Toll-like receptors (TLRs) detect a wide range of conserved pathogen-associated molecular patterns (PAMPs). They play an important role of sensing invading pathogens and subsequent initiation of innate immune responses. There are 10 known members of the TLR family in human, which are type I transmembrane proteins featuring an extracellular leucine-rich domain and a cytoplasmic tail that contains a conserved Toll/ interleukin (IL)-1 receptor (TIR) domain. Within this family, TLR3, TLR7, TLR8 and TLR9 are located within endosomes.

TLR7 can be activated by binding to a specific small molecule ligand (i.e., TLR7 agonist) or its native ligand (i.e., single-stranded RNA, ssRNA). Following binding of ssRNA to TLR7, the receptor in its dimerized form is believed to undergo a structural change leading to the subsequent recruitment of adapter proteins at its cytoplasmic domain, including the myeloid differentiation primary response gene 88 (MyD88). Following the initiation of the receptor signalling cascade via the MyD88 pathway, cytoplasmic transcription factors such as interferon regulatory factor 7 (IRF-7) and nuclear factor kappa B (NF-κB) are activated. These transcription factors then translocate to the nucleus and initiate the transcription of various genes, e.g., IFN-α and other antiviral cytokine genes.

WO201772662 relates to TLR7 agonist-anti HER2 conjugates for the treatment of HER2 positive cancers. Hotz et al, Oncoimmunology 2012, 227-228 relates to cancer treatment with TLR7 agonists. However so far no TLR7 agonist is used systemically for the treatment of cancer. Only topical TLR7 agonist imiquimod is known to induce immune-mediated rejection of skin metastases in patients with breast cancer (Adams S., Kozhaya L., Martiniuk F., Meng T.C., Chiriboga L., Liebes L., Hochman T., Shuman N., Axelrod D., Speyer J., et al. Clin. Cancer Res. 2012;18:6748–6757.

SUMMARY

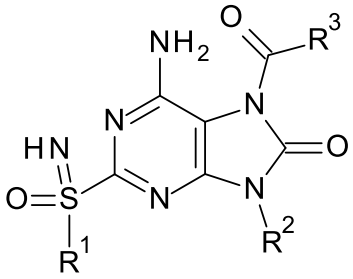
The present disclosure relates to a series of novel 6-amino-2-sulfonimidoyl-9-substituted-7-substituted-purin-8-one compounds with Toll-like receptor agonistic activity and their prodrugs for use in the treatment or prophylaxis (prevention) of liver cancer.

It was found out that the potent and safe TLR7 agonist prodrugs described herein are effective in the treatment of liver cancer either alone or in combination with other agents.

The present disclosure provides a series of novel 6-amino-2-sulfonimidoyl-9-substituted-7-substituted-purin-8-one compounds that have Toll-like receptor agonistic activity and their prodrugs. The disclosure also provides the bio-activity of such compounds

to induce cytokine/chemokine release, SEAP level increase by activating Toll-like receptors, such as TLR7 receptor, the metabolic conversion of prodrugs to parent compounds in the presence of human hepatocytes, and the therapeutic or prophylactic use of such compounds and their pharmaceutical compositions comprising these compounds and their prodrugs to treat or prevent liver cancer. The present disclosure also provides compounds with superior activity. In addition, the compounds of formula (I) also show good solubility and PK profiles.

The present disclosure relates to novel compounds of formula (I),



(I),

wherein

R^1 is C_{1-6}alkyl;

R^2 is benzyl, said benzyl being unsubstituted or substituted by one, two or three substituents independently selected from halogen and C_{1-6}alkyl;

R^3 is $-NR^4R^5$, wherein

R^4 is C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^5 is $(C_{1-6}alkyl)_2NCOOC_{1-6}$alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(phenyl)C_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonyloxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl or pyrrolidinylcarbamoyloxyC_{1-6}alkyl; or

