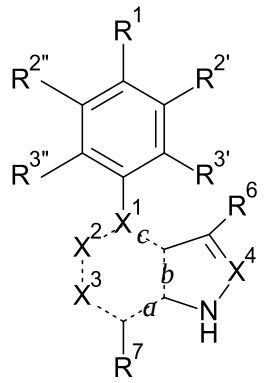
Sulfone derivatives

The present ~~invention~~disclosure provides compounds which are inhibitors of the Human methionine adenosyltransferase 2A (Mat2A), for use in the treatment, prevention and/or delay of progression of Cancer.

In ~~particular~~one aspect, the present ~~invention~~disclosure relates to a compound~~s~~ of formula I



(I)

wherein

X^1 is either N or C

X^2 is either N or CR^4

X^3 is either N or CR^5

X^4 is either N or CH

provided that no more than two of X^1, X^2 and X^3 represent N ;

the dotted lines represent a single or double bond, to enable the six membered rings to be aromatic with the proviso that when X^1 is N and X^2 is C=O then the bond between X^1 and X^2, the bond between X^2 and X^3, the bonds *a* and *c* are single bonds and the bond between X^3 and CR^7 and b are double bonds; and with the proviso that when X^1 is N and X^2 is not C=O then the bond between X^1 and X^2, the bond between X^3 and CR^7, the bonds *b* and *c* are single bonds and the bond between X^2 and X^3 and the bond *a* are double bonds;

R^1 is $-SO_2R^{1a}$ or $–SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $NR^{1'a}R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is $(C_1\text{-}C_6)$alkyl and the other is H or $(C_1\text{-}C_6)$alkyl; or

$R^{2'}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{2''}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3'}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3''}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

R^4 is hydrogen, cyano, oxo, hydroxy, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, -CO_2R^{4a}, -$CONR^{4b}R^{4c}$, -SO_2R^{4d}, -SOR^{4e}, –SR^{4f}, -$SO(NR^{4h})R^{4g}$ or -$SO_2(NR^{4i})R^{4j}$;

R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4h} and R^{4g} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4i} and R^{4j} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^5 is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, oxetanyl or thiophenyl or –SO_2R^{6a} ;

R^{6a} is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or halo(C_1-C_6) alkyl;

R^7 is hydrogen, halogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, halo-(C_1-C_6)alkoxy or $NR^{7'a}$ $R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NH_2, -(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl or -(C_1-C_6)alkyl-NH_2;

and pharmaceutically acceptable salts thereof.

In another aspect, the present disclosure relates to a compound as described herein for use as a therapeutically active substance.

In another aspect, the present disclosure relates to pharmaceutical compositions comprising compounds of formula I as described herein or their pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure relates to compounds of formula I as described herein or their pharmaceutically acceptable salts above for use as therapeutically active substances.

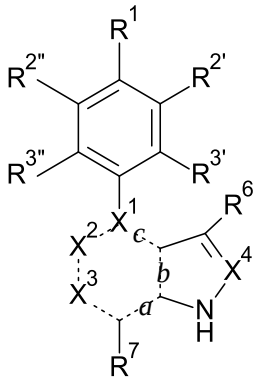
In another aspect, the present disclosure relates to compounds of formula I as described herein or their pharmaceutically acceptable salts for the use in the treatment, prevention and/or delay of progression of Lung Aenocarcinoma, Melanoma, Pancreatic Adenocarcinoma, Head and Neck Squamous Cell Carcinoma, Lung Squamous Cell Carcinoma, Esophageal Carcinoma, Glioblastmoa Multiforme, and Mesothelioma.

In another aspect, the present disclosure relates to use of compounds of formula I as described herein or their pharmaceutically acceptable salts in the preparation of a medicament for the treatment or prevention of Lung Aenocarcinoma, Melanoma, Pancreatic Adenocarcinoma, Head and Neck Squamous Cell Carcinoma, Lung Squamous Cell Carcinoma, Esophageal Carcinoma, Glioblastmoa Multiforme, and Mesothelioma.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

Claims:

1. A compound of formula I



(I)

wherein

X^1 is either N or C

X^2 is either N or CR^4

X^3 is either N or CR^5

X^4 is either N or CH

provided that no more than two of X^1, X^2 and X^3 represent N ;

the dotted lines represent a single or double bond, to enable the six membered rings to be aromatic with the proviso that when X^1 is N and X^2 is C=O then the bond between X^1 and X^2, the bond between X^2 and X^3, the bonds *a* and *c* are single bonds and the bond between X^3 and CR^7 and b are double bonds; and with the proviso that when X^1 is N and X^2 is not C=O then the bond between X^1 and X^2, the bond between X^3 and CR^7, the bonds *b* and *c* are single bonds and the bond between X^2 and X^3 and the bond *a* are double bonds;

