

PYRIMIDO [4,5-B]QUINOLINE-4,5 (3H,10H)-DIONES AS NONSENSE
MUTATION SUPPRESSORSPyrimido[4,5-b]quinoline-4,5(3H,10H)-diones

The invention relates to pyrimido[4,5-b]quinoline-4,5(3H,10H)-diones, to their preparation, to their use as medicaments and to medicaments comprising them.

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Many human genetic diseases are caused by nonsense mutations (see Keeling et al, WIREs RNA, 2011, 2, 837-852; Linde et al, Trends in Genetics, 2008, 24(11), 552-563; and Rose et al, Pharmacology & Therapeutics, 2012 136(2), 227-266).

10 A nonsense mutation is a genetic mutation leading to the transformation of a sense codon into a premature termination codon (hereinafter PTC) upstream from the normal termination codon.

Eukaryotic termination codons are UAA, UAG or UGA.

15 The normal termination codon stops gene translation and enables full-length, wild type protein synthesis. A PTC prevents such wild type protein synthesis and leads to truncated, in many cases inactive, proteins. The resulting partial/total lack of protein leads to the pathology of the disease caused by such a nonsense mutation.

Nonsense mutations can be in-frame mutations, e.g. single nucleic acid exchanges transforming a single codon into a PTC, or frameshift mutations, e.g. a single nucleic acid insertion/deletion transforming the affected codon into a PTC.

20

A compound being able to suppress the effect of a nonsense mutation is herein called a "nonsense mutation suppressor".

25 One mechanism to suppress the effect of nonsense mutations is to increase the rate of readthrough events during translation. A compound having this mechanism of action is herein called a "readthrough activator". In a readthrough event, an aminoacyl tRNA being near-cognate is used to recode a termination codon into a sense codon. Under basal conditions, the recoding of a PTC into a sense codon occurs in less than 1% of translation events, while suppression of a normal stop codon occurs at a frequency of <0.1%. Amino
30 acids inserted by recoding will not necessarily be identical to the corresponding amino acids of the wild-type protein; however many amino acid substitutions are functionally tolerated. Thus, a protein produced by readthrough activation may possess activity strongly similar to the wild-type protein. Consequently, by increasing the rate of PTC-recoding enough functional protein may be restored to provide a therapeutic benefit to patients carrying a
35 nonsense mutation.

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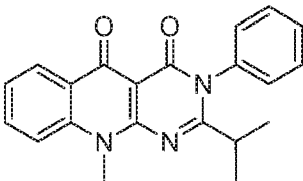
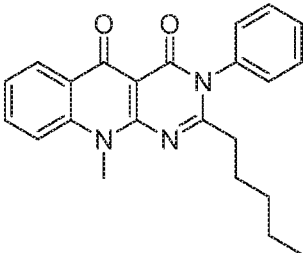
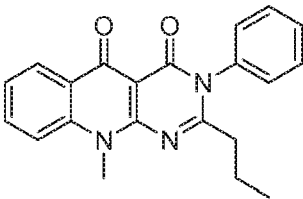
Another mechanism to suppress the effect of nonsense mutations is to inhibit nonsense-mediated mRNA decay (NMD). A compound having this mechanism of action is herein called a "NMD inhibitor". NMD regulates the total level of PTC-bearing transcripts: it detects and

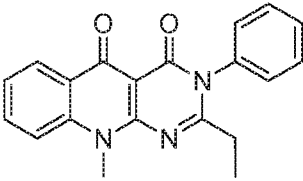
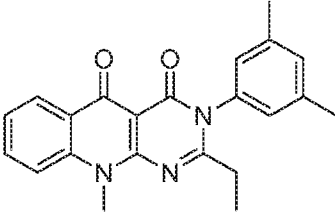
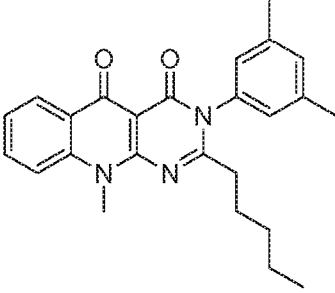
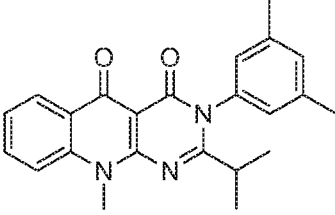
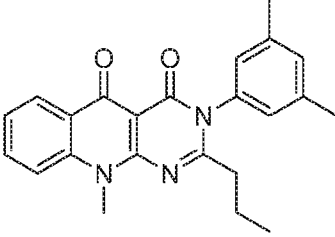
5 degrades such transcripts to prevent synthesis of truncated proteins which might be nonfunctional or deleterious owing to dominant-negative or gain-of-function effects. Inhibition of NMD increases the number of transcripts available which could also be a mechanism to restore enough functional protein for a therapeutic benefit.

- 10 Compounds described as nonsense mutation suppressors are certain aminoglycoside antibiotics, e.g. in WO2007113841, and certain 1,2,4-oxadiazole benzoic acids, e.g. in WO2004091502.

The following pyrimido[4,5-b]quinoline-4,5(3H,10H)-diones have been published in

15 catalogues of suppliers of chemical compounds without indicating usefulness of compounds:

Ex	Structure	Name	CAS number
1.28		2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	883958-40-5
1.29		10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	898913-20-7
1.30		10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	898923-07-4

1.31		2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	883958-38-1
1.33		3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	898921-75-0
1.34		3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	896597-46-9
1.35		3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	883960-31-4
1.36		3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	899404-28-5

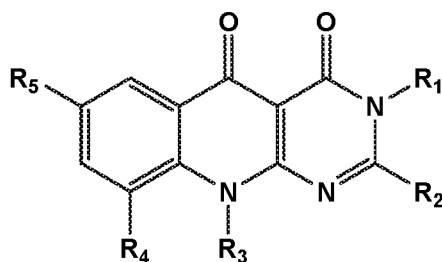
2.15		3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	898918-28-0
2.18		3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	883961-07-7
2.21		3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	883961-12-4
2.24		3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	898912-80-6
2.29		3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	879773-75-8
		3-cyclopentyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	898916-50-2

Nonsense mutation suppressors are considered to be useful in the treatment of a wide range of diseases caused by nonsense mutations. Prominent examples of diseases caused by nonsense mutations are diseases caused by nonsense mutations in lysosomal enzymes, e.g. mucopolysaccharidosis I (Hurler syndrome) caused by nonsense mutations in α -L-iduronidase; hemophilia A or hemophilia B caused by nonsense mutations in coagulation factors 7, 8 or 9; cystic fibrosis caused by nonsense mutations in the chloride channel CFTR; diseases caused by nonsense mutations in structural proteins, e.g. Duchenne or Becker Muscle Dystrophy caused by nonsense mutations in dystrophin; or cancer caused by nonsense mutations in APC or p53.

There is a need to provide new nonsense mutation suppressors that are good drug candidates. In particular, preferred compounds should be potent nonsense mutation suppressors whilst showing little potency in other drug target assays, e.g. GPCR or ion channel assays. They should exhibit a low binding to plasma proteins. They should be well absorbed from the gastrointestinal tract, be sufficiently metabolically stable and possess favorable pharmacokinetic properties. They should be non-toxic and demonstrate few side-effects. Furthermore, the ideal drug candidate will be able to exist in a physical form that is stable, non-hygroscopic and easily formulated.

The compounds of the invention are nonsense mutation suppressors and are therefore potentially useful in the treatment of a wide range of diseases caused by nonsense mutations, particularly wherein the disease is selected from hemophilia A, hemophilia B, cystic fibrosis, mucopolysaccharidosis I, Duchenne Muscle Dystrophy, Becker Muscle Dystrophy, loss of APC caused cancer and loss of p53 caused cancer.