R^4 and R^5 together with the nitrogen they are attached to form a heterocyclyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

for use in the treatment or prophylaxis of liver cancer;

with the proviso that

6-amino-9-benzyl-2-(propylsulfonimidoyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-amino-9-benzyl-7-(piperidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(morpholine-4-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3,3-dimethylpyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

ethyl 1-[6-amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carbonyl]pyrrolidine-2-carboxylate;

6-amino-7-(2-azaspiro[3.3]heptane-2-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;

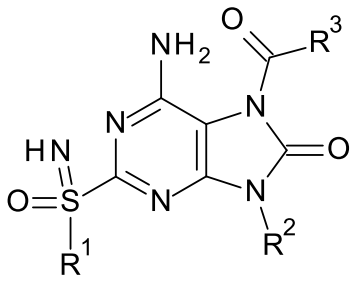
6-amino-9-benzyl-7-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3,3-difluoropyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3-fluoro-3-methyl-pyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

and their enantiomers or diastereomers are excluded.

In one aspect, the disclosure provides use of a compound of formula (I),



(I),

wherein

R^1 is $C_{1\text{-}6}$alkyl;

R^2 is benzyl, said benzyl being unsubstituted or substituted by one, two or three substituents independently selected from halogen and $C_{1\text{-}6}$alkyl;

R^3 is $-NR^4R^5$, wherein

R^4 is $C_{1\text{-}6}$alkyl or $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl;

R^5 is $(C_{1\text{-}6}\text{alkyl})_2\text{NCOOC}_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxycarbonyl($C_{1\text{-}6}$alkyl)amino$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxycarbonyl(phenyl)$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxycarbonyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxycarbonyloxy$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylcarbonyl($C_{1\text{-}6}$alkyl)amino$C_{1\text{-}6}$alkyl or pyrrolidinylcarbamoyloxy$C_{1\text{-}6}$alkyl; or

R^4 and R^5 together with the nitrogen they are attached to form a heterocyclyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

in the manufacture of a medicament for the treatment or prophylaxis of liver cancer;

with the proviso that

6-amino-9-benzyl-2-(propylsulfonimidoyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-amino-9-benzyl-7-(piperidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
6-amino-9-benzyl-7-(morpholine-4-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
6-amino-9-benzyl-7-(3,3-dimethylpyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
ethyl 1-[6-amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carbonyl]pyrrolidine-2-carboxylate;
6-amino-7-(2-azaspiro[3.3]heptane-2-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;
6-amino-9-benzyl-7-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
6-amino-9-benzyl-7-(3,3-difluoropyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
6-amino-9-benzyl-7-(3-fluoro-3-methyl-pyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
and their enantiomers or diastereomers are excluded.

In another aspect, the disclosures provides use of a compound in the manufacture of a medicament for the treatment or prophylaxis of liver cancer, wherein the compound is selected from:
6-Amino-9-benzyl-N-methyl-8-oxo-N-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-9-benzyl-N-(2-methoxyethyl)-N-methyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-9-benzyl-*N*-ethyl-8-*oxo*-*N*-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-9-benzyl-7-[4-(1-piperidyl)piperidine-1-carbonyl]-2-(propylsulfonimidoyl)purin-8-one;
6-Amino-9-benzyl-*N*-ethyl-*N*-(2-methoxyethyl)-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-9-benzyl-*N*-butyl-*N*-ethyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-9-benzyl-*N*-(2-methoxyethyl)-8-*oxo*-*N*-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-9-benzyl-*N*,*N*-bis(2-methoxyethyl)-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;
6-Amino-7-(azetidine-1-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-isopropyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-7-(4-methylpiperazine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-(3-methoxypropyl)-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-isobutyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

Ethyl 2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]acetate;

Ethyl 3-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

tert-Butyl 3-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

tert-Butyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Isopropyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-methyl-butanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

Isopropyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

tert-Butyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

N-[2-[Acetyl(methyl)amino]ethyl]-6-amino-9-benzyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

Methyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

tert-Butyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

Ethyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*-butyl-*N*-methyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl pyrrolidine-1-carboxylate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*-methyl-*N*-propyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*,*N*-diethylcarbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl ethyl carbonate;

