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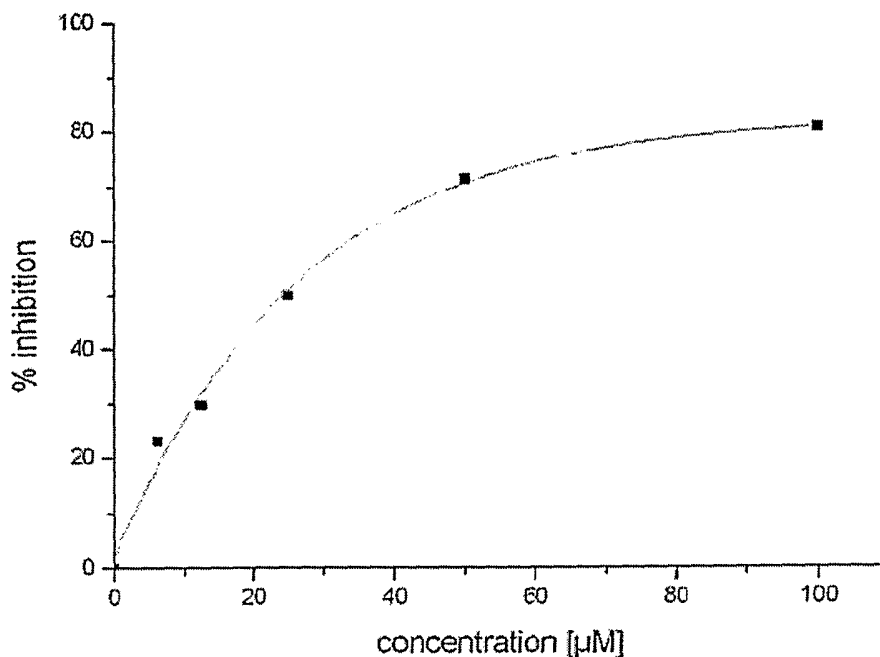
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(54) Title: 2-PHENYLQUINOXALINES AS INHIBITORS FOR MPP1



(57) Abstract: The present invention relates to 2-phenylquinoxaline derivatives as well as pharmaceutical compositions containing at least one of these 2-phenylquinoxaline derivatives together with pharmaceutically acceptable carrier, excipient and/or diluents. Said 2-phenylquinoxaline derivatives have been identified as specific inhibitors of the mitotic kinesin MPP1, and are useful for the treatment of cancers and proliferative diseases including tumor growth and metastases.



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2-Phenylquinoxalines as inhibitors for MPP1

Specification

5

The present invention relates to 2-phenylquinoxaline derivatives and stereoisomeric forms, prodrugs, solvates, hydrates and/or pharmaceutically acceptable salts of these compounds as well as pharmaceutical compositions containing at least one of these 2-phenylquinoxaline derivatives together with pharmaceutically acceptable
10 carrier, excipient and/or diluents. Said 2-phenylquinoxaline derivatives have been identified as specific inhibitors of the mitotic kinesin MPP1, and are useful for the treatment of cancers and proliferative diseases including tumor growth and metastases.

15

Background of the invention

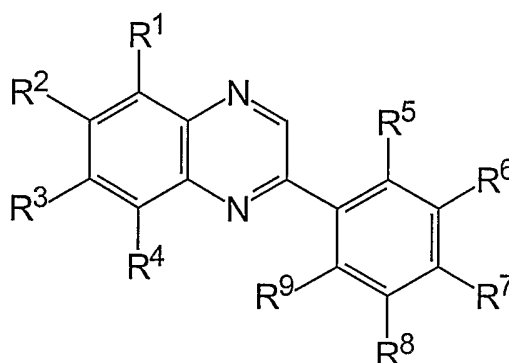
The mechanism by which the cell coordinates the division of the chromosomes (mitosis) and division of the cytoplasm (cytokinesis) remains among the largest unsolved problems in cell biology. Establishment, maintenance and the
20 concerted contraction of the actomyosin structures of the cleavage furrow are continuously regulated by the microtubules of the anaphase spindle and telophase midbody. Many molecules are known to be involved in cytokinesis, but the spatial as well as the temporal regulation and mechanistic roles of the vast majority of these proteins remain unclear. Previously, it has been shown that the activities of
25 the kinesins Mklp1, Mklp2, and MPP1 are essential for cytokinesis. Mklp1 and Mklp2 have been shown to regulate the localization of RhoGAP and Polo kinase to the spindle midzone, respectively. These data suggest that Mklp1 and Mklp2 have regulatory functions during cytokinesis. While RNA interference studies revealed that MPP1 is required late in cytokinesis its exact function remains
30 unknown.

It is object of the present invention to provide compounds and/or pharmaceutically acceptable salts thereof which can be used as pharmaceutically active agents, especially for prophylaxis and/or treatment of proliferative diseases such as
35 cancers.

The object of the present invention is solved by the teaching of the independent claims. Further advantageous features, aspects and details of the invention are

evident from the dependent claims, the description, and the examples of the present application.

The 2-phenylquinoxaline derivatives according to the present invention are represented by the following general formula (I)



wherein

- $R^1, R^2, R^3, R^4, R^5, R^8,$ and R^9 are independently of each other selected from $R^{10} - R^{18}, -CH_2-R^{19}, -C_2H_4-R^{20}, -C_3H_6-R^{21}, -C_4H_8-R^{22}, -C_5H_{10}-R^{23}, -C_6H_{12}-R^{24}, -C_7H_{14}-R^{25}, -CHR^{26}R^{27}, -CR^{28}R^{29}R^{30}, -CHR^{31}-CHR^{32}R^{33}, -CR^{34}R^{35}-CR^{36}R^{37}R^{38}, -CHR^{39}-CHR^{40}-CHR^{41}R^{42}, -CR^{43}R^{44}-CR^{45}R^{46}-CR^{47}R^{48}R^{49},$
- $R^{10} - R^{49}$ represent independently of each other $-H, -OH, -OCH_3, -OC_2H_5, -OC_3H_7, -O-cyclo-C_3H_5, -OCH(CH_3)_2, -OC(CH_3)_3, -OC_4H_9, -OPh, -OCH_2-Ph, -OCPh_3, -SH, -SCH_3, -SC_2H_5, -SC_3H_7, -S-cyclo-C_3H_5, -SCH(CH_3)_2, -SC(CH_3)_3, -NO_2, -F, -Cl, -Br, -I, -N_3, -CN, -OCN, -NCO, -SCN, -NCS, -CHO, -COCH_3, -COC_2H_5, -COC_3H_7, -CO-cyclo-C_3H_5, -COCH(CH_3)_2, -COC(CH_3)_3, -COOH, -COCN, -COOCH_3, -COOC_2H_5, -COOC_3H_7, -COO-cyclo-C_3H_5, -COOCH(CH_3)_2, -COOC(CH_3)_3, -OOC-CH_3, -OOC-C_2H_5, -OOC-C_3H_7, -OOC-cyclo-C_3H_5, -OOC-CH(CH_3)_2, -OOC-C(CH_3)_3, -CONH_2, -CONHCH_3, -CONHC_2H_5, -CONHC_3H_7, -CONH-cyclo-C_3H_5, -CONH[CH(CH_3)_2], -CONH[C(CH_3)_3], -CON(CH_3)_2, -CON(C_2H_5)_2, -CON(C_3H_7)_2, -CON(cyclo-C_3H_5)_2, -CON[CH(CH_3)_2]_2, -CON[C(CH_3)_3]_2, -NH_2, -NHCH_3, -NHC_2H_5, -NHC_3H_7, -NH-cyclo-C_3H_5, -NHCH(CH_3)_2, -NHC(CH_3)_3, -N(CH_3)_2, -N(C_2H_5)_2, -N(C_3H_7)_2, -N(cyclo-C_3H_5)_2, -N[CH(CH_3)_2]_2, -N[C(CH_3)_3]_2, -SOCH_3, -SOC_2H_5, -SOC_3H_7, -SO-cyclo-C_3H_5, -SOCH(CH_3)_2, -SOC(CH_3)_3, -SO_2CH_3, -SO_2C_2H_5, -SO_2C_3H_7, -SO_2-cyclo-C_3H_5, -SO_2CH(CH_3)_2, -SO_2C(CH_3)_3, -SO_3H, -SO_3CH_3, -SO_3C_2H_5, -SO_3C_3H_7, -SO_3-cyclo-C_3H_5, -SO_3CH(CH_3)_2, -SO_3C(CH_3)_3, -OCF_3, -OC_2F_5, -O-COOCH_3, -O-COOC_2H_5, -O-COOC_3H_7, -O-COO-cyclo-C_3H_5, -O-COOCH(CH_3)_2, -O-COOC(CH_3)_3, -NH-CO-NH_2, -NH-CO-NHCH_3,$