R^1 is $-SO_2R^{1a}$ or $-SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $NR^{1'a}R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is $(C_1\text{-}C_6)$alkyl and the other is H or $(C_1\text{-}C_6)$alkyl; or

$R^{2'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{2''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3'}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3''}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

R^4 is hydrogen, cyano, oxo, hydroxy, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, -CO_2R^{4a}, -$CONR^{4b}R^{4c}$, -SO_2R^{4d}, -SOR^{4e}, –SR^{4f}, -$SO(NR^{4h})R^{4g}$ or -$SO_2(NR^{4i})R^{4j}$;

R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4h} and R^{4g} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4i} and R^{4j} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^5 is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

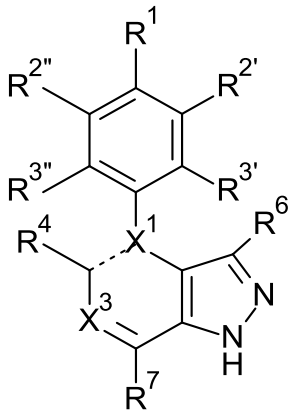
R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, oxetanyl or thiophenyl or –SO_2R^{6a} ;

R^{6a} is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or halo(C_1-C_6) alkyl;

R^7 is hydrogen, halogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, halo-(C_1-C_6)alkoxy or $NR^{7'a}$ $R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NH_2, -(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl or -(C_1-C_6)alkyl-NH_2;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein the compound is of formula Ia



(Ia)

wherein

X^1 is either N or C;

X^3 is either N or CR^5

the dotted line represents a double bond to enable the six membered rings to be aromatic with the proviso that when X^1 is N and R^4 is oxo then the bond is a single bond;

R^1 is $-SO_2R^{1a}$ or $–SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $NR^{1'a}R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is $(C_1\text{-}C_6)$alkyl and the other is H or $(C_1\text{-}C_6)$alkyl; or

$R^{2'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{2''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

R^4 is hydrogen, cyano, oxo, hydroxy, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, $-CO_2R^{4a}$, $-CONR^{4b}R^{4c}$, $-SO_2R^{4d}$, $-SOR^{4e}$, $–SR^{4f}$, $-SO(NR^{4h})R^{4g}$ or $-SO_2(NR^{4i})R^{4j}$;

R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl and oxetanyl;

R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4h} and R^{4g} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4i} and R^{4j} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

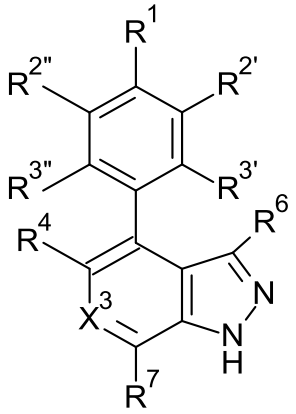
R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, oxetanyl or thiophenyl or $–SO_2R^{6a}$;

R^{6a} is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or halo(C_1-C_6) alkyl;

R^7 is hydrogen, halogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, halo-(C_1-C_6)alkoxy or $NR^{7'a}$ $R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NH_2, -(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl or -(C_1-C_6)alkyl-NH_2; and

pharmaceutically acceptable salts thereof.

3. The compound according to claim 1, wherein the compound is of formula Ib



(Ib)

wherein

X^3 is either N or CR^5

R^1 is $-SO_2R^{1a}$ or $–SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, $NR^{1'a}$ $R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is (C_1-C_6)alkyl and the other is H or (C_1-C_6)alkyl; or

$R^{2'}$ is hydrogen, halogen, $-NH_2$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{2"}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3'}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3"}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

R^4 is hydrogen, cyano, oxo, hydroxy, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, -CO_2R^{4a}, -$CONR^{4b}R^{4c}$, -SO_2R^{4d}, -SOR^{4e}, –SR^{4f}, -$SO(NR^{4h})R^{4g}$ or -$SO_2(NR^{4i})R^{4j}$;

R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4h} and R^{4g} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4i} and R^{4j} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

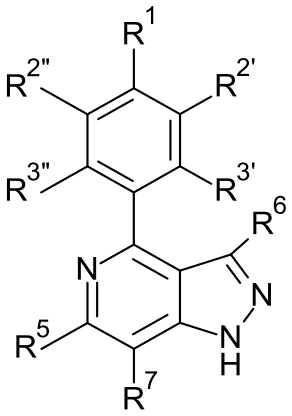
R^5 is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, oxetanyl or thiophenyl or –SO_2R^{6a} ;

R^{6a} is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or halo(C_1-C_6) alkyl;

R^7 is hydrogen, halogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, halo-(C_1-C_6)alkoxy or $NR^{7'a}$ $R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NH_2, -(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl or -(C_1-C_6)alkyl-NH_2;and pharmaceutically acceptable salts thereof.