6-Amino-N-butyl-9-[(4-chlorophenyl)methyl]-N-methyl-8-oxo-2-[S(S)-propylsulfonimidoyl]purine-7-carboxamide;

6-amino-N-butyl-9-[(4-chlorophenyl)methyl]-N-methyl-8-oxo-2-[S(S)-propylsulfonimidoyl]purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-*N*-methyl-8-*oxo*-*N*-propyl-2[S(*S*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-methyl-8-*oxo*-*N*-propyl-2[S(*R*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*S)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-Amino-2-[S(*R)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-Amino-*N*-(2-methoxyethyl)-*N*-methyl-8-*oxo*-2-[S(*S)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-(2-methoxyethyl)-*N*-methyl-8-*oxo*-2-[S(*R)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-butyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-2-[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-2-[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*S*)ethylsulfonimidoyl]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*R*)ethylsulfonimidoyl]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*R*)-ethylsulfonimidoyl]-9-[(4-bromophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*S*)-ethylsulfonimidoyl]-9-[(4-bromophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide; and

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another aspect, the disclosures provides use of a pharmaceutical composition or medicament comprising a compound as defined herein and a therapeutically inert carrier, in the manufacture of a medicament for the treatment or prophylaxis of liver cancer.

In another aspect, the disclosures provides use of a compound as defined herein, or a pharmaceutical composition or a medicament comprising such compound, in the manufacture of a medicament for

a) the treatment or prophylaxis of liver cancer in combination with an antagonistic PD1 antibody or antagonistic PD-L1 antibody,

or

b) the treatment of a patient suffering from liver cancer in combination with an antagonistic PD1 antibody or antagonistic PD-L1 antibody.

In another aspect, the disclosures provides use of a compound as defined herein in the preparation of a medicament for the treatment or prophylaxis of liver cancer wherein the treatment is in combination with an antagonistic PD1 antibody or antagonistic PD-L1 antibody.

In another aspect, the disclosures provides use of a compound as defined herein, or a pharmaceutical composition or a medicament comprising such compound, in the manufacture of a medicament for

a) the treatment or prophylaxis of liver cancer in combination with an anti-angiogenic agent,

or

b) the treatment of a patient suffering from liver cancer in combination with an anti-angiogenic agent.

In another aspect, the disclosures provides use of a compound as defined herein in the preparation of a medicament for the treatment or prophylaxis of liver cancer wherein the treatment is in combination with an anti-angiogenic agent.

These prodrug compounds are especially useful for the treatment of liver cancer as they are activated (converted into their active form) in the liver. They show valuable anti-tumor efficacy in vivo in liver cancer cell models (either alone or in combination with anti-PD1/PD1 antibodies or with anti-angiogenic agents) and in vitro against liver cancer cells (by activation of peripheral blood cells and/or factors).

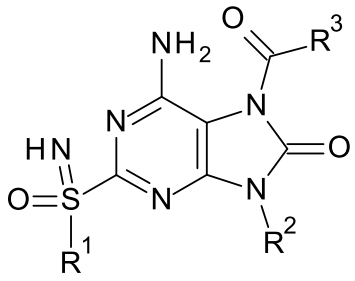
The disclosure also relates to their use for the manufacture of a medicament for the treatment or prophylaxis of liver cancer, medicaments based on a compound in accordance with the disclosure for the treatment or prophylaxis of liver cancer. Accordingly, the compounds of formula (I) are useful for the treatment or prophylaxis of liver cancer, especially for the treatment or prophylaxis of hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, or metastatic liver cancer.

DETAILED DESCRIPTION OF THE INVENTION

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. Furthermore, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention.