- NH-CO-NHC₂H₅, -NH-CO-NHC₃H₇, -NH-CO-NH-cyclo-C₃H₅,
 -NH-CO-NH[CH(CH₃)₂], -NH-CO-NH[C(CH₃)₃], -NH-CO-N(CH₃)₂,
 -NH-CO-N(C₂H₅)₂, -NH-CO-N(C₃H₇)₂, -NH-CO-N(cyclo-C₃H₅)₂,
 -NH-CO-N[CH(CH₃)₂]₂, -NH-CO-N[C(CH₃)₃]₂, -NH-CS-NH₂,
 5 -NH-CS-NH-cyclo-C₃H₅, -NH-CS-NHC₃H₇, -NH-CS-NH[CH(CH₃)₂],
 -NH-CS-NH[C(CH₃)₃], -NH-CS-N(CH₃)₂, -NH-CS-N(C₂H₅)₂, -NH-CS-N(C₃H₇)₂,
 -NH-CS-N(cyclo-C₃H₅)₂, -NH-C(=NH)-NH₂, -NH-CS-NHC₂H₅,
 -NH-CS-NHCH₃, -O-CO-NH₂, -O-CO-NHCH₃, -O-CO-NHC₂H₅,
 -O-CO-NHC₃H₇, -O-CO-NH-cyclo-C₃H₅, -O-CO-NH[CH(CH₃)₂],
 10 -O-CO-NH[C(CH₃)₃], -O-CO-N(CH₃)₂, -O-CO-N(C₂H₅)₂, -O-CO-N(C₃H₇)₂,
 -O-CO-N(cyclo-C₃H₅)₂, -O-CO-N[CH(CH₃)₂]₂, -O-CO-N[C(CH₃)₃]₂,
 -O-CO-OCH₃, -O-CO-OC₂H₅, -O-CO-OC₃H₇, -O-CO-O-cyclo-C₃H₅,
 -O-CO-OCH(CH₃)₂, -O-CO-OC(CH₃)₃, -CH₂F, -CHF₂, -CF₃, -CH₂Cl,
 -CHCl₂, -CCl₃, -CH₂Br, -CHBr₂, -CBr₃, -CPh₃, -CH₂-CH₂F
 15 -CH₂-CHF₂, -CH₂-CF₃, -CH₂-CH₂Cl, -CH₂-CHCl₂, -CH₂-CCl₃,
 -CH₂-CH₂Br, -CH₂-CHBr₂, -CH₂-CBr₃, -CH₃, -C₂H₅, -C₃H₇,
 -CH(CH₃)₂, -C₄H₉, -CH₂-CH(CH₃)₂, -CH(CH₃)-C₂H₅, -C(CH₃)₃,
 -C₅H₁₁, -CH(CH₃)-C₃H₇, -CH₂-CH(CH₃)-C₂H₅, -CH(CH₃)-CH(CH₃)₂,
 -C(CH₃)₂-C₂H₅, -CH₂-C(CH₃)₃, -CH(C₂H₅)₂, -C₂H₄-CH(CH₃)₂,
 20 -C₆H₁₃, -C₃H₆-CH(CH₃)₂, -C₂H₄-CH(CH₃)-C₂H₅, -CH(CH₃)-C₄H₉,
 -CH₂-CH(CH₃)-C₃H₇, -CH(CH₃)-CH₂-CH(CH₃)₂, -CH₂-C(CH₃)₂-C₂H₅,
 -CH(CH₃)-CH(CH₃)-C₂H₅, -CH₂-CH(CH₃)-CH(CH₃)₂, -C(CH₃)₂-C₃H₇,
 -C(CH₃)₂-CH(CH₃)₂, -C₂H₄-C(CH₃)₃, -CH(CH₃)-C(CH₃)₃, -C₇H₁₅, -C₈H₁₇,
 -C₉H₁₉, -C₁₀H₂₁, -Ph, -CH₂-Ph, -C₂H₄-Ph, -C₂H₂-Ph, -C≡C-Ph, -CPh₃,
 25 -CH=CH₂, -CH₂-CH=CH₂, -C(CH₃)=CH₂, -CH=CH-CH₃, -C₂H₄-CH=CH₂,
 -CH₂-CH=CH-CH₃, -CH=CH-C₂H₅, -CH₂-C(CH₃)=CH₂, -CH(CH₃)-CH=CH,
 -CH=C(CH₃)₂, -C(CH₃)=CH-CH₃, -CH=CH-CH=CH₂, -C₃H₆-CH=CH₂,
 -C₂H₄-CH=CH-CH₃, -CH₂-CH=CH-C₂H₅, -C≡CH, -CH=CH-C₃H₇, -C≡C-CH₃,
 -CH₂-C≡CH, -C₂H₄-C≡CH, -CH₂-C≡C-CH₃, -C≡C-C₂H₅, -C₃H₆-C≡CH,
 30 -cyclo-C₃H₅, -cyclo-C₄H₇, -cyclo-C₅H₉, -cyclo-C₆H₁₁;

R⁶ and R⁷ represent -Cl; and

at least one of the substituents R⁵, R⁸, and R⁹ is different from hydrogen;

and stereoisomeric forms, prodrugs, solvates, hydrates and/or pharmaceutically acceptable salts thereof.

35

Preferred are the 2-phenylquinoxaline derivatives wherein R³ represents -CF₃.

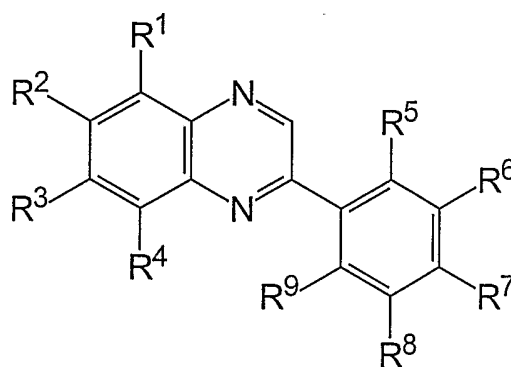
Also preferred are the 2-phenylquinoxaline derivatives wherein R¹ represents -Cl.

Another preferred group of compounds is represented by the general formula (I), wherein the substituents R^1 , R^2 and $R^4 - R^{49}$ have the meanings as disclosed below without the restriction that at least one of the substituents R^5 , R^8 , and R^9 is different from hydrogen (e.g. all substituents R^5 , R^8 , and R^9 can be hydrogen) and wherein R^3 represents $-CF_3$.

Still another preferred subgroup of compounds is represented by the general formula (I), wherein the substituents $R^2 - R^{49}$ have the meanings as disclosed below without the restriction that at least one of the substituents R^5 , R^8 , and R^9 is different from hydrogen (e.g. all substituents R^5 , R^8 , and R^9 can be hydrogen) and wherein R^1 represents $-Cl$.

The above-mentioned 2-phenylquinoxaline derivatives are especially useful as pharmaceutically active agents, most especially for prophylaxis and/or treatment of proliferative diseases and cancers.

Thus, the present invention relates to the use of 2-phenylquinoxaline derivatives of the general formula (I)



wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently of each other selected from $R^{10} - R^{18}$, $-CH_2-R^{19}$, $-C_2H_4-R^{20}$, $-C_3H_6-R^{21}$, $-C_4H_8-R^{22}$, $-C_5H_{10}-R^{23}$, $-C_6H_{12}-R^{24}$, $-C_7H_{14}-R^{25}$, $-CHR^{26}R^{27}$, $-CR^{28}R^{29}R^{30}$, $-CHR^{31}-CHR^{32}R^{33}$, $-CR^{34}R^{35}-CR^{36}R^{37}R^{38}$, $-CHR^{39}-CHR^{40}-CHR^{41}R^{42}$, $-CR^{43}R^{44}-CR^{45}R^{46}-CR^{47}R^{48}R^{49}$; $R^{10} - R^{49}$ represent independently of each other $-H$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-O-cyclo-C_3H_5$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, $-OPh$, $-OCH_2-Ph$, $-OCPh_3$, $-SH$, $-SCH_3$, $-SC_2H_5$, $-SC_3H_7$, $-S-cyclo-C_3H_5$, $-SCH(CH_3)_2$, $-SC(CH_3)_3$, $-NO_2$, $-F$, $-Cl$, $-Br$, $-I$, $-N_3$, $-CN$, $-OCN$, $-NCO$, $-SCN$, $-NCS$, $-CHO$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO-cyclo-C_3H_5$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOH$, $-COCN$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$,

