination with one or more other drugs that treat, prevent, control, ameliorate, or reduce the risk of side effects or toxicity of the compounds of the present invention. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with the compounds of the present invention. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to the compounds of the present invention. The combinations may be administered as part of a unit dosage form combination product, or as a kit or treatment protocol

wherein one or more additional drugs are administered in separate dosage forms as part of a treatment regimen.

Examples of combinations of the compounds include combinations with agents for the treatment of pain, for example steroids such as dexamethasone, cortisone, and fluticasone, non-steroidal anti-inflammatory agents, such as aspirin, diclofenac, duflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, oxaprozin, piroxicam, sulindac and tolmetin; COX-2 inhibitors, such as celecoxib, rofecoxib and valdecoxib; CB-2 agonists; VR-1 antagonists; bradykinin B 1 receptor antagonists; sodium channel blockers and antagonists; nitric oxide synthase (NOS) inhibitors (including iNOS and nNOS inhibitors); glycine site antagonists, including lacosamide; neuronal nicotinic agonists; NMDA antagonists; potassium channel openers; AMPA/kainate receptor antagonists; calcium channel blockers, such as ziconotide; GABA-A receptor IO modulators (e.g., a GABA- A receptor agonist); matrix metalloprotease (MMP) inhibitors; thrombolytic agents; chemotherapeutic agents, opioid analgesics such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene; neutrophil inhibitory factor (NIF); pramipexole, ropinirole; anticholinergics; amantadine; monoamine oxidase Bl5 ("MAO-B") inhibitors; 5HT receptor agonists or antagonists; mGlu5 antagonists; alpha agonists; neuronal nicotinic agonists; NMDA receptor agonists or antagonists; NKI antagonists; selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), such as duloxetine; tricyclic antidepressant drugs, norepinephrine modulators; lithium; valproate; gabapentin; pregabalin; rizatriptan; zolmitriptan; naratriptan and sumatriptan.

Another aspect of the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier. Still another aspect of the present invention is directed to a compound of formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition treatable with an inhibitor of Trk-A and/or Trk-B, such as the disorders, conditions and/or diseases described herein. Still another aspect is directed to use of a compound of formula I or a pharmaceutically acceptable salt thereof in the treatment of pain, cancer, inflammation, neurodegenerative disease or typanosoma cruzi infection.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or

more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of formula (I), is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a

mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 mg to about 500 mg of the active ingredient.

Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Other pharmaceutical compositions include aqueous suspensions, which contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. In addition, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Oily suspensions may also contain various excipients. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions, which may also contain excipients such as sweetening and flavoring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension, or in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can also be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as tablets, capsules, syrups,

suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories.

The terms "effective amount" or "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treatment" or "treating" means any administration of a compound of the present invention and includes (1) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or (2) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

The compositions containing compounds of the present invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term "unit dosage form" is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person administering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration, single dose vials for injection, or suppositories for rectal administration. This list of unit dosage forms is not intended to be limiting in any way, but merely to represent typical examples of unit dosage forms.

The compositions containing compounds of the present invention may conveniently be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person administering the drug to the patient. Such kits may be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

When treating or ameliorating a disorder or disease for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kg of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. The total daily dosage is from about 1.0 mg to about 2000 mg, preferably from about 0.1 mg to about 20 mg per kg of body weight. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg.

This dosage regimen may be adjusted to provide the optimal therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.005 mg to about 2.5 g of active agent, compounded with an appropriate and convenient amount of carrier material. Unit dosage forms will generally contain between from about 0.005 mg to about 1000 mg of the active ingredient, typically 0.005, 0.01 mg, 0.05 mg, 0.25 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg, administered once, twice or three times a day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions hereinabove. Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the schemes and examples herein, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