PATENT CLAIMS

1. Use of a compound of formula (I),



(I),

wherein

R^1 is C_{1-6}alkyl;

R^2 is benzyl, said benzyl being unsubstituted or substituted by one, two or three substituents independently selected from halogen and C_{1-6}alkyl;

R^3 is $-NR^4R^5$, wherein

R^4 is C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^5 is $(C_{1-6}alkyl)_2NCOOC_{1-6}$alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(phenyl)C_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonyloxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl or pyrrolidinylcarbamoyloxyC_{1-6}alkyl; or

R^4 and R^5 together with the nitrogen they are attached to form a heterocyclyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

in the manufacture of a medicament for the treatment or prophylaxis of liver cancer;

with the proviso that

6-amino-9-benzyl-2-(propylsulfonimidoyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-amino-9-benzyl-7-(piperidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(morpholine-4-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3,3-dimethylpyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

ethyl 1-[6-amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carbonyl]pyrrolidine-2-carboxylate;

6-amino-7-(2-azaspiro[3.3]heptane-2-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3,3-difluoropyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3-fluoro-3-methyl-pyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;
and their enantiomers or diastereomers are excluded.

2. The use according to claim 1, wherein
R^1 is C_{1-6}alkyl;
R^2 is benzyl, said benzyl being unsubstituted or substituted by halogen or C_{1-6}alkyl;
R^3 is azetidinyl;
piperazinyl substituted by C_{1-6}alkyl;
piperidinyl substituted by piperidinyl;
pyrrolidinyl; or
$-NR^4R^5$, wherein
R^4 is C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;
R^5 is $(C_{1-6}alkyl)_2NCOOC_{1-6}$alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(phenyl)C_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonyloxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl or pyrrolidinylcarbamoyloxyC_{1-6}alkyl.

3. The use according to claim 1 or 2, wherein
R^1 is ethyl or propyl;
R^2 is benzyl, bromobenzyl, chlorobenzyl, fluorobenzyl or methylbenzyl;
R^3 is azetidinyl;
4-methylpiperazinyl;
piperidinylpiperidinyl;
pyrrolidinyl; or
$-NR^4R^5$, wherein
R^4 is methyl, ethyl, propyl or methoxyethyl;
R^5 is acetyl(methyl)aminoethyl, butyl, butyl(methyl)carbamoyloxyethyl, diethylcarbamoyloxyethyl, ethoxycarbonyl(methyl)aminoethyl, ethoxycarbonylethyl, ethoxycarbonylisobutyl, ethoxycarbonylisopentyl, ethoxycarbonylmethyl, ethoxycarbonyloxyethyl, ethoxycarbonyl(phenyl)ethyl, ethyl, isobutyl, isopropoxycarbonylisopentyl, isopropoxycarbonyl(phenyl)ethyl, isopropyl, methoxycarbonyl(methyl)aminoethyl, methoxyethyl, methoxypropyl, propyl, propyl(methyl)carbamoyloxyethyl, pyrrolidinylcarbamoyloxyethyl, tert-

butoxycarbonyl(methyl)aminoethyl, tert-butoxycarbonylethyl, tert-butoxycarbonylisopentyl or tert-butoxycarbonyl(phenyl)ethyl.

4. The use according to claim 3, wherein R^3 is azetidinyl, 4-methylpiperazinyl, piperidinylpiperidinyl, pyrrolidinyl, acetyl(methyl)aminoethyl(methyl)amino, bis(methoxyethyl)amino, butyl(ethyl)amino, butyl(methyl)amino, butyl(methyl)carbamoyloxyethyl(methyl)amino, diethylcarbamoyloxyethyl(methyl)amino, ethoxycarbonyl(methyl)aminoethyl(methyl)amino, ethoxycarbonylethyl(methyl)amino, ethoxycarbonylisobutyl(methyl)amino, ethoxycarbonylisopentyl(methyl)amino, ethoxycarbonylmethyl(methyl)amino, ethoxycarbonyloxyethyl(methyl)amino, ethoxycarbonyl(phenyl)ethyl(methyl)amino, ethyl(methyl)amino, isobutyl(methyl)amino, isopropoxycarbonylisopentyl(methyl)amino, isopropoxycarbonyl(phenyl)ethyl(methyl)amino, isopropyl(methyl)amino, methoxycarbonyl(methyl)aminoethyl(methyl)amino, methoxyethyl(ethyl)amino, methoxyethyl(methyl)amino, methoxyethyl(propyl)amino, methoxypropyl(methyl)amino, propyl(ethyl)amino, propyl(methyl)amino, propyl(methyl)carbamoyloxyethyl(methyl)amino, pyrrolidinylcarbamoyloxyethyl(methyl)amino, tert-butoxycarbonyl(methyl)aminoethyl(methyl)amino, tert-butoxycarbonylethyl(methyl)amino, tert-butoxycarbonylisopentyl(methyl)amino or tert-butoxycarbonyl(phenyl)ethyl(methyl)amino.

