the market. In addition, a great number of protein kinase inhibitors are currently in various phases of clinical development. In most cases these compounds are either targeting subtypes of the EGF (Epidermal Growth Factor) receptor or of the VEGF (Vascular Endothelial Growth Factor) receptor. All these compounds have been developed with the goal to specifically inhibit one particular protein kinase, for which there is evidence that it interferes with one of the four major molecular processes of tumor progression. These four processes are (1) cell proliferation/cell cycle control, (2) regulation of programmed cell death (apoptosis) and cell survival, (3) tumor angiogenesis and (4) tumor metastasis.

The present invention relates to benzazole derivatives which may be useful for inhibition of protein kinases involved in diseases besides cancer, but which are especially useful as anti-tumor agents. This includes monospecific protein kinase inhibitors, which preferentially inhibit one protein kinase which is causatively involved in tumor progression, but also so-called multi-target protein kinase inhibitors, which inhibit at least two different protein kinases which play a role in two or more different molecular mechanism of tumor progression. As an example, such a compound could be an inhibitor of tumor angiogenesis and, in addition, also a stimulator of apoptosis.

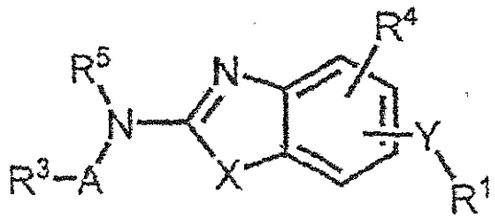
The concept of multi-target protein kinase inhibitors is a new approach although the idea of developing "multiplex protein kinase inhibitors" has already been described by J. Adams et al., Current Opinion in Chemical Biology 6, 486-492, 2002. Therein compounds are described, which, at the same time, inhibit several protein kinases, which however all are involved in one molecular mechanism of tumor progression, namely tumor angiogenesis.

In WO 2004085425 benzazoles are described as kinase inhibitors. In WO 9924035 2-aminobenzothiazoles are described. These compounds have also been published in Das et al., Bioorg. Med. Chem. Lett *13*, **2003**, 2587-2590 and in Das et al., Bioorg. Med. Chem. Lett *13*, **2003**, 2145-2149. In WO 2000061580 benzimidazolyl- and benzoxazolylacetylaminopyridylbutyrates are described as integrin antagonists. In WO 9940072 five-membered, benzo-condensed heterocycles used as antithrombotics of are described.

Summary

The object of the present ~~invention~~disclosure is solved by the teaching of the independent claims.

In a first aspect, there is provided a compound of the general formula (I) or a salt thereof,



formula (I)

wherein

the substituent –Y-R^1 is attached to the 5- or 6-position of the benzazole;

X independently represents S, O, SO, or SO_2;

Y independently represents S, NR^2, SO, or SO_2;

A independently represents ←CO-, ←CS-, ←SO-, ←SO_2-, ←CO_2-, ←$CONR^8$-, ←NR^8CO-, ←NR^8CONR^9-, ←NR^8COO-, ←NR^8NR^9CO-, ←NR^8OCO-, ←ONR^8CO-, or ←NR^8SO_2-, where ← indicates the point of attachment to R^3;

R^2 independently represents H, alkyl, cycloalkyl, -COR^6, -SOR^6, -SO_2R^6, -CN, hydroxyalkyl, haloalkyl, or haloalkyloxy;

R^3 independently represents H, alkyl, cycloalkyl, aryl, or heteroaryl;

R^4 independently represents H;

R^5 independently represents H;