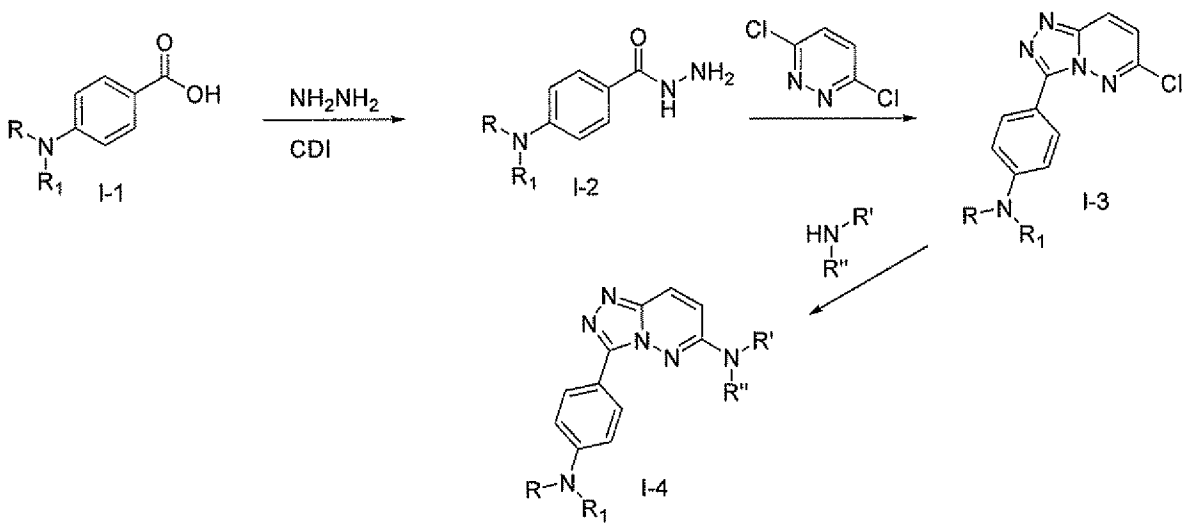
During any of the synthetic sequences it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W.McOmie, Plenum Press, 1973, and T.W. Greene & P/G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient sequent stage using methods known from the art.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

The following abbreviations are used throughout the text:

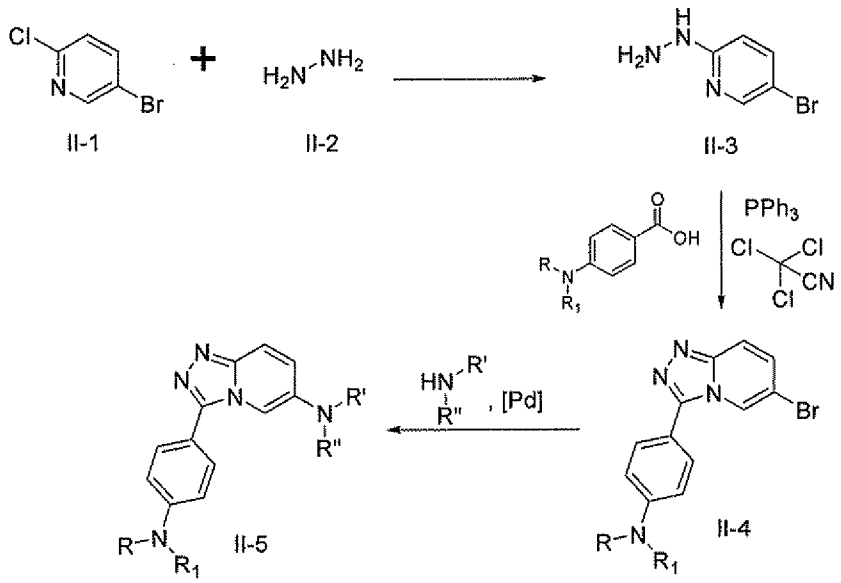
| | |
|---|---|
| Me: | methyl |
| Et: | ethyl |
| Bu: | butyl |
| *t*-Bu: | *tert*-butyl |
| Ar: | aryl |
| Ph: | phenyl |
| Bn: | benzyl |
| Ac: | acetyl |
| DMF•DMA | *N,N*-dimethylformamide dimethyl acetal |
| DMSO | dimethylsulfoxide |
| DMF | *N,N*-dimethylformamide |
| DMEM: | Dulbecco's Modified Eagle Medium (High Glucose) |
| THF: | tetrahydrofuran |
| TEA: | triethylamine |
| rt: | room temperature |
| aq: | aqueous |
| HPLC: | high performance liquid chromatography |
| MS: | mass spectrometry |
| RB: | round bottom |
| CDI | 1,1'-Carbonyldiimidazole |
| DCE | 1,2-Dichlorethane |
| HCl | Hydrochloric acid |
| °C | degrees Celcius |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene |
| DMSO | methyl sulfoxide |
| ATP | adenosine triphosphate |