- COO-cyclo-C₃H₅, -COOCH(CH₃)₂, -COOC(CH₃)₃, -OOC-CH₃, -OOC-C₂H₅,
 -OOC-C₃H₇, -OOC-cyclo-C₃H₅, -OOC-CH(CH₃)₂, -OOC-C(CH₃)₃, -CONH₂,
 -CONHCH₃, -CONHC₂H₅, -CONHC₃H₇, -CONH-cyclo-C₃H₅, -CONH[CH(CH₃)₂],
 -CONH[C(CH₃)₃], -CON(CH₃)₂, -CON(C₂H₅)₂, -CON(C₃H₇)₂, -CON(cyclo-C₃H₅)₂,
 5 -CON[CH(CH₃)₂]₂, -CON[C(CH₃)₃]₂, -NH₂, -NHCH₃, -NHC₂H₅, -NHC₃H₇,
 -NH-cyclo-C₃H₅, -NHCH(CH₃)₂, -NHC(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂,
 -N(C₃H₇)₂, -N(cyclo-C₃H₅)₂, -N[CH(CH₃)₂]₂, -N[C(CH₃)₃]₂, -SOCH₃,
 -SOC₂H₅, -SOC₃H₇, -SO-cyclo-C₃H₅, -SOCH(CH₃)₂, -SOC(CH₃)₃,
 -SO₂CH₃, -SO₂C₂H₅, -SO₂C₃H₇, -SO₂-cyclo-C₃H₅, -SO₂CH(CH₃)₂,
 10 -SO₂C(CH₃)₃, -SO₃H, -SO₃CH₃, -SO₃C₂H₅, -SO₃C₃H₇,
 -SO₃-cyclo-C₃H₅, -SO₃CH(CH₃)₂, -SO₃C(CH₃)₃, -OCF₃, -OC₂F₅,
 -O-COOCH₃, -O-COOC₂H₅, -O-COOC₃H₇, -O-COO-cyclo-C₃H₅,
 -O-COOCH(CH₃)₂, -O-COOC(CH₃)₃, -NH-CO-NH₂, -NH-CO-NHCH₃,
 -NH-CO-NHC₂H₅, -NH-CO-NHC₃H₇, -NH-CO-NH-cyclo-C₃H₅,
 15 -NH-CO-NH[CH(CH₃)₂], -NH-CO-NH[C(CH₃)₃], -NH-CO-N(CH₃)₂,
 -NH-CO-N(C₂H₅)₂, -NH-CO-N(C₃H₇)₂, -NH-CO-N(cyclo-C₃H₅)₂,
 -NH-CO-N[CH(CH₃)₂]₂, -NH-CO-N[C(CH₃)₃]₂, -NH-CS-NH₂,
 -NH-CS-NH-cyclo-C₃H₅, -NH-CS-NHC₃H₇, -NH-CS-NH[CH(CH₃)₂],
 -NH-CS-NH[C(CH₃)₃], -NH-CS-N(CH₃)₂, -NH-CS-N(C₂H₅)₂, -NH-CS-N(C₃H₇)₂,
 20 -NH-CS-N(cyclo-C₃H₅)₂, -NH-C(=NH)-NH₂, -NH-CS-NHC₂H₅,
 -NH-CS-NHCH₃, -O-CO-NH₂, -O-CO-NHCH₃, -O-CO-NHC₂H₅,
 -O-CO-NHC₃H₇, -O-CO-NH-cyclo-C₃H₅, -O-CO-NH[CH(CH₃)₂],
 -O-CO-NH[C(CH₃)₃], -O-CO-N(CH₃)₂, -O-CO-N(C₂H₅)₂, -O-CO-N(C₃H₇)₂,
 -O-CO-N(cyclo-C₃H₅)₂, -O-CO-N[CH(CH₃)₂]₂, -O-CO-N[C(CH₃)₃]₂,
 25 -O-CO-OCH₃, -O-CO-OC₂H₅, -O-CO-OC₃H₇, -O-CO-O-cyclo-C₃H₅,
 -O-CO-OCH(CH₃)₂, -O-CO-OC(CH₃)₃, -CH₂F, -CHF₂, -CF₃, -CH₂Cl,
 -CHCl₂, -CCl₃, -CH₂Br, -CHBr₂, -CBr₃, -CPh₃, -CH₂-CH₂F,
 -CH₂-CHF₂, -CH₂-CF₃, -CH₂-CH₂Cl, -CH₂-CHCl₂, -CH₂-CCl₃,
 -CH₂-CH₂Br, -CH₂-CHBr₂, -CH₂-CBr₃, -CH₃, -C₂H₅, -C₃H₇,
 30 -CH(CH₃)₂, -C₄H₉, -CH₂-CH(CH₃)₂, -CH(CH₃)-C₂H₅, -C(CH₃)₃,
 -C₅H₁₁, -CH(CH₃)-C₃H₇, -CH₂-CH(CH₃)-C₂H₅, -CH(CH₃)-CH(CH₃)₂,
 -C(CH₃)₂-C₂H₅, -CH₂-C(CH₃)₃, -CH(C₂H₅)₂, -C₂H₄-CH(CH₃)₂,
 -C₆H₁₃, -C₃H₆-CH(CH₃)₂, -C₂H₄-CH(CH₃)-C₂H₅, -CH(CH₃)-C₄H₉,
 -CH₂-CH(CH₃)-C₃H₇, -CH(CH₃)-CH₂-CH(CH₃)₂, -CH₂-C(CH₃)₂-C₂H₅,
 35 -CH(CH₃)-CH(CH₃)-C₂H₅, -CH₂-CH(CH₃)-CH(CH₃)₂, -C(CH₃)₂-C₃H₇,
 -C(CH₃)₂-CH(CH₃)₂, -C₂H₄-C(CH₃)₃, -CH(CH₃)-C(CH₃)₃, -C₇H₁₅, -C₈H₁₇,
 -C₉H₁₉, -C₁₀H₂₁, -Ph, -CH₂-Ph, -C₂H₄-Ph, -C₂H₂-Ph, -C≡C-Ph, -CPh₃,
 -CH=CH₂, -CH₂-CH=CH₂, -C(CH₃)=CH₂, -CH=CH-CH₃, -C₂H₄-CH=CH₂,

$-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{C}_2\text{H}_5$, $-\text{CH}_2-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{CH}(\text{CH}_3)-\text{CH}=\text{CH}$,
 $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$, $-\text{C}_3\text{H}_6-\text{CH}=\text{CH}_2$,
 $-\text{C}_2\text{H}_4-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-\text{C}_2\text{H}_5$, $-\text{C}\equiv\text{CH}$, $-\text{CH}=\text{CH}-\text{C}_3\text{H}_7$, $-\text{C}\equiv\text{C}-\text{CH}_3$,
 $-\text{CH}_2-\text{C}\equiv\text{CH}$, $-\text{C}_2\text{H}_4-\text{C}\equiv\text{CH}$, $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_3$, $-\text{C}\equiv\text{C}-\text{C}_2\text{H}_5$, $-\text{C}_3\text{H}_6-\text{C}\equiv\text{CH}$,
 5 $-\text{cyclo}-\text{C}_3\text{H}_5$, $-\text{cyclo}-\text{C}_4\text{H}_7$, $-\text{cyclo}-\text{C}_5\text{H}_9$, $-\text{cyclo}-\text{C}_6\text{H}_{11}$;

and stereoisomeric forms, prodrugs, solvates, hydrates and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of cancers and proliferative diseases.

- 10 The present invention also comprises pharmaceutically acceptable salts of the compounds according to the general formula (I), all stereoisomeric forms of the compounds according to the general formula (I) as well as solvates, especially hydrates or prodrugs thereof. A prodrug is commonly described as an inactive or protected derivative of an active ingredient or a drug, which is converted to the
- 15 active ingredient or drug in the body.

The 2-phenylquinoxaline derivatives are basic and may form salts with organic or inorganic acids. Examples of suitable acids for such acid addition salt formation are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid,

20 citric acid, oxalic acid, malonic acid, salicylic acid, p-aminosalicylic acid, malic acid, fumaric acid, succinic acid, ascorbic acid, maleic acid, sulfonic acid, phosphonic acid, perchloric acid, nitric acid, formic acid, propionic acid, gluconic acid, lactic acid, tartaric acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, methanesulfonic acid,

25 ethanesulfonic acid, nitrous acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, p-toluenesulfonic acid, naphthylsulfonic acid, sulfanilic acid, camphorsulfonic acid, china acid, mandelic acid, o-methylmandelic acid, hydrogen-benzenesulfonic acid, picric acid, adipic acid, d-o-tolyltartaric acid, tartronic acid, (o, m, p)-toluic acid, naphthylamine sulfonic acid, and other mineral or carboxylic acids well

30 known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. In case, the compounds bear acidic substituents, the formation of salts with inorganic or organic bases may be possible. Examples for such bases are NaOH, KOH, NH_4OH , tetraalkylammonium hydroxide, lysine or

35 arginine and the like. Salts may be prepared in a conventional manner using methods well known in the art, for example by treatment of a solution of the compound of the general formula (I) with a solution of an acid, selected out of the group mentioned above.

Some of the compounds of the present invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric
5 solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Some compounds of the general formula (I) may exist in the form of optical isomers, e.g. enantiomers, diastereoisomers and mixtures of isomers in all ratios,
10 e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. Where a compound according to the general formula (I) contains an alkene
15 moiety, the alkene can be presented as a cis or trans isomer or a mixture thereof. When an isomeric form of a compound of the invention is provided substantially free of other isomers, it will preferably contain less than 5% w/w, more preferably less than 2% w/w and especially less than 1% w/w of the other isomer(s). The
afore-mentioned compounds are useful as pharmaceutically active agents, i.d. as
20 drugs or medicine.

The 2-phenylquinoxaline derivatives are specific inhibitors of the mitotic kinesin MPP1. The 2-phenylquinoxaline derivatives were identified as MPP1 inhibitors by means of a malachite-green based in vitro ATPase assay. The human M-Phase
25 Phosphoprotein 1 (MPP1), previously identified through a screening of a subset of proteins specifically phosphorylated at the G2/M transition, is characterized as a plus-end-directed kinesin-related protein. Recombinant MPP1 exhibits in vitro microtubule-binding and microtubule-bundling properties as well as microtubules-stimulated ATPase activity. In gliding experiments using polarity-marked
30 microtubules, MPP1 is a slow molecular motor that moves towards the microtubule plus-end at a 0.07 $\mu\text{m/s}$ speed. In cycling cells, MPP1 localizes mainly to the nuclei in interphase. During mitosis, MPP1 is diffuse throughout the cytoplasm in metaphase and subsequently localizes to the midzone to further concentrate on the midbody. MPP1 suppression by RNA interference induces failure of cell
35 division late in cytokinesis. It is assumed that MPP1 is a new mitotic molecular motor required for completion of cytokinesis.

Concerning the function of MPP1 it is suggested that inhibitors of MPP1 are useful for the treatment of any kind of cancer since MPP1 seems to be essential for mitosis.