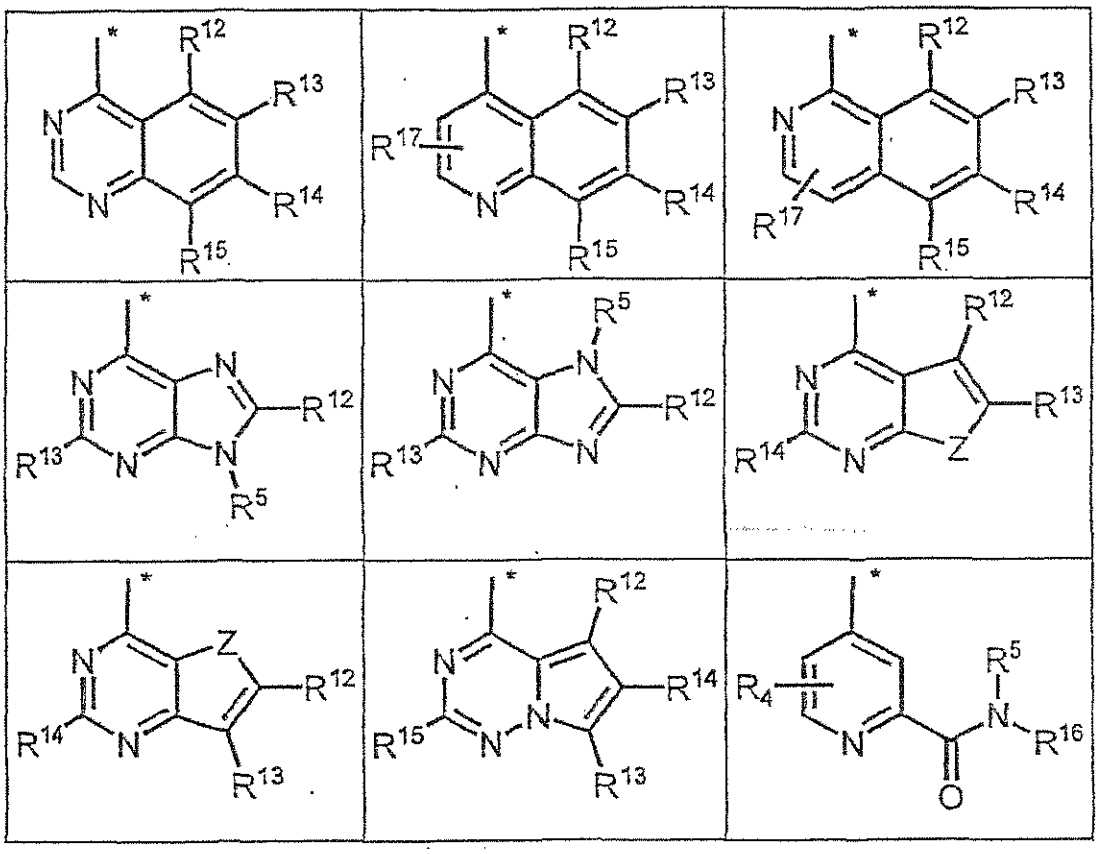
R^{6a} independently represents H, alkyl, cycloalkyl, -$NR^8NR^2R^9$, -ONR^8R^9, -NR^8OR^9, aryl or heteroaryl;

R^6 independently represents H, alkyl, cycloalkyl, aryl or heteroaryl;

R^8 independently represents H, alkyl, cycloalkyl, -COR^6, -SOR^6, -SO_2R^6, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R^9 independently represents H, alkyl, cycloalkyl, -COR^6, -SOR^6, -SO_2R^6, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R^1 independently represents one of the following groups:



where * indicates the point of attachment;

Z independently represents O, NR^8, or S;

R^{12} independently represents H, halogen, nitro, trifluoromethyl, alkyl, aryl, heteroaryl, $-NR^{8a}R^{9a}$, or $-X^2R^{16}$;

R^{8a} independently represents H, alkyl, cycloalkyl, $-COR^{6a}$, $-SOR^6$, $-SO_2R^6$, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R^{9a} independently represents H, alkyl, cycloalkyl, $-COR^{6a}$, $-SOR^6$, $-SO_2R^6$, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R^{13} independently represents H, halogen, nitro, trifluoromethyl, alkyl, aryl, heteroaryl, $-NR^{8a}R^{9a}$, or $-X^2R^{16}$;

R^{14} independently represents H, halogen, nitro, trifluoromethyl, alkyl, aryl, heteroaryl, $-NR^{8a}R^{9a}$, or $-X^2R^{16}$;