General Reaction Scheme I




Reaction Scheme I illustrates the preparation of the compounds of the instant invention, starting with a commercially available carboxylic acid I-1. This material can be converted to the corresponding carboxy hydrazide I-2. Intermediate I-2 reacts with dichloropyridazine under acidic conditions to produce I-3. I-3 can then undergo substitution, in parallel, with a diverse array of amines to provide I-4.

General Reaction Scheme II




Reaction Scheme II illustrates the preparation of the compounds of the instant invention, starting with a commercially available pyridine chloride II-1. This material reacts with hydrazine II-2 to provide to the corresponding hydrozinylpyridine II-3. Intermediate II-3 reacts with

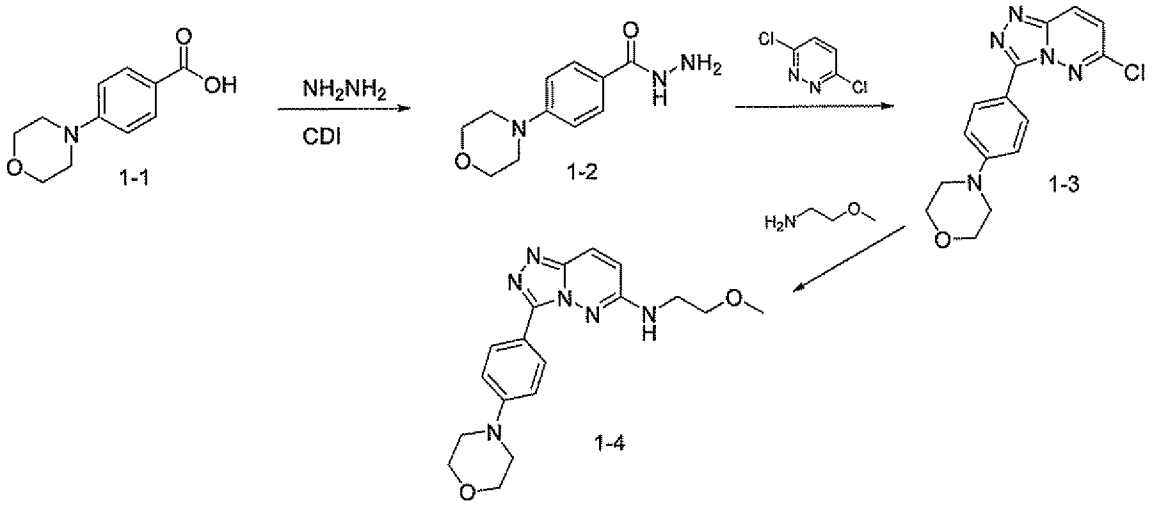
carboxylic acid in the presence of trichloroacetonitrile and triphenylphosphine to produce II-4. II-4 can then undergo substitution, in parallel, with a diverse array of amines to provide II-5.

Specific embodiments of the compounds of the invention, and methods of making them, are described in the Examples herein. Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof. The reagents utilized in synthesizing the compounds depicted in the following Tables are either commercially or are readily prepared by one of ordinary skill in the art.