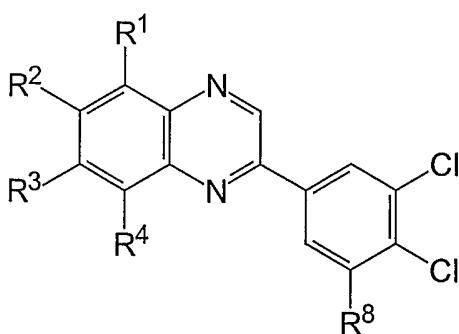
- 5 Preferred as MPP1 inhibitors and preferred for prophylaxis and/or treatment of proliferative diseases are the compounds of general formula (I) wherein R^6 is a chloro substituent. Also preferred are the 2-phenylquinoxaline derivatives wherein R^7 is a chloro substituent. Still preferred are the 2-phenylquinoxaline derivatives wherein R^1 is a chloro substituent. Preferred are also the compounds
10 of general formula (I) wherein R^3 represents $-CF_3$ group.

More preferred are the compounds wherein R^6 and R^7 represent $-Cl$ and these compounds wherein R^1 is a chloro substituent and R^3 is a $-CF_3$ group.

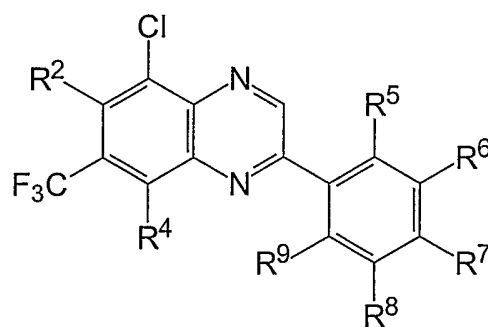
- Still more preferred are compounds wherein R^1 , R^6 and R^7 represent $-Cl$ or
15 wherein R^6 and R^7 represent $-Cl$ and R^3 is a $-CF_3$ group.

Most preferred are the 2-phenylquinoxaline derivatives wherein R^1 , R^6 and R^7 represent $-Cl$ and R^3 represents $-CF_3$.

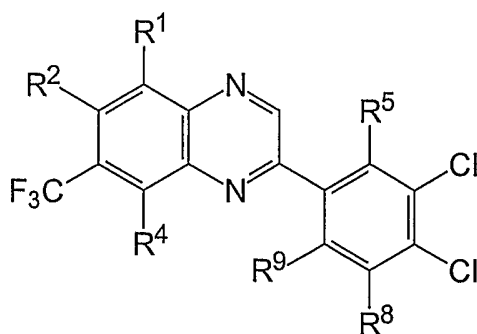
- Furthermore, the compounds belonging to one of the substructures (II) – (VII) of
20 general formula (I) are preferred:



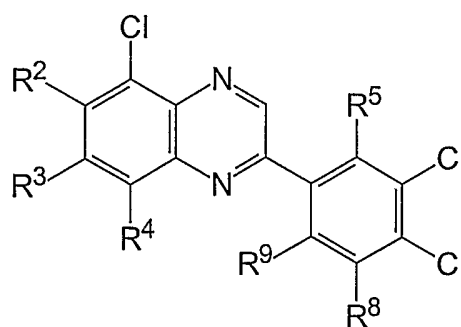
(II)



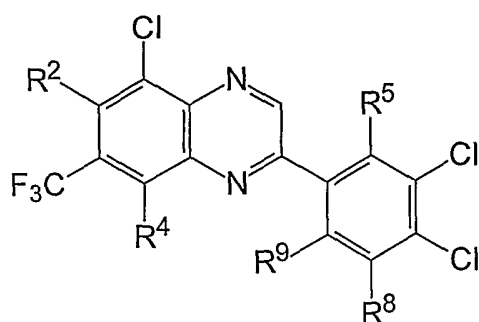
(III)



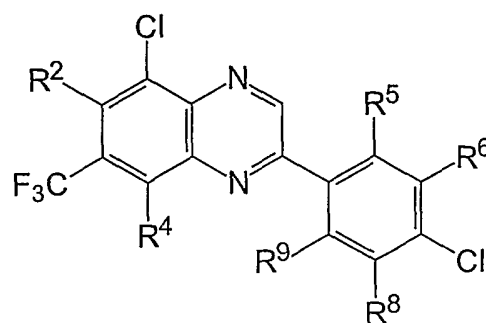
(IV)



(V)



(VI)



(VII)

Within the formula (II) – (VII) R^8 represents preferably $-Cl$, $-CF_3$, $-CH_2F$, $-CH_2Cl$, $-OCF_3$, or $-F$ or an alkyl chain consisting of 1, 2, 3, 4, or 5 carbon atoms wherein said alkyl chain is substituted with at least one hetero atom, preferably with at least one heteroatom having an electronegativity of > 2.2 , preferably > 2.5 . Within the formula (II) – (VII) R^1 represents preferably $-Cl$, $-CF_3$, $-CH_2F$, $-CH_2Cl$, $-OCF_3$, or $-F$ or an alkyl chain consisting of 1, 2, 3, 4, or 5 carbon atoms wherein said alkyl chain is substituted with at least one hetero atom, preferably with at least one heteroatom having an electronegativity of > 2.2 , preferably > 2.5 .

The 2-phenylquinoxaline derivatives disclosed herein are especially useful for the treatment of cancers and proliferative diseases including tumor growth and metastases. As proliferative diseases or cancer types the following can be mentioned:

adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary), colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas, gynecologic tumors, ear, nose and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors (gliomas), brain metastases, testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors (tumors of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer (Hodgkin's/Non-

Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarian carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinaliomas, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumors, urethral cancer, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma and tongue cancer.

15 In further preferred embodiments of the present invention, at least one compound of general formula (I) – (VII) is applied in combination with chemotherapy or any other radiotherapy for the treatment of cancer.

Furthermore, it is preferred to use at least one compound of general formula (I) –
20 (VII) in combination with a cytostatic and/or cytotoxic drug such as actinomycin D, aminoglutethimide, amsacrin, anastrozol, antagonists of purin and pyrimidin bases, anthracycline, aromatase inhibitors, asparaginase, antiestrogenes, bexaroten, bleomycin, buselerin, busulfan, camptothecin derivatives, capecitabin, carboplatin, carmustin, chlorambucil, cisplatin, cladribin, cyclophosphamide, cytarabin, cytosinarabioside, alkylating cytostatics, dacarbacin, dactinomycin,
25 daunorubicin, docetaxel, doxorubicin (adriamycin), doxorubicin lipo, epirubicin, estramustin, etoposid, exemestan, fludarabin, fluorouracil, folic acid antagonists, formestan, gemcitabin, glucocorticoides, goselerin, hormones and hormone antagonists, hycamtin, hydroxy urea, idarubicin, ifosfamid, imatinib, irinotecan, letrozol, leuprorelin, lomustin, melphalan, mercaptopurin, methotrexat, miltefosin,
30 mitomycine, mitosis inhibitors, mitoxantron, nimustine, oxaliplatin, paclitaxel, pentostatin, procarbacin, tamoxifen, temozolomid, teniposid, testolacton, thiotepa, tioguanin, topoisomerase inhibitors, topotecan, treosulfan, tretinoin, triptorelin, trofosfamide, vinblastin, vincristin, vindesin, vinorelbin, antibiotics with cytotoxic activities.
35

Still another aspect of the present invention relates to pharmaceutical compositions comprising at least one compound according to general formula (I) –

(VII) as an active ingredient, together with at least one pharmaceutically acceptable carrier, excipient, binders, disintegrates, glidants, diluents, lubricants, coloring agents, sweetening agents, flavoring agents, preservatives or the like. The pharmaceutical compositions of the present invention can be prepared in a conventional solid or liquid carrier or diluents and a conventional pharmaceutically-made adjuvant at suitable dosage level in a known way. The preferred preparations are adapted for oral application. These administration forms include, for example, pills, tablets, film tablets, coated tablets, capsules, liposomal formulations, micro- and nano-formulations, powders and deposits.

Furthermore, the present invention also includes pharmaceutical preparations for parenteral application, including dermal, intradermal, intragastral, intracutan, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutan, rectal, subcutaneous, sublingual, topical, or transdermal application, which preparations in addition to typical vehicles and/or diluents contain at least one compound according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient. Preparations for oral use are preferred.

The pharmaceutical compositions according to the present invention containing at least one compound according to the present invention and/or a pharmaceutically acceptable salt thereof as active ingredient will typically be administered together with suitable carrier materials selected with respect to the intended form of administration, i.e. for oral administration in the form of tablets, capsules (either solid filled, semi-solid filled or liquid filled), powders for constitution, aerosol preparations consistent with conventional pharmaceutical practices. The pharmaceutical formulation may further contain a cytotoxic and/or cytostatic drug. Other suitable formulations are gels, elixirs, dispersible granules, syrups, suspensions, creams, lotions, solutions, emulsions, suspensions, dispersions, and the like. Suitable dosage forms for sustained release include tablets having layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

As pharmaceutically acceptable carrier, excipient and/or diluents can be used lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid filled capsules).

Suitable binders include starch, gelatine, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes, sugars such as sucrose, starches derived from wheat corn rice and potato, natural gums such as acacia, tragacanth, derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulose materials such as methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose, polyvinylpyrrolidone, and inorganic compounds such as magnesium aluminum silicate.