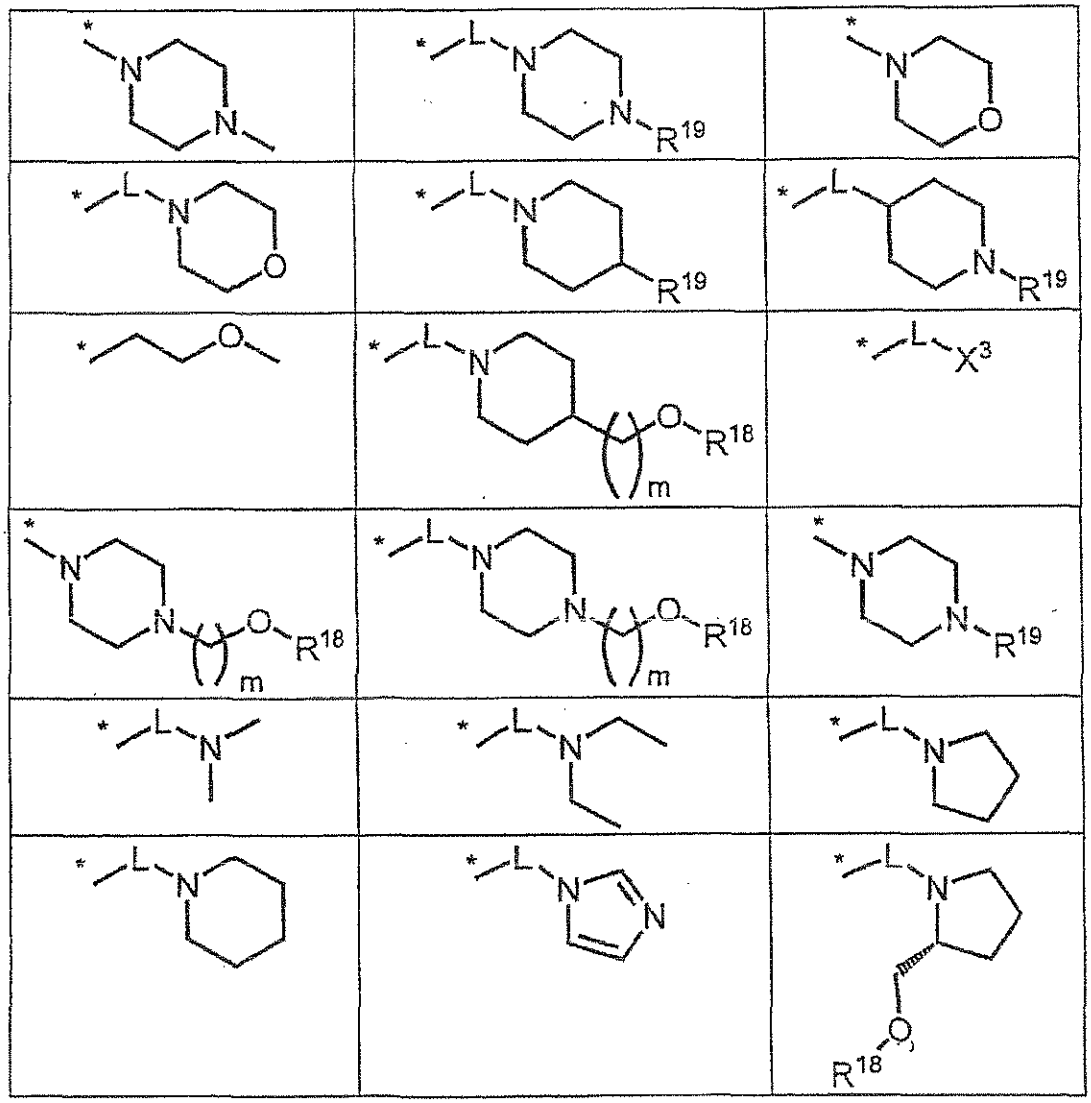
R^{15} independently represents H, halogen, nitro, trifluoromethyl, alkyl, aryl, heteroaryl, $-NR^{8a}R^{9a}$, or $-X^2R^{16}$;