## EXAMPLE 1

*N*-(2,5-difluorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-*b*]pyridazin-6-amine

Example Scheme I




4-(Morpholin-4-yl)benzohydrazide (1-2)

CDI (430 mg, 2.65 mmol) was added to a solution of 4-(morpholin-4-yl)-benzoic acid (500 mg, 2.413 mmol) in $CH_2Cl_2$ (24.100 ml) and the mixture was stirred at room temperature for 2 hrs until gas evolution ceased. Then hydrazine (0.098 ml, 3.14 mmol) was added to the reaction and the mixture was stirred at room temperature for overnight. The reaction mixture was cooled, aqueous sodium hydrogen carbonate (saturated, 20 mL) was added and the mixture was extracted with dichloromethane (3 x 20mL). The combined organic fractions were washed with brine (saturated, 30 mL), dried and filtered. The solvent was evaporated under reduced pressure to give

the title compound; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.0 Hz, 2H), 7.20 (bs, 1 H), 6.89 (d, *J* = 9.0 Hz , 2H), 4.07 (bs, 1H), 3.87 (d, *J* = 4.9 Hz, 2H), 3.86 (d, *J* = 4.8 Hz, 2H), 3.27 (d, *J* = 4.9 Hz, 2H), 3.25 (d, *J* = 4.8 Hz, 2H); MS (ES) m/z M+H calc'd:222, found: 222.

6-Chloro-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-*b*]pyridazine (1-3)

4-(Morpholin-4-yl)benzohydrazide (250 mg, 1.130 mmol), 3,6-dichloropyridazine (168 mg, 1.130 mmol) was added in a 6 mL solution of 5% 4N HCl/EtOH. The vial was irradiated in a microwave reactor at 150 °C for 10 min. The reaction was filtered and the filtration cake was washed with cold EtOH, dried, to provide the title compound; MS (ES) m/z M+H calc'd:316, found: 316.

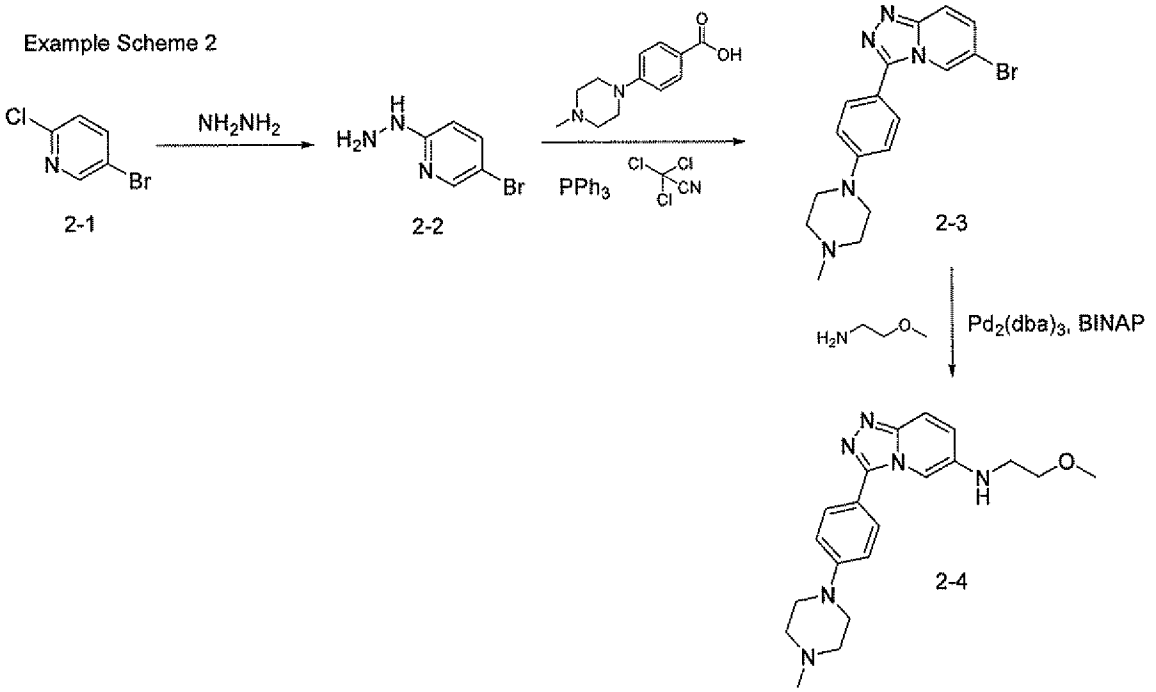
*N*-(2,5-difluorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (1-4)