5 Lubricants such as boric acid, sodium benzoate, sodium acetate, sodium chloride, magnesium stearate, calcium stearate, or potassium stearate, stearic acid, high melting point waxes, and other water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine may be used within the pharmaceutical preparations.

15 Disintegrating agents (disintegrates) such as starch, methylcellulose, guar gum, modified starches such as sodium carboxymethyl starch, natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar, cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, 20 microcrystalline celluloses, and cross-linked microcrystalline celluloses such as sodium croscarmellose, alginates such as alginic acid and sodium alginate, clays such as bentonites, and effervescent mixtures can be used.

Furthermore, coloring agents, sweetening agents, flavoring agents and/or 25 preservatives may be present in the pharmaceutical formulations.

Glidants which can be used are for example silicon dioxide and talc; suitable adsorbent are clay, aluminum oxide.

30 Suitable diluents are water or water/propylene glycol solutions for parenteral injections, juice, sugars such as lactose, sucrose, mannitol, and sorbitol, starches derived from wheat, corn rice, and potato, and celluloses such as microcrystalline cellulose.

35

Description of figures:

- 5 Figure 1 shows the potency study of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline. The inhibitory effect of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline on the *in vitro* ATPase activity of MPP1 was determined by using a malachite green assay,
- 10 Figure 2 shows *in vitro* specificity studies of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline. The inhibitory effect of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline on the ATPase activity of the indicated kinesins was determined using a malachite-green assay,
- 15 Figure 3 shows a test concerning a cellular phenotype of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline.

EXPERIMENTAL PART:

Malachite-green based in vitro ATPase assay:

5 The 2-phenylquinoxaline derivatives were measured by means of a malachite-green based (Itaya K. and Ui, M. (1966), A new micromethod for the colorimetric determination of inorganic phosphate; Clin. Chim. Acta, 14: 362 - 366) in vitro ATPase assay. For this assay the microtubule-stimulated ATPase activity of a His-tagged human MPP1 construct (Aa 1-533) in the presence of small molecules
10 or DMSO as a solvent control were measured. These studies are done in 384-well plates in which individual compounds of a large compound collection are transferred into each well using a liquid handling robot.

15 Potency study:

The potency of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline as a representative example of the 2-phenylquinoxaline derivatives of general formula (I) was determined by measuring MPP1's microtubule-stimulated ATPase activity in vitro in the presence of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)-
20 quinoxaline or DMSO as a solvent control. For these studies a malachite green assay which allows the quantification of free phosphate (Pi) in solution was used.

It was found that 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline inhibits the in vitro ATPase activity of MPP1 with an IC₅₀ of approximately 40 µM
25 (cf. Fig. 1).

Specificity:

The specificity of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline
30 was determined by measuring its effect on the microtubule-stimulated in vitro ATPase activities of the kinesins Eg5, Kif4, Mklp1, and Mklp2.

The compound 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline has no significant effect on the in vitro ATPase activities of Eg5, Kif4, Mklp1, and
35 Mklp2 (cf. Fig. 2).

Cellular phenotype:

Concerning the study the function of MPP1 in living cells, it was tested whether 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline induces a phenotype similar to the one obtained by RNAi-mediated depletion of MPP1. For these studies we treated synchronized BSC-1 (African green monkey) cells with 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline or DMSO as a solvent control.

BSC-1 cells were released from thymidine-block for three hours and then treated with 50µM or the indicated concentrations of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline for 18 hours. Treated cells were fixed with formaldehyde-containing buffer and the DNA and microtubule cytoskeleton were visualized with Hoechst and FITC-labeled anti-tubulin antibody, respectively. The number of binucleated cells was determined by manual counting of at least 200 cells per concentration.

It was found that the compound 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline induces a binucleate phenotype in BSC-1 with an EC₅₀ of about 50 µM. Similarly, 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline induces a binucleate phenotype in Hela S3 cells (cf. Fig. 3).

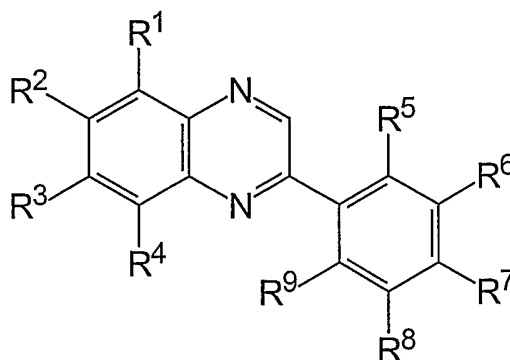
Specificity in vivo:

For the specificity *in vivo* studies, the effect of 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline on cellular processes known to be independent of MPP1 function, e.g. golgi/lysosome localization, actin/microtubule cytoskeleton in interphase, protein synthesis, S to M-phase cell cycle progression, and wound healing was investigated.

The compound 5-chloro-2-(3,4-dichlorophenyl)-7-(trifluoromethyl)quinoxaline had no observable effect on the tested cellular processes.

Claims

1. Compounds having the general formula (I):



5

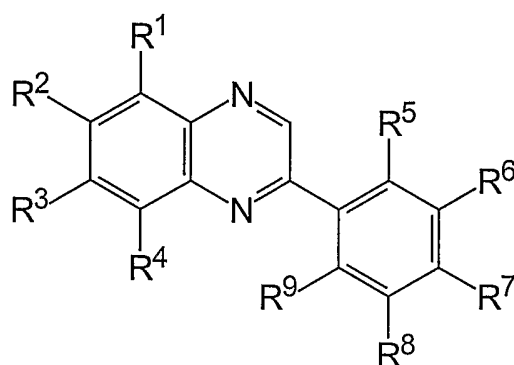
wherein

$R^1, R^2, R^3, R^4, R^5, R^8,$ and R^9 are independently of each other selected from $R^{10} - R^{18}, -CH_2-R^{19}, -C_2H_4-R^{20}, -C_3H_6-R^{21}, -C_4H_8-R^{22}, -C_5H_{10}-R^{23}, -C_6H_{12}-R^{24}, -C_7H_{14}-R^{25}, -CHR^{26}R^{27}, -CR^{28}R^{29}R^{30}, -CHR^{31}-CHR^{32}R^{33}, -CR^{34}R^{35}-CR^{36}R^{37}R^{38}, -CHR^{39}-CHR^{40}-CHR^{41}R^{42}, -CR^{43}R^{44}-CR^{45}R^{46}-CR^{47}R^{48}R^{49};$

$R^{10} - R^{49}$ represent independently of each other $-H, -OH, -OCH_3, -OC_2H_5, -OC_3H_7, -O-cyclo-C_3H_5, -OCH(CH_3)_2, -OC(CH_3)_3, -OC_4H_9, -OPh, -OCH_2-Ph, -OCPh_3, -SH, -SCH_3, -SC_2H_5, -SC_3H_7, -S-cyclo-C_3H_5, -SCH(CH_3)_2, -SC(CH_3)_3, -NO_2, -F, -Cl, -Br, -I, -N_3, -CN, -OCN, -NCO, -SCN, -NCS, -CHO, -COCH_3, -COC_2H_5, -COC_3H_7, -CO-cyclo-C_3H_5, -COCH(CH_3)_2, -COC(CH_3)_3, -COOH, -COCN, -COOCH_3, -COOC_2H_5, -COOC_3H_7, -COO-cyclo-C_3H_5, -COOCH(CH_3)_2, -COOC(CH_3)_3, -OOC-CH_3, -OOC-C_2H_5, -OOC-C_3H_7, -OOC-cyclo-C_3H_5, -OOC-CH(CH_3)_2, -OOC-C(CH_3)_3, -CONH_2, -CONHCH_3, -CONHC_2H_5, -CONHC_3H_7, -CONH-cyclo-C_3H_5, -CONH[CH(CH_3)_2], -CONH[C(CH_3)_3], -CON(CH_3)_2, -CON(C_2H_5)_2, -CON(C_3H_7)_2, -CON(cyclo-C_3H_5)_2, -CON[CH(CH_3)_2]_2, -CON[C(CH_3)_3]_2, -NH_2, -NHCH_3, -NHC_2H_5, -NHC_3H_7, -NH-cyclo-C_3H_5, -NHCH(CH_3)_2, -NHC(CH_3)_3, -N(CH_3)_2, -N(C_2H_5)_2, -N(C_3H_7)_2, -N(cyclo-C_3H_5)_2, -N[CH(CH_3)_2]_2, -N[C(CH_3)_3]_2, -SOCH_3, -SOC_2H_5, -SOC_3H_7, -SO-cyclo-C_3H_5, -SOCH(CH_3)_2, -SOC(CH_3)_3, -SO_2CH_3, -SO_2C_2H_5, -SO_2C_3H_7, -SO_2-cyclo-C_3H_5, -SO_2CH(CH_3)_2, -SO_2C(CH_3)_3, -SO_3H, -SO_3CH_3, -SO_3C_2H_5, -SO_3C_3H_7, -SO_3-cyclo-C_3H_5, -SO_3CH(CH_3)_2, -SO_3C(CH_3)_3, -OCF_3, -OC_2F_5, -O-COOCH_3, -O-COOC_2H_5, -O-COOC_3H_7, -O-COO-cyclo-C_3H_5,$