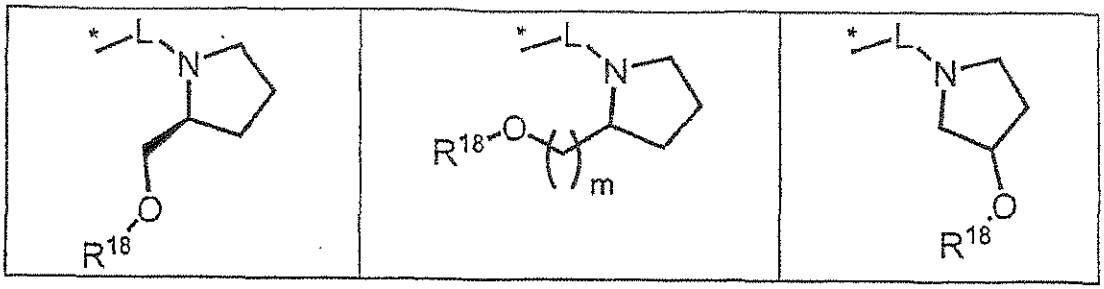
R^{17} independently represents H, halogen, nitro, trifluoromethyl, alkyl, aryl, heteroaryl, $-NR^{8a}R^{9a}$, or $-X^2R^{16}$;

X^2 independently represents a direct bond, -O-, $-CH_2-$, -OCO-, carbonyl, -S-, -SO-,

$-SO_2-$, $-NR^8CO-$, $-CONR^8-$, $-SO_2NR^8-$, $-NR^8SO_2-$ or $-NR^{8a}-$;

R^{16} independently represents H, alkyl, cycloalkyl, $-SOR^6$, $-SO_2R^6$, $-OCH_3$, hydroxyalkyl, haloalkyl, haloalkyloxy, or one of the following groups:





where * indicates the point of attachment;

m independently represents an integer from 1-3;

L is absent or represents a divalent linkage group comprising alkylene, cycloalkylene, heterocyclylene, arylene, or heteroarylene, wherein one or more of the (-CH_2-) groups may be replaced by an oxygen or a NR^8, and wherein one or more carbon atoms may be independently substituted by one or two substituents, wherein each substituent is halogen, hydroxy, alkoxy, halo-alkyloxy, phoshonooxy, or phoshonooxyalkyl;

X^3 independently represents –COOH, -COOalkyl, -OH, -SH, -SO_3H or -$SO_2NR^8R^9$;

R^{18} independently represents H, phosphonooxy, or phosphonooxyalkyl;

R^{19} independently represents H, alkyl, cycloalkyl, alkylamino, or alkoxy;

with the proviso that the following compounds are excluded:
N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide, N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-benzothiazol-2-yl]-2-phenyl-acetamide, N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-3-phenyl-propionamide, N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-(3-trifluoromethyl-phenyl)-acetamide, 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-acetamide, 2-(2-chloro-5-trifluoromethyl-phenyl)-N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-acetamide;

wherein an alkyl group, if not stated otherwise, denotes a linear or branched C_1-C_6-alkyl, a linear or branched C_2-C_6-alkenyl or a linear or branched C_2-C_6-alkynyl group, which can be substituted by one or more substituents R';

wherein R' independently represents H, -CO_2R", -CONHR", -CR"O, -SO_2NR", -NR"-CO-haloalkyl, -NO_2, -NR"-SO_2-haloalkyl, -NR"-SO_2-alkyl, -SO_2-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

wherein R" independently represents H, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

wherein a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, wherein one or more of the carbon atoms in the ring can be substituted by a group E, E being O, S, SO, SO_2, N, or NR", R" being as defined above;

wherein an alkoxy group denotes an O-alkyl group, the alkyl group being as defined above;

wherein an alkylthio group denotes an S-alkyl group, the alkyl group being as defined above;

wherein an haloalkyl group denotes an alkyl group which is substituted by one to five halogen atoms, the alkyl group being as defined above;

wherein a hydroxyalkyl group denotes an HO-alkyl group, the alkyl group being as defined above;

wherein a haloalkyloxy group denotes an alkoxy group which is substituted by one to five halogen atoms, the alkyl group being as defined above;

wherein a hydroxyalkylamino group denotes an $(HO\text{-alkyl})_2$-N- group or HO-alkyl-NH-group, the alkyl group being as defined above;