In a first aspect, the invention relates to a compound of formula (I)



(I);

or a salt thereof, wherein

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R₁ is a five- to seven-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

5 and

R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;

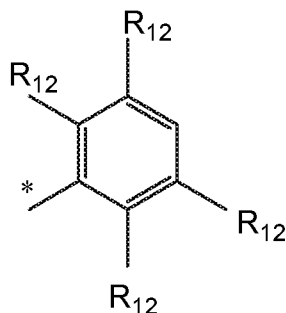
or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl which may be substituted once or more than once by R₁₀;

10 or R₂ is a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₁;

or

15

R₁ is



wherein the phenyl ring is attached via the bond marked with an asterisk;

20 each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

25 and

R₂ is C₂₋₇alkyl which may be substituted once or more than once by R₁₃;

or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl which may be substituted once or more than once by R₁₆;

or R₂ is a three- to seven-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₇;

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R₃ is hydrogen or -CH₂R₁₈;

R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or aminoC₁₋₃alkyl;

and

- 10 R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
- or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
- 15 nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

- 20 R₃ and R₄ taken together are -CH₂-CH₂-;

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl, C₁₋₄alkoxy or C₁₋₄halogenalkoxy; or C₃₋₄cycloalkyl, wherein one carbon

- 25 atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₄cycloalkyl may be substituted once or more than once by halogen;

R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

- 30 or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl
- 35 may be substituted once or more than once by halogen;

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or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

5 R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

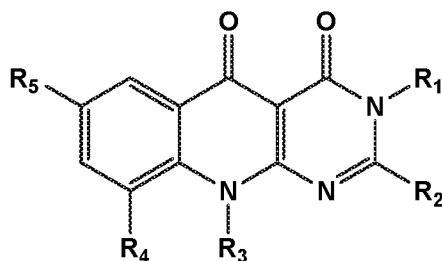
10 or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

for use as a medicament for the treatment of a disease caused by a nonsense mutation.

15

In a second aspect, the invention relates to a compound of formula (I)



(I);

or a salt thereof, wherein

20 R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

and

25 R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;

or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl which may be substituted once or more than once by R₁₀;

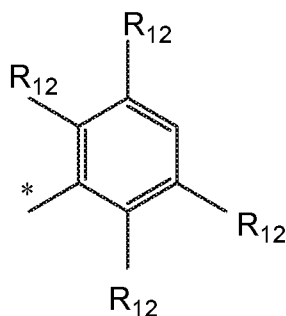
or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} ;

or

5

R_1 is



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;

15 and

R_2 is C_{2-7} alkyl which may be substituted once or more than once by R_{13} ;

or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ;

R_3 is hydrogen or $-CH_2R_{18}$;

25 R_{18} is hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy C_{1-3} alkyl, hydroxy C_{1-3} alkyl, or amino C_{1-3} alkyl;

and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

R₃ and R₄ taken together are -CH₂-CH₂-;

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

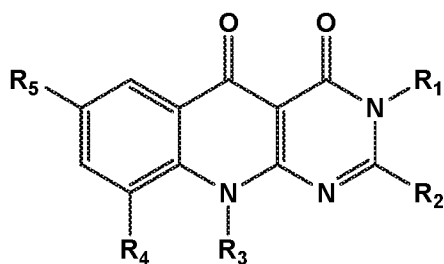
or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

for use as a medicament.

In a third aspect, the invention relates to a compound of formula (I)



(I);

or a salt thereof, wherein

R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

and

R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;

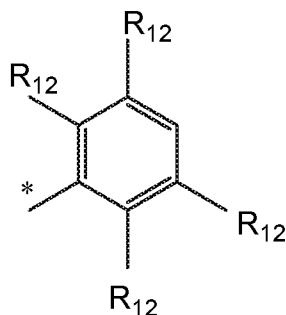
or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl which may be substituted once or more than once by R₁₀;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₁;

or

R₁ is

- 12 -



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋

5 4alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

and

10 R₂ is C₂₋₇alkyl which may be substituted once or more than once by R₁₃;

or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl which may be substituted once or more than once by R₁₆;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

15 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or

20 aminoC₁₋₃alkyl;

and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

25 or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

R₃ and R₄ taken together are -CH₂-CH₂-;

5

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

10 R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the

15 C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

20

R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl

25 may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

30 provided the compound is not

2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

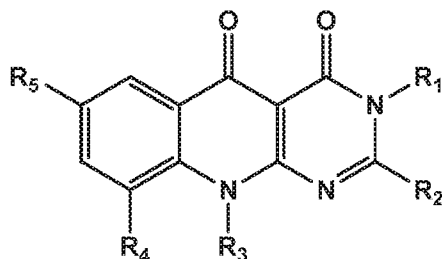
2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

35 3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 5 3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
 3-cyclopentyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione.

10

In a fourth aspect, the invention relates to a compound of formula (I)



(I);

or a salt thereof, wherein

15 R_1 is a five- to seven-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_6 ;

and

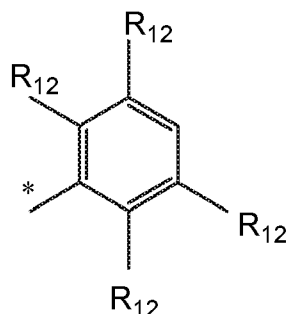
20 R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 ;
 or R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ;

or R_2 is a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms
 25 selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} ;

or

- 15 -

R₁ is



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋

5 4halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋
4alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋
4alkyl)amino; or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen
atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein
the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

10 and

R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₁₃;

or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl
which may be substituted once or more than once by R₁₆;

or R₂ is a three- to seven-membered monocyclic saturated or unsaturated non-aromatic ring
15 system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

20 R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl or C₃₋₆cycloalkyl;

and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋
4hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-
amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

25 or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic
ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋
2alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

R₃ and R₄ taken together are -CH₂-CH₂-;

5

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl, C₁₋₄alkoxy or C₁₋₄halogenalkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached

10 directly or via a C₁₋₂alkylene, and wherein the C₃₋₄cycloalkyl may be substituted once or more than once by halogen;

R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

15

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

20 or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

25

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

30

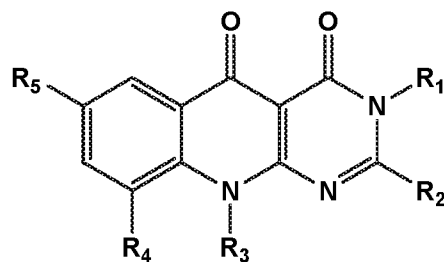
or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

for use as a medicament for the treatment of a disease caused by a nonsense mutation.

35

In a fifth aspect, the invention relates to a compound of formula (I)

- 17 -



(I);

or a salt thereof, wherein

R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system,
 5 wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen,
 oxygen and sulfur, and wherein said ring system may be substituted once or more than once
 by R₆;

and

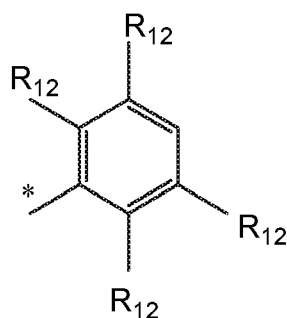
R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;

10 or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl
 which may be substituted once or more than once by R₁₀;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring
 system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
 15 than once by R₁₁;

or

R₁ is



20

wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;

and

R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_{13} ;

or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ;

R_3 is hydrogen or $-CH_2R_{18}$;

R_{18} is hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl or C_{3-6} cycloalkyl;

and

R_4 is hydrogen, halogen, hydroxyl, amino, cyano, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino;

or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C_{1-2} alkylene, and wherein said ring system may be substituted once or more than once by R_{19} ;

or

R_3 and R_4 taken together are $-CH_2-CH_2-$;

R_5 is hydrogen, halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkinyl or C_{1-4} alkoxy; or C_{3-4} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-4} cycloalkyl may be attached directly or via a C_{1-2} alkylene;

- 19 -

R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

- 5 or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;
 or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;
 or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form
 10 a C₃₋₆cycloalkyl;

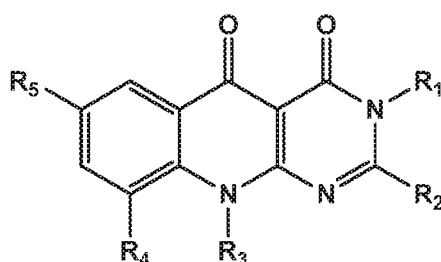
R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

- or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the
 15 C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;
 or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;
 or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

20

for use as a medicament.