- O-COOCH(CH₃)₂, -O-COOC(CH₃)₃, -NH-CO-NH₂, -NH-CO-NHCH₃,
 -NH-CO-NHC₂H₅, -NH-CO-NHC₃H₇, -NH-CO-NH-cyclo-C₃H₅,
 -NH-CO-NH[CH(CH₃)₂], -NH-CO-NH[C(CH₃)₃], -NH-CO-N(CH₃)₂,
 -NH-CO-N(C₂H₅)₂, -NH-CO-N(C₃H₇)₂, -NH-CO-N(cyclo-C₃H₅)₂,
 5 -NH-CO-N[CH(CH₃)₂]₂, -NH-CO-N[C(CH₃)₃]₂, -NH-CS-NH₂,
 -NH-CS-NH-cyclo-C₃H₅, -NH-CS-NHC₃H₇, -NH-CS-NH[CH(CH₃)₂],
 -NH-CS-NH[C(CH₃)₃], -NH-CS-N(CH₃)₂, -NH-CS-N(C₂H₅)₂,
 -NH-CS-N(C₃H₇)₂, -NH-CS-N(cyclo-C₃H₅)₂, -NH-C(=NH)-NH₂,
 -NH-CS-NHC₂H₅, -NH-CS-NHCH₃, -O-CO-NH₂, -O-CO-NHCH₃,
 10 -O-CO-NHC₂H₅, -O-CO-NHC₃H₇, -O-CO-NH-cyclo-C₃H₅,
 -O-CO-NH[CH(CH₃)₂], -O-CO-NH[C(CH₃)₃], -O-CO-N(CH₃)₂,
 -O-CO-N(C₂H₅)₂, -O-CO-N(C₃H₇)₂, -O-CO-N(cyclo-C₃H₅)₂,
 -O-CO-N[CH(CH₃)₂]₂, -O-CO-N[C(CH₃)₃]₂, -O-CO-OCH₃,
 -O-CO-OC₂H₅, -O-CO-OC₃H₇, -O-CO-O-cyclo-C₃H₅,
 15 -O-CO-OCH(CH₃)₂, -O-CO-OC(CH₃)₃, -CH₂F -CHF₂, -CF₃, -CH₂Cl,
 -CHCl₂, -CCl₃, -CH₂Br -CHBr₂, -CBr₃, -CPh₃, -CH₂-CH₂F
 -CH₂-CHF₂, -CH₂-CF₃, -CH₂-CH₂Cl, -CH₂-CHCl₂, -CH₂-CCl₃,
 -CH₂-CH₂Br -CH₂-CHBr₂, -CH₂-CBr₃, -CH₃, -C₂H₅, -C₃H₇,
 -CH(CH₃)₂, -C₄H₉, -CH₂-CH(CH₃)₂, -CH(CH₃)-C₂H₅, -C(CH₃)₃,
 20 -C₅H₁₁, -CH(CH₃)-C₃H₇, -CH₂-CH(CH₃)-C₂H₅, -CH(CH₃)-CH(CH₃)₂,
 -C(CH₃)₂-C₂H₅, -CH₂-C(CH₃)₃, -CH(C₂H₅)₂, -C₂H₄-CH(CH₃)₂,
 -C₆H₁₃, -C₃H₆-CH(CH₃)₂, -C₂H₄-CH(CH₃)-C₂H₅, -CH(CH₃)-C₄H₉,
 -CH₂-CH(CH₃)-C₃H₇, -CH(CH₃)-CH₂-CH(CH₃)₂, -CH₂-C(CH₃)₂-C₂H₅,
 -CH(CH₃)-CH(CH₃)-C₂H₅, -CH₂-CH(CH₃)-CH(CH₃)₂, -C(CH₃)₂-C₃H₇,
 25 -C(CH₃)₂-CH(CH₃)₂, -C₂H₄-C(CH₃)₃, -CH(CH₃)-C(CH₃)₃, -C₇H₁₅,
 -C₈H₁₇, -C₉H₁₉, -C₁₀H₂₁, -Ph, -CH₂-Ph, -C₂H₄-Ph, -C₂H₂-Ph,
 -C≡C-Ph, -CPh₃, -CH=CH₂, -CH₂-CH=CH₂, -C(CH₃)=CH₂, -CH=CH-CH₃,
 -C₂H₄-CH=CH₂, -CH₂-CH=CH-CH₃, -CH=CH-C₂H₅, -CH₂-C(CH₃)=CH₂,
 -CH(CH₃)-CH=CH, -CH=C(CH₃)₂, -C(CH₃)=CH-CH₃, -CH=CH-CH=CH₂,
 30 -C₃H₆-CH=CH₂, -C₂H₄-CH=CH-CH₃, -CH₂-CH=CH-C₂H₅, -C≡CH,
 -CH=CH-C₃H₇, -C≡C-CH₃, -CH₂-C≡CH, -C₂H₄-C≡CH,
 -CH₂-C≡C-CH₃, -C≡C-C₂H₅, -C₃H₆-C≡CH, -cyclo-C₃H₅,
 -cyclo-C₄H₇, -cyclo-C₅H₉, -cyclo-C₆H₁₁;
 R⁶ and R⁷ represent -Cl; and
 35 at least one of the substituents R⁵, R⁸, and R⁹ is different from hydrogen;
 and stereoisomeric forms, prodrugs, solvates, hydrates and/or
 pharmaceutically acceptable salts thereof.

2. Compound according to claim 1 wherein R^1 represents $-\text{Cl}$.
3. Compound according to claim 1 or 2 wherein R^3 represents $-\text{CF}_3$.
- 5 4. Compound according to any previous claim for use as a pharmaceutically active agent.
5. Use of a compound having the general formula (I):



wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently of each other selected from $R^{10} - R^{18}$, $-\text{CH}_2-R^{19}$, $-\text{C}_2\text{H}_4-R^{20}$, $-\text{C}_3\text{H}_6-R^{21}$, $-\text{C}_4\text{H}_8-R^{22}$, $-\text{C}_5\text{H}_{10}-R^{23}$, $-\text{C}_6\text{H}_{12}-R^{24}$, $-\text{C}_7\text{H}_{14}-R^{25}$, $-\text{CHR}^{26}R^{27}$, $-\text{CR}^{28}R^{29}R^{30}$, $-\text{CHR}^{31}-\text{CHR}^{32}R^{33}$, $-\text{CR}^{34}R^{35}-\text{CR}^{36}R^{37}R^{38}$, $-\text{CHR}^{39}-\text{CHR}^{40}-\text{CHR}^{41}R^{42}$, $-\text{CR}^{43}R^{44}-\text{CR}^{45}R^{46}-\text{CR}^{47}R^{48}R^{49}$,

$R^{10} - R^{49}$ represent independently of each other $-\text{H}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{OC}_3\text{H}_7$, $-\text{O-cyclo-C}_3\text{H}_5$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OC}(\text{CH}_3)_3$, $-\text{OC}_4\text{H}_9$, $-\text{OPh}$, $-\text{OCH}_2-\text{Ph}$, $-\text{OCPh}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SC}_2\text{H}_5$, $-\text{SC}_3\text{H}_7$, $-\text{S-cyclo-C}_3\text{H}_5$, $-\text{SCH}(\text{CH}_3)_2$, $-\text{SC}(\text{CH}_3)_3$, $-\text{NO}_2$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{OCN}$, $-\text{NCO}$, $-\text{SCN}$, $-\text{NCS}$, $-\text{CHO}$, $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$, $-\text{COC}_3\text{H}_7$, $-\text{CO-cyclo-C}_3\text{H}_5$, $-\text{COCH}(\text{CH}_3)_2$, $-\text{COC}(\text{CH}_3)_3$, $-\text{COOH}$, $-\text{COCN}$, $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$, $-\text{COOC}_3\text{H}_7$, $-\text{COO-cyclo-C}_3\text{H}_5$, $-\text{COOCH}(\text{CH}_3)_2$, $-\text{COOC}(\text{CH}_3)_3$, $-\text{OOC-CH}_3$, $-\text{OOC-C}_2\text{H}_5$, $-\text{OOC-C}_3\text{H}_7$, $-\text{OOC-cyclo-C}_3\text{H}_5$, $-\text{OOC-CH}(\text{CH}_3)_2$, $-\text{OOC-C}(\text{CH}_3)_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CONHC}_2\text{H}_5$, $-\text{CONHC}_3\text{H}_7$, $-\text{CONH-cyclo-C}_3\text{H}_5$, $-\text{CONH}[\text{CH}(\text{CH}_3)_2]$, $-\text{CONH}[\text{C}(\text{CH}_3)_3]$, $-\text{CON}(\text{CH}_3)_2$, $-\text{CON}(\text{C}_2\text{H}_5)_2$, $-\text{CON}(\text{C}_3\text{H}_7)_2$, $-\text{CON}(\text{cyclo-C}_3\text{H}_5)_2$, $-\text{CON}[\text{CH}(\text{CH}_3)_2]_2$, $-\text{CON}[\text{C}(\text{CH}_3)_3]_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHC}_2\text{H}_5$, $-\text{NHC}_3\text{H}_7$, $-\text{NH-cyclo-C}_3\text{H}_5$, $-\text{NHCH}(\text{CH}_3)_2$, $-\text{NHC}(\text{CH}_3)_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{C}_2\text{H}_5)_2$, $-\text{N}(\text{C}_3\text{H}_7)_2$, $-\text{N}(\text{cyclo-C}_3\text{H}_5)_2$, $-\text{N}[\text{CH}(\text{CH}_3)_2]_2$, $-\text{N}[\text{C}(\text{CH}_3)_3]_2$, $-\text{SOCH}_3$,