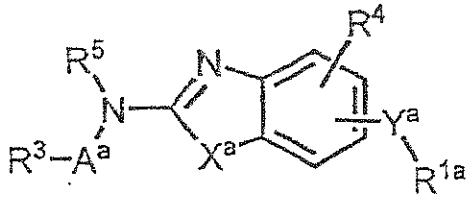
wherein an alkylamino group denotes an HN-alkyl or N-dialkyl group, the alkyl group being as defined above;

wherein a halogen group is chlorine, bromine, fluorine or iodine;

wherein an aryl group denotes an aromatic group having five to fifteen carbon atoms, which can be substituted by one or more substituents R', wherein R' is as defined above;

wherein a heteroaryl group denotes a 5- or 6-membered heterocyclic group which contains at least one heteroatom, wherein the heterocyclic group can be fused to another ring, and wherein the heterocyclic group can be substituted by one or more substituents R', wherein R' is as defined above.

In a second aspect, there is provided a compound of the general formula (Ia) or a salt thereof,



formula (Ia)

wherein

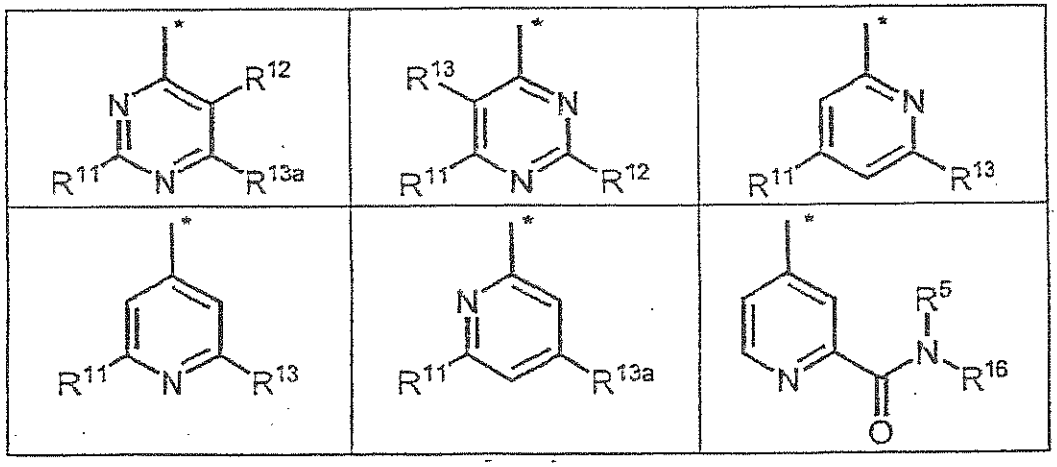
the substituent $-Y^a-R^{1a}$ is attached to the 5- or 6-position of the benzazole;

X^a independently represents S, O, SO, or SO_2;

Y^a independently represents S, NR^2, SO, or SO_2;