In a sixth aspect, the invention relates to a compound of formula (I)



(I);

- 25 or a salt thereof, wherein

R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen,

- 20 -

oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_6 ;

and

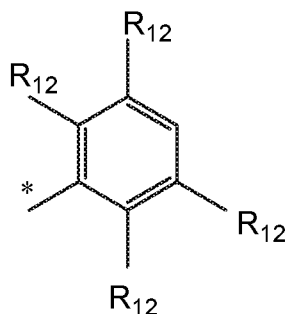
R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 ;

5 or R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
10 than once by R_{11} ;

or

R_1 is



15

wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein

20

the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;

and

R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_{13} ;

25 or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

- 5 R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl or C₃₋₆cycloalkyl;
and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

- 10 or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

- 15 or

R₃ and R₄ taken together are -CH₂-CH₂-;

- 20 R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

- 25 R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

- 30 or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;
or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

- 35 R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

- 22 -

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

- 5 or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

provided the compound is not

- 2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10 10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 15 3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 20 3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
- 3-cyclopentyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione.

- Unless specified otherwise, the term "compounds of the invention" refers to compounds of
- 25 formula (I) and subformulae thereof; salts of the compounds; hydrates or solvates of the compounds and/or salts; as well as all stereoisomers (including diastereoisomers), tautomers and isotopically labeled compounds (including deuterium substitutions); as well as inherently formed moieties (e.g. polymorphs, solvates and/or hydrates).

- 30 Unless indicated otherwise, the expressions used in this invention have the following meaning:

- "Alkyl" represents a straight-chain or branched-chain alkyl group and, for example, may be methyl, ethyl, n- or iso-propyl or n-, iso-, sec- or tert-butyl; C₂₋₇alkyl preferably represents a
- 35 straight-chain or branched-chain C₂₋₄alkyl with particular preference given to ethyl, n-propyl,

iso-propyl and tert-butyl. C₁₋₄alkyl preferably represents a straight-chain or branched-chain C₁₋₃alkyl with particular preference given to methyl, ethyl, n-propyl and iso-propyl.

Each alkyl part of "alkoxy", "halogenalkyl", "hydroxyalkyl", "aminoalkyl", "alkoxyalkyl" and so on shall have the same meaning as described in the above-mentioned definition of "alkyl", especially regarding linearity and preferential size, unless the size is further specified.

"C₃₋₆cycloalkyl" represents a saturated alicyclic moiety having from three to six carbon atoms. This term refers to groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

A substituent being substituted "once or more than once", e.g. as defined in connection with R₁, is preferably substituted by one to three substituents.

Halogen is generally fluorine, chlorine, bromine or iodine; preferably fluorine, chlorine or bromine. Halogenalkyl groups preferably have a chain length of 1 to 4 carbon atoms and are, for example, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, 2-chloroethyl, pentafluoroethyl, 1,1-difluoro-2,2,2-trichloroethyl, 2,2,2-trichloroethyl, 1,1,2,2-tetrafluoroethyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl or 2,2,3,4,4,4-hexafluorobutyl.

In the context of the invention, the definition of R₁ as a "five- to seven-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms" encompasses five- to seven-membered monocyclic non-aromatic hydrocarbon groups and heterocyclic ring systems of the same sizes.

In the context of the invention, the definition of R₂ or R₄ as a "three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms" encompasses (i) three- to seven-membered monocyclic aromatic or non-aromatic hydrocarbon groups and aromatic or non-aromatic heterocyclic ring systems of the same sizes.

Examples of heterocyclic ring systems are: pyrrole, pyrroline, pyrrolidine, pyrazole, pyrazoline, pyrazolidine, imidazole, imidazoline, imidazolidine, triazole, triazoline, triazolidine, tetrazole, furane, dihydrofurane, tetrahydrofurane, oxadiazole, dioxolane, thiophene, dihydrothiophene, tetrahydrothiophene, oxazole, oxazoline, oxazolidine, isoxazole,

isoxazoline, isoxazolidine, thiazole, thiazoline, thiazolidine, isothiazole, isothiazoline, isothiazolidine, thiadiazole, thiadiazoline, thiadiazolidine, pyridine, piperidine, pyridazine, pyrazine, pyrimidine, piperazine, triazine, pyrane, tetrahydropyrane, thiopyrane, tetrahydrothiopyrane, oxazine, thiazine, morpholine.

5

Compounds of formula I may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures or diastereomeric mixtures. In particular, asymmetrical carbon atom(s) may be present in the compounds of formula I and their salts. Unless otherwise provided herein, all optical isomers and their mixtures, including the

10

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo

15 isomeric configurations which may exist for a given compound of the invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes

20 enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is

25 specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. The compounds described herein may contain one or

30 more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless otherwise provided herein, the invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral

35 reagents, or resolved using conventional techniques.

If the compound contains a double bond, the substituent may be E or Z configuration.

If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a
5 cis- or trans-configuration.

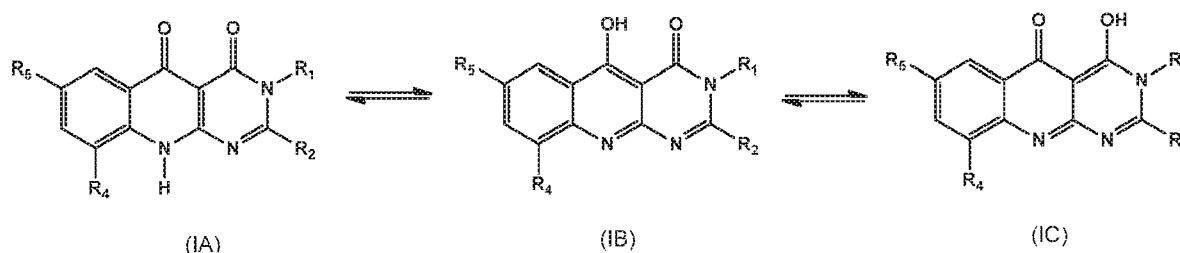
Any asymmetric atom (e.g. carbon or the like) of the compound(s) of the invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 %
10 enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

15 Accordingly, as used herein, a compound of the invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

20 Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

25 Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the
30 compounds of the invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Depending on substituent definition, compounds of formula I may occur in various tautomeric forms. All tautomeric forms of the compounds of formula I are embraced by the invention. For example, compounds of formula I, in which R_1 , R_2 , R_4 and R_5 are as defined under formula I, and R_3 is hydrogen, may exist in tautomeric forms (IA), (IB) or (IC):



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As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound of the invention. “Salts” include in particular “pharmaceutically acceptable salts”. The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. The compounds of the invention may be capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

10

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

20

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

25

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

30

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

When both a basic group and an acid group are present in the same molecule, the compounds of the invention may also form internal salts, e.g., zwitterionic molecules.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I respectively. The invention includes various isotopically labeled compounds as defined

herein, for example those into which radioactive isotopes, such as ^3H and ^{14}C , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O , d_6 -acetone, d_6 -DMSO.

Compounds of the invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-

melting, or contacting in solution compounds of formula I with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

5

The invention also envisages the use of pro-drugs of the compounds of the invention that convert in vivo to the compounds of the invention. A pro-drug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of the invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-

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drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See The Practice of Medicinal Chemistry, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001).