- SOC₂H₅, -SOC₃H₇, -SO-cyclo-C₃H₅, -SOCH(CH₃)₂, -SOC(CH₃)₃,
 -SO₂CH₃, -SO₂C₂H₅, -SO₂C₃H₇, -SO₂-cyclo-C₃H₅, -SO₂CH(CH₃)₂,
 -SO₂C(CH₃)₃, -SO₃H, -SO₃CH₃, -SO₃C₂H₅, -SO₃C₃H₇,
 -SO₃-cyclo-C₃H₅, -SO₃CH(CH₃)₂, -SO₃C(CH₃)₃, -OCF₃, -OC₂F₅,
 5 -O-COOCH₃, -O-COOC₂H₅, -O-COOC₃H₇, -O-COO-cyclo-C₃H₅,
 -O-COOCH(CH₃)₂, -O-COOC(CH₃)₃, -NH-CO-NH₂, -NH-CO-NHCH₃,
 -NH-CO-NHC₂H₅, -NH-CO-NHC₃H₇, -NH-CO-NH-cyclo-C₃H₅,
 -NH-CO-NH[CH(CH₃)₂], -NH-CO-NH[C(CH₃)₃], -NH-CO-N(CH₃)₂,
 -NH-CO-N(C₂H₅)₂, -NH-CO-N(C₃H₇)₂, -NH-CO-N(cyclo-C₃H₅)₂,
 10 -NH-CO-N[CH(CH₃)₂]₂, -NH-CO-N[C(CH₃)₃]₂, -NH-CS-NH₂,
 -NH-CS-NH-cyclo-C₃H₅, -NH-CS-NHC₃H₇, -NH-CS-NH[CH(CH₃)₂],
 -NH-CS-NH[C(CH₃)₃], -NH-CS-N(CH₃)₂, -NH-CS-N(C₂H₅)₂,
 -NH-CS-N(C₃H₇)₂, -NH-CS-N(cyclo-C₃H₅)₂, -NH-C(=NH)-NH₂,
 -NH-CS-NHC₂H₅, -NH-CS-NHCH₃, -O-CO-NH₂, -O-CO-NHCH₃,
 15 -O-CO-NHC₂H₅, -O-CO-NHC₃H₇, -O-CO-NH-cyclo-C₃H₅,
 -O-CO-NH[CH(CH₃)₂], -O-CO-NH[C(CH₃)₃], -O-CO-N(CH₃)₂,
 -O-CO-N(C₂H₅)₂, -O-CO-N(C₃H₇)₂, -O-CO-N(cyclo-C₃H₅)₂,
 -O-CO-N[CH(CH₃)₂]₂, -O-CO-N[C(CH₃)₃]₂, -O-CO-OCH₃,
 -O-CO-OC₂H₅, -O-CO-OC₃H₇, -O-CO-O-cyclo-C₃H₅,
 20 -O-CO-OCH(CH₃)₂, -O-CO-OC(CH₃)₃, -CH₂F -CHF₂, -CF₃, -CH₂Cl,
 -CHCl₂, -CCl₃, -CH₂Br -CHBr₂, -CBr₃, -CPh₃, -CH₂-CH₂F
 -CH₂-CHF₂, -CH₂-CF₃, -CH₂-CH₂Cl, -CH₂-CHCl₂, -CH₂-CCl₃,
 -CH₂-CH₂Br -CH₂-CHBr₂, -CH₂-CBr₃, -CH₃, -C₂H₅, -C₃H₇,
 -CH(CH₃)₂, -C₄H₉, -CH₂-CH(CH₃)₂, -CH(CH₃)-C₂H₅, -C(CH₃)₃,
 25 -C₅H₁₁, -CH(CH₃)-C₃H₇, -CH₂-CH(CH₃)-C₂H₅, -CH(CH₃)-CH(CH₃)₂,
 -C(CH₃)₂-C₂H₅, -CH₂-C(CH₃)₃, -CH(C₂H₅)₂, -C₂H₄-CH(CH₃)₂,
 -C₆H₁₃, -C₃H₆-CH(CH₃)₂, -C₂H₄-CH(CH₃)-C₂H₅, -CH(CH₃)-C₄H₉,
 -CH₂-CH(CH₃)-C₃H₇, -CH(CH₃)-CH₂-CH(CH₃)₂, -CH₂-C(CH₃)₂-C₂H₅,
 -CH(CH₃)-CH(CH₃)-C₂H₅, -CH₂-CH(CH₃)-CH(CH₃)₂, -C(CH₃)₂-C₃H₇,
 30 -C(CH₃)₂-CH(CH₃)₂, -C₂H₄-C(CH₃)₃, -CH(CH₃)-C(CH₃)₃, -C₇H₁₅,
 -C₈H₁₇, -C₉H₁₉, -C₁₀H₂₁, -Ph, -CH₂-Ph, -C₂H₄-Ph, -C₂H₂-Ph,
 -C≡C-Ph, -CPh₃, -CH=CH₂, -CH₂-CH=CH₂, -C(CH₃)=CH₂, -CH=CH-CH₃,
 -C₂H₄-CH=CH₂, -CH₂-CH=CH-CH₃, -CH=CH-C₂H₅, -CH₂-C(CH₃)=CH₂,
 -CH(CH₃)-CH=CH, -CH=C(CH₃)₂, -C(CH₃)=CH-CH₃, -CH=CH-CH=CH₂,
 35 -C₃H₆-CH=CH₂, -C₂H₄-CH=CH-CH₃, -CH₂-CH=CH-C₂H₅, -C≡CH,
 -CH=CH-C₃H₇, -C≡C-CH₃, -CH₂-C≡CH, -C₂H₄-C≡CH,
 -CH₂-C≡C-CH₃, -C≡C-C₂H₅, -C₃H₆-C≡CH, -cyclo-C₃H₅,
 -cyclo-C₄H₇, -cyclo-C₅H₉, -cyclo-C₆H₁₁;

and stereoisomeric forms, prodrugs, solvates, hydrates and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of cancers and proliferative diseases.

- 5 6. Use of a compound according to claim 5 as an inhibitor of the mitotic kinesin MPP1.
7. Use of a compound according to claim 5 or 6 wherein R⁶ and/or R⁷ represent(s) -Cl.
- 10 8. Use of a compound according to any one of claims 5 – 7 wherein R¹ represents -Cl.
- 15 9. Use of a compound according to any one of claims 5 – 8 wherein R³ represents -CF₃.
- 20 10. Use of a compound according to any one of claims 5 – 9, wherein the proliferative disease or cancer is selected from the group comprising:
adenocarcinoma, choroidal melanoma, acute leukemia, acoustic
neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell
carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial
carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-
syndrome (carcinoma of unknown primary), colorectal cancer, small
intestine cancer, small intestinal tumors, ovarian cancer, endometrial
25 carcinoma, ependymoma, epithelial cancer types, Ewing's tumors,
gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder
carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas,
gynecologic tumors, ear, nose and throat tumors, hematologic neoplasias,
hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain
30 tumors (gliomas), brain metastases, testicle cancer, hypophysis tumor,
carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone
cancer, colorectal carcinoma, head and neck tumors (tumors of the ear,
nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer
(cancer in the mouth area and on lips), cancer of the central nervous
35 system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer,
lymph node cancer (Hodgkin's/Non-Hodgkin's), lymphomas, stomach
cancer, malignant melanoma, malignant neoplasia, malignant tumors
gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas,

melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarian carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinaliomas, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumors, urethral cancer, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma and tongue cancer.

11. Use of a compound according to any one of claims 5 – 10 in combination with chemotherapy or radiotherapy.

12. Use of a compound according to any one of claims 5 – 11 in combination with actinomycin D, aminoglutethimide, amsacrin, anastrozol, antagonists of purin and pyrimidin bases, anthracycline, aromatase inhibitors, asparaginase, antiestrogenes, bexaroten, bleomycin, buselerin, busulfan, camptothecin derivates, capecitabin, carboplatin, carmustin, chlorambucil, cisplatin, cladribin, cyclophosphamide, cytarabin, cytosinarabinoside, alkylating cytostatics, dacarbacin, dactinomycin, daunorubicin, docetaxel, doxorubicin (adriamycin), doxorubicin lipo, epirubicin, estramustin, etoposid, exemestan, fludarabin, fluorouracil, folic acid antagonists, formestan, gemcitabin, glucocorticoides, goselerin, hormones and hormone antagonists, hycamtin, hydroxy urea, idarubicin, ifosfamid, imatinib, irinotecan, letrozol, leuprorelin, lomustin, melphalan, mercaptopurin, methotrexat, miltefosin, mitomycine, mitosis inhibitors, mitoxantron, nimustine, oxaliplatin, paclitaxel, pentostatin, procarbacin, tamoxifen, temozolomid, teniposid, testolacton, thiotepa, tioguanin, topoiso­merase inhibitors, topotecan, treosulfan, tretinoin, triptorelin, trofosfamide, vinblastin, vincristin, vindesin, vinorelbin, antibiotics with cytotoxic activities.

13. Pharmaceutical composition comprising at least one compound of general formula (I) as an active ingredient, together with at least one pharmaceutically acceptable carrier, excipient and/or diluents.