5. The use according to any one of claims 1 to 4, wherein R^1 is ethyl.

6. The use according to claim 1 or 2, wherein R^2 is benzyl substituted by halogen or C_{1-6}alkyl.

7. The use according to any one of claims 2 to 6, wherein R^2 is bromobenzyl, chlorobenzyl, fluorobenzyl or methylbenzyl.

8. The use according to claim 7, wherein R^2 is bromobenzyl, chlorobenzyl or fluorobenzyl.

9. The use according to claim 1 or 2, wherein R^3 is $-NR^4R^5$, wherein R^4 is C_{1-6}alkyl, R^5 is C_{1-6}alkyl.

10. The use according to claim 9, wherein R^3 is propyl(methyl)amino or ethyl(methyl)amino.

11. The use according to any one of claims 1, 2, 6 and 9, wherein

R^1 is C_{1-6}alkyl;
R^2 is benzyl, said benzyl being substituted by halogen or C_{1-6}alkyl;
R^3 is $-NR^4R^5$, wherein R^4 is C_{1-6}alkyl, R^5 is C_{1-6}alkyl.

12. The use according to claim 11, wherein
R^1 is ethyl;
R^2 is methylbenzyl, bromobenzyl, chlorobenzyl or fluorobenzyl;
R^3 is propyl(methyl)amino or ethyl(methyl)amino.

13. Use of a compound in the manufacture of a medicament for the treatment or prophylaxis of liver cancer, wherein the compound is selected from:
6-Amino-9-benzyl-N-methyl-8-oxo-N-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-N-(2-methoxyethyl)-N-methyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-ethyl-8-*oxo*-*N*-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-7-[4-(1-piperidyl)piperidine-1-carbonyl]-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-ethyl-*N*-(2-methoxyethyl)-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-butyl-*N*-ethyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-(2-methoxyethyl)-8-*oxo*-*N*-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*,*N*-bis(2-methoxyethyl)-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-7-(azetidine-1-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-isopropyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-7-(4-methylpiperazine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-(3-methoxypropyl)-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-isobutyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

Ethyl 2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]acetate;

Ethyl 3-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

tert-Butyl 3-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

tert-Butyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Isopropyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-methyl-butanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

Isopropyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

tert-Butyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

N-[2-[Acetyl(methyl)amino]ethyl]-6-amino-9-benzyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

Methyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

tert-Butyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

Ethyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*-butyl-*N*-methyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl pyrrolidine-1-carboxylate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*-methyl-*N*-propyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*,*N*-diethylcarbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl ethyl carbonate;

6-Amino-N-butyl-9-[(4-chlorophenyl)methyl]-N-methyl-8-oxo-2-[S(S)-propylsulfonimidoyl]purine-7-carboxamide;