4. The compound according to claim 1, wherein the compound is of formula Ic



(Ic)

wherein

R^1 is $-SO_2R^{1a}$ or $-SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $NR^{1'a}R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is $(C_1\text{-}C_6)$alkyl and the other is H or $(C_1\text{-}C_6)$alkyl; or

$R^{2'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{2''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

R^5 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

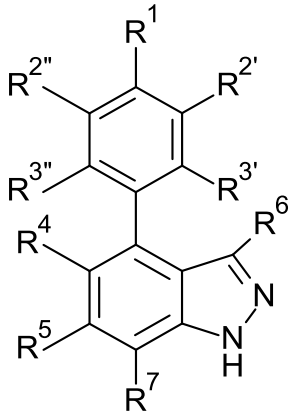
R^6 is halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, cyano, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, oxetanyl or thiophenyl or $-SO_2R^{6a}$;

R^{6a} is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl or halo$(C_1\text{-}C_6)$ alkyl;

R^7 is hydrogen, halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo-$(C_1\text{-}C_6)$alkyl, halo-$(C_1\text{-}C_6)$alkoxy or $NR^{7'a}R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, -$(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl-NHCO-$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl-NH_2, -$(C_1\text{-}C_6)$alkyl-NHCO-$(C_1\text{-}C_6)$alkyl or -$(C_1\text{-}C_6)$alkyl-NH_2; and

pharmaceutically acceptable salts thereof.

5. The compound according to claim 1, wherein the compound is of formula Id,



(Id)

wherein

R^1 is $-SO_2R^{1a}$ or $–SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, -, $NR^{1'a}R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is $(C_1\text{-}C_6)$alkyl and the other is H or $(C_1\text{-}C_6)$alkyl; or

$R^{2'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{2''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3'}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

$R^{3''}$ is hydrogen, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkoxy;

R^4 is hydrogen, cyano, oxo, hydroxy, halogen, $-NH_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, $-CO_2R^{4a}$, $-CONR^{4b}R^{4c}$, $-SO_2R^{4d}$, $-SOR^{4e}$, $–SR^{4f}$, $-SO(NR^{4h})R^{4g}$ or $-SO_2(NR^{4i})R^{4j}$;

R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl and oxetanyl;

R^{4d}, R^{4e} and R^{4f} are independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl and oxetanyl;

R^{4h} and R^{4g} are independently selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl and oxetanyl;

R^{4i} and R^{4j} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^5 is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

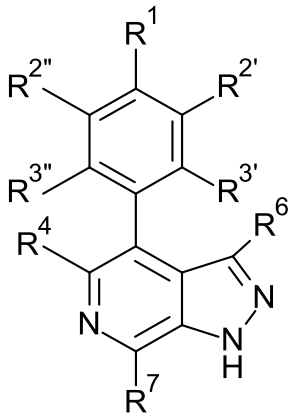
R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, oxetanyl or thiophenyl or $–SO_2R^{6a}$;

R^{6a} is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or halo(C_1-C_6) alkyl;

R^7 is hydrogen, halogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, halo-(C_1-C_6)alkoxy or $NR^{7'a}$ $R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NH_2, -(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl or -(C_1-C_6)alkyl-NH_2; and

pharmaceutically acceptable salts thereof.

6. The compound according to claim 1, wherein the compound is of formula Ie



(Ie)

wherein

R^1 is $-SO_2R^{1a}$ or $–SOR^{1b}$;

R^{1a} and R^{1b} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, $NR^{1'a}$ $R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is (C_1-C_6)alkyl and the other is H or (C_1-C_6)alkyl; or

$R^{2'}$ is hydrogen, halogen, $-NH_2$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{2"}$ is hydrogen, halogen, $-NH_2$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3'}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

$R^{3''}$ is hydrogen, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or halo(C_1-C_6)alkoxy;

R^4 is hydrogen, cyano, oxo, hydroxy, halogen, -NH_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, -CO_2R^{4a}, -$CONR^{4b}R^{4c}$, -SO_2R^{4d}, -SOR^{4e}, -$SO(NR^{4h})R^{4g}$ or -$SO_2(NR^{4i})R^{4j}$;

R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4h} and R^{4g} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^{4i} and R^{4j} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and oxetanyl;

R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, oxetanyl or thiophenyl or $-SO_2R^{6a}$;

R^{6a} is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or halo(C_1-C_6) alkyl;

R^7 is hydrogen, halogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, halo-(C_1-C_6)alkoxy or $NR^{7'a}$ $R^{7'b}$, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-NH_2, -(C_1-C_6)alkyl-NHCO-(C_1-C_6)alkyl or -(C_1-C_6)alkyl-NH_2; and

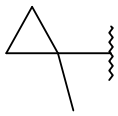
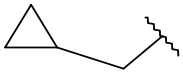
pharmaceutically acceptable salts thereof.