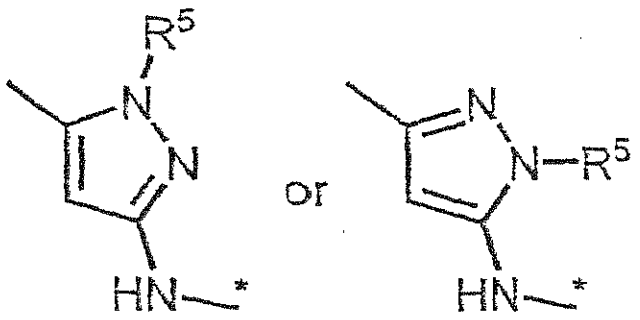
A^a independently represents $\leftarrow CO-$, $\leftarrow CS-$, $\leftarrow SO-$, $\leftarrow SO_2-$, $\leftarrow CO_2-$, $\leftarrow CONR^8-$, $\leftarrow NR^8CO-$, $\leftarrow NR^8CONR^9-$, $\leftarrow NR^8COO-$, $\leftarrow NR^8NR^9CO-$, $\leftarrow NR^8OCO-$, $\leftarrow ONR^8CO-$, or $\leftarrow NR^8SO_2-$, where $\leftarrow$ indicates the point of attachment to R^3;

R^{1a} independently represents one of the following groups:



where * indicates the point of attactment;

R^{11} independently represents H, $-NHR^{8a}$, or one of the groups:

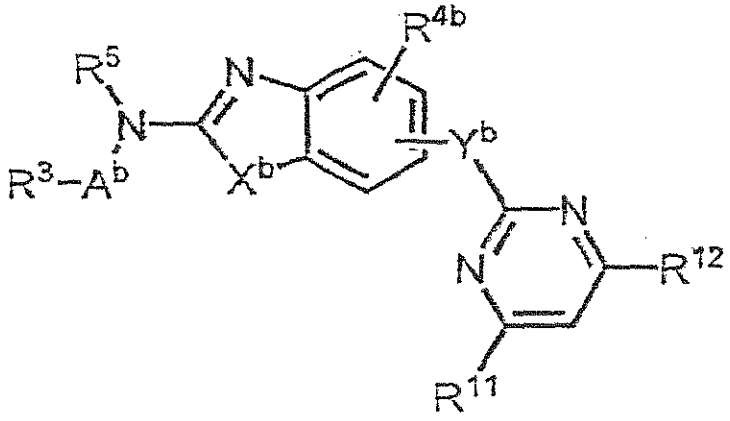


where * indicates the point of attachment;

R^{13a} independently represents H, halogen, nitro, trifluoromethyl, alkyl, $-NR^{8a}R^{9a}$, or $-X^2R^{16}$; and

R^2, R^3, R^4, R^5, R^6, R^{6a}, R^8, R^{8a}, R^9, R^{9a}, R^{12}, R^{13}, R^{16}, or X^2, are as defined above.

In a third aspect, there is provided a compound of the general formula (II) or a salt thereof,



formula (II)

wherein

the substituent $-Y^b-$ is attached to the 5- or 6-position of the benzazole;

X^b independently represents S, O, SO, or SO_2;

Y^b independently represents S, NR^2, SO, or SO_2;

A^b independently represents $\leftarrow CO-$, $\leftarrow CS-$, $\leftarrow SO-$, $\leftarrow SO_2-$, $\leftarrow CO_2-$, $\leftarrow CONR^8-$, $\leftarrow NR^8CO-$, $\leftarrow NR^8CONR^9-$, $\leftarrow NR^8COO-$, $\leftarrow NR^8NR^9CO-$, $\leftarrow NR^8OCO-$, $\leftarrow ONR^8CO-$, or $\leftarrow NR^8SO_2-$, where $\leftarrow$ indicates the point of attachment to R^3;

R^{4b} independently represents H;

R^2, R^3, R^5, R^6, R^{6a}, R^8, R^{8a}, R^9, R^{9a}, R^{11}, R^{12}, R^{16}, X^2 are as defined above.

In a fourth aspect, there is provided the compound as defined above, or a salt thereof, for use as a medicament for the treatment or prevention of a disease characterized by proliferation of keratinocytes, T-cells or both.

In a fifth aspect, there is provided the compound as defined above, or a salt thereof, for use in the treatment of cell proliferation disorders; the prophylaxis of immunological diseases and conditions; the treatment of diseases caused by malignant cell proliferation; the support of cell generation poiesis; the therapeutic control of tissue generation and degeneration; the therapeutic modification of cell and tissue maintenance; or blood cell homeostasis.