6-Chloro-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-*b*]pyridazine (17 mg, 0.054 mmol), 2,5-difluorobenzylamine (38.5 mg, 0.269 mmol) was added in a 1 mL EtOH. The reaction mixture was irradiated in a microwave reactor at 150 °C for 2hr. The reaction mixture was dried and purified by HPLC to provide the title compound; $^1$H-NMR (400 MHz, $CD_3OD$) δ 8.30 (bd, *J* = 9.1 Hz, 2H), 7.92 (d, *J* = 10.0 Hz, 1H), 7.14 (bd, *J* = 9.1 Hz, 2H), 7.11 (d, *J* = 10.0 Hz, 1H), 3.88-3.83 (m, 4 H), 3.71-3.66 (m, 2H), 3.64-3.59 (m, 2H), 3.40 (s, 3H), 3.36-3.30 (m, 4H); HRMS (ES) m/z M+H calc'd:355.1804, found: 355.1880.

## EXAMPLE 2

*N*-(2,5-difluorobenzyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-*a*]pyridin-6-amine

Example Scheme 2




5-Bromo-2-hydrazinylpyridine (2-2)

Hydrazine (1.633 mL, 52.0 mmol) was mixed with a stirred, room temperature of 5-bromo-2-chloropyridine (2000 mg, 10.39 mmol) in dioxane (13 mL). The reaction mixture was stirred for 110 °C for overnight. The reaction mixture was quenched with aqueous sodium hydrogen carbonate (saturated, 50 mL). The reaction mixture was extracted with EtOAc (3 x 30mL). The combined organic fractions were washed with brine (saturated, 40 mL), dried and filtered. The solvent was evaporated under reduced pressure to provide the title compound; MS (ES) m/z M calc'd:188, found: 188.

6-bromo-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-*a*]pyridine (2-3)

4-(4-methylpiperazin-1-yl)benzoic acid (400 mg, 1.816 mmol), 5-bromo-2-hydrazinylpyridine (341 mg, 1.816 mmol) in $CH_2Cl_2$ (3 mL) and DCE (3 mL) was added polymer-bonded Triphenylphosphine (1429 mg, 5.45 mmol) followed by Hunig's base (634 mL, 3.63 mmol) and Trichloroacetonitrile (364 mL, 3.63 mmol). The reaction mixture was irradiated in a microwave reaction at 150 °C for 20 min. The reaction mixture was filtered and aqueous sodium hydrogen carbonate (saturated, 20 mL) was added. The reaction mixture was extracted with

dichloromethane (3 x 20mL). The combined organic fractions were washed with brine (saturated, 30 mL), dried and filtered. The solvent was evaporated under reduced pressure and purified via column chromatography to provide the title compound; $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.66 (bs, 1H), 7.83-7.77 (m, 3 H), 7.68 (dd, $J$ = 9.7 Hz, $J$ = 1.6 Hz, 1H), 7.28 (d, $J$ = 6.9 Hz, 2H), 4.16-4.04 (m, 2H), 3.70-3.62 (m, 2H), 3.36-3.26 (m, 2H), 3.24-3.14 (m, 2H), 3.00 (s, 3H); HRMS (ES) m/z M+H calc'd:372.0818, found: 372.0822.

*N*-(2,5-difluorobenzyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-*a*]pyridin-6-amine (2-4)