15

Furthermore, the compounds of the invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

20

The compounds of the invention, including salts, hydrates and solvates thereof, may

25

inherently or by design form polymorphs.

Preferred substituents, preferred ranges of numerical values or preferred ranges of the radicals present in compounds of the formula I and the corresponding intermediate compounds are defined below.

30

The definition of the substituents applies to compounds of the first, second and third aspect; i.e. compounds of formula (I) for use as a medicament for the treatment of a disease caused by a nonsense mutation, compounds of formula (I) for use as a medicament and compounds of formula (I) per se, respectively.

The definition of the substituents applies to the end-products as well as to the corresponding intermediates.

35

- 30 -

The definitions of the substituents may be combined at will, e.g. preferred substituents R_1 and particularly preferred substituents R_2 .

In one embodiment, R_1 is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_6 ;

and

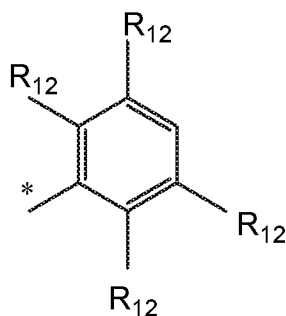
R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 ;

or R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} ;

or

R_1 is



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;

and

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R₂ is C₂₋₇alkyl which may be substituted once or more than once by R₁₃;
 or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl
 which may be substituted once or more than once by R₁₆;
 or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring
 5 system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
 than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

10 R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or
 aminoC₁₋₃alkyl;
 and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄
 hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-
 15 amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
 or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic
 ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
 nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂
 alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;
 20 or

R₃ and R₄ taken together are -CH₂-CH₂-;

25 R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or
 C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the
 C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl,
 30 C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄
 alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄
 alkyl)amino;
 or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the
 C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl
 35 may be substituted once or more than once by halogen;

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or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

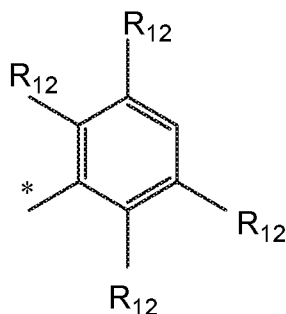
5 R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

10 or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl.

In one embodiment, R₁ is



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wherein the phenyl ring is attached via the bond marked with an asterisk;

each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

20 or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

and

R₂ is C₂₋₇alkyl which may be substituted once or more than once by R₁₃;

25 or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl which may be substituted once or more than once by R₁₆;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

- 5 R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or aminoC₁₋₃alkyl;

and

- R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-
- 10 amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
- or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

- 15 or

R₃ and R₄ taken together are -CH₂-CH₂-;

- 20 R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

- R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
- 25 or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;
- or two R₁₃ or R₁₆ at the same carbon atom together are oxo;
- 30 or two R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋

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₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl

5 may be substituted once or more than once by halogen;

or two R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl.

10 In one embodiment, R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

and

15 R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;

or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl which may be substituted once or more than once by R₁₀;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

20 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₁;

R₃ is hydrogen or -CH₂R₁₈;

R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl or C₃₋₆cycloalkyl;

25 and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-

amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic

30 ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

35

R₃ and R₄ taken together are -CH₂-CH₂-;

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the

5 C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

R₇ and R₁₀ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the

10 C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₇ or R₁₀ at the same carbon atom together are oxo;

or two R₇ or R₁₀ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

15

R₆, R₁₁ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

20 or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₆, R₁₁ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl.

25

In one embodiment, R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted

30 once or more than once by R₆; each R₆ independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by

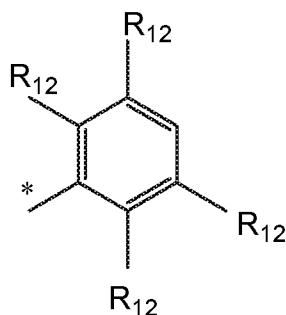
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halogen; or two R_6 at the same ring atom together are oxo; or two R_6 at the same ring carbon atom together with said carbon atom form a C_{3-6} cycloalkyl.

5 In one embodiment, R_1 is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_6 ; each R_6 independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

10 In one embodiment, R_1 is



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} alkoxy; or C_{3-6} cycloalkyl.

15

In one embodiment, R_2 is C_{2-7} alkyl which may be substituted once or more than once by R_7 .

In one embodiment, R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 .

20 In one embodiment, R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 ; each R_7 independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

In one embodiment, R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} .

25

In one embodiment, R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ; each R_{10} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

In one embodiment, R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$ or $-S-$; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ; each R_{10} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

5

In one embodiment, R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$ or $-S-$; and R_8 is C_{1-6} alkyl.

In one embodiment, R_2 is $-X_1-R_8$; $-X_1-$ is $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ; each R_{10} independently is

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halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

In one embodiment, or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} .

15

In one embodiment, or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} ; each R_{11} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

20

In one embodiment, R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_{13} .

25

In one embodiment, R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_{13} ; each R_{13} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

In one embodiment, R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} .

30

In one embodiment, R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ; each R_{16} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

35

In one embodiment, R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$ or $-S-$; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ; each R_{16} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

5

In one embodiment, R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$ or $-S-$; and R_{14} is C_{1-6} alkyl.

In one embodiment, R_2 is $-X_2-R_{14}$; $-X_2-$ is $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ; each R_{16} independently is

10

halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

In one embodiment, R_2 is $-X_2-R_{14}$; $-X_2-$ is $-N(R_{15})-$; R_{15} is C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl.

In one embodiment, or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} .

15

In one embodiment, or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ; each R_{17} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

20

In one embodiment, R_3 is hydrogen or $-CH_2R_{18}$; R_{18} is hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl or C_{3-6} cycloalkyl; and R_4 is hydrogen, halogen, hydroxyl, amino, cyano, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C_{1-2} alkylene, and wherein said ring system may be substituted once or more than once by R_{19} ; each R_{19} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-}

25

30

35

₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen; or two R₁₉ at the same ring atom together are oxo; or two R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl.

In one embodiment, R₄ is hydrogen.

In one embodiment, R₃ is hydrogen or -CH₂R₁₈; R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl or C₃₋₆cycloalkyl; and R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄alkoxy, or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur.

In one embodiment, R₃ is hydrogen.

In one embodiment, R₃ is -CH₂R₁₈; R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, or C₃₋₆cycloalkyl.

In one embodiment, R₃ is -CH₂R₁₈; R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or aminoC₁₋₃alkyl.

In one embodiment, R₃ is -CH₂R₁₈; and R₁₈ is hydrogen.

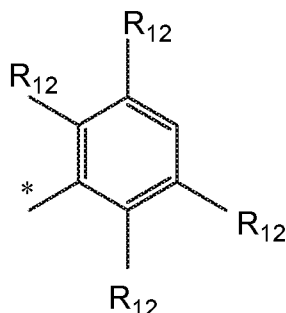
In one embodiment, R₃ and R₄ taken together are -CH₂-CH₂-.

In one embodiment, R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene.

In one embodiment, R₅ is hydrogen.

In one embodiment, R₁ is

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wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} alkoxy; or C_{3-6} cycloalkyl;

5 and

R_2 is C_{2-7} alkyl which may be substituted once or more than once by R_{13} ;

or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ; each R_{16} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl;

10 or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ;

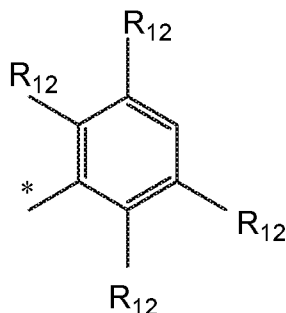
R_3 is $-CH_2R_{18}$; and R_{18} is hydrogen;

15 R_4 and R_5 are both hydrogen;

each R_{13} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkoxy or C_{3-6} cycloalkyl;

each R_{17} independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy or C_{3-6} cycloalkyl.

20 In one embodiment, R_1 is



wherein the phenyl ring is attached via the bond marked with an asterisk;
 each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄alkoxy; or C₃₋₆cycloalkyl;
 and

- 5 R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₁₃;
 or R₂ is is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl which may be substituted once or more than once by R₁₆; each R₁₆ independently is
 halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy or C₃₋₆cycloalkyl;
 or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring
 10 system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
 than once by R₁₇;
 R₃ is -CH₂R₁₈; and R₁₈ is hydrogen;
 R₄ and R₅ are both hydrogen;
 15 each R₁₃ independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy or C₃₋₆cycloalkyl;
 each R₁₇ independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄alkoxy or C₃₋₆cycloalkyl.

- In one embodiment, R₁ is a five- to six-membered monocyclic saturated or unsaturated non-
 20 aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms
 selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted
 once or more than once by R₆; each R₆ independently is halogen, hydroxyl, amino, cyano,
 nitro, C₁₋₄alkyl, C₁₋₄alkoxy or C₃₋₆cycloalkyl;
 R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;
 25 or R₂ is is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl
 which may be substituted once or more than once by R₁₀; each R₁₀ independently is halogen,
 hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy or C₃₋₆cycloalkyl;
 or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring
 system, wherein said ring system may contain from 1 to 4 hetero atoms selected from
 30 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
 than once by R₁₁; each R₁₁ independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl,
 C₁₋₄alkoxy or C₃₋₆cycloalkyl;
 R₃ is -CH₂R₁₈; and R₁₈ is hydrogen;
 R₄ and R₅ are both hydrogen.

Further examples of suitable compounds of the invention are compounds selected from the following group P:

Group P: suitable compounds of the invention:

- 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 5 10-allyl-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-allyl-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-2-(3-methylcyclobutyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10 2-(3,3-dimethylcyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-(3-methoxycyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-2-(pentan-3-yl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-cyclopentyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-cyclopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 15 2-butyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-(3-methoxypropyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-(4-methoxybutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(2-fluorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(2-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 20 3-(2,6-dichlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-10-methyl-3-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-3-(2-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-10-methyl-3-(2-(trifluoromethyl)phenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 25 3-(3-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-3-(3-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 7-fluoro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 7-chloro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 7-bromo-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 30 2-isopropyl-7,10-dimethyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 9-isopropyl-8-phenyl-1H-pyrimido[4,5-b]pyrrolo[3,2,1-ij]quinoline-6,7(2H,8H)-dione;
- 2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 35 2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 2-cyclohexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
5 3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-(2-aminoethyl)-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-3-(2-isopropylphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-cyclobutyl-10-(2-hydroxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(2-bromophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10 10-(2-aminoethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-(2-hydroxyethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-10-(2-methoxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-3-phenyl-10-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-3-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
15 dione;
2-cyclobutyl-3-(2,6-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-hexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-heptyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
20 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-ethyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(sec-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isobutyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(tert-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
25 2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-4-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione;
2-isopropyl-10-methyl-3-(piperidin-1-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-9-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-7-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
30 7-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
7-bromo-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-7-ethynyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-10-methyl-4,5-dioxo-3,4,5,10-tetrahydropyrimido[4,5-b]quinoline-7-
carbonitrile;
35 3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 3-cyclohexyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(3-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
5 3-cyclohexyl-2-(furan-2-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10 3-cycloheptyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-2-(4-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-cyclohexyl-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
15 2-(3-bromophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-(4-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
20 2-(2-chlorophenyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(p-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(2-chlorophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
25 3-cyclopentyl-10-methyl-2-(p-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-(3,4,5-trimethoxyphenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione;
3-cyclopentyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
30 2-(4-chlorophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(4-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-(3-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-2-(4-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
35 3-cyclopentyl-2-(furan-2-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 2-(3-bromophenyl)-3-cycloheptyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 9-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
 5 2-(dimethylamino)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 or salts of these compounds.

Further examples of suitable compounds of the invention are compounds selected from the following group Q:

- 10 Group Q: suitable compounds of the invention:
 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-allyl-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-allyl-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 15 2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-methyl-2-(3-methylcyclobutyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(3,3-dimethylcyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(3-methoxycyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-methyl-2-(pentan-3-yl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 20 2-cyclopentyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-cyclopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-butyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(3-methoxypropyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(4-methoxybutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 25 3-(2-fluorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(2-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(2,6-dichlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-isopropyl-10-methyl-3-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-isopropyl-3-(2-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 30 2-isopropyl-10-methyl-3-(2-(trifluoromethyl)phenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
 dione;
 3-(3-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-isopropyl-3-(3-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 7-fluoro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 35 7-chloro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 7-bromo-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-7,10-dimethyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
9-isopropyl-8-phenyl-1H-pyrimido[4,5-b]pyrrolo[3,2,1-ij]quinoline-6,7(2H,8H)-dione;
10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
5 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-ethyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(sec-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isobutyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(tert-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10 2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-4-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione;
2-isopropyl-10-methyl-3-(piperidin-1-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-9-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-7-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
15 7-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
7-bromo-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-7-ethynyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-10-methyl-4,5-dioxo-3,4,5,10-tetrahydropyrimido[4,5-b]quinoline-7-
carbonitrile;
20 9-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
2-(dimethylamino)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-(2-aminoethyl)-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
25 2-isopropyl-3-(2-isopropylphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-cyclobutyl-10-(2-hydroxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(2-bromophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-(2-aminoethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-(2-hydroxyethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
30 2-isopropyl-10-(2-methoxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-3-phenyl-10-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-3-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione;
2-cyclobutyl-3-(2,6-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
35 2-hexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-heptyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
or salts of these compounds.

Compounds of the formula I can be prepared by conventional processes, e.g. as described in
5 the Examples, which processes are further aspects of the invention. Furthermore,
compounds of formula I or their precursors may be obtainable from compounds which are
described in the Examples, e.g. by reduction, oxidation and/or other functionalization of
resulting compounds and/or by cleavage of any protecting group(s) optionally present, and of
recovering the so obtainable compound of the formula I or the intended precursor. The
10 reactions can be effected according to conventional methods, for example as described in
the Examples. The work-up of the reaction mixtures and the purification of the compounds
thus obtainable may be carried out in accordance with known procedures. Acid addition salts
may be produced from the free bases in known manner, and vice-versa. Starting materials,
e.g. starting materials as described in the Examples, may be known or prepared according to
15 conventional procedures starting from known compounds.

The invention also contemplates that compounds of formula (I) may be formed by in vivo
biotransformation from pro-drugs.

20 In another aspect, the invention provides a pharmaceutical composition comprising a
compound of the invention and a pharmaceutically acceptable carrier. The pharmaceutical
composition can be formulated for particular routes of administration such as oral
administration, parenteral administration, and rectal administration, etc. In addition, the
pharmaceutical compositions of the invention can be made up in a solid form including
25 capsules, tablets, pills, granules, powders or suppositories, or in a liquid form including
solutions, suspensions or emulsions. The pharmaceutical compositions can be subjected to
conventional pharmaceutical operations such as sterilization and/or can contain conventional
inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as
preservatives, stabilizers, wetting agents, emulsifiers and buffers etc.

30 Typically, the pharmaceutical compositions are tablets and gelatin capsules comprising the
active ingredient together with

a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or
glycine;

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b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if
5 desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

10 Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible
powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions

15 intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with nontoxic
20 pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The
25 tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium
30 phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said
35 compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing,

wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with carrier. Carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, e.g., to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, e.g., for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g., for the treatment of skin cancer, e.g., for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They are conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

The invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity

conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e. g., vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, such like materials and combinations thereof, as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The compounds of formula I or pharmaceutical acceptable salts thereof exhibit valuable pharmacological properties and are therefore useful as pharmaceuticals.

Furthermore, compounds of formula I may be useful for research on diseases caused by nonsense mutations, e.g. as tool compounds.

In particular, compounds of formula I act as nonsense mutation suppressors on frequent PTCs, e.g. on Y122X in the mRNA of the cystic fibrosis conductance regulator protein (CFTR). This can be determined in vitro, for example, using cell lines expressing GFP-CFTR-Y122X-Renilla constructs as described herein.

The compounds of the invention may be therefore useful in the prevention, treatment or delay of progression of diseases caused by nonsense mutations

The term "disease caused by nonsense mutation" is known in the field. It relates to a disease being present in patients carrying a nonsense mutation in a disease-relevant gene wherein the nonsense mutation causes a partial/total lack of protein which then causes the pathology of the disease.

- 5 In one embodiment, the disease is selected from hemophilia A, hemophilia B, cystic fibrosis, mucopolysaccharidosis I, Duchenne Muscle Dystrophy, Becker Muscle Dystrophy, loss of APC caused cancer and loss of p53 caused cancer.

For the above-mentioned indications (the conditions and disorders) the appropriate dosage
10 will vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.01 to about 100 mg/kg body weight, preferably from about 0.1 to about 10 mg/kg body weight, e.g. 1 mg/kg. In larger mammals, for example humans, an indicated daily
15 dosage is in the range from about 0.1 to about 1000 mg, preferably from about 1 to about 400 mg, most preferably from about 10 to about 100 mg of the compound of the invention conveniently administered, for example, in divided doses up to four times a day.

For use according to the invention, a compound of the invention, especially a compound as
20 defined in group P, may be administered as single active agent or in combination with other active agents, in any usual manner, e.g. orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injection solutions or suspensions. A combination comprising a compound of the invention and another active agent will be referred to as "combination of the invention".

25 A compound of the invention, especially being a compound as defined in group P, may be combined with a readthrough activator, e.g. negamycin, RT13, RT14, ataluren or an aminoglycoside readthrough activator, e.g. paromomycin, amikacin, G418, NB30, NB54 or NB84. An example of a combination is the first compound as defined in group P, i.e. 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione, and negamycin.
30

A compound of the invention, especially being a compound as defined in group P, may be combined with a nonsense-mediated mRNA decay inhibitor, e.g. NMDI-1. An example of a combination is the first compound as defined in group P, i.e. 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione, and NMDI-1.
35

A compound of the invention, especially being a compound as defined in group Q, may be combined with a readthrough activator, e.g. negamycin, RT13, RT14, ataluren or an aminoglycoside readthrough activator, e.g. paromomycin, amikacin, G418, NB30, NB54 or NB84.

A compound of the invention, especially being a compound as defined in group Q, may be combined with a nonsense-mediated mRNA decay inhibitor, e.g. NMDI-1.

Negamycin, RT13, RT14, ataluren, aminoglycoside readthrough activators and NMDI-1 are described e.g. in Keeling et al, WIREs RNA, 2011, 2, 837-852.

The compounds of the invention may be useful for the prevention of diseases caused by nonsense mutations.

The compounds of the invention may be useful for the treatment of diseases caused by nonsense mutations.

The compounds of the invention may be useful for the delay of progression of diseases caused by nonsense mutations.

In another embodiment, the invention provides a method of treating a disease caused by a nonsense mutation comprising administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a method of treating a disease caused by a nonsense mutation comprising administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the disease is selected from the afore-mentioned list, suitably hemophilia A, hemophilia B, cystic fibrosis and mucopolysaccharidosis I (Hurler syndrome).

The term "a therapeutically effective amount" of a compound of the invention refers to an amount of the compound of the invention that will elicit the biological or medical response of a subject, for example, ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the invention that, when administered to a subject, is effective to at least partially alleviating, inhibiting, preventing and/or ameliorating a disease caused by nonsense mutations. In another non-

limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially suppress the effect of nonsense mutations.

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As used herein, the term "subject" refers to an animal. Preferably, the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In a preferred embodiment, the subject is a human.

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As used herein, the term "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

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As used herein, the term "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (*i.e.*, slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

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The pharmaceutical composition or combination of the invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

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The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the invention can be applied *in vitro* in the form of solutions, e.g., preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

- 10 The activity of a compound of the invention can be assessed by *in vitro* & *in vivo* methods described herein.

The compound of the invention may be administered either simultaneously with, or before or after, at least one other therapeutic agent. The compound of the invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition.

The following Examples illustrate the invention, but do not limit it.

20 **Experimental part:**

Abbreviations:

DCM	dichloromethane
DMF	dimethylformamide
DMA	dimethylacetamide
25 TBME	tert.butylmethylether

LC-MS Method:

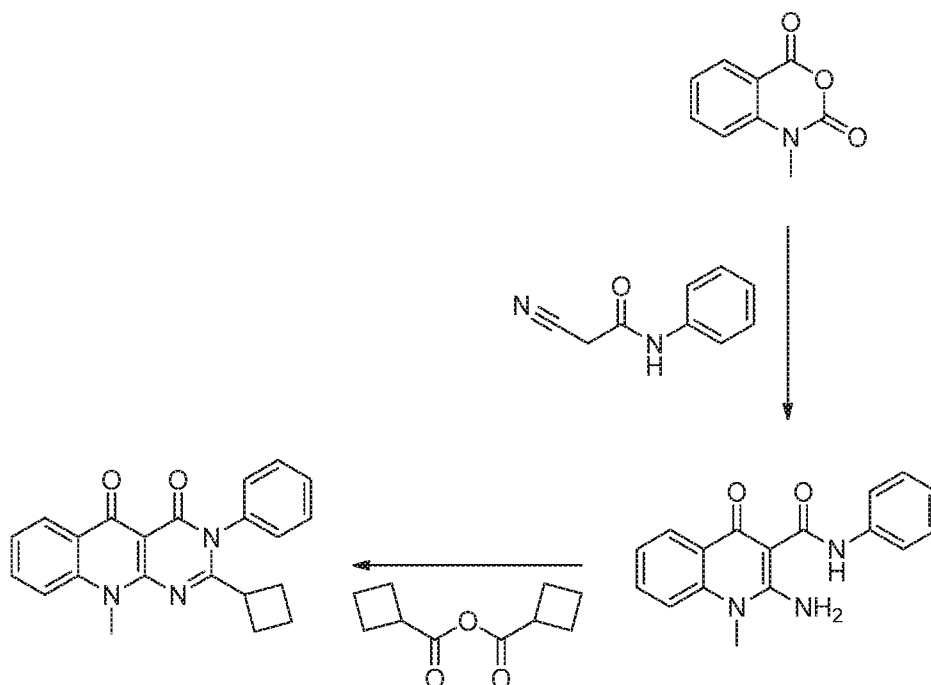
Waters Acquity UPLC-SQD system; mobile phase: A: water (0.05% formic acid) B: methanol (0.04% formic acid); gradient: from 2% B to 8% B in 0.1 min, from 8% B to 98% B in 0.5 min, 98% B for 0.1 min; flow rate 1 mL / min; column Waters Acquity UPLC BEH C18, 30x2.1 mm, 1.7 mM; oven temperature 60 °C.

NMR device :

Bruker Avance 400MHz Ultrashield

35 **Examples:**

Example 1.1: 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione



a) 2-amino-1-methyl-4-oxo-N-phenyl-1,4-dihydroquinoline-3-carboxamide:

- 5 2.235 g of a 60% suspension of NaH in mineral oil (55.9 mmol) was suspended in 100 mL dry DMA and 4.48 g 2-cyanoacetanilide (27.9 mmol) were added in portions within 15 minute at 5-10 °C and stirred for 30 minutes at room temperature. The mixture was cooled to 0 °C and 5 g 1-methyl-1H-benzo[d][1,3]oxazine-2,4-dione (25.4 mmol) were added in portions within 5 minutes and stirred at room temperature for 60 minutes. 27.9 mL aqueous
- 10 hydrochloric acid (2 M, 55.9 mmol) were added within 10 minutes and the mixture was heated to 50 °C for 1 hour. The reaction mixture was cooled to room temperature, poured into 450 mL 10% aqueous potassium hydrogencarbonate solution and stirred for 30 minutes. The resulting solid was filtered, washed with water, diethyl ether / pentane 3:2, and pentane and dried to yield 5.0 g 2-amino-1-methyl-4-oxo-N-phenyl-1,4-dihydroquinoline-3-
- 15 carboxamide (16.71 mmol, 66%) as a yellow powder.

b) 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:

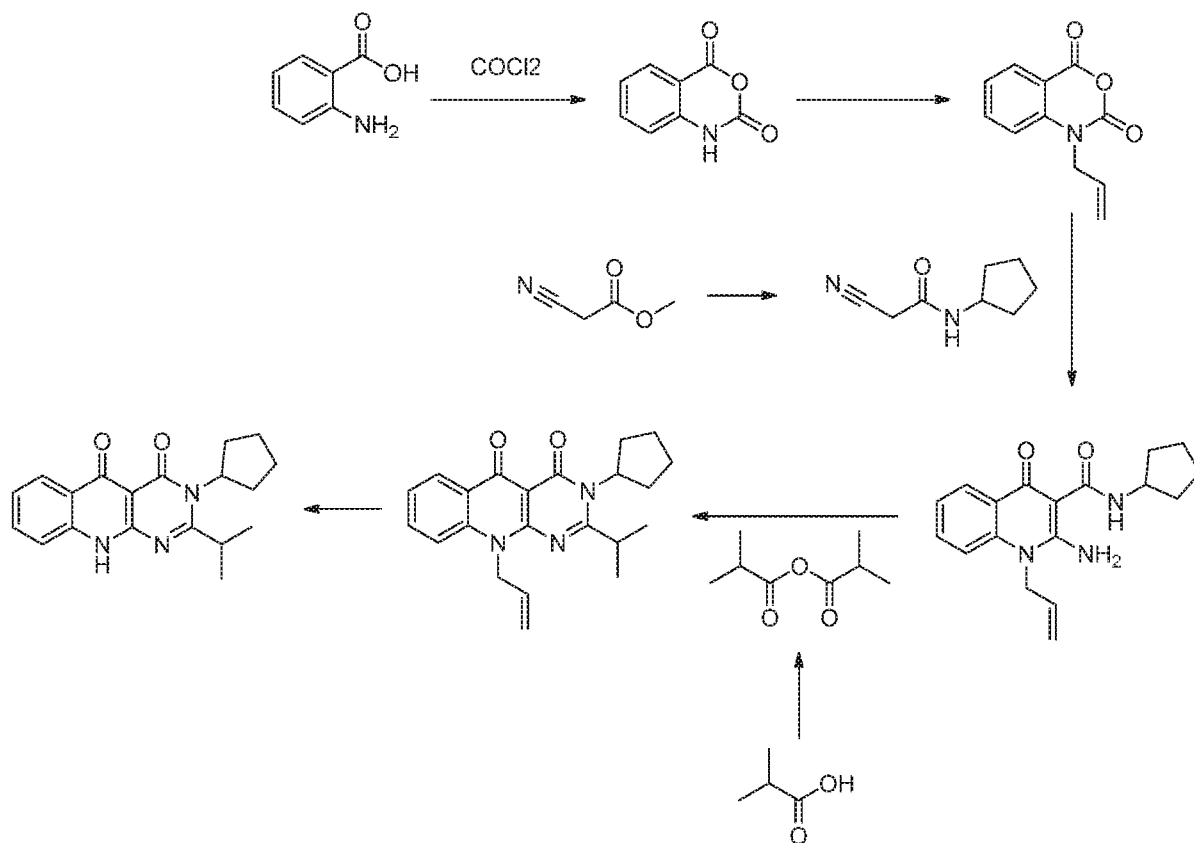
- To a suspension of 130 mg 2-amino-1-methyl-4-oxo-N-phenyl-1,4-dihydroquinoline-3-carboxamide (0.443 mmol) in 1.3 mL cyclobutyric acid (1.36 mL, 13.3 mmol) 242 mg cyclobutyric anhydride (1.33 mmol) and 129 µL propane phosphonic acid anhydride 50% in
- 20 DMF (70 mg, 0.22 mmol) were added subsequently and the mixture was heated to 150 °C for 90 minutes. The solution was cooled to 70 °C, one mL methanol added and stirred for

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one hour. The reaction mixture was cooled to room temperature, 5 mL diethyl ether and 1 mL pentane added and the resulting mixture was stirred for 15 minutes, filtered and the resulting solid washed with diethyl ether / pentane 3:2. The solid was dissolved in DCM and extracted with 0.1M sodium hydroxide solution, the organic phases dried with sodium sulfate, filtered and evaporated. The resulting solid was stirred with 5 mL diethyl ether, filtered, washed with diethyl ether / pentane 3:2 and dried under vacuum to yield 135 mg 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (0.37 mmol, 84%) as a white powder.

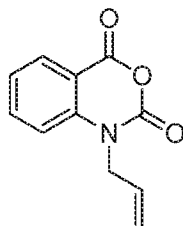
¹H-NMR (400 MHz, D₆-DMSO): δ(ppm) = 8.23 (d, 1H, ³J = 7.65 Hz), 7.89 – 7.80 (m, 2H), 7.59 – 7.49 (m, 3H), 7.44 (t, 1H, ³J = 7.15 Hz), 7.36 (d, 2H, ³J = 6.65 Hz), 4.11 (s, 3H), 3.28 – 3.20 (m, 1H), 2.48 – 2.38 (m, 2H), 1.81 – 1.61 (m, 4H).

Example 2.1 / Example 2.2: 10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione / 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:



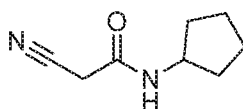
15 a) 1-allyl-1H-benzo[d][1,3]oxazine-2,4-dione:

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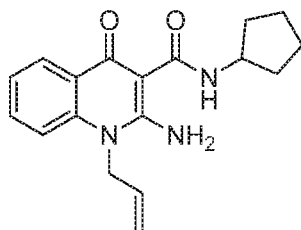
0.485 g of a 60% suspension of NaH in mineral oil (12.14 mmol) was suspended in 48.2 mL dry DMA, cooled to 0 °C and 2 g 1H-benzo[d][1,3]oxazine-2,4-dione (90% technical grade, 11.03 mmol) were added in portions and stirred for 1 hour. Then, 1.315 mL allyl iodide (2.41 g, 14.34 mmol) were slowly added and stirred at room temperature for 1.5 hours. The reaction mixture was poured into 250 mL 0.1 M aqueous hydrochloric acid and stirred for 10 minutes. The resulting solid was filtered and washed with 60 mL water and 20 mL diethyl ether / pentane (8:2) and dried under vacuum at 65 °C to yield 1.88 g 1-allyl-1H-benzo[d][1,3]oxazine-2,4-dione (9.25 mmol, 84%) as an off-white solid.