In a sixth aspect, there is provided a pharmaceutical composition comprising the compound as defined above, or a salt thereof, together with a pharmaceutically acceptable diluent or carrier.

In a seventh aspect, there is provided the pharmaceutical composition as defined above, for the treatment, relief or prevention of cancer.

In an eighth aspect, there is provided the use of the compound as defined above, or a salt thereof, in the preparation of a medicament for the treatment, relief or prevention of cancer.

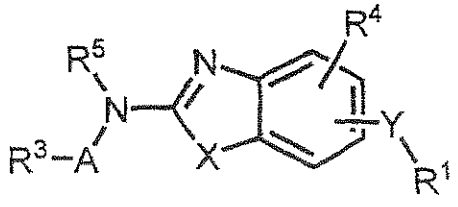
Further advantageous features, ~~aspects~~embodiments and details of the ~~invention~~present disclosure are evident from the dependent claims, the description, the figures, and the examples of the present application. Considering the lack of currently available treatment options for the majority of the conditions associated with protein kinases like ABL1, ACV-R1, AKT1, AKT2, AKT3,

ARK5, Aurora-A, Aurora-B, Aurora-C, B-RAF, BRK, CDC42BPB, CDK1, CDK2 CDK3, CDK4, CDK5, CDK6, CDK7, CDK9, CHK1, CK2, COT, CSK, DAPK1, EGF-R EPHA1, EPHA2, EPHA4, EPHB1, EPHB2, EPHB3, EPHB4, ERBB2, ERBB4, FAK FGF-R1, FGF-R3, FGF-R4, FGR, FLT3, GSK3-beta, HCK, IGF1-R, IKK-beta, IKK epsilon, INS-R, IRAK4, ITK, JAK2, JAK3, JNK3, KIT, LCK, LYN, MAPKAPK5, MET MST4, MUSK, NEK2, NEK6, NLK, PAK1, PAK2, PAK4, PBK, PCTAIRE1, PDGFR alpha, PDGFR-beta, PDK1, PIM1, PIM2, PKC-alpha, PKC-beta1, PKC-beta2, PKC-delta PKC-epsilon, PKC-eta, PKC-gamma, PKC-iota, PKC-mu, PKC-theta, PKC-zeta, PLK1 PRK1, RET, ROCK2, S6K, SAK, SGK1, SGK3, SNK, SRC, SRPK2, SYK, TGFB-R1 TIE2, TSF1, TSK2, TTK, VEGF-R1, VEGF-R2, VEGF-R3, VRK1, WEE1, YES, ZAP70 especially with protein kinases like EGF-R (cell proliferation), ERBB2 (cell proliferation) PDGFR (cell proliferation), FLT3 (cell proliferation), Aurora-A (cell cycle control) Aurora-B (cell cycle control), IGF1-R (apoptosis), VEGF-R2 (angiogenesis), VEGF-R3 (angiogenesis), TIE2 (angiogenesis), EPHB4 (angiogenesis), FAK (metastasis), and SRC kinase (metastasis), there is still a great need for new therapeutic agents that inhibit these protein targets.

Herein described benzazole derivatives are a new group of protein kinase inhibitors which show differential inhibition of protein kinases, each of which can be assigned to one of the four molecular mechanism of tumor development.

Detailed Description

The present invention relates to compounds of the general formula (I) or a salt or a physiologically functional derivative or a stereoisomer thereof,



formula (I)

wherein

the substituent $-Y-R^1$ is attached to the 5- or 6-position of the benzazole;

X independently represents S, O, SO, or SO_2;

Y independently represents S, O, NR^2, SO, or SO_2;

A independently represents $\leftarrow CO-$, $\leftarrow CS-$, $\leftarrow SO-$, $\leftarrow SO_2-$, $\leftarrow CO_2-$, $\leftarrow CONR^8-$, $\leftarrow NR^8CO-$, $\leftarrow NR^8CONR^9-$, $\leftarrow NR^8CO_2-$, $\leftarrow NR^8NR^9CO-$, $\leftarrow NR^8OCO-$