Combined $Pd_2(dba)_3$ (9.84 mg, 10.75 μmol), BINAP (10.04 mg, 0.016 mmol) and sodium tert-butoxide (7.74 mg, 0.081 mmol) in a sealed tube. Evacuated and back filled the reaction vessel with nitrogen three times. Added degassed toluene (537 μl) to the reaction and allowed to stir for 10 min. 6-Bromo-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-*a*]pyridine (20 mg, 0.054 mmol) and 2,5-difluorobenzylamine (30.8 mg, 0.215 mmol) in degassed toluene (537 μl) was added and the reaction mixture was then heated to 100 °C for 16 hr. The reaction mixture was quenched with aqueous sodium hydrogen carbonate (saturated, 20 mL). The reaction mixture was extracted with EtOAc (3 x 20mL). The combined organic fractions were washed with brine (saturated, 30 mL), dried and filtered. The solvent was evaporated under reduced pressure and purified via HPLC to provide the title compound; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.83 (bd, $J$ = 8.9 Hz, 2H), 7.76 (d, $J$ = 9.3 Hz, 1H), 7.64-7.59 (m, 2H), 7.30 (d, $J$ = 8.9 Hz, 2H), 4.16-4.06 (m, 2H), 3.64-3.60 (m, 6H), 3.38 (s, 3H), 3.26-3.22 (m, 4H), 3.00 (s, 3H); HRMS (ES) m/z M+H calc'd:367.2241, found: 367.2247.

**Biological Utility**

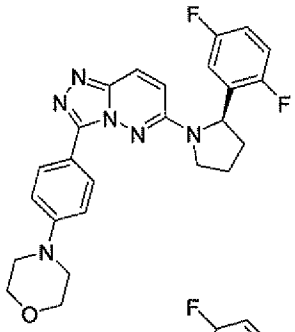
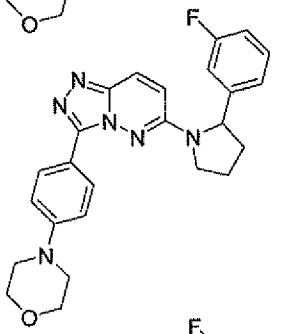
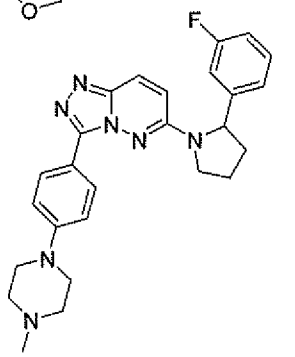
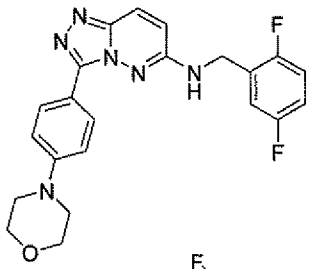
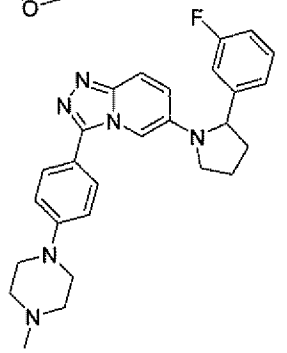
TrkA kinase activity was measured as the ability of the enzyme to phosphorylate a fluorescently labeled peptide substrate. Buffer salts, reagents, and fluorescently labeled peptides were purchased from Carna Biosciences and were of the highest quality available (QSS Assist TRKA_MSA Kit). Enzyme was purchased from Cell Signaling, and was used without further purification. 384-well round bottom assay plates were prepared by the

addition of 200 nl of a DMSO solution of compound at various concentrations to final inhibitor concentrations ranging from 100 μM to 0.2 μM. Next, assay buffer (10 μl) containing substrate and ATP were added, followed by addition of 10 μl of enzyme in assay buffer. Final assays concentrations were: [E]=0.37nM, [S]=1μM, [ATP]=2mM. The reactions were incubated at room temperature for 3 hours resulting in approximately 15 % substrate phosphorylation and were terminated by the addition of 5 μl of stop buffer. Substrates and products were separated on the Caliper EZReader II (Caliper LifeSciences, Inc.) using standard separation protocols. The percent inhibition was calculated for each compound concentration and the $IC_{50}$ was determined using equation 1.