6-amino-N-butyl-9-[(4-chlorophenyl)methyl]-N-methyl-8-oxo-2-[S(S)-propylsulfonimidoyl]purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-*N*-methyl-8-*oxo*-*N*-propyl-2[S(*S*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-methyl-8-*oxo*-*N*-propyl-2[S(*R*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*S)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-Amino-2-[S(*R)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-Amino-*N*-(2-methoxyethyl)-*N*-methyl-8-*oxo*-2-[S(*S)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-(2-methoxyethyl)-*N*-methyl-8-*oxo*-2-[S(*R)*-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-butyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-2-[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-2-[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*S*)ethylsulfonimidoyl]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*R*)ethylsulfonimidoyl]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*R*)-ethylsulfonimidoyl]-9-[(4-bromophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*S*)-ethylsulfonimidoyl]-9-[(4-bromophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide; and

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

14. The use according to claim 13, wherein the compound is selected from:
6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;
6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;
6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide; and

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

15. The use according to claim 13, wherein the compound is
6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

16. The use according to any one of claims 1 to 15, wherein the liver cancer is hepatocellular carcinoma, hepatoma, cholangiocarcinoma, hepatoblastoma, hepatic carcinoma, hepatic angiosarcoma, or metastatic liver cancer.

17. The use according to any one of claims 1 to 15, wherein the liver cancer is hepatocellular carcinoma.

18. Use of a pharmaceutical composition or medicament comprising a compound according to any one of claims 1 to 15 and a therapeutically inert carrier, in the manufacture of a medicament for the treatment or prophylaxis of liver cancer.

19. Use of a compound as defined in any one of claims 1 to 15, or a pharmaceutical composition or a medicament comprising such compound, in the manufacture of a medicament for

a) the treatment or prophylaxis of liver cancer in combination with an antagonistic PD1 antibody or antagonistic PD-L1 antibody,

or

b) the treatment of a patient suffering from liver cancer in combination with an antagonistic PD1 antibody or antagonistic PD-L1 antibody.

20. Use of a compound as defined in any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of liver cancer wherein the treatment is in combination with an antagonistic PD1 antibody or antagonistic PD-L1 antibody.

21. The use according to any one of claims 19 or 20, wherein the treatment is in combination with an antagonistic PD1 antibody.

22. The use,according to claim 21, wherein the antagonistic PD1 antibody is nivolumab or

pemprolizumab.

23. The use according to claim 22, wherein the compound is 6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide

24. The use according to claim 21, wherein the antagonistic PD1 antibody comprises a heavy chain variable domain VH with an amino acid sequence of SEQ ID NO: 5 and a light chain variable domain VL with an amino acid sequence of SEQ ID NO:6.

25. The use according to claim 23, wherein the compound is 6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide.

26. The use according to claim 19 or 20, wherein the treatment is in combination with an antagonistic PD-L1 antibody.

27. The use according to claim 26, wherein the antagonistic PD-L1 antibody to be used in the combination therapy is atezolizumab or durvalumab or avelumab (in one preferred embodiment atezolizumab)

28. The use according to claim 27, wherein the compound is 6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide.

29. The use according to any one of claims 19 to 28 wherein additionally an anti-angiogenic agent is to be used in the combination therapy

30. The use according to any one of claims 19 to 28 wherein additionally an anti-angiogenic agent selected from is sorafenib, regorafenib, sunitinib or bevacizumab (in one preferred embodiment the anti-angiogenic agent is sorafenib; in one preferred embodiment the anti-angiogenic agent is bevacizumab) is to be used in the combination therapy.

31. Use of a compound as defined in any one of claims 1 to 15, or a pharmaceutical composition or a medicament comprising such compound, in the manufacture of a medicament for

a) the treatment or prophylaxis of liver cancer in combination with an anti-angiogenic agent,

or

b) the treatment of a patient suffering from liver cancer in combination with an anti-angiogenic agent.

32. Use of a compound as defined in any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of liver cancer wherein the treatment is in combination with an anti-angiogenic agent.

33. The use according to claim 31 or 32 wherein the anti-angiogenic agent selected from is sorafenib, regorafenib, sunitinib or bevacizumab (in one preferred embodiment the anti-angiogenic agent is sorafenib; in one preferred embodiment the anti-angiogenic agent is bevacizumab).

34. The use according to claim 33, wherein the compound is 6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide.