

SULFAMOYL-PHENYL-UREIDO BENZAMIDINE-DERIVATIVES AS ANTIMALARIAL AGENTS

The present invention relates to compounds which are suitable for the therapy of infections caused by protozoa and in particular uncomplicated or severe malaria caused by plasmodia.

Malaria is a life-threatening parasitic disease transmitted from person to person through the bite of a female anopheles mosquito (Tuteja R.; Malaria - an overview. *FEBS J.*, **274** (2007), 4670-4679). The disease is a public health problem in more than 90 countries and more than 2 billion people are at risk, most of them living in tropical Africa. High risk groups include children, pregnant women, migrant workers and tourist or business travellers entering into endemic areas (Snow R.W., *et al.*; The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* **434** (2005), 214-217). A resurgence of this serious disease is currently registered. It is caused by several factors such as increased drug resistance by the parasites, increased mosquito resistance to insecticide, demographic or environmental changes caused by the human population.

By far, the most important factor for malaria resurgence in sub-Saharan Africa and Southeast Asia is the development of resistance by *Plasmodium falciparum* to the cheap and effective drugs in use, notably chloroquine and sulfadoxine/pyrimethamine. Lethal *Plasmodium falciparum* strains resistant to amodiaquine, mefloquine, and quinine have been observed as well (Hyde J.E.; Drug-resistant malaria - an insight. *FEBS J.*, **274** (2007), 4688-4698). At this time, the recommended new treatments for malaria in these parts of the globe are the so-called ACT (artemisinin-based combination therapy) which combines the rapid effect of an artemisinin compound with a longer-half-life drug selected from a pool of known drugs. For example Coartem® combines arthemether and lumefantrine whereas Coarsucam® combines artesunate and amodiaquine; other drugs of this type are currently being released or at late clinical development stage (Wells T.N.C., *et al.*; New medicines to improve control and contribute to the eradication of malaria. *Nature Reviews Drug Discovery*, **8** (2009), 879-891). The World Health Organization (WHO) has recently endorsed ACT as the "policy standard" for all malaria infections in areas where *Plasmodium falciparum* is the predominant infecting species. The large use of ACT and the positive results registered reinforces the hopes to achieve, within the next years, the goal of controlling the spread of malaria.

In 2007 the Bill and Melinda Gates Foundation called for a renewed global effort to eradicate malaria worldwide (Mills A., *et al.*; Malaria eradication: the economic, financial and institutional challenge. *Malaria Journal*, 7(Suppl 1):S11 (2008)). Initiatives to eliminate malaria are critically dependent on the efficacy of these ACT therapies. Unfortunately, there is recent worrying evidence that artemisinin resistance has arisen at the Thai-Cambodian border (Dondrop A.M., *et al.*; Artemisinin Resistance in *Plasmodium falciparum* Malaria. *New England Journal of Medicine*, 361 (2009) 455-467). The Thai-Cambodian border area is historically the source of the global diaspora of anti-malarial drug resistance. Resistance to chloroquine and sulphadoxine-pyrimethamine in *Plasmodium falciparum* originated there, spread across Asia and Africa, and caused millions of deaths.

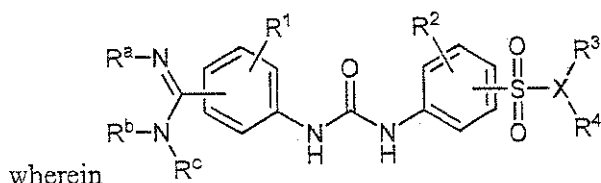
Clearly, to achieve the goal of malaria control and eradication, antimalaria drug discovery must continue working on the development of new medicines to treat malaria, mainly targeting the asexual blood stages of the parasite. Preferentially these new drugs should possess a mode of action diverse from all known and used drugs to prevent the phenomenon of resistance and to open the possibility to combined therapies.

We discovered diaryl-urea compounds which possess antiparasite properties (Leban J., *et al.*; Sulfonyl-phenyl-ureido benzamidines: a novel structural class of potent antimalarial agents. *Bioorganic & Medicinal Chemistry Letters*, 14 (2004), 1979-1982.; Aschenbrenner A., *et al.*; Derivatives of diphenylurea, diphenyloxalic acid diamide and diphenylsulfuric acid diamide and their use as medicaments. PCT Int. Appl. (2002) WO 02/070467). Several of these compounds were able to kill a chloroquine-resistant strain of *Plasmodium falciparum*, cultured *in vitro*. Unfortunately, these compounds lack the ability to clear completely the parasites from circulating blood of infected animal models and this was attributed to the poor physico-chemical and pharmacokinetic properties. Unexpectedly we found a new class of compounds with improved absorption, distribution, metabolism, and excretion ("ADME") properties as well as better physico-chemical characteristics, which still displayed high antiparasite and antimalaria activity most likely with a new mechanism of action.

SUMMARY

In a first aspect, there is provided a compound of the formula (I)

or a physiologically acceptable salt thereof,



R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, $-OCOR'$, $C(O)R'$, $CONHR'$ or $-CO_2R'$;

R^b and R^c independently are alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, cycloalkyl, aryl and heteroaryl, heterocyclyl or $-CO_2R'$;

or

R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or entirely unsaturated heterocyclic ring selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'' , where chemically appropriate, two R'' taken together can form a group $=O$; this heterocyclic group is preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, S,S-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl

R' independently represents hydrogen, $-CO_2R''$, $-CONHR''$, $-CR''O$, $-SO_2N(R'')_2$, $-SO_2NHR''$, $-NR''-CO-haloalkyl$, $-NO_2$, $-NR''-SO_2-haloalkyl$, $-NR''-SO_2-alkyl$, $-SO_2-alkyl$, $-NR''-CO-alkyl$, $-CN$, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, $-OH$, $-SH$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' independently represents hydrogen, $-(CH_2)_mR'$, $-CO_2R'$, $-CON(R')_2$, $-CR'O$, $-SO_2N(R')_2$, $-NR'-CO-haloalkyl$, $-NO_2$, $-NR'-SO_2-haloalkyl$, $-NR'-SO_2-alkyl$, $-NR'-SO_2-aryl$, $-NR'-SO_2-heteroaryl$, $-SO_2-alkyl$, $-SO_2-aryl$, $-SO_2-heteroaryl$, $-NR'-$

CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group =O; wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represent hydrogen, (CH₂)_mR', -CO₂R', -CON(R')₂, CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, NO₂, -NR'-SO₂-haloalkyl, NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or -CO₂R';

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

or wherein if

X is N, then

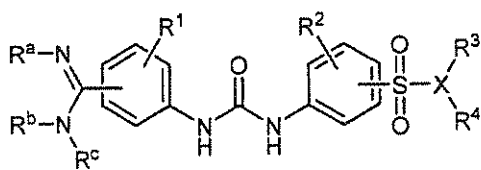
R^3 forms together with R^4 a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''

In a second aspect, there is provided a pharmaceutical composition, comprising a compound as defined above and a pharmaceutically acceptable carrier or diluent.

In a third aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for treating or preventing or ameliorating a disease or condition.

DETAILED DESCRIPTION

The present invention relates to compounds of the formula (I):



formula (I)

or a physiologically acceptable salt or derivative thereof, wherein

R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, $-OCOR'$, $-C(O)R'$, $-CONHR'$ or $-CO_2R'$;

R^b and R^c independently are alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, cycloalkyl, aryl and heteroaryl, heterocyclyl or $-CO_2R'$;

or

R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or entirely unsaturated heterocyclic ring selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'' , where chemically appropriate, two R'' taken together can form a group $=O$; this heterocyclic group is preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, *S,S*-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl

R' independently represents hydrogen, $-CO_2R''$, $-CONHR''$, $-CR''O$, $-SO_2N(R'')_2$, $-SO_2NHR''$, $-NR''-CO-haloalkyl$, $-NO_2$, $-NR''-SO_2-haloalkyl$, $-NR''-SO_2-alkyl$, $-SO_2-alkyl$, $-NR''-CO-alkyl$, $-CN$, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, $-OH$, $-SH$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' is independently hydrogen, $-(CH_2)_mR'$, $-CO_2R'$, $-CON(R')_2$, $-CR'O$, $-SO_2N(R')_2$, $-NR'-CO-haloalkyl$, $-NO_2$, $-NR'-SO_2-haloalkyl$, $-NR'-SO_2-alkyl$, $-NR'-SO_2-aryl$, $-NR'-SO_2-heteroaryl$, $-SO_2-alkyl$, $-SO_2-aryl$, $-SO_2-heteroaryl$, $-NR'-CO-alkyl$, $-NR'-CO-aryl$, $-NR'-CO-heteroaryl$, $-NR'-CO-N(R')_2$, $-CN$, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, $-SH$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where

chemically appropriate, two R'' taken together can form a group =O; wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represent hydrogen, -(CH₂)_mR', -CO₂R', -CON(R')₂, -CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, NO₂, -NR'-SO₂-haloalkyl, NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or -CO₂R';

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

or wherein if

X is N, then

or R^3 forms together with R^4 a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''

In another preferred embodiment, the present invention relates to a compound of formula (I) or a physiologically acceptable salt or derivative thereof, where

R_a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or $-CO_2R'$;

R^1 and R^2 are hydrogen;

R^b and R^c independently are alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl and heteroaryl, heterocycloalkyl or $-CO_2R'$;

or R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated or partially or entirely unsaturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R'' ;

R' is independently hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl or an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl and heteroaryl;

R'' independently represents hydrogen, $-(CH_2)_mR'$, $-CO_2R'$, $-CON(R')_2$, $-CR'O$, $-SO_2N(R')_2$, $-NR'-CO$ -haloalkyl, $-NO_2$, $-NR'-SO_2$ -haloalkyl, $-NR'-SO_2$ -alkyl, $-NR'-SO_2$ -aryl, $-NR'-SO_2$ -heteroaryl, $-SO_2$ -alkyl, $-SO_2$ -aryl, $-SO_2$ -heteroaryl, $-NR'-CO$ -alkyl, $-NR'-CO$ -aryl, $-NR'-CO$ -heteroaryl, $-NR'-CO-N(R')_2$, $-CN$, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, $-SH$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group $=O$; wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR^5 , then

R^3 forms together with R^4 an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'' , and wherein if X is part of a double bond, R^5 is absent;

or wherein if

X is N, then

R^3 is independently hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or $-CO_2R'$;

R^4 is independently hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

R^5 is H, OH, halogen, C1-4 alkyl;

or R^3 forms together with R^4 a 3-, 4-, 5-, 6- or 7-membered saturated or partially or entirely unsaturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R'' as defined herein;

Preferably, $R^3 = H$, $R^4 = \text{arylalkyl}$, $R^a = H$, and R^b forms together with R^c a 6-membered saturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R'' .

More preferably $R^3 = H$, $R^4 = \text{benzyl}$, substituted with aminosulfonyl, $R^a = H$, and R^b forms together with R^c a piperazinyl, substituted with n-butyl.

In another preferred embodiment, the present invention relates to a compound of formula (I) and the pharmaceutically acceptable salt or solvate thereof,

wherein

R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, $-OCOR'$, $-C(O)R'$, $-CONHR'$ or $-CO_2R'$;

R^b and R^c independently are alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, cycloalkyl, aryl and heteroaryl, heterocyclyl or $-CO_2R'$;

R' independently represents hydrogen, $-CO_2R''$, $-CONHR''$, $-CR''O$, $-SO_2N(R'')_2$, $-SO_2NHR''$, $-NR''-CO$ -haloalkyl, $-NO_2$, $-NR''-SO_2$ -haloalkyl, $-NR''-SO_2$ -alkyl,

-SO₂-alkyl, -NR''-CO-alkyl, -CN, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' is independently hydrogen, -(CH₂)_mR', -CO₂R', -CON(R')₂, -CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, -NO₂, -NR'-SO₂-haloalkyl, -NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group =O; wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represents hydrogen, -(CH₂)_mR', -CO₂R', -CON(R')₂, -CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, NO₂, -NR'-SO₂-haloalkyl, NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or -CO₂R';

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

or wherein if

X is N, then

or R³ forms together with R⁴ a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''

In another preferred embodiment, the present invention relates to a compound of formula (I) and the pharmaceutically acceptable salt or solvate thereof, wherein

R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, -OCOR', -C(O)R', -CONHR' or -CO₂R';

R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or entirely unsaturated heterocyclic ring selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', where chemically appropriate, two R'' taken together can form a group =O; this heterocyclic group is preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, *S,S*-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl

R' independently represents hydrogen, -CO₂R'', -CONHR'', -CR''O, -SO₂N(R'')₂, -SO₂NHR'', -NR''-CO-haloalkyl, -NO₂, -NR''-SO₂-haloalkyl, -NR''-SO₂-alkyl, -SO₂-alkyl, -NR''-CO-alkyl, -CN, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' independently hydrogen, $-(CH_2)_mR'$, $-CO_2R'$, $-CON(R')_2$, $-CR'O$, $-SO_2N(R')_2$, $-NR'-CO$ -haloalkyl, $-NO_2$, $-NR'-SO_2$ -haloalkyl, $-NR'-SO_2$ -alkyl, $-NR'-SO_2$ -aryl, $-NR'-SO_2$ -heteroaryl, $-SO_2$ -alkyl, $-SO_2$ -aryl, $-SO_2$ -heteroaryl, $-NR'-CO$ -alkyl, $-NR'-CO$ -aryl, $-NR'-CO$ -heteroaryl, $-NR'-CO-N(R')_2$, $-CN$, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, $-SH$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group $=O$; wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represents hydrogen, $-(CH_2)_mR'$, $-CO_2R'$, $-CON(R')_2$, $-CR'O$, $-SO_2N(R')_2$, $-NR'-CO$ -haloalkyl, NO_2 , $-NR'-SO_2$ -haloalkyl, $NR'-SO_2$ -alkyl, $-NR'-SO_2$ -aryl, $-NR'-SO_2$ -heteroaryl, $-SO_2$ -alkyl, $-SO_2$ -aryl, $-SO_2$ -heteroaryl, $-NR'-CO$ -alkyl, $-NR'-CO$ -aryl, $-NR'-CO$ -heteroaryl, $-NR'-CO-N(R')_2$, $-CN$, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, $-SH$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR^5 , then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or $-CO_2R'$;

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

or wherein if

X is N, then

R³ forms together with R⁴ a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''

In another preferred embodiment, the present invention relates to a compound of formula (I) and the pharmaceutically acceptable salt or solvate thereof, wherein

R^a is hydrogen or alkyl;

R^b and R^c independently are alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, or -CO₂R';

R' independently represents hydrogen, -CO₂R'', -SO₂N(R'')₂, -SO₂NHR'', -CN, alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl;

R'' independently represent hydrogen, -SO₂N(R')₂, -NO₂, alkyl, amino, alkylamino, alkoxyalkyl, hydroxyl, hydroxyalkyl, halogen, wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represent hydrogen, alkyl, amino, hydroxyl, halogen, or haloalkyl, wherein R' groups are as defined above and may be selected independently from each other;

wherein if

X is CR⁵, then

R^3 forms together with R^4 an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'' , and wherein if X is part of a double bond, R^5 is absent;

R^5 is H, OH, halogen, C_1 - C_4 -alkyl;

or wherein if

X is N, then

R^3 is hydrogen or alkyl;

R^4 is hydrogen, amino, alkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl

or wherein if

X is N, then

R^3 forms together with R^4 a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'' .

In another preferred embodiment, the present invention relates to a compound of formula (I) and the pharmaceutically acceptable salt or solvate thereof,

wherein

R^a is hydrogen or alkyl;

R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or entirely unsaturated heterocyclic ring selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'' , where chemically appropriate, two R'' taken together can form a group =O; this heterocyclic group is preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, *S,S*-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl

R' independently represents hydrogen, $-CO_2R''$, $-SO_2N(R'')_2$, $-SO_2NHR''$, $-CN$, alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl;

R'' independently represent hydrogen, $-\text{SO}_2\text{N}(\text{R}')_2$, $-\text{NO}_2$, alkyl, amino, alkylamino, alkoxyalkyl, hydroxyl, hydroxyalkyl, halogen, wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represent hydrogen, alkyl, amino, hydroxyl, halogen, or haloalkyl, wherein R' groups are as defined above and may be selected independently from each other;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen or alkyl;

R⁴ is hydrogen, amino, alkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl

or wherein if

X is N, then

R³ forms together with R⁴ a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''.

Preferably, R³ = H, R⁴ = alkylaryl, R^a = H, and R^b forms together with R^c a 6-membered saturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R''.

Preferably, $R^3 = H$, $R^4 = \text{alkylaryl}$, $R^a = H$, and R^b forms together with R^c a piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, *S,S*-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl, which optionally has 0, 1, 2 or 3 substituents R'' .

More preferably $R^3 = H$, $R^4 = \text{benzyl}$, substituted with aminosulfonyl, $R^a = H$, and R^b forms together with R^c a piperazinyl, which optionally has 0, 1, 2 or 3 substituents R'' .

In another preferred embodiment, the present invention relates to a compound of formula (I) and the pharmaceutically acceptable salt or solvate thereof,

wherein

$R^3 = H$, $R^4 = \text{aryl}$, $R^a = H$, and R^b forms together with R^c a 6-membered saturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R'' .

Preferably, $R^3 = H$, $R^4 = \text{aryl}$, $R^a = H$, and R^b forms together with R^c a piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, *S,S*-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl, which optionally has 0, 1, 2 or 3 substituents R'' .

More preferably $R^3 = H$, $R^4 = \text{phenyl}$, substituted with aminosulfonyl, $R^a = H$, and R^b forms together with R^c a piperazinyl, which optionally has 0, 1, 2 or 3 substituents R'' .

Another embodiment of the invention is a pharmaceutical composition, comprising a compound according to formula (I) and a pharmaceutically acceptable carrier or diluent.

Another embodiment of the invention is a method of treating or preventing or ameliorating a disease or condition in a subject comprising the administration of a compound according to formula (I)..

In a preferred embodiment the disease or condition is malaria.

In a more preferred embodiment the disease or condition is malaria, caused by a strain of *Plasmodium falciparum*.

An aryl group denotes an aromatic group having five to fifteen carbon atoms, which may be substituted by one or more substituents R', and may be fused to another aromatic ring; the aryl group is preferably a phenyl group, -o-C₆H₄-R', -m-C₆H₄-R', -p-C₆H₄-R', 1-naphthyl, 2-naphthyl, 1-anthracenyl or 2-anthracenyl;

a heteroaryl group denotes a 5- or 6-membered heterocyclic group which contains at least one heteroatom like O, S or N, wherein the heteroatom N is optionally substituted with R', and/or the heteroatom S is optionally bonded to =O or (=O)₂. This heterocyclic group can be fused to another aromatic ring. For example, this group can be selected from a thiadiazole, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isooxazol-3-yl, isooxazol-4-yl, isooxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,5-oxadiazol-3-yl, benzooxazol-2-yl, benzooxazol-4-yl, benzooxazol-5-yl, benzoisooxazol-3-yl, benzoisooxazol-4-yl, benzoisooxazol-5-yl, 1,2,5-oxadiazol-4-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, benzoisothiazol-3-yl, benzoisothiazol-4-yl, benzoisothiazol-5-yl, 1,2,5-thiadiazol-3-yl, 1-imidazolyl, 2-imidazolyl, 1,2,5-thiadiazol-4-yl, 4-imidazolyl, benzoimidazol-4-yl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyranyl, 3-pyranyl, 4-pyranyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-5-yl, pyrid-6-yl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1H-tetrazol-2-yl, 1H-tetrazol-3-yl, tetrazolyl, acridyl, phenazinyl, carbazolyl, phenoxazinyl, indolizine, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl, 1-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl, 2-indolinyl, 3-indolinyl, 4-indolinyl, 5-indolinyl, 6-indolinyl, 7-indolinyl, benzo[b]furanyl, benzofurazane, benzothiofurazane, benzotriazol-1-yl, benzotriazol-4-yl, benzotriazol-5-yl, benzotriazol-6-yl, benzotriazol-7-yl, benzotriazine, benzo[b]thiophenyl, benzimidazolyl, benzothiazolyl, quinazolinyl, quinoxalinyl, cinnoline, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, purine, phthalazine, pteridine, thiatetraazaindene, thiatriazaindene, isothiazolopyrazine, 6-pyrimidinyl,

2,4-dimethoxy-6-pyrimidinyl, benzimidazol-2-yl, 1*H*-benzimidazolyl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl, benzimidazol-7-yl, tetrahydro-thieno[3,4-*d*]imidazol-2-one, pyrazolo[5,1-*c*][1,2,4]triazine, isothiazolopyrimidine, pyrazolotriazine, pyrazolopyrimidine, imidazopyridazine, imidazopyrimidine, imidazopyridine, imidazolotriazine, triazolotriazine, triazolopyridine, triazolopyrazine, triazolopyrimidine, or 4-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl, 1-furo[2,3-*c*]pyridin-4-yl, 1-furo[2,3-*c*]pyridin-5-yl, 1-furo[2,3-*c*]pyridin-3-yl, and triazolopyridazine group. This heterocyclic group can be substituted by one or more substituents R', wherein R' is as defined above;

a heterocyclyl or heterocycloalkyl group denotes a 3- to 8-membered heterocyclic non-aromatic group which contains at least one heteroatom selected from O, N, and S, wherein the heterocyclyl group may be fused to another non-aromatic ring and may be substituted by one or more substituents R', wherein R' is as defined above; the C₃-C₈-heterocyclyl residue may be selected from the group consisting of -cyclo-C₃H₅, -cyclo-C₄H₇, -cyclo-C₅H₉, -cyclo-C₆H₁₁, -cyclo-C₇H₁₃, -cyclo-C₈H₁₅, morpholine-4-yl, piperazinyl, morpholine-4-yl, 1-alkylpiperazine-4-yl, pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, thiazolidinyl, piperidin-4-one-1-yl, S,S-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, azepanyl and pyranlyl;

a heterocycloaryl group denotes a 5- or 6-membered heterocyclic non-aromatic group which contains at least one heteroatom selected from O, N, and S, wherein the heterocyclyl group may be fused to an aromatic ring and may be substituted by one or more substituents R', wherein R' is as defined above;

To keep the definitions as short as possible, in the following paragraphs "alkyl" is to be understood to encompass alkyl, alkenyl and alkynyl.

In the context of the present invention, an alkyl group, if not stated otherwise, denotes a linear or branched C₁-C₈-alkyl, preferably a linear or branched chain of one to five carbon atoms; an alkenyl group, if not stated otherwise, denotes a linear or branched C₂-C₈-alkenyl; and an alkynyl group, if not stated otherwise, denotes a linear or branched C₂-C₈-alkynyl group, which may be substituted by one or more substituents R'.

The C₁-C₈-alkyl, C₂-C₈-alkenyl and C₂-C₈-alkynyl residue may be selected from the group consisting of -CH₃, -C₂H₅, -CH=CH₂, -C≡CH, -C₃H₇, -CH(CH₃)₂, -CH₂-CH=CH₂, -C(CH₃)=CH₂, -CH=CH-CH₃, -C≡C-CH₃, -CH₂-C≡CH, -C₄H₉, -CH₂-CH(CH₃)₂, -CH(CH₃)-C₂H₅, -C(CH₃)₃, -C₅H₁₁, -C₆H₁₃, -C(R')₃, -C₂(R')₅, -CH₂-C(R')₃, -C₃(R')₇, -C₂H₄-C(R')₃, -C₂H₄-CH=CH₂, -CH=CH-C₂H₅, -CH=C(CH₃)₂, -CH₂-CH=CH-CH₃, -CH=CH-CH=CH₂, -C₂H₄-C≡CH, -C≡C-C₂H₅, -CH₂-C≡C-CH₃, -C≡C-CH=CH₂, -CH=CH-C≡CH, -C≡C-C≡CH, -C₂H₄-CH(CH₃)₂, -CH(CH₃)-C₃H₇, -CH₂-CH(CH₃)-C₂H₅, -CH(CH₃)-CH(CH₃)₂, -C(CH₃)₂-C₂H₅, -CH₂-C(CH₃)₃, -C₃H₆-CH=CH₂, -CH=CH-C₃H₇, -C₂H₄-CH=CH-CH₃, -CH₂-CH=CH-C₂H₅, -CH₂-CH=CH-CH=CH₂, -CH=CH-CH=CH-CH₃, -CH=CH-CH₂-CH=CH₂, -C(CH₃)=CH-CH=CH₂, -CH=C(CH₃)-CH=CH₂, -CH=CH-C(CH₃)=CH₂, -CH₂-CH=C(CH₃)₂, -C(CH₃)=C(CH₃)₂, -C₃H₆-C≡CH, -C≡C-C₃H₇, -C₂H₄-C≡C-CH₃, -CH₂-C≡C-C₂H₅, -CH₂-C≡C-CH=CH₂, -CH₂-CH=CH-C≡CH, -CH₂-C≡C-C≡CH, -C≡C-CH=CH-CH₃, -CH=CH-C≡C-CH₃, -C≡C-C≡C-CH₃, -C≡C-CH₂-CH=CH₂, -CH=CH-CH₂-C≡CH, -C≡C-CH₂-C≡CH, -C(CH₃)=CH-CH=CH₂, -CH=C(CH₃)-CH=CH₂, -CH=CH-C(CH₃)=CH₂, -CH=CH-C(CH₃)=CH₂, -C(CH₃)=CH-C≡CH, -CH=C(CH₃)-C≡CH, -C≡C-C(CH₃)=CH₂, -C₃H₆-CH(CH₃)₂, -C₂H₄-CH(CH₃)-C₂H₅, -CH(CH₃)-C₄H₉, -CH₂-CH(CH₃)-C₃H₇, -CH(CH₃)-CH₂-CH(CH₃)₂, -CH(CH₃)-CH(CH₃)-C₂H₅, -CH₂-CH(CH₃)-CH(CH₃)₂, -CH₂-C(CH₃)₂-C₂H₅, -C(CH₃)₂-C₃H₇, -C(CH₃)₂-CH(CH₃)₂, -C₂H₄-C(CH₃)₃, -CH(CH₃)-C(CH₃)₃, -C₄H₈-CH=CH₂, -CH=CH-C₄H₉, -C₃H₆-CH=CH-CH₃, -CH₂-CH=CH-C₃H₇, -C₂H₄-CH=CH-C₂H₅, -CH₂-C(CH₃)=C(CH₃)₂, -C₂H₄-CH=C(CH₃)₂, -C₄H₈-C≡CH, -C≡C-C₄H₉, -C₃H₆-C≡C-CH₃, -CH₂-C≡C-C₃H₇, and -C₂H₄-C≡C-C₂H₅;

an arylalkyl group denotes a linear or branched C₁-C₈-alkyl substituted with at least one aryl group as defined herein. Exemplary arylalkyl groups include benzyl, phenylethyl, 1-(1-phenylethyl), 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl, and the like. This arylalkyl group can be substituted by one or more substituents R', wherein R' is as defined above;

a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, preferably four to eight carbon atoms, wherein one or more of the carbon atoms in the ring may be substituted by a group E, E being O, S, SO, SO₂, N, or NR'', R'' being as defined above; the C₃-C₈-cycloalkyl residue may be selected from the group consisting of -cyclo-C₃H₅, -cyclo-C₄H₇, -cyclo-C₅H₉, -cyclo-C₆H₁₁, -cyclo-C₇H₁₃, -cyclo-C₈H₁₅, morpholine-4-yl, piperazinyl, and

1-alkylpiperazine-4-yl. This cycloalkyl group can be substituted by one or more substituents R', wherein R' is as defined above;

an alkoxy group denotes an O-alkyl group, the alkyl group being as defined above; the alkoxy group is preferably a methoxy, ethoxy, isopropoxy, *t*-butoxy or pentoxy group;

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

a haloalkyl group denotes a alkyl group as defined above substituted by one or more halogen atoms, preferably substituted by one to five halogen atoms, the haloalkyl group is preferably a $-C(R^{10})_3$, $-CR^{10}(R^{10'})_2$, $-CR^{10}(R^{10'})R^{10''}$, $-C_2(R^{10})_5$, $-CH_2-C(R^{10})_3$, $-C(R^{10'})_2-CH(R^{10'})_2$, $-CH_2-CR^{10}(R^{10'})_2$, $-CH_2-CR^{10}(R^{10'})R^{10''}$, $-C_3(R^{10})_7$, or $-C_2H_4-C(R^{10})_3$, wherein R^{10} , $R^{10'}$, $R^{10''}$ represent F, Cl, Br or I, preferably F;

a haloaryl group denotes a aryl group as defined above substituted by one or more halogen atoms, preferably substituted by one to five halogen atoms;

a haloarylalkyl group denotes a linear or branched C_1 - C_8 -alkyl substituted with at least one haloaryl group as defined herein;

a cyanoalkyl group denotes a NC-alkyl group, the alkyl group being as defined above;

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

a haloalkoxy group denotes an alkoxy group as defined above substituted by one or more halogen atoms, preferably substituted by one to five halogen atoms, the haloalkoxy group is preferably a $-OC(R^{10})_3$, $-OCR^{10}(R^{10'})_2$, $-OCR^{10}(R^{10'})R^{10''}$, $-OC_2(R^{10})_5$, $-OCH_2-C(R^{10})_3$, $-OCH_2-CR^{10}(R^{10'})_2$, $-OCH_2-CR^{10}(R^{10'})R^{10''}$, $-OC_3(R^{10})_7$ or $-OC_2H_4-C(R^{10})_3$, wherein R^{10} , $R^{10'}$, $R^{10''}$ represent F, Cl, Br or I, preferably F;

a hydroxyalkylamino group denotes a $(HO-alkyl)_2-N$ - group or HO-alkyl-NH- group, the alkyl group being as defined above;

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

an aminoalkyl group denotes an -alkyl-NH₂ group, the alkyl group being as defined above;

an alkylaminoalkyl group denotes an alkyl-NH-alkyl or alkyl-N-dialkyl group, the alkyl group being as defined above

a halo or halogen group denotes fluorine, chlorine, bromine, or iodine; preferably chlorine or fluorine.

Compounds having infinite chains consisting for instance of repeating R' and R'' units and the like are not encompassed by this invention. Thus, the longest chain allowed in each side chain R^a, R^b, R^c, R¹, R², R³, and R⁴ of the compounds according to the invention are three coupled substituents R' and/or R'', e.g. R' substituted with R'' further substituted with R' or the like;

this is to be understood such that oligomeric or polymeric side chains comprising more repeating R' and/or R'' units as above outlined are not within the scope of the present invention.

Constituents which are optionally substituted as stated herein may be substituted, unless otherwise noted, at any chemically possible position.

Unless otherwise noted, any heteroatom of a heterocyclic ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences.

When any variable occurs more than one time in any constituent, each definition is independent.

The person skilled in the art is aware on account of his/her expert knowledge that certain combinations of the variable characteristics mentioned in the description of this invention lead to chemically less stable compounds. This can apply, for example, to certain compounds, in which - in a manner being disadvantageous for chemical stability- two heteroatoms (S, N or O) would directly meet or would only be separated by one carbon atom. Those compounds according to this invention, in which the combination of the abovementioned variable substituents does not lead to chemically less stable compounds, are therefore preferred.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), in free form or in the form of pharmaceutically acceptable salts and physiologically functional derivatives, together with a pharmaceutically acceptable diluent or carrier therefore.

In another aspect, the present invention also provides a method for the treatment or prophylaxis of diseases which occur due to the attack of humans by protozoa which comprises the administration of an effective amount of a compound of formula (I) and physiologically acceptable salts or physiologically functional derivatives thereof.

The invention is also directed to the use of compounds of the formula (I) and of their pharmacologically tolerable salts or physiologically functional derivatives for the production of a medicament for the prevention and treatment of diseases, where reduction of parasites is of benefit.

Suitable salts for compounds of formula (I) according to this invention - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are, depending on substitution, also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds of formula (I) according to this invention on an

industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of formula (I) according to this invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula (I) according to this invention as well as all solvates and in particular all hydrates of the salts of the compounds of formula (I) according to this invention. For instance, the mono-, di-, tri-, and tetrahydrates of formula (I) are encompassed.

The compounds of the formula (I) and their pharmacologically acceptable salts can be administered to animals, preferably to mammals, and in particular to humans, as therapeutics *per se*, as mixtures with one another or in the form of pharmaceutical preparations which allow entreat or parenteral use and which as active constituent contain an effective dose of at least one compound of the formula (I) or a salt thereof, in addition to customary pharmaceutically innocuous excipients and additives. The compounds of formula (I) can also be administered in form of their salts, which are obtainable by reacting the respective compounds with physiologically acceptable acids and bases.

The therapeutics can be administered orally, e.g. in the form of pills, tablets, coated tablets, sugar coated tablets, hard and soft gelatin capsules, solutions, syrups, emulsions or suspensions or as aerosol mixtures. Administration, however, can also be carried out rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injections or infusions, or percutaneously, e.g. in the form of ointments, creams or tinctures.

In addition to the active compounds of formula (I), the pharmaceutical composition can contain further customary, usually inert carrier materials or excipients. Thus, the pharmaceutical preparations can also contain additives, such as, for example, fillers, extenders, disintegrants, binders, glidants, wetting agents, stabilizers, emulsifiers, preservatives, sweetening agents, colorants, flavorings or aromatizers, buffer substances, and furthermore solvents or solubilizers or agents for achieving a depot effect, as well as salts for changing the osmotic pressure, coating

agents or antioxidants. They can also contain two or more compounds of the formula (I) or their pharmacologically acceptable salts and also other therapeutically active substances.

Thus, the compounds of the present invention can be used in the form of one substance alone or in combination with other active compounds – for example with medicaments already known for the treatment of the aforementioned diseases, whereby in the latter case a favorable additive, amplifying effect is noticed.

To prepare the pharmaceutical preparations, pharmaceutically inert inorganic or organic excipients can be used. To prepare pills, tablets, coated tablets and hard gelatin capsules, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. can be used. Excipients for soft gelatin capsules and suppositories are, for example, fats, waxes, semi-solid and liquid polyols, natural or hardened oils etc. Suitable excipients for the production of solutions and syrups are, for example, water, sucrose, invert sugar, glucose, polyols etc. Suitable excipients for the production of injection solutions are, for example, water, alcohols, glycerol, polyols or vegetable oils.

The physiologically functional derivatives also include prodrugs of the compounds of the invention. Such prodrugs may be metabolized *in vivo* to a compound of the invention. These prodrugs may or may not be active themselves.

Prodrugs of the compounds of the present invention include but are not limited to: esters, which are transformed *in vivo* into the corresponding active alcohol, esters, which are transformed *in vivo* into the corresponding active acid, imines, which are transformed *in vivo* into the corresponding amines, imines which are metabolized *in vivo* into the corresponding active carbonyl derivative (e.g. aldehyde or ketone), 1-carboxy-amines, which are decarboxylated *in vivo* into the active amine, phosphoryloxy-compounds, which are dephosphorylated *in vivo* by phosphatases into the active alcohols, amidoxime which are transformed into the corresponding amidine, and amides which are metabolized into the corresponding active amine or acid respectively.

For a definition of prodrugs see for example Han Han H.K., Amidon G.L.; Targeted Prodrug Design to Optimize Drug Delivery. *AAPS PharmSci.*, 2(1): article 6. (2000), DOI:

10.1208/ps020106 and Clement B.; Reduction of N-Hydroxylated Compounds: Amidoximes (N-Hydroxyamidines) as prodrugs of amidines. *Drug Metabolism Reviews*, **34** (2002), 565-579.

The physiologically functional derivatives furthermore include, for example, glucuronides, sulfuric acid esters, glycosides and ribosides.

The compounds of formula (I) can also be used in the form of a precursor (prodrug) or a suitably modified form that releases the active compound *in vivo*.

The compounds according to the invention and medicaments prepared therewith are generally suitable for the treatment of diseases which occur due to attack of humans or animals by protozoa. Veterinary- and human-pathogenic protozoa of this type are preferably intracellularly active parasites of the classes Apicomplexa and Zoomastigophora, in particular trypanosomes, plasmodia (malarial parasites), leishmaniasis, babesiasis and theileriasis, cryptosporidiidae, sarcocystidae, amoebae, coccidia and trichomonads. The compounds or corresponding medicaments are particularly preferably suitable for the treatment of diseases caused by plasmodia, in particular for the treatment of tropical malaria, which is caused by *Plasmodium falciparum*, for the treatment of benign tertian malaria, caused by *Plasmodium vivax* and *Plasmodium ovale* and for the treatment of quartan malaria, caused by *Plasmodium malariae*; Most preferred is the use of the compounds according to the invention for the treatment of coccidiosis or malarial diseases or for the production of a medicament or, if appropriate, of a feed for the treatment of coccidiosis or malarial diseases. The treatment can in this case be carried out prophylactically or curatively.

The invention thus makes available novel medicaments for the treatment of the various forms of malaria, in particular for the treatment of tropical malaria. It was surprising that the compounds proved active not only against chloroquine-sensitive, but also against chloroquine-resistant, *Plasmodium falciparum* strains.

The compounds of the present invention are also useful for the treatment of diseases which are caused by eukaryotic protists of the genus *Plasmodium*.

The invention relates to the use of a composition according to the invention for the manufacture of a medicament.

The compounds of the present invention can be used alone or in combination with other antimalarial compounds such as chloroquine, sulfadoxine/pyrimethamine, dapson/pyrimethamine, sulfonamides, halofantrine, amodiaquine, mefloquine, quinine, quinidine, doxycycline, lumefantrine, primaquine, proguanil, atovaquone, pyronaridine, chlorproguanil, artemesinin, arteflene, artemether, artesunate or trimethoprim.

Exemplary compounds according to this invention may include any one selected from

1. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide
2. 4-(3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide
3. 4-(3-(3-(imino(piperazin-1-yl)methyl)phenyl)ureido)benzenesulfonamide
4. 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)urea
5. 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea
6. 1-(3-(imino(morpholino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea
7. 1-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea
8. 1-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea
9. 1-(3-(imino(thiazolidin-3-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea
10. 1-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea
11. 1-(4-(4-chlorophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea
12. 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-(hydroxymethyl)piperidin-1-yl)(imino)methyl)phenyl)urea
13. 3-(3-(4-(4-bromophenylsulfonyl)phenyl)ureido)-N,N-bis(2-methoxyethyl)benzimidamide
14. 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(imino(thiomorpholino)methyl)phenyl)urea
15. 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)urea

16. 1-((3-(3-(4-(4-bromophenylsulfonyl)phenyl)ureido)phenyl)(imino)methyl)piperidine-4-carboxamide
17. 1-(4-(4-aminophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea
18. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-methylbenzenesulfonamide
19. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-propylbenzenesulfonamide
20. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N,N-bis(2-hydroxyethyl)benzenesulfonamide
21. 1-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)-3-(4-(morpholinosulfonyl)phenyl)urea
22. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(7-chloroquinolin-4-yl)benzenesulfonamide
23. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide
24. methyl 4-(imino(3-(3-(4-(N-(4-sulfamoylphenyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
25. 4-(3-(3-(imino(morpholino)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide
26. 4-(3-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide
27. 4-(3-(3-(imino(4-oxopiperidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
28. 4-(3-(3-((4-(2-hydroxyethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
29. 4-(3-(3-((4-(hydroxymethyl)piperidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
30. N-ethyl-N-(2-hydroxyethyl)-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide
31. 4-(3-(3-(imino(thiomorpholino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
32. N,N-bis(2-methoxyethyl)-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide

33. 1-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)-phenyl)ureido)phenyl)methyl)piperidine-4-carboxamide
34. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
35. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(2,3,6-trifluorobenzyl)benzenesulfonamide
36. N-benzyl-4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide
37. 4-(3-(3-((4-ethylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
38. 4-(3-(3-(imino(4-propylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
39. 4-(3-(3-((4-allylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
40. 4-(2-(4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonyl)hydrazinyl)benzenesulfonamide
41. 2-(4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonyl)isoindoline-5-sulfonamide
42. 4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(1-(4-sulfamoylphenyl)ethyl)benzenesulfonamide
43. 4-(3-(3-(imino(morpholino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
44. 4-(3-(3-((1,1-dioxidothiomorpholino)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
45. 4-(3-(3-(imino(4-(pyridin-4-yl)methyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
46. 4-(3-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
47. N-(2-(diethylamino)ethyl)-N-methyl-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide
48. 4-(3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide

49. 4-(3-(3-((3-(dimethylamino)pyrrolidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
50. 4-(3-(3-(imino(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
51. tert-butyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
52. 4-(3-(3-(imino(piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
53. 4-(3-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
54. 4-(3-(3-(imino(4-isopropylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
55. 4-(3-(3-(imino(4-pentylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
56. 4-(3-(3-((4-heptylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
57. 4-(3-(3-((4-acetylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
58. 4-(3-(3-(imino(4-propionylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
59. 4-(3-(3-(imino(4-pentanoylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
60. methyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
61. ethyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
62. propyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
63. 4-(3-(3-((4-butyl-3-oxopiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
64. N,N-dimethyl-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide

65. 4-(3-(3-((4-(2-cyanoethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
66. 4-(3-(3-((4-(cyclopropylmethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
67. 4-(3-(3-((4-((1,3-dioxolan-2-yl)methyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
68. 4-(3-(3-(imino(4-((tetrahydrofuran-2-yl)methyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
69. 4-(3-(3-(imino(4-(2-methoxyethyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
70. 5-((4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonamido)methyl)thiophene-2-sulfonamide
71. 4-(3-(4-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide
72. methyl 4-((acetylimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
73. methyl 4-((octanoylimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate
74. methyl 4-((hydroxyimino)(4-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate

Experimental Part

Abbreviations index

The following abbreviations are presently used:

DCM = dichloromethane; DMF = N,N'-dimethylformamide; MeOH = methanol;
EtOH = ethanol; DIEA = diisopropylethylamide; TFA = trifluoroacetic acid;
MeCN = acetonitrile; HPLC = high-performance liquid chromatography; rt = room temperature;
eq = molar equivalents; h = hours; TLC = Thin layer chromatography; DMSO-*d*₆ = Deuterated
methylsulfoxide; HPLC-MS = high-performance liquid chromatography/mass spectrometry.

Reagents used

The following chemicals were obtained from Fisher Scientific, Germany: Isopropanol, DMA, DCM, DMF, DIEA, 3-nitrobenzamidine, 3-aminobenzamidine; tin(II) dichloride dihydrate, formic acid, acetonitrile, 4-trifluoro-methylaniline, 3-chloroaniline, 2-bromoaniline, 2-aminobenzonitrile, 2-bromo-4,6-difluoroaniline, 3-tri-fluoromethyl-4-chloraniline, 3-trifluoromethylaniline, 2-bromo-4-trifluoromethylaniline, 3,6-bis-trifluoro-methylaniline, 2,4-dibromoaniline, butylamine, benzyl-amine, adamantylamine, oxalamide and sulphamide.

The following chemicals were obtained from Acros Organics, Belgium: 4-aminosulfonamide, 3-isocyanatobenzonitrile, n-butylpiperazine, N-chlorosuccinimide, 4-hydroxypiperidine, piperazine, hydroxylamine, 3-nitrobenzaldehyde, silica gel, 4-(4-bromophenylsulfonyl)aniline, 4-(4-nitrophenylsulfonyl)aniline, 4-(4-chlorophenylsulfonyl)aniline, methyl sulfoxide-*d*₆.

The following chemicals were obtained from Sigma-Aldrich Chemie GmbH, Germany: 4-(Chlorosulphonyl)phenyl isocyanate and 4-nitro-sulphonyl-4-aniline, pyrrolidine, 1-methylpiperazine, thiazolidine, piperidin-4-ylmethanol, bis(2-methoxyethyl)amine, thiomorpholine, piperidine-4-carboxamide, methyl piperazine-1-carboxylate, morpholine, 4-piperidone, 2-(piperazin-1-yl)ethanol, 2-(ethylamino)ethanol, 1-ethylpiperazine, n-propylpiperazine, 1-allylpiperazine, 1-(pyridin-4-ylmethyl)piperazine, tert-butyl piperazine-1-carboxylate, 1-isopropylpiperazine, n-pentylpiperazine, n-heptylpiperazine, 1-butylpiperazin-2-one, N,N-dimethylamine.

The following chemicals were obtained from Maybridge Chemical Comp. Ltd., United Kingdom: 1,1-Dioxo-1H-benzothiophen-6-ylamine, 4-benzene-sulphonylphenylamine and 3H-benzimidazol-5-ylamine.

Analytical determination

Analytical HPLC-MS determinations were performed with Waters 2700 Autosampler, Waters 1525 Multisolvant Delivery System and Micromass ZQ single quadrupole mass spectrometer with electrospray source. Column: Chromolith Fast Gradient C18 (Merck), 50 x 2 mm, with stainless steel 2 µm prefilter. Eluent A, H₂O + 0.1% HCOOH; eluent B, MeCN.

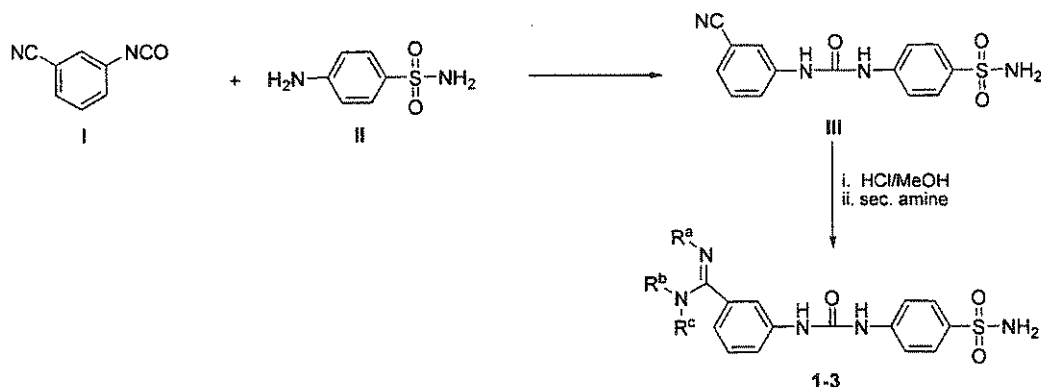
Preparative HPLC-MS were performed with a Waters 2700 Autosampler, Waters 600 Multisolvant Delivery System with preparative pump heads (500 µL), Waters 600S Controller and Waters ZQ single quadrupole mass spectrometer with electrospray source. Column: Waters X-Terra RP18, 5 µm, 19 x 150 mm. Eluent A, H₂O + 0.1% HCOOH; eluent B, MeCN. Different linear gradients, individually adapted to sample.

¹H-NMR were performed with a Bruker AV300 (300.13 Mhz) at temperature of 305 K. Abbreviations used for the peak identification were: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; J = ¹H-¹H coupling constant.

Preparation process

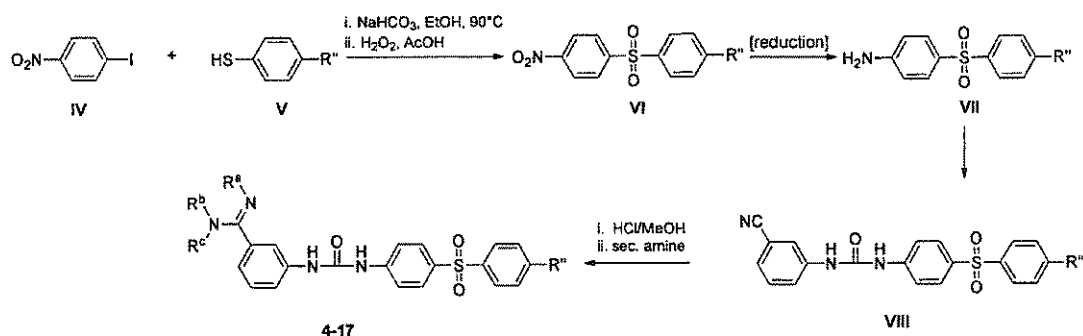
The compounds described in this document were prepared according to methods described in the following synthesis methods.

Procedure A - General procedure for the synthesis of compounds 1-3



1 equivalent of 4-aminosulfonamide(II) was dissolved in DCM/DMF (3:1 solution). 1 equivalent of 3-isocyanatobenzonitrile (I) was added portionwise at rt and the reaction mixture was allowed to stir overnight. The 4-(3-(3-cyanophenyl)ureido)benzenesulfonamide (III) precipitated and was filtered. Under argon atmosphere, the dried cyano compound (III) was dissolved in a 4 M HCl solution in dioxane/MeOH 5:1 and was allowed to stir overnight at rt. The solvent was removed, the residue was washed with diethylether and the obtained methyl 3-(3-(4-sulfamoylphenyl)ureido) benzimidate was reacted further with the corresponding secondary amine in DMF at temperatures ranging between 55 to 75°C. The product (1-3) was obtained after preparative-HPLC, using a reverse-phase column and a gradient of acetonitrile in 0.1% HCOOH_{aq}.

Procedure B1 - General procedure for the synthesis of compounds 4-17 with synthesis of the 4-(substituted)-sulfonylaniline



The multistep syntheses of these compounds follow the methods already described in literature (for example: E. D. Amstutz, *et al.*, *J. Am. Chem. Soc.*, **69** (8), pp 1922-1925, 1947) and require the preparation of the 4-(substituted)-sulfonylaniline which is then reacted with 3-isocyanatobenzonitrile (I) to form the urea which is finally converted to the required products.

Step 1. Synthesis of (4-bromophenyl)(4-nitrophenyl)sulfane

1 equivalent of 1-iodo-4-nitrobenzene (IV) and 4-bromobenzenethiol (or a corresponding 4-substituted-benzenethiol) (V) were dissolved in EtOH. 8 equivalents of sodium bicarbonate were added and the mixture was stirred at reflux for 22 hours. The solvent was removed and the residue was suspended in water. The precipitate was filtered and washed with 1 M sodium

hydroxide and water. The final product was obtained after re-crystallization from ethanol/water (yield: 60%).

Step 2. Synthesis of 1-bromo-4-(4-nitrophenylsulfonyl)benzene (VI)

(4-bromophenyl)(4-nitrophenyl)sulfane [or a correspondent (4-substituted)(4-nitrophenyl)sulfane] was dissolved in concentrated acetic acid and a 30% solution of water peroxide was slowly added (18 ml for 12 g sulfane). The solution was refluxed for 2 h. A precipitate formed upon cooling of the solution to room temperature and addition of EtOH. The precipitate was filtered, washed with ice-cold EtOH and dried (yield: 91%).

Step 3. Synthesis of 4-(4-bromophenylsulfonyl)aniline (VII)

A suspension of Tin(II) chloride dihydrate in concentrated acetic acid (66.1 g in 180 ml) was treated with a 3 M solution of chloridric acid in MeOH for 30 minutes. The resulting suspension was added portionwise during 40 minutes to a suspension of the 1-bromo-4-(4-nitrophenylsulfonyl)benzene (IV) compound (28.6 g) [or a correspondent 1-substituted-4-(4-nitrophenylsulfonyl)benzene] dissolved in acetic acid and was stirred at 80°C for 2 h. 2 litres of water were added and a precipitate formed overnight, which was filtered and washed with 10% aqueous sodium hydroxide and water. The product was crystallized from hot-cold EtOH (yield: 69%).

Step 4. Synthesis of 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-cyanophenyl)urea (VIII)

4-(4-bromophenylsulfonyl)aniline (VII) [or a correspondent (4-substituted)sulfonylaniline] (1 equivalent) was dissolved in a 3:1 solution of DCM/DMF. A solution of 3-isocyanatobenzonitrile (I) (1 equivalent) in DCM was added dropwise. The solution was stirred overnight at rt and, after removal of the solvent, the product was crystallized from hot-cold MeOH (yield: 97%).

Step 5. Synthesis of 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea (4-17)

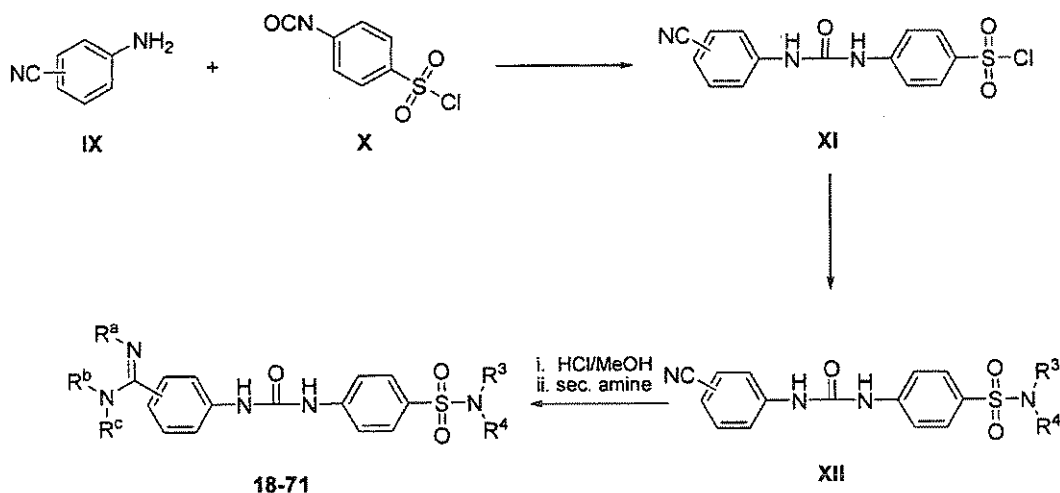
Under argon atmosphere, 1 equivalent of 1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-cyanophenyl)urea (VIII) [or a correspondent 1-(4-(4-substituted-phenylsulfonyl)phenyl)-3-(3-cyanophenyl)urea] was dissolved in of 4 M HCl in dioxane/MeOH 5:1. The solution was stirred overnight at rt then the solvent was removed *in vacuo*. The residue was washed with diethylether,

dried *in vacuo*, dissolved in dry MeOH (or DMF) and reacted with 1.1 to 2 equivalents of piperidin-4-ol (or 1.1 to 2 equivalents of the corresponding secondary amine) at temperature between 55 and 70°C for a minimum of 4 h to a maximum of 22 h. The products were purified either by flash chromatography, using a silica gel column and an appropriate gradient of MeOH in DCM as eluent, or by preparative HPLC, using a reverse-phase column and a gradient of acetonitrile in 0.1% HCOOH_{aq}.

Procedure B2 - General procedure for the synthesis of compounds 4-17 when the 4-(substituted)-sulfonylaniline were commercially available

If the 4-(substituted)-sulfonylaniline (VII) were available from commercial source, the syntheses were performed as described in Procedure B1, *Step 4 and Step 5*.

Procedure C - General procedure for the synthesis of compounds 18-71



Step 1. Production of the cyanourea compound (XII)

28 mmol of 3-aminobenzonitrile (IX) were dissolved in 40 ml DCM. 27 mmol of 4-isocyanatobenzene-1-sulfonyl chloride (X) were added portionwise over 20 minutes and the mixture was allowed to stir at room temperature overnight. The urea product (XI) precipitated, was filtered, washed with cold DCM and was used directly in the next step (yield 93%).

An appropriate amine or aniline compound was dissolved in MeCN and DIEA was added (from 1.2 to 3 equivalents, depending on the amine or aniline compound). The solution was cooled to 0°C and, under vigorous stirring, 1 equivalent of the ureido-sulfonylchloride compound (XI) was added portionwise. The reaction was allowed to stir overnight, allowing the temperature to

increase to rt. The solvent was evaporated and the product (XII) was obtained by precipitation with ethylacetate/petrol ether or MeOH/diethylether. If necessary, the product was further purified by flash chromatography using a gradient of MeOH in DCM mixtures as eluent.

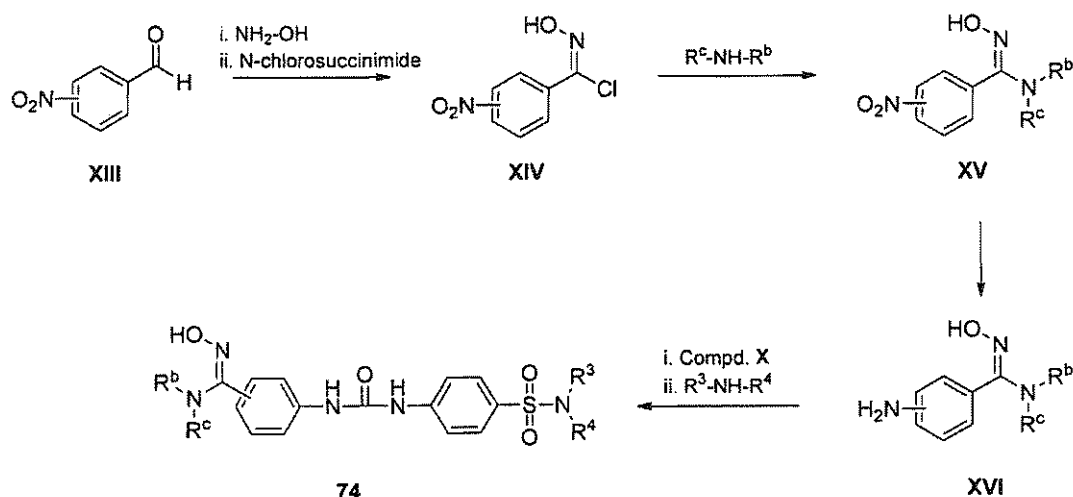
Step 2 – Conversion of the cyano compound to functionalized benzamidine

Under argon atmosphere, 1 equivalent of the cyanoureido (XII) compound was dissolved with 20 ml of dry MeOH. 4 M HCl in dioxane was added and the solution was stirred overnight at rt. The solvent was removed; the residue was taken in diethylether which was evaporated. This operation was repeated three times to yield either a solid or an oily product.

1 equivalent of the dried benzimidate was dissolved in DMF and variable amounts of the chosen secondary amine were added (1.1 to 3 equivalents). The solution was stirred overnight at temperatures ranging from 55 to 70°C. The solvent was removed and the product was purified by preparative HPLC and a gradient of acetonitrile in 0.1% HCOOH_{aq}.

Procedure D - General procedure for the synthesis of compound 74

Compound 74 and analogues can be prepared in a multistep synthesis following methods known and described in literature (for example: Liu K.-C., *et al.*; A particularly convenient preparation of benzohydroximinoyl chlorides (nitrile oxide precursors). *Journal of Organic Chemistry*, **45** (1980), 3916-3918; Johnson J.E., *et al.*; Bisamidoximes: Synthesis and Complexation with Iron(III). *Australian Journal of Chemistry*, **60** (2007), 685-690; Moehrle H., *et al.*; Assistance of N,N-disubstituted amidoximes in cyclodehydrogenation reactions. *Zeitschrift fuer Naturforschung, B: Chemical Sciences*, **47** (1992), 1333-1340).



0.13 mol of compound **XIII** were dissolved in dry DMF. 0.14 mol each of sodium acetate and hydroxylamine hydrochloride were added and the mixture was stirred overnight at rt. After removal of the solvent, the oxime was precipitate from MeOH/diethylether (yield 70%). This compound was dissolved in dry DMF and 1.1 eq of *N*-chlorosuccinimide was added portionwise over 30 min. The mixture was stirred overnight at rt, then it was poured into ice-water. The suspension was extracted with ethylacetate and the organic solution was washed with water and brine. Compound **XIV** was obtained after removal of the organic solvent. Compound **XIV** was dissolved in DCM and 1 eq of methyl piperazine-1-carboxylate (or another secondary amine) were added in the presence of 2.1 eq of DIEA. The mixture was stirred for 24 h at rt, the solvent was removed and the residue was taken into ethylacetate. The organic solution was washed with water and brine and was evaporated. The obtained oil was purified by flash chromatography with silica gel and a mixture DCM/MeOH 95:5 as eluent. The nitro compound **XV** was reduced by hydrogenation with palladium catalyst to produce the corresponding amino compound **XVI**. Compound **XVI** was reacted with 1 eq of compound **X** in DCM until complete conversion to the corresponding diarylurea. The solvent was removed and the residue was dissolved in dry DMF. To this solution, 1 eq of the corresponding amino compound and 1 eq of DIEA was added. The solution was stirred at 70°C overnight, then the solvent was removed and compound **74** was obtained after purification by preparative HPLC.

List of compounds**4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide (1)**

The title compound was obtained following procedure A and using 3 equivalents of n-butylpiperazine as secondary amine.

Yield: 15%.

$[M+H]^+$: 459.1.

^1H NMR ($\text{DMSO}-d_6$): 11.45 (s, 1H, NH), 11.44 (s, 1H, NH), 7.87 (t broad, 1H, ArH), 7.77-7.68 (m, 5H, ArH), 7.49 (t, 1H, $J = 7.9$ Hz, ArH), 7.14 (s, 2H, NH_2), 7.10 (d, 1H, $J = 7.1$ Hz, ArH), water signal partially covers a group of signals, 2.34 (t, 2H, $J=7.2$ Hz, NCH_2), 1.40 (m, 2H, CH_2), 1.29 (m, 2H, CH_2), 0.88 (t, 3H, $J=7.2$, CH_3).

4-(3-(3-((4-hydroxypiperazin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide (2)

The title compound was obtained following procedure A and using 2 equivalents of 4-hydroxypiperidine as secondary amine.

Yield: 2%.

$[M+H]^+$: 418.0.

4-(3-(3-(imino(piperazin-1-yl)methyl)phenyl)ureido)benzenesulfonamide (3)

The title compound was obtained following procedure A and using 2 equivalents of piperazine as secondary amine.

Yield: 13%.

$[M+H]^+$: 403.0.

1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)urea (4)

The title compound was obtained following procedure B2 (with 4-(4-bromophenylsulfonyl)aniline) and using 1.14 equivalents of 4-hydroxypiperidine as secondary amine. The product was purified by flash chromatography.

Yield: 27%.

[M+H]⁺: 599.1.

1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea (5)

The title compound was obtained following procedure B1 or B2 (with 4-(4-bromophenylsulfonyl)aniline) and using 2 equivalents of 4-hydroxypiperidine as secondary amine. The product was purified by preparative HPLC.

Yield: 9%.

[M+H]⁺: 556.6 .

¹H NMR (DMSO-*d*₆): 9.59 (s, 1H, NH); 9.42 (s, 1H, NH); 9.30 (s, 1H, NH); 9.02 (s, 1H, NH); 7.82-7.43 (m, 11H, Ar-H); 7.13 (m, 1H, Ar-H); 4.88 (d, 1H, J=3.5 Hz, OH); 3.84-3.13 (m, 5H, CH+2CH₂) water signal partly covers this group of signals; 1.92-1.34 (m, 4H, 2CH₂).

1-(3-(imino(morpholino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea (6)

The title compound was obtained following procedure B2 with 4-(4-nitrophenylsulfonyl)aniline and using 0.8 equivalents of morpholine as secondary amine. The product was purified by flash chromatography.

Yield: 2%.

[M+H]⁺: 510.1.

1-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea (7)

The title compound was obtained following procedure B2 with 4-(4-nitrophenylsulfonyl)aniline and using 0.8 equivalents of pyrrolidine as secondary amine. The product was purified by flash chromatography.

Yield: 5%.

$[M+H]^+$: 494.0.

^1H NMR ($\text{DMSO}-d_6$): 10.09 (s, 1H, NH); 9.86 (s, 1H, NH); 9.25-8.65 (broad, 2H, NH_2); 8.31 (m, 2H, Ar-H); 8.10 (m, 2H, Ar-H); 7.85 (m, 2H, Ar-H); 7.73 (m, 1H, Ar-H); 7.63 (m, 2H, Ar-H); 7.52 (m, 1H, Ar-H); 7.43 (m, 1H, Ar-H); 7.14 (m, 1H, Ar-H); 3.46-3.28 (broad, 4H, 2NCH_2) water signal partly covers this group of signals; 1.96-1.80 (broad, 4H, 2CH_2).

1-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea (8)

The title compound was obtained following procedure B2 with 4-(4-nitrophenylsulfonyl)aniline and using 1.5 equivalents of 1-methylpiperazine. The product was purified by flash chromatography.

Yield: 18%.

$[M+H]^+$: 523.2

^1H NMR ($\text{DMSO}-d_6$): 10.18 (broad, 1H, NH); 9.96 (broad, 1H, NH); 9.51 (broad, 1H, NH); 9.26 (broad, 1H, NH); 8.39 (m, 2H, Ar-H); 8.18 (m, 2H, Ar-H); 7.94 (m, 2H, Ar-H); 7.76 (m, 1H, Ar-H); 7.71 (m, 2H, Ar-H); 7.63 (m, 1H, Ar-H); 7.53 (m, 1H, Ar-H); 7.18 (m, 1H, Ar-H); 3.76-3.28 (broad, 4H, 2NCH_2) water signal partly covers this group of signals; 2.55-2.38 (broad, 4H, 2NCH_2) DMSO signal partly covers this group of signals; 2.23 (s, 3H, CH_3).

1-(3-(imino(thiazolidin-3-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea (9)

The title compound was obtained following procedure B2 with 4-(4-nitrophenylsulfonyl)aniline and using 1.5 equivalents of thiazolidine as secondary amine. The product was purified by flash chromatography.

Yield: 1%.

[M+H]⁺: 512.1.

1-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea (10)

The title compound was obtained following procedure B1 or B2 with 4-(4-nitrophenylsulfonyl)aniline and using 1.5 equivalents of 4-hydroxypiperidine as secondary amine. The product was purified by flash chromatography.

Yield: 10%.

[M+H]⁺: 524.1.

¹H NMR (DMSO-*d*₆): 10.13 (s, 1H, NH); 9.91 (s, 1H, NH); 9.37-9.16 (broad, 2H, NH); 8.29 (AB, 4H, J=63.3 Hz, 8.9 Hz, Ar-H); 7.82 (AB, 4H, J=67.0 Hz, 8.9 Hz, Ar-H); 7.78 (s, 1H, Ar-H); 7.61 (m, 1H, Ar-H); 7.52 (t, 1H, J=7.9 Hz, Ar-H); 7.19 (m, 1H, Ar-H); 4.95 (d, 1H, J=3.6 Hz, OH); 3.87-3.83 (broad, 1H, CH); 3.60-3.10 (broad, 4H, 2NCH₂) water signal partly covers this group of signals; 2.00-1.40 (broad, 4H, 2CH₂).

1-(4-(4-chlorophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea (11)

The title compound was obtained following procedure B2 with 4-(4-chlorophenylsulfonyl)aniline and using 1.2 equivalents of piperidin-4-ol as secondary amine. The product was purified by preparative HPLC.

Yield: 14%.

[M+H]⁺: 513.0.

¹H NMR (DMSO-*d*₆): 10.44 (s, 1H, NH); 9.33 (broad, 1H, NH); 9.26 (s, 1H, NH); 9.05 (broad, 1H, NH); 7.91-7.80 (m, 5H, Ar-H); 7.70-7.64 (m, 4H, Ar-H); 7.56-7.47 (m, 2H, Ar-H); 7.18-7.16 (m, 1H, Ar-H); 4.91 (d, 1H, J=3.6 Hz, OH); 3.86-3.79 (broad, 1H, CH); water signal covers the group of 2NCH₂ signals; 1.84-1.52 (broad, 4H, 2CH₂).

1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-(hydroxymethyl)piperidin-1-yl)(imino)methyl)phenyl)urea (12)

The title compound was obtained following procedure B2 with 4-(4-bromophenylsulfonyl)aniline and using 1.14 equivalents of piperidin-4-ylmethanol as secondary amine. The residue was taken into ethylacetate and washed with 5% NaHCO₃, water and brine. The product was obtained after crystallization with methanol/ethyl ether.

Yield: 20%.

[M+H]⁺: 570.9.

¹H NMR (DMSO-*d*₆): 10.22 (broad, 1H, NH); 10.03 (broad, 1H, NH); 9.40 (broad, 2H, NH); 8.11-7.86 (m, 9H, Ar-H); 7.84-7.79 (m, 1H, Ar-H); 7.76-7.68 (m, 1H, Ar-H); 7.39-7.35 (m, 1H, Ar-H); 4.76 (t, 1H, J=5.0 Hz, OH); 4.07-4.02 (broad, 2H, CH₂); water signal partially covers the group of 2NCH₂ signals; 2.01-1.94 (broad, 3H, CH+CH₂); 1.50-1.40 (broad, 2H, CH₂).

3-(3-(4-(4-bromophenylsulfonyl)phenyl)ureido)-N,N-bis(2-methoxyethyl)benzimidamide (13)

The title compound was obtained following procedure B2 with 4-(4-bromophenylsulfonyl)aniline and using 1.14 equivalents of bis(2-methoxyethyl)amine as secondary amine. The residue was taken into ethylacetate and washed with 5% NaHCO₃, water and brine. The product was obtained by crystallization with MeOH/ethyl ether.

Yield: 30%.

[M+H]⁺: 589.1.

1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(imino(thiomorpholino)methyl)phenyl)urea (14)

The title compound was obtained following procedure B2 with 4-(4-bromophenylsulfonyl)aniline and using 1.14 equivalents of thiomorpholine as secondary amine. The product was purified by flash chromatography.

Yield: 25%.

$[M+H]^+$: 559.0.

1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)urea (15)

The title compound was obtained following procedure B2 with 4-(4-bromophenylsulfonyl)aniline and using 1.14 equivalents of pyrrolidine as secondary amine. The product was purified by flash chromatography.

Yield: 38%.

$[M+H]^+$: 527.0.

1-((3-(3-(4-(4-bromophenylsulfonyl)phenyl)ureido)phenyl)(imino)methyl)piperidine-4-carboxamide (16)

The title compound was obtained following procedure B2 with 4-(4-bromophenylsulfonyl)aniline and using 1.14 equivalents of piperidine-4-carboxamide as secondary amine. The product precipitated directly from the reaction mixture and was filtered, washed with cold diethylether and dried.

Yield: 54%.

$[M+H]^+$: 584.0.

1-(4-(4-aminophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea (17)

A suspension of tin(II) chloride dihydrate (3 equivalents) in concentrated acetic acid was treated with a 3 M solution of chloridric acid in methanol for 30 minutes. The resulting suspension was added portionwise to a solution of 1-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea (10) in acetic acid. The resulting solution was stirred 2 hours at 85°C. The reaction mixture was quenched with a 5% NaOH aqueous solution, and extracted with ethyl acetate. The title compound was obtained after preparative HPLC.

Yield: 18%.

$[M+H]^+$: 494.1.

¹H NMR (DMSO-*d*₆): 11.30 (s, 1H, NH); 11.22 (s, 1H, NH); 7.81 (m, 1H, Ar-H); 7.72-7.66 (m, 5H, Ar-H); 7.52-7.41 (m, 3H, Ar-H); 7.10-7.06 (m, 1H, Ar-H); 6.62-6.57 (m, 2H, Ar-H); 6.05 (s broad, 2H, NH₂); 3.87-3.76 (m, 1H, CH); 3.75-3.67 (m, 2H, NCH₂); water signal partially covers a group of signals; 1.90-1.78 (broad, 2H, CH₂); 1.58-1.44 (broad, 2H, CH₂).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-methylbenzene sulfonamide (18)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-methylbenzenesulfonamide following procedure C and using 2.2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 1%.

[M+H]⁺: 473.2.

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-propylbenzene sulfonamide (19)

The title compound was prepared from 3-(3-(4-(N-propylsulfamoyl)phenyl)ureido)benzimidamide following procedure C and using 2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 13%.

[M+H]⁺: 501.3.

¹H NMR (DMSO-*d*₆): 9.77-9.27 (m broad, 3H, NH); 7.86 (broad, 1H, Ar-H); 7.66-7.46 (m, 6H, NH+Ar-H); 7.32 (m, 1H, Ar-H); 7.18-7.13 (m, 1H, Ar-H); water signal partially covers a group of signals; 2.65-2.57 (m, 2H, CH₂); 1.58-1.44 (broad, 2H, CH₂); 1.36-1.20 (m, 4H, 2CH₂); 0.84 (t, 3H, J=7.3 Hz, CH₃); 0.72 (t, 3H, J=7.4 Hz, CH₃).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N,N-bis(2-hydroxyethyl)benzenesulfonamide (20)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N,N-bis(2-hydroxyethyl)benzenesulfonamide following procedure C and using 2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 18%.

$[M+H]^+$: 547.2.

^1H NMR ($\text{DMSO}-d_6$): 9.81 (broad, 2H, NH); 9.48 (broad, 1H, NH); 7.97 (broad, 1H, Ar-H); 7.79-7.57 (m, 6H, Ar-H); 7.29-7.24 (m, 1H, Ar-H); 3.55 (t, 4H, $J=6.3$ Hz, 2CH_2); 3.18 (t, 4H, $J=6.3$ Hz, 2CH_2); water signal partially covers a group of signals; 1.68-1.56 (broad, 2H, CH_2); 1.43-1.31 (m, 2H, CH_2); 0.95 (t, 3H, $J=7.3$ Hz, CH_3).

1-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)-3-(4-(morpholinosulfonyl)phenyl)urea (21)

The title compound was prepared from 1-(3-cyanophenyl)-3-(4-(morpholinosulfonyl)phenyl)urea following procedure C and using 2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 72%.

$[M+H]^+$: 529.2.

^1H NMR ($\text{DMSO}-d_6$): 9.83-9.13 (broad, 3H, 3NH); 7.90 (broad, 1H, Ar-H); 7.80-7.56 (m, 6H, Ar-H); 7.28-7.22 (m, 1H, Ar-H); 3.67 (m, 4H, 2CH_2); 2.89 (m, 4H, 2CH_2); water signal partially covers a group of signals; 1.60-1.42 (broad, 2H, CH_2); 1.41-1.28 (m, 2H, CH_2); 0.93 (t, 3H, $J=7.2$ Hz, CH_3).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(7-chloroquinolin-4-yl)benzenesulfonamide (22)

The title compound was prepared from N-(7-chloroquinolin-4-yl)-4-(3-(3-cyanophenyl)ureido)benzenesulfonamide following procedure C and using 2.2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 25%.

$[M+H]^+$: 620.2.

^1H NMR ($\text{DMSO}-d_6$): 9.78-9.59 (broad, 2H, 2NH); 8.38 (d, 1H, $J=8.9$ Hz, Quin-H); 8.26 (s, 1H, NH); 8.14 (d, 1H, $J=6.1$ Hz, Quin-H); 7.83 (m, 1H, Ar-H); 7.72 (m, 2H, Ar-H); 7.64 (d, 1H, $J=2.1$ Hz, Quin-H); 7.62-7.46 (m, 4H, Ar-H); 7.33 (dd, 1H, $J=8.9$ Hz, 2.2 Hz, Quin-H); 7.13 (m,

1H, Ar-H); 6.91 (d, 1H, J=6.1 Hz, Quin-H); water signal partially covers a group of signals; 1.46-1.22 (m, 4H, 2CH₂); 0.88 (t, 3H, J=7.2 Hz, CH₃).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide (23)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide following procedure C and using 1.2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 16.5%.

[M+H]⁺: 614.2.

¹H NMR (DMSO-*d*₆): 10.10-9.31 (broad, 3H, 3NH); 7.82-7.48 (m, 9H, Ar-H); 7.25-7.16 (m, 3H, Ar-H); 7.15 (s broad, 2H, NH₂); water signal partially covers a group of signals; 2.33 (t, 2H, J=7.2 Hz, CH₂); 1.46-1.22 (2m, 4H, 2CH₂); 0.88 (t, 3H, J=7.2 Hz, CH₃).

methyl 4-(imino(3-(3-(4-(N-(4-sulfamoylphenyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate (24)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide following procedure C and using 1 equivalent of methyl piperazine-1-carboxylate as secondary amine and 1 equivalent of DIEA as base. The product was purified by preparative HPLC.

Yield: 5.3%.

[M+H]⁺: 616.0.

4-(3-(3-(imino(morpholino)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide (25)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide following procedure C and using 1 equivalent of morpholine as secondary amine and 0.5 equivalent of DIEA as base. The product was purified by preparative HPLC.

Yield: 31.6%.

[M+H]⁺: 559.1.

¹H NMR (DMSO-*d*₆): 10.69-9.10 (broad, 3H, 3NH); 8.44 (broad, 1H, NH); 7.81 (m, 1H, Ar-H); 7.75-7.59 (m, 7H, Ar-H); 7.49 (m, 1H, Ar-H); 7.22-7.08 (m, 5H, Ar-H+NH₂); 3.73 (broad, 4H, 2CH₂); 3.54 (broad, 4H, 2CH₂); water signal interferes with these two signals.

4-(3-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide (26)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide following procedure C and using 1 equivalent of 1-methylpiperazine as secondary amine and 1 equivalent of DIEA as base. The product was purified by preparative HPLC.

Yield: 33.8%.

[M+H]⁺: 572.1.

¹H NMR (DMSO-*d*₆): 10.45 (broad, 1H, NH); 10.34 (broad, 1H, NH); 8.21 (s, 1H, NH); 7.77-7.60 (m, 8H, Ar-H); 7.51 (m, 1H, Ar-H); 7.27-7.21 (m, 2H, Ar-H); 7.19-7.12 (m, 3H, Ar-H+NH₂); water signal partially covers a group of signals; 2.23 (s, 3H, CH₃).

4-(3-(3-(imino(4-oxopiperidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (27)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of both 4-piperidone as secondary amine and DIEA as base. The product was purified first by preparative HPLC and finally with a preparative TLC (eluent: petrolether/DCM/MeOH 2:3:1 containing 2% of a 7 M NH₃ solution in MeOH).

Yield: 3%.

[M+H]⁺: 585.2.

¹H NMR (DMSO-*d*₆): 9.69 (broad, 1H, NH); 9.62 (broad, 1H, NH); 8.08 (t, 1H, J=6.3 Hz, NH); 7.92 (m, 1H, Ar-H); 7.77-7.52 (m, 8H, Ar-H); 7.46-7.41 (m, 2H, Ar-H); 7.30-7.23 (m, 3H, Ar-H+NH₂); 4.03 (d, 2H, J=6.3 Hz, CH₂); 3.82 (broad, 4H, 2CH₂); 2.64 (broad, 4H, 2CH₂).

4-(3-(3-((4-(2-hydroxyethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (28)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1.2 equivalent of 2-(piperazin-1-yl)ethanol as secondary amine. The product was purified by preparative TLC (eluent: petrolether/DCM/MeOH 2:3:1 containing 2% of a 7 M NH₃ solution in MeOH).

Yield: 2%.

[M+H]⁺: 616.1.

¹H NMR (DMSO-*d*₆): 10.12 (broad, 1H, NH); 10.05 (broad, 1H, NH); 8.09 (t, 1H, J=6.2 Hz, NH); 7.79-7.62 (m, 8H, Ar-H); 7.53 (m, 1H, Ar-H); 7.47-7.41 (m, 2H, Ar-H); 7.29 (s broad, 2H, NH₂); 7.19-7.15 (m, 1H, Ar-H); 4.47 (t, 1H, J=5.3 Hz, OH); 4.03 (d, 2H, J=6.0 Hz, CH₂); 3.51 (m, 2H, OCH₂); water signal partially covers a group of signals; 2.59 (broad, 4H, 2CH₂).

4-(3-(3-((4-(hydroxymethyl)piperidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (29)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalents of 4-piperidinylmethanol as secondary amine. The product was purified by preparative HPLC.

Yield: 40%.

[M+H]⁺: 601.1.

¹H NMR (DMSO-*d*₆): 9.61 (broad, 1H, NH); 9.54 (broad, 1H, NH); 8.08 (t, 1H, J=6.2 Hz, NH); 7.83 (m, 1H, Ar-H); 7.79-7.41 (m, 11H, Ar-H); 7.28 (s broad, 2H, NH₂); 7.20-7.16 (m, 1H, Ar-H); 4.57 (t, 1H, J=5.1 Hz, OH); 4.03 (d, 2H, J=6.1 Hz, CH₂); water signal partially covers a group of signals; 1.89-1.70 (broad, 3H, CH+CH₂); 1.40-1.20 (broad, 2H, CH₂).

N-ethyl-N-(2-hydroxyethyl)-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide (30)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide following procedure C and using 1.1 equivalents of 2-(ethylamino)ethanol as secondary amine. The product was purified by preparative HPLC.

Yield: 7%.

$[M+H]^+$: 575.1.

4-(3-(3-(imino(thiomorpholino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (31)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide following procedure C and using 1.1 equivalents of thiomorpholine as secondary amine. The product was purified by preparative TLC (eluent DCM/MeOH 8:2).

Yield: 28%.

$[M+H]^+$: 589.0.

^1H NMR (DMSO- d_6): 9.74 (broad, 1H, NH); 9.67 (broad, 1H, NH); 8.08 (t, 1H, $J=6.3$ Hz, NH); 7.87 (m, 1H, Ar-H); 7.77-7.51 (m, 8H, Ar-H); 7.46-7.41 (m, 2H, Ar-H); 7.28 (s broad, 2H, NH_2); 7.24-7.20 (m, 1H, Ar-H); 4.03 (d, 2H, $J=6.2$ Hz, CH_2); water signal partially covers a group of signals; 2.85-2.80 (m, 4H, 2CH_2).

N,N-bis(2-methoxyethyl)-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide (32)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide following procedure C and using 1.1 equivalents of bis(2-methoxyethyl)amine as secondary amine. The product was purified by preparative HPLC.

Yield: 11%.

$[M+H]^+$: 619.1.

^1H NMR (DMSO- d_6): 9.62 (broad, 1H, NH); 9.56 (broad, 1H, NH); 8.07 (t, 1H, $J=6.3$ Hz, NH); 7.79-7.41 (m, 13H, Ar-H); 7.28 (s broad, 2H, NH_2); 7.14-7.11 (m, 1H, Ar-H); 4.03 (d, 2H, $J=6.2$ Hz, CH_2); 3.82-3.48 (broad, 8H, 4CH_2); water signal partially covers a group of signals.

1-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)-phenyl)ureido)phenyl)methyl)piperidine-4-carboxamide (33)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide following procedure C and using 2.2 equivalents of piperidine-4-carboxamide as secondary amine. The product was purified by preparative HPLC.

Yield: 40%.

$[M+H]^+$: 614.1.

^1H NMR ($\text{DMSO}-d_6$): 9.63 (broad, 1H, NH); 9.56 (broad, 1H, NH); 8.08 (broad, 1H, NH); 7.84 (m, 1H, Ar-H); 7.77-7.42 (m, 10H, Ar-H); 7.32 (broad, 1H, NH_2); 7.28 (broad, 2H, NH_2); 7.21-7.18 (m, 1H, Ar-H); 6.87 (broad, 1H, NH_2); 4.04-4.02 (broad, 2H, CH_2); water signal partially covers a group of signals; 1.92-1.62 (broad, 4H, Ar-H).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (34)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide following procedure C and using 1.1 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 21%.

$[M+H]^+$: 628.1.

^1H NMR ($\text{DMSO}-d_6$): 9.81 (broad, 1H, NH); 9.77 (broad, 1H, NH); 9.44 (broad, 1H, NH); 8.08 (t, 1H, $J=6.3$ Hz, NH); 7.93 (m, 1H, Ar-H); 7.76-7.53 (m, 8H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.28 (broad, 2H, NH_2); 7.25-7.21 (m, 1H, Ar-H); 4.03 (d, 2H, $J=6.3$ Hz, CH_2); water signal partially covers a group of signals; 1.64-1.53 (broad, 2H, CH_2); 1.33 (m, 2H, CH_2); 0.91 (t, 3H, $J=7.3$ Hz, CH_3).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(2,3,6-trifluorobenzyl) benzenesulfonamide (35)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(2,3,6-trifluorobenzyl)benzenesulfonamide following procedure C and using 3 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield (8%)

$[M+H]^+$: 603.2.

^1H NMR ($\text{DMSO}-d_6$): 11.00 (broad, 1H, NH); 10.97 (broad, 1H, NH); 8.03 (broad, 1H, NH); 7.83 (m, 1H, Ar-H); 7.74-7.63 (m, 5H, Ar-H); 7.51-7.33 (m, 2H, Ar-H); 7.13-7.00 (m, 2H, Ar-H); 4.02 (broad, 2H, CH_2); water signal partially covers a group of signals; 2.33 (m, 2H, CH_2); 1.46-1.23 (m, 4H, 2 CH_2); 0.88 (t, 3H, $J=7.2$ Hz, CH_3).

N-benzyl-4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido) benzenesulfonamide (36)

The title compound was prepared from N-benzyl-4-(3-(3-cyanophenyl)ureido)benzenesulfonamide following procedure C and using 3 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 6%.

$[M+H]^+$: 549.2.

^1H NMR ($\text{DMSO}-d_6$): 11.28-11.14 (broad, 2H, 2NH); 8.52 (s broad, 1H, NH); 7.94-7.87 (broad, 1H, NH); 7.83 (m, 1H, Ar-H); 7.75-7.67 (m, 5H, Ar-H); 7.47 (m, 1H, Ar-H); 7.32-7.19 (m, 5H, Ar-H); 7.11-7.07 (m, 1H, Ar-H); 3.95 (s broad, 2H, CH_2); water signal partially covers a group of signals; 2.33 (m, 2H, CH_2); 1.46-1.23 (m, 4H, 2 CH_2); 0.88 (t, 3H, $J=7.2$ Hz, CH_3).

4-(3-(3-((4-ethylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (37)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1.5 equivalents of 1-ethylpiperazine as secondary amine. The product was purified by flash chromatography on silica gel.

Yield: 30%.

$[M+H]^+$: 600.1.

4-(3-(3-(imino(4-propylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (38)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of n-propylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 30%.

$[M+H]^+$: 614.1.

^1H NMR ($\text{DMSO}-d_6$): 9.80 (s broad, 1H, NH); 9.75 (s broad, 1H, NH); 9.70 (s broad, 1H, NH); 9.45 (s broad, 1H, NH); 8.08 (t, 1H, $J=6.3$ Hz, NH); 7.93 (m, 1H, Ar-H); 7.76-7.62 (m, 7H, Ar-H); 7.56 (m, 1H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.28 (s broad, 2H, NH_2); 7.25-7.21 (m, 1H, Ar-H); 4.04 (d, 2H, $J=6.3$ Hz, CH_2); water signal partially covers a group of signals; 1.70-1.58 (m broad, 2H, CH_2); 0.92 (t, 3H, $J=7.4$ Hz, CH_3).

4-(3-(3-((4-allylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (39)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 5 equivalents of 1-allylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 3%.

$[M+H]^+$: 612.1.

4-(2-(4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonyl)hydrazinyl)benzenesulfonamide (40)

The title compound was prepared from 4-(2-(4-(3-(3-cyanophenyl)ureido)phenylsulfonyl)hydrazinyl)benzenesulfonamide following procedure C and using 2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 10%.

$[M+H]^+$: 629.1.

2-(4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonyl)isoindoline-5-sulfonamide (41)

The title compound was prepared from 2-(4-(3-(3-cyanophenyl)ureido)phenylsulfonyl)isoindoline-5-sulfonamide following procedure C and using 3 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 12%.

$[M+H]^+$: 640.2.

^1H NMR ($\text{DMSO}-d_6$): 11.37-11.17 (broad, 2H, 2NH), 7.81-7.87 (m, 7H, Ar-H); 7.50-7.41 (m, 2H, Ar-H); 7.28 (broad, 2H, NH_2); 7.12-7.09 (m, 1H, Ar-H); 4.64-4.59 (m, 4H, 2 CH_2); water signal partially covers a group of signals; 2.33 (m, 2H, CH_2); 1.45-1.22 (m, 4H, 2 CH_2); 0.88 (t, 3H, $J=7.2$ Hz, CH_3).

4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(1-(4-sulfamoylphenyl)ethyl) benzenesulfonamide (42)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(1-(4-sulfamoylphenyl)ethyl)benzenesulfonamide following procedure C and using 2 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 8%.

$[M+H]^+$: 642.2.

4-(3-(3-(imino(morpholino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (43)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of morpholine as secondary amine. The product was purified by preparative HPLC.

Yield: 38%.

$[M+H]^+$: 573.1.

^1H NMR ($\text{DMSO}-d_6$): 9.81 (s broad, 1H, NH); 9.74 (s broad, 1H, NH); 9.37 (broad, 1H, NH); 8.07 (t, 1H, $J=6.2$ Hz, NH); 7.85 (m, 1H, Ar-H); 7.76-7.62 (m, 7H, Ar-H); 7.55-7.42 (m, 3H, Ar-H); 7.28 (s broad, 2H, NH_2); 7.28-7.18 (m, 3H, NH_2 +Ar-H); 4.03 (d, 2H, $J=6.0$ Hz, CH_2); 3.74-3.72 (m broad, 4H, 2 CH_2); 3.54-3.58 (m broad, 4H, 2 CH_2).

4-(3-(3-(imino(1,1-dioxidothiomorpholine)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (44)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1.5 equivalents of 1,1-dioxothiomorpholine as secondary amine. The product was purified by preparative HPLC.

Yield: 13%.

$[M+H]^+$: 621.1.

4-(3-(3-(imino(4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (45)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of 1-(pyridin-4-ylmethyl)piperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 11%.

$[M+H]^+$: 663.2.

^1H NMR ($\text{DMSO}-d_6$): 9.63-9.52 (broad, 3H, 3NH), 9.25 (broad, 1H, NH); 8.67-8.65 (m, 2H, Pyr-H); 8.09 (t, 1H, $J=6.1$ Hz, NH); 7.88 (m, 1H, Ar-H); 7.77-7.52 (m, 10H, Ar-H+Pyr-H); 7.46-7.41 (m, 2H, Ar-H); 7.30 (broad, 2H, NH_2); 7.22-7.18 (m, 1H, Ar-H); 4.04 (d, 2H, $J=6.2$ Hz, CH_2); water signal partially covers a group of signals; 2.80-2.57 (m, 4H, 2 CH_2).

4-(3-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (46)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of pyrrolidine as secondary amine. The product was purified by preparative HPLC.

Yield: 16%.

$[M+H]^+$: 557.1.

¹H NMR (DMSO-*d*₆): 9.51 (s broad, 1H, NH); 9.42 (s broad, 1H, NH); 9.26 (broad, 1H, NH); 8.75 (s broad, 1H, NH); 8.08 (t, 1H, J=6.4 Hz, NH); 7.90 (m, 1H, Ar-H); 7.76-7.41 (m, 10H, Ar-H); 7.28 (s broad, 2H, NH₂); 7.25-7.21 (m, 1H, Ar-H); 4.04 (d, 2H, J=6.3 Hz, CH₂); 3.56 (t, 2H, J=6.9 Hz, CH₂); 3.41 (t, 2H, J=6.7 Hz, CH₂); 2.11-1.84 (m, 4H, 2CH₂).

N-(2-(diethylamino)ethyl)-N-methyl-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido) benzimidamide (47)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of N¹,N¹-diethyl-N²-methylethane-1,2-diamine as secondary amine. The product was purified by preparative HPLC.

Yield: 12%.

[M+H]⁺: 616.2.

¹H NMR (DMSO-*d*₆): 9.87-9.17 (very broad, 4H, 4NH), 8.09 (t, 1H, J=6.3 Hz, NH); 7.96 (m, 1H, Ar-H); 7.77-7.55 (m, 8H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.28 (broad, 2H, NH₂); 7.25-7.21 (m, 1H, Ar-H); 4.04 (d, 2H, J=6.3 Hz, CH₂); water signal partially covers a group of signals; 1.07 (m broad, 6H, 2CH₃).

4-(3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (48)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide following procedure C and using 1.3 equivalents of 4-hydroxy-piperidine as secondary amine. The product was purified by preparative HPLC.

Yield: 42%.

[M+H]⁺: 587.1.

¹H NMR (DMSO-*d*₆): 9.67 (s, 1H, NH); 9.61 (s, 1H, NH); 8.08 (t, 1H, J=6.3 Hz, NH); 7.86 (m, 1H, Ar-H); 7.76-7.51 (m, 8H, Ar-H); 7.45-7.42 (m, 2H, Ar-H); 7.28 (broad, 2H, NH₂); 7.21-7.18 (m, 1H, Ar-H); 4.95 (d broad, 1H, J=3.4 Hz, OH); 4.03 (d, 2H, J=6.2 Hz, CH₂); 3.90-3.83 (m broad, 1H, CH); water signal partially covers a group of signals; 1.94-1.48 (broad, 4H, 2CH₂).

4-(3-(3-((3-(dimethylamino)pyrrolidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (49)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of N,N-dimethylpyrrolidin-3-amine as secondary amine. The product was purified by preparative HPLC. Yield: 9%.

$[M+H]^+$: 600.2.

^1H NMR (DMSO- d_6): 9.80-9.55 (broad, 3H, 3NH), 9.04 (broad, 1H, NH); 8.08 (t, 1H, $J=6.4$ Hz, NH); 7.94 (m, 1H, Ar-H); 7.76-7.51 (m, 8H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.28 (broad, 2H, NH_2); 7.25-7.21 (m, 1H, Ar-H); 4.03 (d, 2H, $J=6.2$ Hz, CH_2); 3.84-3.54 (broad, 4H, 2 CH_2); water signal partially covers a group of signals; 2.84-2.70 (broad, 6H, 2 CH_3); 2.37-2.01 (broad, 2H, CH_2).

4-(3-(3-(imino(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (50)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of 1-(pyrrolidin-2-ylmethyl)pyrrolidine as secondary amine. The product was purified by preparative HPLC.

Yield: 12%

$[M+H]^+$: 640.2.

tert-butyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate (51)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of tert-butyl piperazine-1-carboxylate as secondary amine. The product was purified by preparative HPLC.

Yield: 15%.

$[M+H]^+$: 672.2.

¹H NMR (DMSO-*d*₆): 9.58 (s broad, 1H, NH); 9.52 (s broad, 1H, NH); 9.45 (broad, 1H, NH); 9.22 (s broad, 1H, NH); 8.08 (t, 1H, J=6.4 Hz, NH); 7.89 (m, 1H, Ar-H); 7.76-7.41 (m, 10H, Ar-H); 7.28 (s broad, 2H, NH₂); 7.23-7.20 (m, 1H, Ar-H); 4.03 (d, 2H, J=6.3 Hz, CH₂); 3.74 (m broad, 2H, CH₂); 3.63 (m broad, 2H, CH₂); water signal partially covers a group of signals; 1.42 (s, 9H, 3CH₃).

4-(3-(3-(imino(piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (52)

The title compound was obtained after removal of the tert-butyl-carboxylate group from compound **51**. 60 mg of N-protected compound were dissolved in 5 ml of tetrahydrofurane and 5 ml of 4 M HCl in dioxane were slowly added under stirring at 0°C. After 2 hours stirring at rt, the solvent was removed. The product was purified by preparative HPLC.

Yield: 85%.

[M+H]⁺: 572.1.

¹H NMR (DMSO-*d*₆): 9.83-9.41 (very broad, 4H, 4NH); 8.09 (t, 1H, J=6.4 Hz, NH); 7.93 (broad, 1H, Ar-H); 7.76-7.53 (m, 8H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.29 (s broad, 2H, NH₂); 7.27-7.23 (m, 1H, Ar-H); 4.04 (d, 2H, J=6.3 Hz, CH₂); 3.95 (m broad, 2H, CH₂); 3.58 (m broad, 2H, CH₂); water signal partially covers a group of signals.

4-(3-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (53)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of N-methyl-piperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 12%.

[M+H]⁺: 586.1.

¹H NMR (DMSO-*d*₆): 9.79 (s broad, 1H, NH); 9.66 (s broad, 1H, NH); 9.61 (broad, 1H, NH); 9.44 (s broad, 1H, NH); 8.09 (t, 1H, J=6.3 Hz, NH); 7.93 (m, 1H, Ar-H); 7.76-7.54 (m, 8H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.29 (s broad, 2H, NH₂); 7.24-7.21 (m, 1H, Ar-H); 4.04 (d, 2H, J=6.2 Hz, CH₂); water signal partially covers a group of signals.

4-(3-(3-(imino(4-isopropylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (54)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1.5 equivalents of 1-isopropylpiperazine as secondary amine. The product was purified by preparative HPLC. Yield: 3%.

$[M+H]^+$: 614.2.

4-(3-(3-(imino(4-pentylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (55)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalents of n-pentylpiperazine as secondary amine. The product was purified by preparative HPLC. Yield: 13%.

$[M+H]^+$: 642.1.

^1H NMR ($\text{DMSO}-d_6$): 9.75 (very broad, 1H, NH); 9.54 (broad, 1H, NH); 9.50 (broad, 1H, NH); 9.40 (very broad, 1H, NH); 8.08 (t, 1H, $J=6.3$ Hz, NH); 7.92 (broad, 1H, Ar-H); 7.76-7.53 (m, 8H, Ar-H); 7.44-7.40 (m, 2H, Ar-H); 7.27 (broad, 2H, NH_2); 7.25-7.20 (m, 1H, Ar-H); 4.03 (d, 2H, $J=6.3$ Hz, CH_2); water signal partially covers a group of signals; 1.65-1.53 (broad, 2H, CH_2); 1.35-1.24 (m, 4H, 2CH_2); 0.88 (t, 3H, $J=6.8$ Hz, CH_3).

4-(3-(3-((4-heptylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (56)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1.5 equivalents of n-heptylpiperazine as secondary amine. The product was purified by preparative HPLC. Yield: 10%.

$[M+H]^+$: 670.1.

4-(3-(3-((4-acetylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (57)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1 equivalent of 1-(piperazin-1-yl)ethanone as secondary amine. The product was purified by preparative HPLC. Yield: 14%.

$[M+H]^+$: 614.1.

4-(3-(3-(imino(4-propionylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (58)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1 equivalent of 1-(piperazin-1-yl)propan-1-one as secondary amine. The product was purified by preparative HPLC.

Yield: 16%.

$[M+H]^+$: 628.0.

^1H NMR ($\text{DMSO}-d_6$): 10.52 (very broad, 2H, 2NH); 9.38 (broad, 1H, NH); 8.05 (t broad, 1H, NH); 7.85 (broad, 1H, Ar-H); 7.76-7.66 (m, 7H, Ar-H); 7.54-7.41 (m, 3H, Ar-H); 7.29 (broad, 2H, NH_2); 7.19-7.14 (m, 1H, Ar-H); 4.03 (d broad, 2H, CH_2); 3.67-3.50 (broad, 8H, 4 H_2); 2.35 (q, 2H, $J=7.4$ Hz, CH_2); 1.00 (t, 3H, $J=7.4$ Hz, CH_3).

4-(3-(3-(imino(4-pentanoylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (59)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1 equivalent of 1-(piperazin-1-yl)pentan-1-one as secondary amine. The product was purified by preparative HPLC.

Yield: 9%.

$[M+H]^+$: 656.0.

¹H NMR (DMSO-*d*₆): 10.05-9.32 (very broad, 4H, 4NH); 8.07 (t, 1H, J=6.3 Hz, NH); 7.85 (broad, 1H, Ar-H); 7.76-7.62 (m, 7H, Ar-H); 7.57-7.51 (m, 1H, Ar-H); 7.46-7.40 (m, 2H, Ar-H); 7.29 (broad, 2H, NH₂); 7.23-7.19 (m, 1H, Ar-H); 4.03 (d, 2H, J=5.9 Hz, CH₂); 3.69-3.52 (broad, 8H, 4H₂); 2.33 (t, 2H, J=7.4 Hz, CH₂); 1.49 (m, 2H, 7.4 Hz, CH₂); 1.30 (m, 2H, 7.4 Hz, CH₂); 0.88 (t, 3H, J=7.4 Hz, CH₃).

methyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido) phenyl)methyl) piperazine-1-carboxylate (60)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1 equivalent of methyl piperazine-1-carboxylate as secondary amine. The product was purified by preparative HPLC.

Yield: 13%.

[M+H]⁺: 630.1.

¹H NMR (DMSO-*d*₆): 10.87 (s broad, 1H, NH); 10.81 (s broad, 1H, NH); 8.05 (t broad, 1H, NH); 7.85 (m broad, 1H, Ar-H); 7.77-7.69 (m, 7H, Ar-H); 7.53-7.42 (m, 3H, Ar-H); 7.30 (broad, 2H, NH₂); 7.17-7.13 (m, 1H, Ar-H); 4.03 (d broad, 2H, CH₂); 3.63 (s, 3H, CH₃); water signal covers a group of signals.

ethyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate (61)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2 equivalent of ethyl piperazine-1-carboxylate as secondary amine. The product was purified by preparative HPLC.

Yield: 8%.

[M+H]⁺: 644.1.

¹H NMR (DMSO-*d*₆): 9.61-9.21 (very broad, 4H, 4NH); 8.08 (t, 1H, NH); 7.89-7.87 (m, 1H, Ar-H); 7.77-7.52 (m, 8H, Ar-H); 7.45-7.41 (m, 2H, Ar-H); 7.28 (broad, 2H, NH₂); 7.24-7.20 (m, 1H, Ar-H); 4.12-4.02 (m, 4H, CH₂+OCH₂); 3.82-3.40 (broad, 8H, 4CH₂); 1.20 (t, 3H, J=7.1 Hz, CH₃).

propyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl) piperazine-1-carboxylate (62)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 1 equivalent of propyl piperazine-1-carboxylate. The product was purified by preparative HPLC.

Yield (5%)

$[M+H]^+$: 658.1.

^1H NMR (DMSO- d_6): 11.06-10.71 (s broad, 2H, 2NH); 8.03 (t, 1H, $J=6.1\text{ Hz}$, NH); 7.85-7.81 (m broad, 1H, Ar-H); 7.77-7.66 (m, 7H, Ar-H); 7.51-7.41 (m, 3H, Ar-H); 7.29 (broad, 2H, NH_2); 7.14-7.10 (m, 1H, Ar-H); 4.03 (d, 2H, $J=6.0\text{ Hz}$, CH_2); 3.98 (t, 2H, $J=6.6\text{ Hz}$, OCH_2); water signal covers a group of signals; 1.59 (m, 2H, CH_2); 0.89 (t, 3H, $J=7.4\text{ Hz}$, CH_3).

4-(3-(3-((4-butyl-3-oxopiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (63)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of 1-butylpiperazin-2-one as secondary amine. The product was purified by preparative HPLC.

Yield: 35%.

$[M+H]^+$: 642.1.

^1H NMR (DMSO- d_6): 10.59 (very broad, 2H, 2NH); 8.06 (t broad, 1H, NH); 7.85-7.82 (m broad, 1H, Ar-H); 7.77-7.66 (m, 7H, Ar-H); 7.54-7.41 (m, 3H, Ar-H); 7.29 (s broad, 2H, NH_2); 7.18-7.13 (m, 1H, Ar-H); 4.16 (broad, 1H, $\text{CO-CH}_2\text{-N}$); 4.03 (d broad, 2H, CH_2); 3.68-3.44 (broad, 4H, 2 CH_2); 3.35 (t, 2H, $J=7.2\text{ Hz}$, CH_2); water signal covers a group of signals; 1.54-1.21 (m, 4H, 2 CH_2); 0.90 (t, 3H, $J=7.3\text{ Hz}$, CH_3).

N,N-dimethyl-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide (64)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of N,N-dimethylamine as secondary amine. The product was purified by preparative HPLC.

Yield: 54%.

$[M+H]^+$: 531.1.

^1H NMR ($\text{DMSO}-d_6$): 10.90 (s broad, 1H, 1NH); 10.85 (s broad, 1H, 1NH); 10.85 (s broad, 1H, 1NH); 9.14 (broad, 1H, NH); 8.05 (t broad, 1H, NH); 7.83 (m broad, 1H, Ar-H); 7.76-7.68 (m, 7H, Ar-H); 7.54-7.41 (m, 3H, Ar-H); 7.30 (s broad, 2H, NH_2); 7.16-7.11 (m, 1H, Ar-H); 4.03 (broad, 2H, CH_2); 3.11 (s broad, 6H, 2CH_3).

4-(3-(3-((4-(2-cyanoethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (65)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of 3-piperazinopropionitrile as secondary amine. The product was purified by preparative HPLC. Yield: 57%.

$[M+H]^+$: 625.1.

4-(3-(3-((4-(cyclopropylmethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (66)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of 1-(cyclopropylmethyl)piperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 57%.

$[M+H]^+$: 625.1.

^1H NMR ($\text{DMSO}-d_6$): 11.52 (s, 1H, 1NH); 11.50 (s broad, 1H, 1NH); 8.03 (t broad, 1H, NH); 7.86 (m broad, 1H, Ar-H); 7.79-7.67 (m, 7H, Ar-H); 7.52-7.41 (m, 3H, Ar-H); 7.30 (s broad, 2H, NH_2); 7.14-7.09 (m, 1H, Ar-H); 4.03 (broad, 2H, CH_2); 3.57 (broad, 4H, 2CH_2); 2.60 (broad, 4H, 2CH_2); 2.26 (d, 2H, $J=6.6$ Hz, CH_2); 0.84 (m, 1H, CH); 0.47 (m, 2H, CH_2); 0.09 (m, 2H, CH_2).

4-(3-(3-((4-((1,3-dioxolan-2-yl)methyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (67)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of 1-(1,3-

dioxolan-2-ylmethyl)piperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 43%.

$[M+H]^+$: 658.1.

1H NMR (DMSO- d_6): 11.53 (s, 1H, 1NH); 11.49 (s broad, 1H, 1NH); 8.02 (t broad, 1H, NH); 7.83 (m broad, 1H, Ar-H); 7.78-7.67 (m, 7H, Ar-H); 7.50-7.40 (m, 3H, Ar-H); 7.30 (s broad, 2H, NH₂); 7.11-7.06 (m, 1H, Ar-H); 4.93 (t, 1H, J=4.4 Hz, CH); 4.02 (broad, 2H, CH₂); 3.90-3.74 (m, 4H, 2CH₂); 3.51 (broad, 4H, 2CH₂); 2.65 (broad, 4H, 2CH₂); 2.57 (d, 2H, J=4.4 Hz, CH₂).

4-(3-(3-(imino(4-((tetrahydrofuran-2-yl)methyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (68)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of 1-(tetrahydro-2-furylmethyl)piperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 48%.

$[M+H]^+$: 656.1.

1H NMR (DMSO- d_6): 11.38 (s, 1H, 1NH); 11.35 (s broad, 1H, 1NH); 8.03 (t broad, 1H, NH); 7.85 (m broad, 1H, Ar-H); 7.77-7.67 (m, 7H, Ar-H); 7.52-7.41 (m, 3H, Ar-H); 7.30 (s broad, 2H, NH₂); 7.13-7.09 (m, 1H, Ar-H); 4.02 (broad, 2H, CH₂); 3.98-3.90 (m, 1H, CH); 3.77-3.50 (group of signals, 6H, OCH₂+2pipCH₂); DMSO signal covers a group of signals; 1.98-1.41 (group of multiplets, 4H, 2CH₂).

4-(3-(3-(imino(4-(2-methoxyethyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl) benzenesulfonamide (69)

The title compound was prepared from 4-(3-(3-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 2.2 equivalent of 1-(2-methoxyethyl)piperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 41.5%.

$[M+H]^+$: 630.1.

¹H NMR (DMSO-*d*₆): 11.43 (s, 1H, 1NH); 11.40 (s broad, 1H, 1NH); 8.03 (t broad, 1H, NH); 7.85 (m broad, 1H, Ar-H); 7.78-7.67 (m, 7H, Ar-H); 7.52-7.41 (m, 3H, Ar-H); 7.30 (s broad, 2H, NH₂); 7.13-7.09 (m, 1H, Ar-H); 4.03 (broad, 2H, CH₂); 3.55 (broad, 4H, 2CH₂); 3.45 (t, 2H; J=5.6 Hz, OCH₂); 3.23 (s, 3H, CH₃); 2.62-2.53 (broad+q, 6H, 3CH₂).

5-((4-(3-(4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonamido)methyl thiophene-2-sulfonamide (70)

The title compound was prepared from 5-((4-(3-(3-cyanophenyl)ureido)phenylsulfonamido)methyl)thiophene-2-sulfonamide following procedure C and using 2.2 equivalent of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 58%.

[M+H]⁺: 634.1.

¹H NMR (DMSO-*d*₆): 11.22 (s, 1H, 1NH); 11.17 (s broad, 1H, 1NH); 8.23 (broad, 1H, NH); 7.84 (m broad, 1H, Ar-H); 7.76-7.47 (m, 8H, NH₂+6 Ar-H); 7.33 (d, 1H, J=3.7 Hz, CH); 7.14-7.10 (m, 1H, Ar-H); 6.91 (d, 1H, J=3.7 Hz, CH); 4.17 (broad, 2H, CH₂); 3.55 (broad, 4H, 2CH₂); DMSO signal covers a group of signals; 2.34 (t, 2H, J=7.2 Hz, CH₂); 1.46-1.23 (m, 4H, 2CH₂); 0.88 (t, 3H, J=7.2 Hz, CH₃).

4-(3-(4-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide (71)

The title compound was prepared from 4-(3-(4-cyanophenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide following procedure C and using 3 equivalents of n-butylpiperazine as secondary amine. The product was purified by preparative HPLC.

Yield: 2.4%.

[M+H]⁺: 628.1.

methyl 4-((acetylimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate (72)

100 mg of compound 60 were dissolved in 2 ml of DCM/DMF 1:1 solution, containing 2 eq of DIEA. Under stirring and at 0°C, 6 eq of acetylchloride were added portionwise during 30

minutes. The solution was stirred overnight at rt, then water was added and a precipitate formed. The precipitate was separated and the title compound was obtained after preparative HPLC purification.

Yield: 19 %.

$[M+H]^+$: 672.2.

methyl 4-((octanoylimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate (73)

The title compound was obtained as described for compound 72 and using 4 eq of octanoylchloride. The product was purified by preparative HPLC.

Yield: 1 %.

$[M+H]^+$: 756.3.

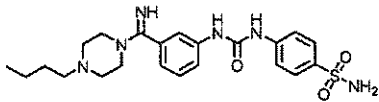
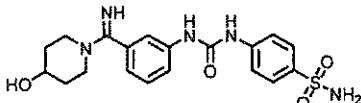
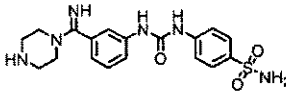
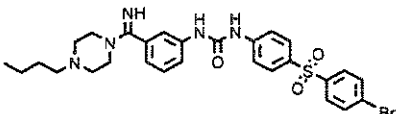
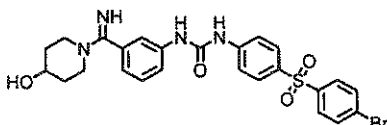
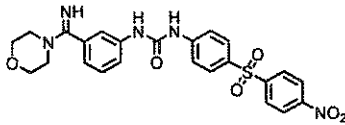
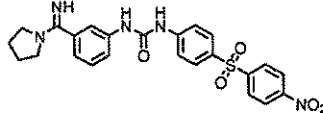
methyl 4-((hydroxyimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate (74)

The title compound was obtained following procedure D, starting from 3-nitrobenzaldehyde and using 1 eq of 4-(aminomethyl)benzenesulfonamide as final amino reagent. The product was purified by preparative HPLC

Yield: 1% (overall over 6 steps)

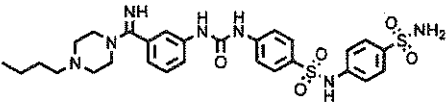
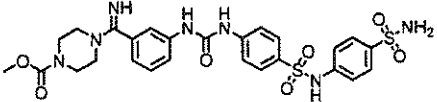
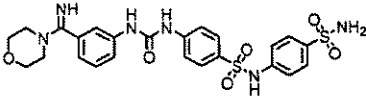
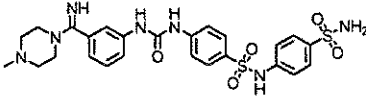
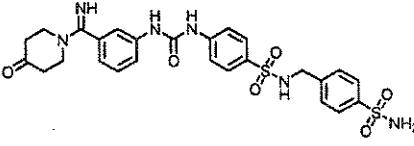
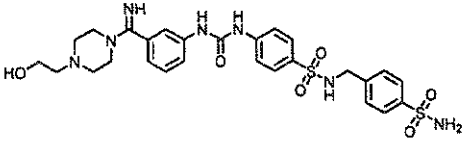
$[M+H]^+$: 646.2.

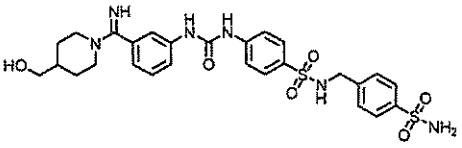
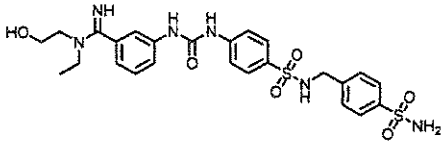
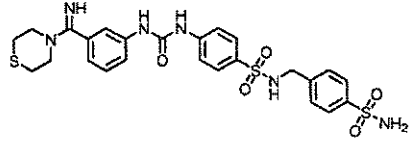
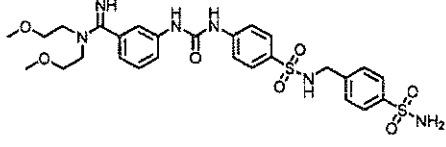
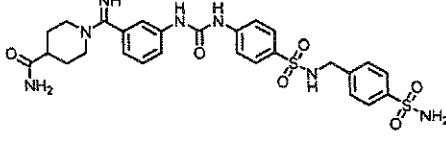
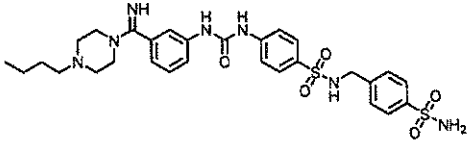
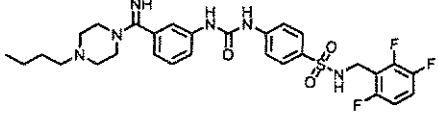
Table 1 Exemplary compounds of formula (I) of the present invention include, but not limited to the followings:

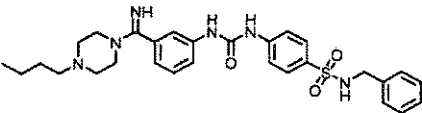
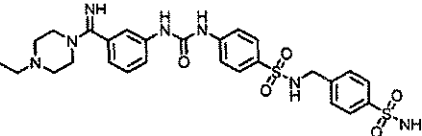
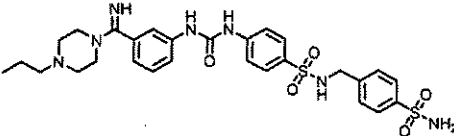
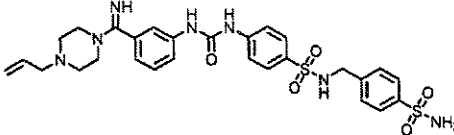
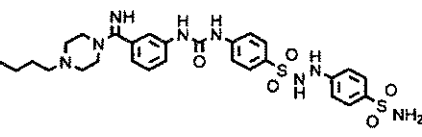
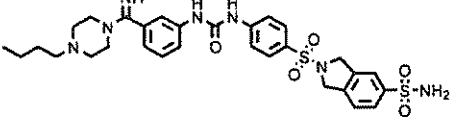
No	Structure	Name	LC/MS [M+H] +
1		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide	459.1
2		4-(3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide	418.0
3		4-(3-(3-(imino(piperazin-1-yl)methyl)phenyl)ureido)benzenesulfonamide	403.0
4		1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)urea	599.1
5		1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea	557.0
6		1-(3-(imino(morpholino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea	510.1
7		1-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea	494.0

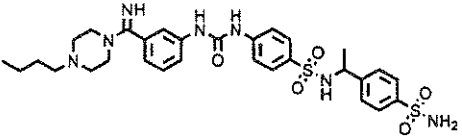
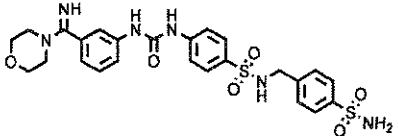
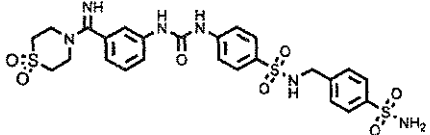
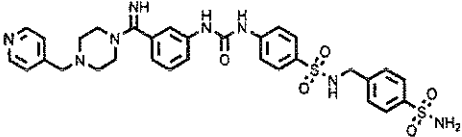
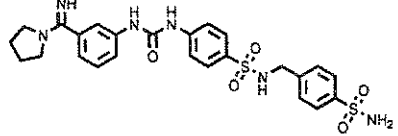
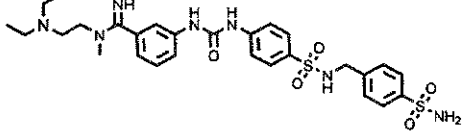
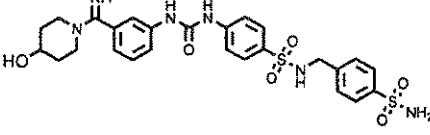
8		1-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea	523.1
9		1-(3-(imino(thiazolidin-3-yl)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea	512.1
10		1-(3-(((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)-3-(4-(4-nitrophenylsulfonyl)phenyl)urea	524.1
11		1-(4-(4-chlorophenylsulfonyl)phenyl)-3-(3-(((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea	513.0
12		1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(((4-hydroxymethyl)piperidin-1-yl)(imino)methyl)phenyl)urea	570.9
13		3-(3-(4-(4-bromophenylsulfonyl)phenyl)urido)-N,N-bis(2-methoxyethyl)benzimidamide	589.1
14		1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(imino(thiomorpholino)methyl)phenyl)urea	559.0
15		1-(4-(4-bromophenylsulfonyl)phenyl)-3-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)urea	527.0

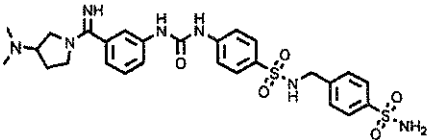
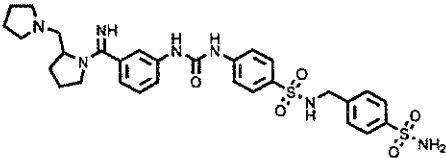
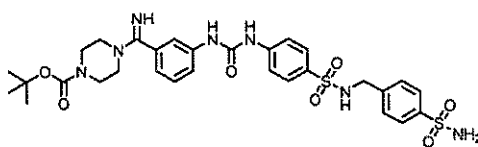
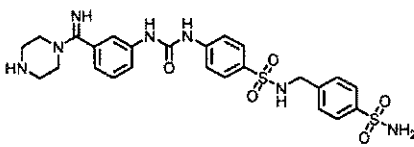
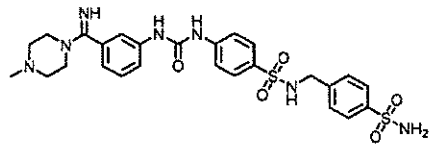
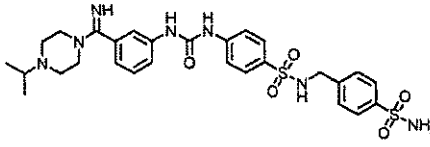
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16		1-((3-(3-(4-(4-bromophenylsulfonyl)phenyl)ureido)phenyl)(imino)methyl)piperidine-4-carboxamide	584.0
17		1-(4-(4-aminophenylsulfonyl)phenyl)-3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)urea	494.1
18		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-methylbenzenesulfonamide	473.2
19		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-propylbenzenesulfonamide	501.3
20		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N,N-bis(2-hydroxyethyl)benzenesulfonamide	547.2
21		1-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)-3-(4-(morpholinosulfonyl)phenyl)urea	529.2
22		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(7-chloroquinolin-4-yl)benzenesulfonamide	620.2

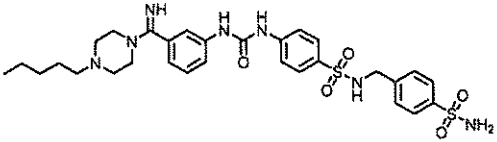
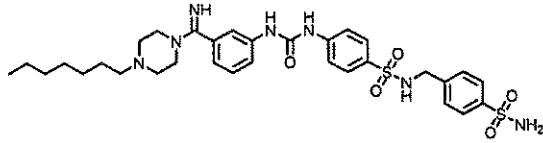
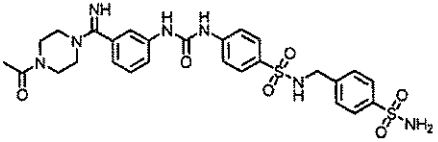
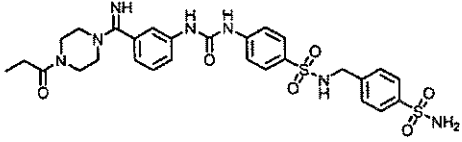
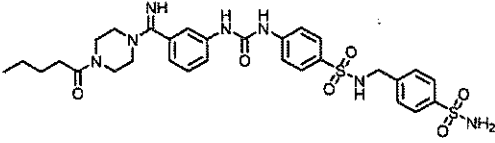
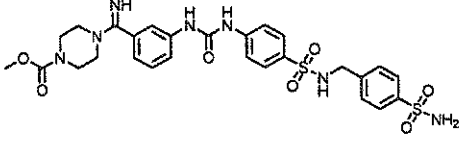
23		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide	614.2
24		methyl 4-(imino(3-(3-(4-(N-(4-sulfamoylphenyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	616.0
25		4-(3-(3-(imino(morpholino)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide	559.1
26		4-(3-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylphenyl)benzenesulfonamide	572.1
27		4-(3-(3-(imino(4-oxopiperidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	585.2
28		4-(3-(3-((4-(2-hydroxyethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	616.1

29		4-(3-(3-((4-(hydroxymethyl)piperidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	601.1
30		N-ethyl-N-(2-hydroxyethyl)-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide	575.1
31		4-(3-(3-(imino(thiomorpholino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	589.0
32		N,N-bis(2-methoxyethyl)-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide	619.1
33		1-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperidine-4-carboxamide	614.1
34		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	628.1
35		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(2,3,6-	603.2

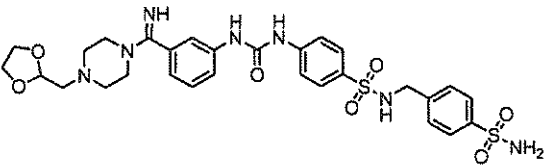
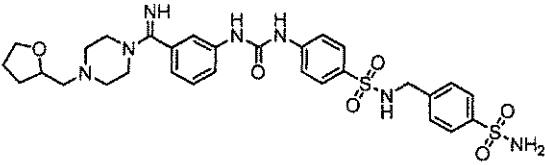
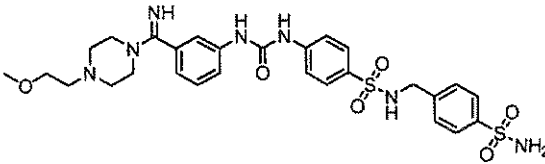
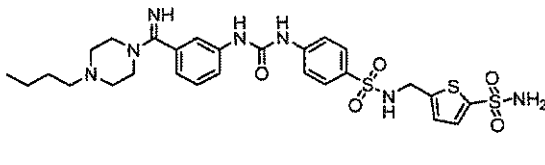
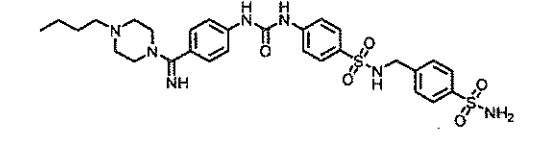
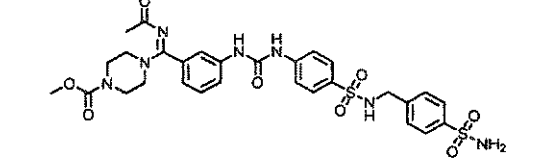
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36		N-benzyl-4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)benzenesulfonamide	549.2
37		4-(3-(3-((4-ethylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	600.1
38		4-(3-(3-(imino(4-propylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	614.1
39		4-(3-(3-((4-allylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	612.1
40		4-(2-(4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonyl)hydrazinyl)benzenesulfonamide	629.2
41		2-(4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)phenylsulfonyl)isoindoline-5-sulfonamide	640.2

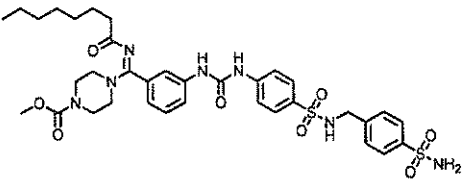
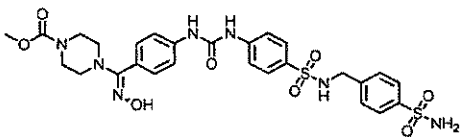
42		4-(3-(3-((4-butylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(1-(4-sulfamoylphenyl)ethyl)benzenesulfonamide	642.2
43		4-(3-(3-(imino(morpholino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	573.1
44		4-(3-(3-((1,1-dioxidothiomorpholino)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	621.1
45		4-(3-(3-(imino(4-(pyridin-4-yl)methyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	663.2
46		4-(3-(3-(imino(pyrrolidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	557.1
47		N-(2-(diethylamino)ethyl)-N-methyl-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide	616.2
48		4-(3-(3-((4-hydroxypiperidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-	587.1

		sulfamoylbenzyl)benzenesulfonamide	
49		4-(3-(3-((3-(dimethylamino)pyrrolidin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	600.2
50		4-(3-(3-(imino(2-(pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	640.2
51		tert-butyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	672.2
52		4-(3-(3-(imino(piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	572,1
53		4-(3-(3-(imino(4-methylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	586.1
54		4-(3-(3-(imino(4-isopropylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	614.2

		amide	
55		4-(3-(3-(imino(4-pentylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	642.1
56		4-(3-(3-((4-heptylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	670.1
57		4-(3-(3-((4-acetylpiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	614.1
58		4-(3-(3-(imino(4-propionylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	628.0
59		4-(3-(3-(imino(4-pentanoylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	656.0
60		methyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	630.1

61		ethyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	644.1
62		propyl 4-(imino(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	658.1
63		4-(3-(3-((4-butyl-3-oxopiperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	642.1
64		N,N-dimethyl-3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)benzimidamide	531.1
65		4-(3-(3-((4-(2-cyanoethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	625.1
66		4-(3-(3-((4-(cyclopropylmethyl)piperazin-1-yl)(imino)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	626.1

67		4-(3-(3-((4-((1,3-dioxolan-2-yl)methyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	658.1
68		4-(3-(3-(imino(4-((tetrahydrofuran-2-yl)methyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	656.1
69		4-(3-(3-(imino(4-(2-methoxyethyl)piperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	630.1
70		5-((4-(3-(3-((4-butylpiperazin-1-yl)methyl)phenyl)ureido)phenyl)sulfonamido)methyl)thiophene-2-sulfonamide	634.1
71		4-(3-(4-((4-butylpiperazin-1-yl)methyl)phenyl)ureido)-N-(4-sulfamoylbenzyl)benzenesulfonamide	628.1
72		methyl 4-((acetylimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperate	672.2.

		azine-1-carboxylate	
73		methyl 4-((octanoylimino)(3-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	756.3
74		methyl 4-((hydroxyimino)(4-(3-(4-(N-(4-sulfamoylbenzyl)sulfamoyl)phenyl)ureido)phenyl)methyl)piperazine-1-carboxylate	646.2

In vitro* assays*Antiplasmodial activity against Dd2 strain of *Plasmodium falciparum***

For the determination of the antiplasmodial activity of the compounds described above, the multiresistant Dd2 strain of *Plasmodium falciparum* was used. The incorporation of [^3H]hypoxanthine into the parasitic nucleic acids was measured. The plasmodia were incubated at 0.3% parasitaemia and an erythrocyte haematocrit of 2.5% in the presence of different concentrations of the compounds in a final volume of 200 μl . The medium employed was RPMI 1640 which contained 10% of heat-treated human serum and 3 mg/l of gentamycin. In the incubations, the concentrations of the compounds varied from 0.001 to 100 μM . After 48 h, each batch was treated with 50 μl of [^3H]hypoxanthine (1 mCi/ml) and incubated for a further 18 h. The cells were filtered off, washed and suspended in 20 μl of scintillation fluid. The radioactive hypoxanthine absorbed by the parasites was then quantified using a scintillation counter. The results were presented graphically and the IC_{50} value was determined using a fitting function. The value IC_{50} , the 'inhibition constant', indicates the value in $\mu\text{Mol/l}$ at which 50% parasite growth inhibition occurs (R.E. Desjardins, *et al.*, *Antimicrobiol. Agent Chemother.* **16**, pp. 710-718, 1979; J. D. Chulay, *et al.*, *Exp.Parasitol.* **55**, pp. 138-146, 1983). In table 2, the antimalaria activity was defined as following: A: IC_{50} value $\geq 1 \mu\text{M}$; B: IC_{50} value between 0.99 μM and 0.21 μM ; C: IC_{50} value between 0.20 μM and 0.02 μM ; D: IC_{50} value $< 0.02 \mu\text{M}$.

Table 2 *In vitro* antiplasmodia activity;

Antiplasmodia activity	Compound
A	1, 2, 3, 8, 9, 12, 13, 17, 18, 19, 20, 21, 22, 24, 25, 26, 40;
B	4, 23, 27, 29, 30, 31, 32, 35, 36, 42, 45, 51, 53, 64, 65;
C	5, 6, 7, 10, 11, 14, 15, 16, 28, 33, 37, 41, 43, 44, 46, 47, 48, 49, 50, 52, 54, 56, 57, 59, 67, 68, 69, 70, 71;
D	34, 38, 39, 55, 58, 60, 61, 62, 63, 66;

Solubility and solubility-range determination in 50 mM phosphate buffer at different pH

The compounds were dissolved in DMSO at a concentration of 20 mg/ml. These stock solutions were further diluted 1:1 with DMSO (50 μ l solution + 50 μ l DMSO) in seven steps. Subsequently, these solutions were diluted 1:100 (5 μ l DMSO-stock + 495 μ l 50 mM phosphate buffer) in all four pH buffers (respectively: pH = 4; pH = 6; pH = 7.4; pH = 9) resulting in a final DMSO concentration of 1% in the buffers. These dilutions were vigorously mixed and transferred into 96-well reading plate. The plates were incubated in a shaker (600 rpm) at 23°C for 24 hours. After that, the contents of the wells were mixed with a pipette and optical density (OD) was recorded at wavelengths of 550 nm; 600 nm; 650 nm and 700 nm in the Tecan Sunrise plate reader. The cut-off OD sum for an undissolved concentration of a compound was defined as follows: Cut off OD sum = mean blank OD + 0.050 OD. For the determination of the solubility range, the following rule was applied:

OD > cut off => compound not dissolved at this concentration

OD < cut-off => compound dissolved at this concentration

For the determination of the solubility, a titration curve (OD/concentration) was prepared and the concentrations were determined based on the measured OD of the mixture supernatant after centrifugation. The solubility values are given in μ g/ml (table 3).

Determination of *in vitro* clearance using human liver microsomes

These experiments were performed at Nikem Research (Via Zambelletti 25; Baranzate, Milan, Italy).

Test compounds in duplicate at the final concentration of 1 μ M were dissolved in DMSO and pre-incubated for 10 min at 37°C in phosphate buffer pH 7.4, 3 mM MgCl₂, with human liver microsomes at the final concentration of 0.5 mg/ml. After the pre-incubation period, reaction was started by adding the cofactor mixture (NADP, Glc6P, G6P-DH); samples were taken at time 0, 5, 10, 15, 20 and 30 min and added to acetonitrile to quench the metabolic reaction, centrifuged and supernatant analysed and quantified by HPLC/MS. A control sample without cofactors was always added in order to check the chemical stability of test compounds. 7-ethoxycoumarin was added as reference standard. A fixed concentration of verapamil was added in every sample as

internal standard for HPLC/MS. The concentration of the remaining compound at different times was determined by HPLC/MS.

The rate constant, k (min^{-1}) derived for the exponential decay equation (peak area vs time) was used to calculate the rate of intrinsic clearance (Cli) of the compounds using the following equations: $\text{Cli} (\mu\text{l}/\text{min}/\text{mg compound}) = k \times V$; where:

$V (\mu\text{l}/\text{mg compound}) = \text{incubation volume}/\text{mg compound added}$.

In table 3 the clearance (*in vitro* metabolic stability) classification was as follows: $\text{Cli} < 10$ = compound stable; Cli between 10 and 60 = low metabolism; Cli between 60 and 600 = medium metabolism $\text{Cli} > 600$ = high metabolism.

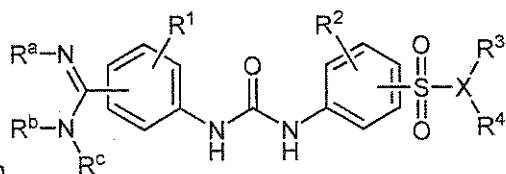
Table 3 Solubility and *in vitro* metabolic stability

No.	Solubility or solubility range	<i>In vitro</i> metabolism as determined from Cli
1		<i>low</i>
23		<i>low</i>
34	pH 4 = 960 $\mu\text{g}/\text{ml}$ pH 6 = 960 $\mu\text{g}/\text{ml}$ pH 7.4 = 750 $\mu\text{g}/\text{ml}$ pH 9 = 540 $\mu\text{g}/\text{ml}$	<i>medium</i>
37		<i>medium</i>
38	pH 4 = > 200 $\mu\text{g}/\text{ml}$ pH 6 = > 200 $\mu\text{g}/\text{ml}$ pH 7.4 = > 200 $\mu\text{g}/\text{ml}$ pH 9 = > 200 $\mu\text{g}/\text{ml}$	<i>medium</i>
41		<i>medium</i>
43		<i>medium</i>

44	pH 4 = > 200 µg/ml pH 6 = > 200 µg/ml pH 7.4 = > 200 µg/ml pH 9 = > 200 µg/ml	
52	pH 4 = > 200 µg/ml pH 6 = > 200 µg/ml pH 7.4 = > 200 µg/ml pH 9 = > 200 µg/ml	<i>low</i>
53		<i>low</i>
54		<i>medium</i>
58	pH 4 = > 200 µg/ml pH 6 = > 200 µg/ml pH 7.4 = > 200 µg/ml pH 9 = > 200 µg/ml	<i>low</i>
60	pH 4 = 1480 µg/ml pH 6 = 1286 µg/ml pH 7.4 = 763 µg/ml pH 9 = 456 µg/ml	<i>medium</i>
63		<i>medium</i>
64		<i>low</i>
65		<i>medium</i>
66		<i>medium</i>
69		<i>medium</i>
70		<i>medium</i>

Claims

1. A compound of the formula (I)
or a physiologically acceptable salt thereof,



wherein

formula (I)

R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, -OCOR', C(O)R', CONHR' or -CO₂R';

R^b and R^c independently are alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, cycloalkyl, aryl and heteroaryl, heterocyclyl or -CO₂R';

or

R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or entirely unsaturated heterocyclic ring selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', where chemically appropriate, two R'' taken together can form a group =O; this heterocyclic group is preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, S,S-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl

R' independently represents hydrogen, -CO₂R'', -CONHR'', -CR''O, -SO₂N(R'')₂, -SO₂NHR'', -NR''-CO-haloalkyl, -NO₂, -NR''-SO₂-haloalkyl, -NR''-SO₂-alkyl, -SO₂-alkyl, -NR''-CO-alkyl, -CN, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' independently represents hydrogen, -(CH₂)_mR', -CO₂R', -CON(R')₂, -CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, -NO₂, -NR'-SO₂-haloalkyl, -NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-

CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group =O; wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represent hydrogen, (CH₂)_mR', -CO₂R', -CON(R')₂, CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, NO₂, -NR'-SO₂-haloalkyl, NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or -CO₂R';

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

or wherein if

X is N, then

R^3 forms together with R^4 a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''

2. A compound according to claim 1, wherein

R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, $-\text{OCOR}'$, $-\text{C}(\text{O})\text{R}'$, $-\text{CONHR}'$ or $-\text{CO}_2\text{R}'$;

R^b and R^c independently are alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, cycloalkyl, aryl and heteroaryl, heterocyclyl or $-\text{CO}_2\text{R}'$;

R' independently represents hydrogen, $-\text{CO}_2\text{R}''$, $-\text{CONHR}''$, $-\text{CR}''\text{O}$, $-\text{SO}_2\text{N}(\text{R}'')_2$, $-\text{SO}_2\text{NHR}''$, $-\text{NR}''-\text{CO}-\text{haloalkyl}$, $-\text{NO}_2$, $-\text{NR}''-\text{SO}_2-\text{haloalkyl}$, $-\text{NR}''-\text{SO}_2-\text{alkyl}$, $-\text{SO}_2-\text{alkyl}$, $-\text{NR}''-\text{CO}-\text{alkyl}$, $-\text{CN}$, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, $-\text{OH}$, $-\text{SH}$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' is independently hydrogen, $-(\text{CH}_2)_m\text{R}'$, $-\text{CO}_2\text{R}'$, $-\text{CON}(\text{R}')_2$, $-\text{CR}'\text{O}$, $-\text{SO}_2\text{N}(\text{R}')_2$, $-\text{NR}'-\text{CO}-\text{haloalkyl}$, $-\text{NO}_2$, $-\text{NR}'-\text{SO}_2-\text{haloalkyl}$, $-\text{NR}'-\text{SO}_2-\text{alkyl}$, $-\text{NR}'-\text{SO}_2-\text{aryl}$, $-\text{NR}'-\text{SO}_2-\text{heteroaryl}$, $-\text{SO}_2-\text{alkyl}$, $-\text{SO}_2-\text{aryl}$, $-\text{SO}_2-\text{heteroaryl}$, $-\text{NR}'-\text{CO}-\text{alkyl}$, $-\text{NR}'-\text{CO}-\text{aryl}$, $-\text{NR}'-\text{CO}-\text{heteroaryl}$, $-\text{NR}'-\text{CO}-\text{N}(\text{R}')_2$, $-\text{CN}$, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, $-\text{SH}$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group $=\text{O}$; wherein R' groups are as defined above and may be selected independently from each other;

R^1 and R^2 independently represents hydrogen, $(\text{CH}_2)_m\text{R}'$, $-\text{CO}_2\text{R}'$, $-\text{CON}(\text{R}')_2$, $-\text{CR}'\text{O}$, $-\text{SO}_2\text{N}(\text{R}')_2$, $-\text{NR}'-\text{CO}-\text{haloalkyl}$, NO_2 , $-\text{NR}'-\text{SO}_2-\text{haloalkyl}$, $\text{NR}'-\text{SO}_2-\text{alkyl}$, $-\text{NR}'-\text{SO}_2-\text{aryl}$, $-\text{NR}'-\text{SO}_2-\text{heteroaryl}$, $-\text{SO}_2-\text{alkyl}$, $-\text{SO}_2-\text{aryl}$, $-\text{SO}_2-\text{heteroaryl}$, $-\text{NR}'-\text{CO}-\text{alkyl}$, $-\text{NR}'-\text{CO}-\text{aryl}$, $-\text{NR}'-\text{CO}-\text{heteroaryl}$, $-\text{NR}'-\text{CO}-\text{N}(\text{R}')_2$, $-\text{CN}$, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, $-\text{SH}$, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl,

arylalkyl or heteroaryl wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, C₁-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or -CO₂R';

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R'' as defined herein;

or wherein if

X is N, then

or R³ forms together with R⁴ a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R''

3. A compound according to claim 1, wherein

R^a is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, -OCOR', -C(O)R', -CONHR' or -CO₂R';

R^b forms together with R^c a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or entirely unsaturated heterocyclic ring selected from the group consisting of cycloalkyl, aryl, heterocycloalkyl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'', where chemically appropriate, two R'' taken

together can form a group =O; this heterocyclic group is preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiazolidinyl, thiomorpholinyl, piperidin-4-one-1-yl, *S,S*-dioxo-thio-morpholinyl, piperazin-3-one-1-yl, or azepanyl

R' independently represents hydrogen, -CO₂R'', -CONHR'', -CR''O, -SO₂N(R'')₂, -SO₂NHR'', -NR''-CO-haloalkyl, -NO₂, -NR''-SO₂-haloalkyl, -NR''-SO₂-alkyl, -SO₂-alkyl, -NR''-CO-alkyl, -CN, alkyl, cycloalkyl, amino, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, haloaryl, haloarylalkyl, arylalkyl, heterocyclyl or heteroaryl;

R'' independently hydrogen, -(CH₂)_mR', -CO₂R', -CON(R')₂, -CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, -NO₂, -NR'-SO₂-haloalkyl, -NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, alkoxyalkyl, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl; where chemically appropriate, two R'' taken together can form a group =O; wherein R' groups are as defined above and may be selected independently from each other;

R¹ and R² independently represents hydrogen, (CH₂)_mR', -CO₂R', -CON(R')₂, -CR'O, -SO₂N(R')₂, -NR'-CO-haloalkyl, NO₂, -NR'-SO₂-haloalkyl, NR'-SO₂-alkyl, -NR'-SO₂-aryl, -NR'-SO₂-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -NR'-CO-alkyl, -NR'-CO-aryl, -NR'-CO-heteroaryl, -NR'-CO-N(R')₂, -CN, alkyl, amino, amide, cycloalkyl, aminoalkyl, alkylamino, alkoxy, hydroxyl, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkoxy, aryl, arylalkyl or heteroaryl wherein R' groups are as defined above and may be selected independently from each other;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

wherein if

X is CR⁵, then

R³ forms together with R⁴ an unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl which optionally

has 0, 1, 2 or 3 substituents R", and wherein if X is part of a double bond, R⁵ is absent;

R⁵ is H, OH, halogen, Ci-C₄-alkyl;

or wherein if

X is N, then

R³ is hydrogen, alkyl, alkoxy, hydroxyl, hydroxyalkyl, alkoxyalkyl, or -CO₂R';

R⁴ is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, amino, alkyl, arylalkyl or a partially or entirely unsaturated or saturated cyclic group selected from the group consisting of cycloalkyl, aryl, arylalkyl, heterocyclyl, haloarylalkyl and heteroaryl which is optionally substituted with R" as defined herein;

or wherein if

X is N, then

R³ forms together with R⁴ a 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated or entirely unsaturated heterocyclic ring consisting of cycloalkyl, aryl, heterocyclyl, heterocycloaryl and heteroaryl which optionally has 0, 1, 2 or 3 substituents R'.

4. A compound according to claim 1, wherein R³ = H, R⁴ = alkylaryl, R^a = H, and R^b forms together with R^c a 6-membered saturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R".
5. A compound according to claim 1, wherein R³ = H, R⁴ = aryl, R^a = H, and R^b forms together with R^c a 6-membered saturated heterocyclic ring which optionally has 0, 1, 2 or 3 substituents R".
6. A pharmaceutical composition, comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.
7. Use of a compound according to claim 1 in the manufacture of a medicament for treating or preventing or ameliorating a disease or condition.

8. Use according to claim 7, wherein the disease or condition is malaria.
9. Use according to claim 7, wherein the disease or condition is malaria, caused by a strain of *Plasmodium falciparum*.
10. Use according to claims 6 to 9, wherein the compound is administered in combination with another antimalaria compound.
11. Use according to claim 10, wherein the other antimalaria compound is selected from chloroquine, sulfadoxine/pyrimethamine, dapsone/pyrimethamine, sulfonamides, halofantrine, amodiaquine, mefloquine, quinine, quinidine, doxycycline, lumefantrine, primaquine, proguanil, atovaquone, pyronaridine, chlorproguanil, artemesinin, arteflene, artemether, artesunate or trimethoprim.