7. The compound according to claim 1, wherein X^4 is N.
8. The compound according to claim 1, wherein wherein X^1 is N or C, X^2 is N or CR^4 and X^3 is N or CR^5.
9. The compound according to any one of claims 1 to 8, wherein the compound is of wherein R^1 is -SO_2R^{1a}.
10. The compound according to any one of claims 1 to 9, wherein R^{1a} and R^{1b} are independently selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-

C_6)alkyl, $NR^{1'a}$ $R^{1'b}$, oxetanyl, furanyl and pyranyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is (C_1-C_6)alkyl and the other is H or (C_1-C_6)alkyl.

11. The compound according to any one of claims 1 to 10, wherein R^{1a} is selected from (C_1-C_3)alkyl, (C_3-C_4)cycloalkyl, (C_3-C_4)cycloalkyl-(C_1-C_3)alkyl, halo(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_3)alkoxy-(C_1-C_3)alkyl, $NR^{1'a}$ $R^{1'b}$ and oxetanyl, wherein at least one of $R^{1'a}$ and $R^{1'b}$ is (C_1-C_3)alkyl and the other is H or (C_1-C_3)alkyl .

12. The compound according to any one of claims 1 to 11, wherein R^{1a} is selected from

methyl, ethyl, propyl, i-propyl, i-butyl, cyclopropyl,  ,  ., fluoromethyl, difluoromethyl, fluoro-ethanyl, difluoro-ethanyl, 1,2 difluoroethanyl, 1,1,2-trifluoroethanyl, 1,2,2-trifluoroethanyl, Hydroxymethyl, hydroxyethyl, metoxymethyl, methylaminyl (-$NHCH_3$), dimethylaminyl (-$N(CH_3)_2$) and oxetanyl.

13. The compound according to any one of claims 1 to 12, wherein R^{1a} is selected from from ethyl, propyl, i-propyl, i-butyl, cyclopropyl, fluoromethyl, difluoromethyl, fluoro-ethanyl, difluoro-ethanyl, 1,2 difluoroethanyl, 1,1,2-trifluoroethanyl and 1,2,2-trifluoroethanyl.

14. The compound according to any one of claims 1 to 13, wherein R^{1a} is selected from methyl, ethyl cyclopropyl and difluoromethyl.

15. The compound according to any one of claims 1 to 14, wherein R^{1b} is (C_1-C_6)alkyl, more particularly is (C_1-C_3)alkyl, most particularly methyl.

16. The compound according to any one of claims 1 to 14, wherein if $R^{2'}$ is other than hydrogen as defined according to any claims 1 to 6, than $R^{3'}$ is hydrogen, $R^{2''}$ is hydrogen and $R^{3''}$ is as defined according to any claims 1 to 6.

17. The compound according to any one of claims 1 to 15, wherein one of $R^{2'}$ and $R^{2''}$ is hydrogen, halogen, -NH_2, (C_1-C_2)alkyl, (C_1-C_2)alkoxy or halo(C_1-C_2)alkyl, while the other one is hydrogen.

18. The compound according to any one of claims 1 to 17, wherein $R^{2'}$ is is hydrogen, halogen, -NH_2, methyl, ethyl, methoxy fluoromethyl, difluoromethyl, fluoro-ethanyl, difluoro-ethanyl or 1,2 difluoroethanyl and $R^{2''}$ is hydrogen.

19. The compound according to any one of claims 1 to 18, wherein $R^{2'}$ is methyl, ethyl, fluoromethyl, difluoromethyl, fluoro-ethanyl, difluoro-ethanyl, 1,2 difluoroethanyl and $R^{2''}$ is hydrogen.

20. The compound according to any one of claims 1 to 19, wherein $R^{2'}$ is methyl or difluoromethyl and $R^{2''}$ is hydrogen.

21. The compound according to any one of claims 1 to 20, wherein one of $R^{3'}$ and $R^{3''}$ is hydrogen, halogen, $-NH_2$, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo(C_1-C_3)alkyl, while the other one is hydrogen.

22. The compound according to any one of claims 1 to 21, wherein $R^{3''}$ is hydrogen, halogen or (C_1-C_3)alkyl and $R^{3'}$ is hydrogen.

23. The compound according to any one of claims 1 to 22, wherein $R^{3''}$ is hydrogen or fluorine and $R^{3'}$ is hydrogen.

24. The compound according to any one of claims 1 to 23, wherein both $R^{3'}$ and $R^{3''}$ are hydrogen.

25. The compound according to any one of claims 1 to 24, wherein R^4 is cyano, oxo, hydroxy, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkyl, halo(C_1-C_6)alkoxy, (C_1-C_3)alkoxy-(C_1-C_3)alkyl, (C_3-C_4)cycloalkyl, $-CO_2R^{4a}$, $--CONR^{4b}R^{4c}$, $-SO_2R^{4d}$, $-SOR^{4e}$, $-SR^{4f}$ or $-SO(NR^{4h})R^{4g}$.

26. The compound according to any one of claims 1 to 25, wherein R^4 is cyano, oxo, hydorxy, (C_1-C_2)alkoxy, halo(C_1-C_2)alkyl, halo(C_1-C_2)alkoxy, (C_1-C_2)alkoxy-(C_1-C_2)alkyl, cyclopropyl, $-CO_2H$, $--CONR^{4b}R^{4c}$, $-SO_2R^{4d}$, $-SOR^{4e}$, $-SR^{4f}$, $-SO(NH)CH_3$ or $-SO_2(NH)CH_3$.

27. The compound according to any one of claims 1 to 26, wherein R^4 is cyano, oxo, hydorxy, methoxy, $-CF_3$, $-OCF_3$, -methyl-methoxy, cyclopropyl, $-CO_2H$, $--CONR^{4b}R^{4c}$, $-SO_2R^{4d}$, $-SOR^{4e}$ or $-SR^{4f}$.

28. The compound according to any one of claims 1 to 27, wherein R^4 is cyano, oxo, $-CONHR^{4c}$ or $-SO_2R^{4d}$.

29. The compound according to any one of claims 1 to 28, wherein R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_3)alkyl, (C_3-C_4)cycloalkyl, and oxetanyl.

30. The compound according to any one of claims 1 to 29, wherein R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_3)alkyl, cyclopropyl, and oxetanyl.

31. The compound according to any one of claims 1 to 30, wherein R^{4a}, R^{4b} and R^{4c} are independently selected from hydrogen, (C_1-C_3)alkyl and cyclopropyl.

32. The compound according to any one of claims 1 to 31, wherein R^{4a} is hydrogen.

33. The compound according to any one of claims 1 to 32, wherein R^{4b} is hydrogen and R^{4c} is hydrogen or methyl.

34. The compound according to any one of claims 1 to 28, wherein R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_3)alkyl, (C_3-C_4)cycloalkyl, and oxetanyl.

35. The compound according to any one of claims 1 to 28, wherein R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_3)alkyl, cyclopropyl, and oxetanyl.

36. The compound according to any one of claims 1 to 28, wherein R^{4d}, R^{4e} and R^{4f} are independently selected from (C_1-C_3)alkyl and cyclopropyl, most particularly R^{4d} is methyl or cyclopropyl.

37. The compound according to any one of claims 1 to 28, wherein R^{4d} is methyl or cyclopropyl..

38. The compound according to any one of claims 1 to 37, wherein R^{4d} is methyl.

39. The compound according to any one of claims 1 to 25, wherein R^{4h} and R^{4g} are independently selected from hydrogen and (C_1-C_6)alkyl.

40. The compound according to any one of claims 1 to 25, wherein R^{4h} and R^{4g} are independently selected from hydrogen and (C_1-C_3)alkyl.

41. The compound according to any one of claims 1 to 25, wherein R^{4h} is hydrogen and R^{4g} is (C_1-C_3)alkyl.

42. The compound according any none of claims 1 to 25, wherein R^{4h} is hydrogen and R^{4g} is methyl.

43. The compound according to any one of claims 1 to 25, wherein R^{4i} and R^{4j} are independently selected from hydrogen and (C_1-C_6)alkyl.

44. The compound according to any one of claims 1 to 25, wherein R^{4i} and R^{4j} are independently selected from hydrogen and (C_1-C_3)alkyl.

45. The compound according to any one of claims 1 to 25, wherein R^{4i} is hydrogen and R^{4j} is (C_1-C_3)alkyl.

46. The compound according any none of claims 1 to 25, wherein R^{4i} is hydrogen and R^{4j} is methyl.

47. The compound according to any one of claims 1 to 46, wherein R^5 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_3-C_6)cycloalkyl.

48. The compound according to any one of claims 1 to 47, wherein R^5 is hydrogen, halogen, (C_1-C_2)alkyl, (C_1-C_2)alkoxy or (C_3-C_4)cycloalkyl.

49. The compound according to any one of claims 1 to 48, wherein R^5 is hydrogen, fluoro, chloro, cylclopropyl, methyl or methoxy.

50. The compound according to any one of claims 1 to 49, wherein R^5 is hydrogen.

51. The compound according to any one of claims 1 to 50, wherein R^6 is halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, thiophenyl, oxetanyl or $-SO_2R^{6a}$.

52. The compound according to any one of claims 1 to 51, wherein R^6 is bromo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, cyano, halo(C_1-C_3)alkyl, halo(C_1-C_3)alkoxy, (C_3-C_4)cycloalkyl, thiophenyl, oxetanyl or $-SO_2R^{6a}$.

53. The compound according to any one of claims 1 to52, wherein R^6 is halo(C_1-C_3)alkyl, halo(C_1-C_3)alkoxy or (C_3-C_4)cycloalkyl.

54. The compound according to any one of claims 1 to 52, wherein R^6 is trifluoromethyl, trifluoromethoxy, difluoromethoxy or cyclopropyl.

55. The compound according to any one of claims 1 to 54, wherein R^{6a} is (C_1-C_6)alkyl.

56. The compound according to any one of claims 1 to 55, wherein R^{6a} is methyl.

57. The compound according to any one of claims 1 to 56, wherein R^7 is hydrogen, halogen, hydroxy or (C_1-C_6)alkyl.

58. The compound according to any one of claims 1 to 57, wherein R^7 is hydrogen, halogen or hydroxy.

59. The compound according to any one of claims 1 to 58, wherein R^7 is hydrogen.

60. The compound according to any one of claims 1 to 56, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -(C_1-C_3)alkyl-O-(C_1-C_3)alkyl-NHCO-(C_1-C_3)alkyl, -(C_1-C_3)alkyl-O-(C_1-C_3)alkyl-NH_2, -(C_1-C_3)alkyl-NHCO-(C_1-C_3)alkyl or -(C_1-C_3)alkyl-NH_2.

61. The compound according to any one of claims 1 to 56, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_6)alkyl, or(C_1-C_6)alkoxy.

62. The compound according to any one of claims 1 to 56, wherein one of $R^{7'a}$ and $R^{7'b}$ is hydrogen and the other is hydrogen, (C_1-C_3)alkyl, or(C_1-C_3)alkoxy.

63. The compound according to any one of claims 1 to 62, selected from the group consisting of:

3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(3-methoxy-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
4-(3-chloro-4-(methylsulfonyl)phenyl)-3-cyclopropyl-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(4-(methylsulfonyl)-3-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
4-(3-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N,2-trimethylbenzenesulfonamide;
3-cyclopropyl-5-methoxy-4-(4-methylsulfonylphenyl)-1H-pyrazolo[3,4-c]pyridine;
3-cyclopropyl-4-(4-(cyclopropylsulfonyl)-3-methylphenyl)-1H-pyrazolo[4,3-c]pyridine;
4-(3-chloro-4-(cyclopropylsulfonyl)phenyl)-3-cyclopropyl-1H-pyrazolo[4,3-c]pyridine;

2-chloro-4-(3-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N-dimethylbenzenesulfonamide;
4-(3-methyl-4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine;
4-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(3-(difluoromethyl)-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(3-(fluoromethyl)-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-bromo-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrrolo[3,2-c]pyridine;
3-cyclopropyl-4-(3-methyl-4-(oxetan-3-ylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-methoxy-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
5-(3-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-4-yl)-2-(methylsulfonyl)aniline;
4-(3-methyl-4-(methylsulfonyl)phenyl)-3-(methylsulfonyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
3-(1,1-difluoroethyl)-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine-3-carbonitrile;
3-(difluoromethyl)-4-(3-methyl-4-methylsulfonylphenyl)-1H-pyrazolo[4,3-c]pyridine;
3-isopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(4-ethylsulfonyl-3-methyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(2-fluoro-5-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-4-(2,5-dimethyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-c]pyridine hydrochloride;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxylic acid
3-cyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-1H-indazole-5-carbonitrile;
3-cyclopropyl-4-(3-methyl-4-methylsulfinyl-phenyl)-1H-pyrazolo[4,3-c]pyridine hydrochloride
3-cyclopropyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-c]pyridin-7-ol
4-(3-methyl-4-(methylsulfonyl)phenyl)-3-(thiophen-3-yl)-1H-pyrazolo[4,3-c]pyridine;

3-cyclopropyl-5-methoxy-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine;
3-ethoxy-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-1H-pyrazolo[4,3-c]pyridine;
4-(4-cyclopropylsulfonyl-3-methyl-phenyl)-3-(difluoromethoxy)-1H-pyrazolo[4,3-c]pyridine;
3-cyclopropyl-7-fluoro-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-(4-ethylsulfonyl-3-methyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
4-(3-methyl-4-methylsulfonyl-phenyl)-3-(oxetan-3-yl)-1H-pyrazolo[4,3-c]pyridine;
4-[4-(cyclopropylmethylsulfonyl)-3-methyl-phenyl]-3-(difluoromethoxy)-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-(3-methyl-4-propylsulfonyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-[3-(difluoromethyl)-4-methylsulfonyl-phenyl]-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-(4-isopropylsulfonyl-3-methyl-phenyl)-1H-pyrazolo[4,3-c]pyridine;
4-[3-(difluoromethoxy)-1H-pyrazolo[4,3-c]pyridin-4-yl]-N,2-dimethyl-benzenesulfonamide;
3-methoxy-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-indazole-5-carbonitrile;
3-(difluoromethoxy)-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-indazole-5-carbonitrile;
6-chloro-3-cyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-1H-pyrazolo[4,3-c]pyridine;
3-(difluoromethoxy)-4-[3-methyl-4-(oxetan-3-ylsulfonyl)phenyl]-1H-pyrazolo[4,3-c]pyridine;
2-[4-[3-(difluoromethoxy)-1H-pyrazolo[4,3-c]pyridin-4-yl]-2-methyl-phenyl]sulfonylethanol
3-cyclopropyl-6-methoxy-4-(3-methyl-4-methylsulfonylphenyl)-1H-pyrazolo[4,3-c]pyridine 2,2,2-trifluoroacetic acid;
3-(difluoromethoxy)-4-[3-methyl-4-(1-methylcyclopropyl)sulfonyl-phenyl]-1H-pyrazolo[4,3-c]pyridine;
4-(3-methyl-4-(methylsulfonyl)phenyl)-3-(trifluoromethoxy)-1H-pyrazolo[4,3-c]pyridine;