Equation 1: $$\% \text{ Inhibition} = (Max + \frac{(Max - Min)}{1 + (\frac{Conc}{IC_{50}})^{Hill}})$$

IC50 values from the aforementioned assay for the compounds of this invention range between 20 nM to 10000 nM.. IC50 values for particular compounds of this invention are provided below in Table 2 below:

Table 2

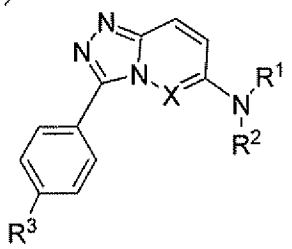
| | TrkA Caliper IC50 (nM) | IUPAC name |
|---|---|---|
|  | 27 | 6-[(2R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine |
|  | 52 | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine |
|  | 102 | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine |
|  | 234 | N-(2,5-difluorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine |
|  | 568 | 6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine |

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that

the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

What is claimed is:

1. A compound of formula (I):



(I)

and pharmaceutically acceptable salts thereof, wherein

X is –N or –CH;

R represents hydrogen or -$C_{1-6}$alkyl;

$R^1$, $R^2$, $R^{1'}$, and $R^{2'}$ are independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, –S-$C_{1-6}$ alkyl, –C(=O)-$(O)_n$-R, OR; $(CHR)_nC_{3-10}$ cycloalkyl, $(CHR)_nC_{6-10}$ aryl, $(CHR)_nC_{5-10}$ heterocycle, said alkyl, cycloalkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$;

or $R^1$ and $R^2$, or $R^{1'}$ and $R^{2'}$ together with the nitrogen atom to which they are attached can combine to form a 3 to 6 membered cyclic group which is optionally substituted with $R^4$;

$R^3$ represents -$C_{1-6}$ alkyl, -$NR^{1'}R^{2'}$, –$NRCOR^1$, -$NRCO_2R^1$, -$NRSO_2R^1$, –$NRCONR^1R^2$, $(CHR)_nC_{5-10}$ heterocycle, said alkyl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$;

$R^4$ is $R^1$;

$R^a$ represents –CN, $NO_2$, -$C_{1-4}$haloalkyl, -$OC_{1-4}$haloalkyl, -$C_{1-6}$alkyl, -$C_{1-6}$alkenyl, -$C_{1-6}$alkynyl, -$(CHR)_nC_{6-10}$ aryl, -$(CHR)_nC_{5-10}$ heterocycle, -O-$C_{6-10}$ aryl, -O-$C_{5-10}$ heterocycle, -O-, -$C(O)CF_3$, -$(CH_2)_n$halo, –OR, –$NRR^1$,–$NRCOR^1$, -$NRCO_2R^1$, -$NRSO_2R^1$, –$NRCONR^1R^2$, -$COR^1$, -$CO_2R^1$, or –$CONR^1R^2$, said aryl and heterocycle optionally substituted with 1 to 3 groups of $R^b$;

$R^b$ represents, -$C_{1-6}$alkyl,, halo, $SO_2R^3$, $NRSO_2R^3$, and

n represents 0-6.

2. The compound according to claim 1 wherein X is –N-

3. The compound according to claim 1 whererin X is –CH.

4. The compound according to claim 1 wherein one of $R^1$ and $R^2$ is hydrogen or methyl and the other is $C_{1-6}$ alkyl, $(CHR)_nC_{6-10}$ aryl, or $(CHR)_nC_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$.

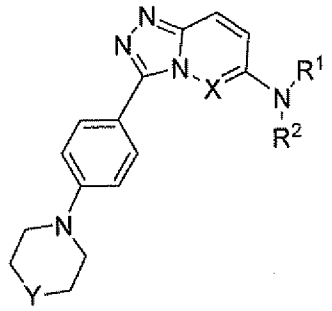
5. The compound according to claim 1 wherein $R^1$ and $R^2$ combine with the nitrogen to which they are attached to form a 3 to 6 membered cyclic ring optionally substituted with 1 to 3 groups of $R^4$.

6. The compound according to claim 5 wherein the cyclic ring is pyrrolidinyl optionally with 1 to 3 groups of $R^a$.

7. The compound according to claim 1 wherein $R^3$ is $(CHR)_nC_{5-10}$ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of $R^a$.

8. The compound according to claim 7 wherein $R^3$ is morpholinyl or piperazinyl optionally substituted with 1 to 3 groups of Ra.