FIGURES

Figure 1 / 3

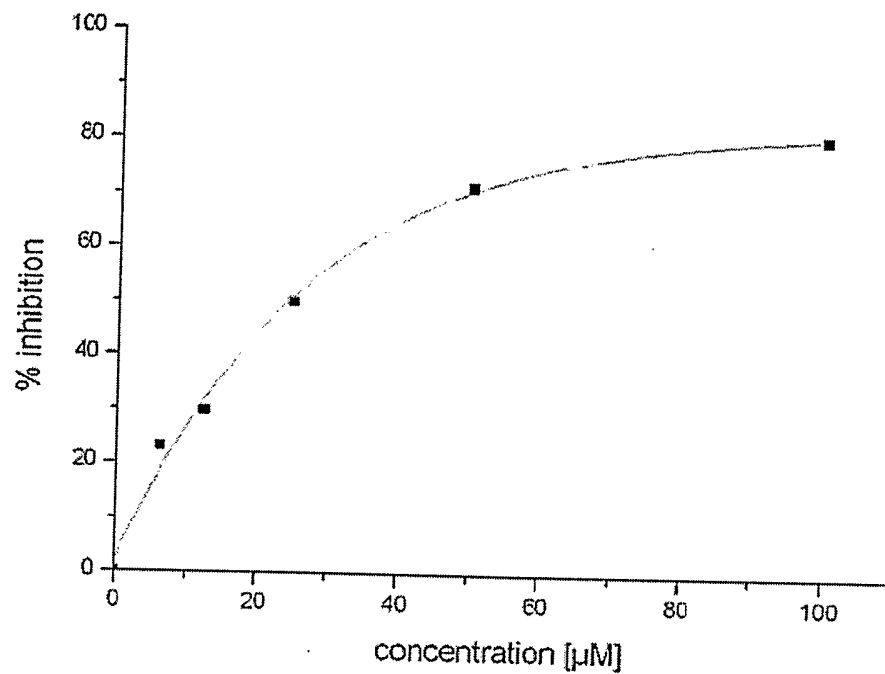


Figure 2 / 3

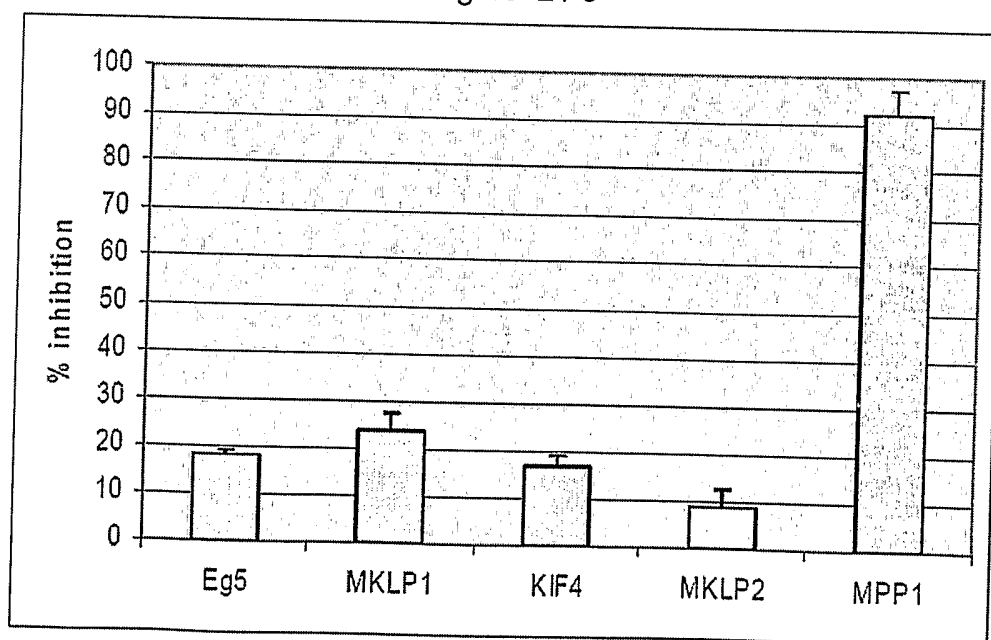
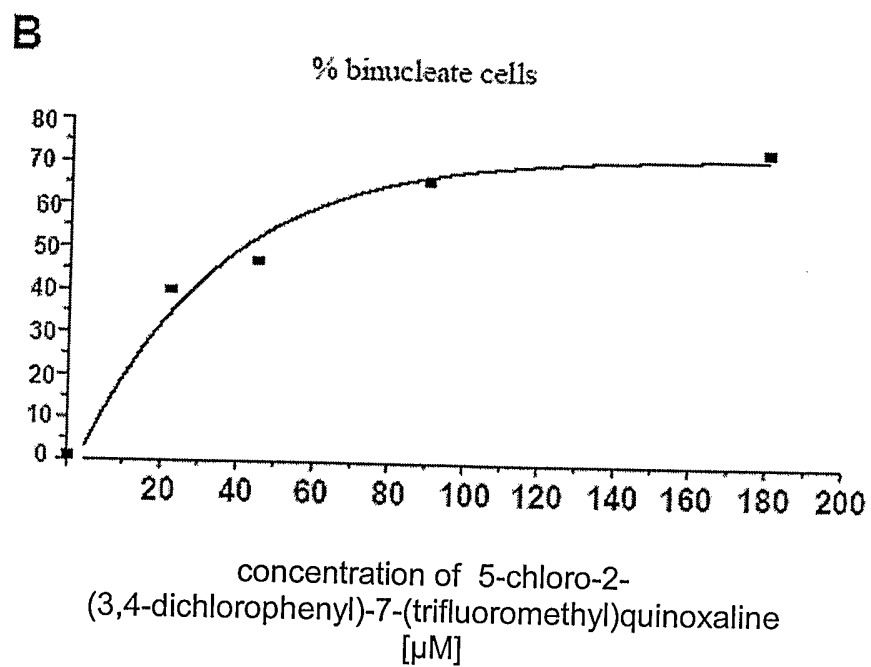


Figure 3 / 3



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/000459

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/498 C07D241/42 A61P35/00

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)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIM ANTHONY C ET AL: "Complete genomic organization of the human erythroid p55 gene (MPP1), a membrane-associated guanylate kinase homologue" 1996, GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, PAGE(S) 223-229, XP002204146 ISSN: 0888-7543 the whole document	1-13
X	WHATMORE, JACQUELINE L. ET AL: "Comparative study of isoflavone, quinoxaline and oxindole families of anti-angiogenic agents" ANGIOGENESIS, 5(1-2), 45-51 CODEN: AGIOFT; ISSN: 0969-6970, 2002, XP002332504 page 49-compounds 3-6 page 45 - page 46 ----- -/--	5-12

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* 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 document 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.

Z document member of the same patent family

Date of the actual completion of the international search

18 May 2006

Date of mailing of the international search report

29/05/2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/000459

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG, SHOUMING ET AL: "Structure-activity relationships for analogues of the phenazine-based dual topoisomerase I/II inhibitor XR11576" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 12(3), 415-418 CODEN: BMCLE8; ISSN: 0960-894X, 2002, XP002332505 teable 1-compounds 12a and 12b page 415 - page 418	5-12
X	GAZIT, AVIV ET AL: "Tyrphostins. 5. Potent Inhibitors of Platelet-Derived Growth Factor Receptor Tyrosine Kinase: Structure-Activity Relationships in Quinoxalines, Quinolines, and Indole Tyrphostins" JOURNAL OF MEDICINAL CHEMISTRY , 39(11), 2170-7 CODEN: JMCMAR; ISSN: 0022-2623, 1996, XP002332506 Tables 3-compounds 24-27, 39-40, 43-45, 52, 54 page 2170 - page 2174	5-12
X	WO 95/15758 A (RHONE-POULENC RORER PHARMACEUTICALS INC; MYERS, MICHAEL, R; SPADA, ALF) 15 June 1995 (1995-06-15) the whole document	5-12
X	WO 2004/043458 A (ABBOTT LABORATORIES) 27 May 2004 (2004-05-27) see compounds with rn: 693775-27-8P, 693775-28-9p, 689292-09-9P, 689292-10-2P page 72, lines 16-24; claim 42	5-12
X	WO 03/062234 A (YAMANOUCHI PHARMACEUTICAL CO., LTD; TAKAYAMA, KAZUHISA; MASUDA, NAOYUK) 31 July 2003 (2003-07-31) table 2-compounds 40, 6, 43-46; table 11; table 16; abstract	5-12
X	WO 03/007959 A (FUJISAWA PHARMACEUTICAL CO., LTD; HATTORI, KOUJI; YAMAMOTO, HIROFUMI;) 30 January 2003 (2003-01-30) table 1; table 2 compounds 1-3, 7-8; table 3; table 5 page 25, lines 7-12	5-12
X	WO 02/080855 A (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 17 October 2002 (2002-10-17) figure 14d page 1	5-12
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/000459

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/030635 A (TARGESEN, INC; WRASIDLO, WOLFGANG; DOUKAS, JOHN; ROYSTON, IVOR; NORONH) 15 April 2004 (2004-04-15) compounds with rn: 32044-95-4P, 102554-55-2P, 126988-00-9p, 677297-85-7p, 677297-86-8p, 677298-50-9p page 44 - page 52 pages 1-5 -----	5-12
X	US 6 331 555 B1 (HIRTH KLAUS P ET AL) 18 December 2001 (2001-12-18) fig. 1g-1-compoundsG10, G13G14, G17, G19, -G21, G23, G24, G27, column 3 - column 6 -----	5-12
X	WO 95/21613 A (SUGEN, INC; YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW) 17 August 1995 (1995-08-17) compounds with rn77093-88-0, 146535-11-7 page 61 - page 63 -----	5-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/000459

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-12 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/000459

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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