3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-cyclopropyl-N-methyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyridazine;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylthio)-1H-indazole;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfinyl)-1H-indazole;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-1H-indazole;
3-(difluoromethoxy)-4-[4-(methoxymethylsulfonyl)-3-methyl-phenyl]-1H-pyrazolo[4,3-c]pyridine formic acid;
5-methoxy-4-(3-methyl-4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazolo[3,4-c]pyridine;
4-(3-methyl-4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridine;
3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-b]pyridin-5-one
3-cyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-c]pyridine;
3-cyclopropyl-6-methyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-b]pyridin-5-one;
3,6-dicyclopropyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-b]pyridin-5-one;
3-cyclopropyl-5-(difluoromethoxy)-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine;
3-cyclopropyl-N,N-dimethyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-cyclopropyl-5-(methoxymethyl)-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine;
3-cyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-N-(oxetan-3-yl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3,5-dicyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-1H-pyrazolo[3,4-c]pyridine;
N,3-dicyclopropyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-cyclopropyl-6-fluoro-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-indazole-5-carbonitrile;

3-cyclopropyl-4-(4-ethylsulfonyl-3-methyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
3-cyclopropyl-4-(4-cyclopropylsulfonyl-3-methyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-3-(trifluoromethyl)-1H-indazole
3-cyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-1H-indole-5-carbonitrile;
3-cyclopropyl-4-(4-cyclopropylsulfonyl-3-methyl-phenyl)-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-cyclopropyl-6-fluoro-N-methyl-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-indazole-5-carboxamide;
3-cyclopropyl-6-fluoro-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-indazole-5-carboxamide;
6-chloro-3-cyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-1#H!-indazole-5-carbonitrile;
3-cyclopropyl-4-(2-fluoro-5-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
4-(3-methyl-4-methylsulfonyl-phenyl)-3-(trifluoromethoxy)-1H-pyrazolo[4,3-b]pyridin-5-one;
3-cyclopropyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-5-one;
4-[3-(difluoromethoxy)-1H-pyrazolo[4,3-c]pyridin-4-yl]-2-(difluoromethyl)-N,N-dimethyl-benzenesulfonamide;
3-(difluoromethoxy)-4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-1H-indazole;
3-cyclopropyl-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-3-(trifluoromethoxy)-1H-indazole;
3-cyclopropyl-4-[3-(difluoromethyl)-4-methylsulfonyl-phenyl]-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
3-(difluoromethoxy)-4-[5-(difluoromethyl)-2-methyl-4-methylsulfinyl-phenyl]-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;

4-[3-(difluoromethyl)-4-methylsulfonyl-phenyl]-5-methoxy-3-(trifluoromethyl)-1H-pyrazolo[3,4-c]pyridine;
3-cyclopropyl-4-(3-(difluoromethyl)-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-1H-indazole;
3-(difluoromethoxy)-N-methyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-cyclopropyl-4-(4-cyclopropylsulfonyl-2-fluoro-5-methyl-phenyl)-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
4-(4-cyclopropylsulfonyl-3-methyl-phenyl)-3-(difluoromethoxy)-5-methylsulfonyl-1H-indazole;
3-cyclopropyl-4-(2-fluoro-5-methyl-4-methylsulfonyl-phenyl)-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-(4-((difluoromethyl)sulfonyl)-3-methylphenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;
3-(difluoromethoxy)-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-N-(oxetan-3-yl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-N-(2-methoxyethyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-N-methyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;
3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-5-(oxetan-3-ylsulfonyl)-1H-indazole;
[3-cyclopropyl-4-(3-methyl-4-methylsulfonylphenyl)-1H-indazol-5-yl]-imino-methyl-oxo-sulfane;
[3-cyclopropyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-indazol-5-yl]-methyl-methylimino-oxo-λ^6-sulfane;
3-cyclopropyl-N,N-dimethyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-indazole-5-sulfonamide;

3-cyclopropyl-N-methyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-indazole-5-sulfonamide;

4-(4-cyclopropylsulfonyl-3-methyl-phenyl)-3-(difluoromethoxy)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;

3-(difluoromethoxy)-4-(4-((difluoromethyl)sulfonyl)-3-methylphenyl)-5-(methylsulfonyl)-1H-indazole;

5-cyclopropylsulfonyl-3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-indazole;

3-(difluoromethoxy)-4-(2-fluoro-5-methyl-4-methylsulfonyl-phenyl)-5-methylsulfonyl-1H-indazole; or

4-(4-cyclopropylsulfonyl-3-methyl-phenyl)-3-(difluoromethoxy)-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide

and pharmaceutically acceptable salts thereof.