9. The compound of formula I of Claim 1 represented by structural formula II:



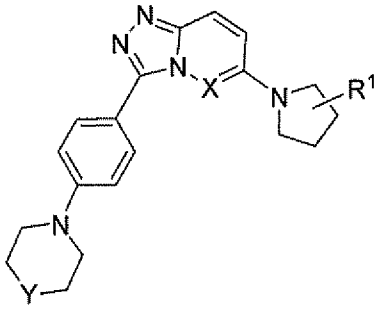
II

and pharmaceutically acceptable salts thereof, wherein Y is –NR, or –O-.

10. The compound according to claim 9 wherein one of $R^1$ and $R^2$ is hydrogen or $C_{1-6}$ alkyl and the other is $C_{1-6}$ alkyl, $(CHR)_nC_{6-10}$ aryl, $(CHR)_nC_{5-10}$ heterocycle, said alkyl, cycloalkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of $R^a$.

11. The compound according to claim 9 wherein $R^1$ and $R^2$ combine with the nitrogen to which they are attached to form a 3 to 6 membered cyclic ring optionally substituted with 1 to 3 groups of $R^4$.

12. The compound according to claim 1 represented by structural formula IIa



IIa

and pharmaceutically acceptable salts thereof.

13. The compound according to claim 12 wherein Y is –NR or –O- $R^1$ is phenyl optionally substituted with 1 to 3 groups of $R^a$ and X is –N or –CH.

14. A compound of claim 1, which is selected from the group consisting of

6-[2-(3-chlorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine,
6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine,
N-(3-chlorobenzyl)-N-methyl-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridin-6-amine,
N-(2-methoxyethyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridin-6-amine,
6-[(2R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine,
6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-a]pyridine,
N-(3-chlorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
N-(3-chlorobenzyl)-N-methyl-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
6-[2-(3-chlorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine,
N-(3-methoxybenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
2-({3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)ethanol,
N-(2-methoxyethyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
N-(3,4-dimethoxybenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine,
N-[2-({3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)ethyl]acetamide,
N-[3-(difluoromethoxy)benzyl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
N-(2,5-difluorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,

3-[4-(morpholin-4-yl)phenyl]-N-(pyridin-3-ylmethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-amine,
N-(3-chlorobenzyl)-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
N-(3-chlorobenzyl)-N-methyl-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
6-[2-(3-fluorophenyl)pyrrolidin-1-yl]-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine,
N-(2,5-difluorobenzyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
N-(2-methoxyethyl)-3-[4-(4-methylpiperazin-1-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazin-6-amine,
6-[(2R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]-3-[4-(morpholin-4-yl)phenyl][1,2,4]triazolo[4,3-b]pyridazine,
and pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for the manufacture of a medicament for the treatment of a disease or disorder mediated by the Trk receptors, wherein said disease or disorder is selected from the group consisting of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.

17. A method of treating a disease or disorder mediated by the TrK receptors, wherein said disease or disorder is selected from the group consisting of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/28977

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 249/00 (2012.01)
USPC - 548/262.4
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07D 249/00 (2012.01)
USPC -548/262.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/248, 303; 544/235 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST Google Patents, WIPO (ngf, trk, receptor, cancer, pain, formula, pyridotriazole, benztriazole, fused, kinase, inhibitors, compositions, methods)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 7,268,136 B2 (GREEN, et al.) 11 September 2007 (11.09.2007) entire document, especially col 1, ln 15-19; col 13, ln 1-10, 31-50; col 18, ln 60-61; col 22, ln 54-63; col 58, ln 64-col 59, ln 11. | 1-2, 4-6, 15<br>----------<br>3, 7-14, 16-17 |
| Y | US 2009/0215817 A1 (RUCKER, et al.) 27 August 2009 (17.08.2009) entire document, especially para[0002], [0008], [0023], [0026], [0033]-[0034], [0045], [0173]-[0199], [0210], [0290]. | 3, 7-14 |
| Y | WO 2009/140128 A2 (ALBAUGH, et al.) 19 November 2009 (19.11.2009) entire document, especially para[0008], [00028]. | 16-17 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 June 2012 (11.06.2012) | 25 JUN 2012 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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