64. The compound according to any one of claims 1 to 63, selected from the group consisting of:

3-(difluoromethoxy)-4-(3-methyl-4-(methylsulfonyl)phenyl)-1H-indazole-5-carbonitrile;

3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[4,3-b]pyridin-5-one;

3-cyclopropyl-4-(4-ethylsulfonyl-3-methyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;

4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-3-(trifluoromethyl)-1H-indazole;

3-(difluoromethoxy)-4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-1H-indazole;

3-cyclopropyl-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;

4-(3-methyl-4-(methylsulfonyl)phenyl)-5-(methylsulfonyl)-3-(trifluoromethoxy)-1H-indazole;

3-cyclopropyl-4-[3-(difluoromethyl)-4-methylsulfonyl-phenyl]-N-methyl-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;

3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carbonitrile;

3-(difluoromethoxy)-N-methyl-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide;

3-(difluoromethoxy)-4-(3-methyl-4-methylsulfonyl-phenyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide; or

3-(difluoromethoxy)-4-[4-(difluoromethylsulfonyl)-3-methyl-phenyl]-1H-pyrazolo[3,4-c]pyridine-5-carboxamide

and pharmaceutically acceptable salts thereof.

65. A compound according to any one of claims 1 to 64 for use as a therapeutically active substance.

66. Pharmaceutical compositions comprising compounds of formula I according to any one of claims 1 to 64 or their pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients.

67. Compounds of formula I according to any of claims 1 to 64 or their pharmaceutically acceptable salts above for use as therapeutically active substances.

68. Compounds of formula I according to any of claims 1 to 64 or their pharmaceutically acceptable salts for the use in the treatment, prevention and/or delay of progression of Lung Aenocarcinoma, Melanoma, Pancreatic Adenocarcinoma, Head and Neck Squamous Cell Carcinoma, Lung Squamous Cell Carcinoma, Esophageal Carcinoma, Glioblastmoa Multiforme, and Mesothelioma.

69. Compounds for the use according to claim 68 ~~for the use~~ in the treatment, prevention and/or delay of progression of Lung Adenocarcinoma, Lung Squamous Carcinoma, Pancreatic Adenocarcinoma, Glioblastoma Multiforme, and Head and Neck Squamous Carcinoma.

~~70. A method for the treatment or prevention of Lung Aenocarcinoma, Melanoma, Pancreatic Adenocarcinoma, Head and Neck Squamous Cell Carcinoma, Lung Squamous Cell Carcinoma, Esophageal Carcinoma, Glioblastmoa Multiforme, and Mesothelioma, which method comprises administering compounds of formula I according to any of one claims 1 to 64 or their pharmaceutically acceptable salts as defined above to a subject.~~

~~71. A method according to claim 70 for the treatment or prevention of Lung Adenocarcinoma, Lung Squamous Carcinoma, Pancreatic Adenocarcinoma, Glioblastoma Multiforme, and Head and Neck Squamous Carcinoma.~~

~~72. The use of compounds of formula I according to any one of claims 1 to 64 or their pharmaceutically acceptable salts for the treatment, prevention and/or delay of progression of Lung Aenocarcinoma, Melanoma, Pancreatic Adenocarcinoma, Head and~~

~~Neck Squamous Cell Carcinoma, Lung Squamous Cell Carcinoma, Esophageal Carcinoma, Glioblastmoa Multiforme, and Mesothelioma.~~

~~73. The use of compounds according to claim 72, for the treatment, prevention and/or delay of progression of Lung Adenocarcinoma, Lung Squamous Carcinoma, Pancreatic Adenocarcinoma, Glioblastoma Multiforme, and Head and Neck Squamous Carcinoma.~~

~~74.~~70. ~~The use~~Use of compounds of formula I according to any one of claims 1 to 64 or their pharmaceutically acceptable salts ~~for~~ in the preparation of a medicament~~s~~ for the treatment or prevention of Lung Aenocarcinoma, Melanoma, Pancreatic Adenocarcinoma, Head and Neck Squamous Cell Carcinoma, Lung Squamous Cell Carcinoma, Esophageal Carcinoma, Glioblastmoa Multiforme, and Mesothelioma.

~~75.~~71. The use of compounds according to claim ~~74~~70, wherein the medicament is for the treatment, prevention and/or delay of progression of Lung Adenocarcinoma, Lung Squamous Carcinoma, Pancreatic Adenocarcinoma, Glioblastoma Multiforme, and Head and Neck Squamous Carcinoma.