10 b) 2-cyano-N-cyclopentylacetamide:



To 5.98 mL cyclopentylamine (5.155 g, 60.5 mmol) under an atmosphere of nitrogen 5.32 mL methyl 2-cyanoacetate (6 g, 60.5 mmol) were added dropwise maintaining a reaction temperature below 30 °C. After 30 min the suspension was diluted with 8 mL diethyl ether and 2 mL pentane, stirred for 40 min, filtered and the remaining solid washed with diethyl ether and pentane and dried to yield 4.343 g of 2-cyano-N-cyclopentylacetamide (28.5 mmol, 47 %) as a white solid.

c) 1-allyl-2-amino-N-cyclopentyl-4-oxo-1,4-dihydroquinoline-3-carboxamide:

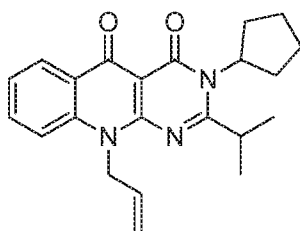


20 0.39 g of a 60% suspension of NaH in mineral oil (9.74 mmol) was suspended in 20.4 mL dry DMA and 0.742 g 2-cyano-N-cyclopentylacetamide (4.87 mmol) were added in portions and stirred for 50 minutes. The solution was cooled to 0 °C and 0.9 g 1-allyl-1H-

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benzo[d][1,3]oxazine-2,4-dione (4.43 mmol) were added in portions and stirred for 50 minutes. 9.74 mL aqueous hydrochloric acid (2 M, 19.5 mmol) were added and the mixture was heated to 60 °C for 2 hours. The reaction mixture was cooled to room temperature, poured into 10% aqueous potassium hydrogen carbonate solution and stirred for 10 min. The resulting solid was filtered, washed with water and diethyl ether and dried to yield 1.2 g 1-allyl-2-amino-N-cyclopentyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (4.13 mmol, 94%) as an off-white solid.

d) 10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:

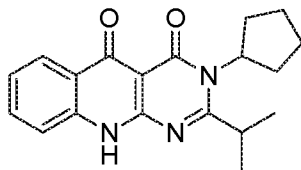


To a suspension of 396 mg 1-allyl-2-amino-N-cyclopentyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (1.273 mmol) in 4.733 mL isobutyric acid (4.487 g, 50.9 mmol) 0.844 mL isobutyric acid anhydride (0.806 g, 5.09 mmol) and 0.186 mL of a 50% solution of propane phosphonic acid anhydride in DMF (0.203 g, 0.637 mmol) were added subsequently and the mixture was heated to 150 °C for 5.5 h. The solution was cooled to 70 °C, 1 mL methanol added, stirred for 15 min and cooled to room temperature. 15 mL diethyl ether and 5 mL pentane were added, stirred for 5 min and another 5 mL pentane was added to the suspension and stirred for another 15 min. The mixture was filtered, the solid washed with diethyl ether / pentane 3:2 and dried to yield 0.398 g 10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (1.095 mmol, 86%) as an off-white solid.

¹H-NMR (400 MHz, D₆-DMSO): δ(ppm) = 8.22 (dd, 1 H, ³J = 8.0 Hz ⁴J = 1.5 Hz), 7.78 – 7.68 (m, 2 H), 7.41 – 7.36 (m, 1H), 6.12 – 6.00 (m, 1H), 5.30 (bs, 2H), 5.19 (dd, 1H, ³J = 10.6 Hz ⁴J = 1.5 Hz), 5.09 (dd, 1H, ³J = 17.1 Hz ⁴J = 1.5 Hz), 4.89 (quint, 1H, ³J = 8.3 Hz), 3.45 (sept, 1H, ³J = 6.4 Hz), 2.22 – 2.12 (m, 2H), 2.06 – 1.95 (m, 2H), 1.95 – 1.85 (m, 2H), 1.68 – 1.57 (m, 2H), 1.30 (d, 6H, 6.8 Hz).

e) 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:

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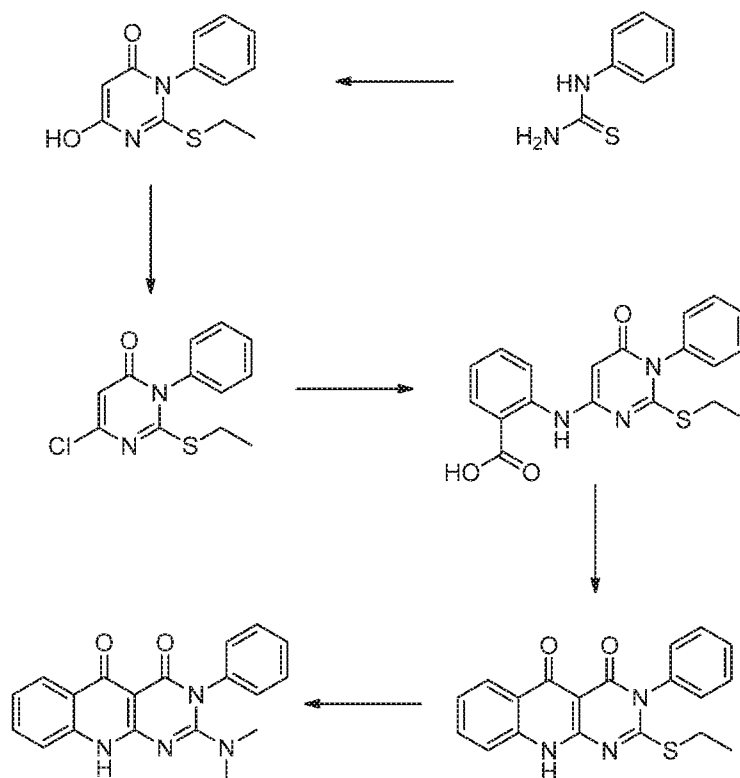


To 51 mg 10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (0.14 mmol) and 11.3 mg tetrakis(triphenylphosphine)-palladium(0) (0.01 mmol) in 3.5 mL DCM 25 mg p-toluene sulfonic acid (0.16 mmol) were added under an atmosphere of argon and stirred at room temperature for 93 h. Another 4.8 mg tetrakis(triphenylphosphine)-palladium(0) (0.004 mmol) and 11 mg p-toluene sulfonic acid (0.07 mmol) were added and stirred for another 97 h. The solution was diluted with 30 mL ethyl acetate / TBME 1:1 and extracted twice with 10 mL 1M aqueous sodium carbonate solution. The aqueous phases were extracted with 30 mL ethyl acetate / TBME 1:1 and 30 mL TBME. Combined organic layers were dried over sodium sulfate, filtered and evaporated to dryness. The resulting oil was purified by SFC and target fractions were evaporated to yield 10.4 mg 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (0.032 mmol, 23 %) as an off-white solid.

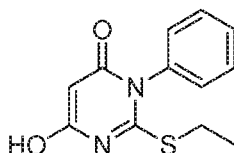
¹H-NMR (400 MHz, D₆-DMSO): δ(ppm) = 11.93 (bs, 1H), 8.08 (dd, 1H, ³J = 8.3 Hz ⁴J = 1.5 Hz), 7.66 (dt, 1H, ³J = 7.9 Hz ⁴J = 1.5 Hz), 7.59 (d, 1H, ³J = 7.4), 7.29 (dt, 1H, ³J = 7.3 ⁴J = 1.0 Hz), 4.87 (quint, 1H, ³J = 8.3), 3.41 (quint, 1H, ³J = 6.9), 2.20-2.11 (m, 2H), 2.05-1.94 (m, 2H), 1.94-1.83 (m, 2H), 1.67 - 1.57 (m, 2H), 1.31 (d, 6H, ³J = 6.8).

Example 3.1 / Example 3.2: 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione / 2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:

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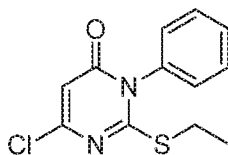
a) 2-(ethylthio)-6-hydroxy-3-phenylpyrimidin-4(3H)-one:



27.5 mL 1M sodium methylate in methanol (1.49 g, 27.5 mmol) were added at room temperature to a solution of 1.56 mL dimethyl malonate (1.8 g, 13.1 mmol) in 20 mL methanol and stirred for 30 minutes. To this solution 1.6 g phenylthiourea (10.5 mmol) were added in portions, stirred at room temperature for 15 minutes and then refluxed for 3.5 h. Heating was removed and 1.06 mL ethyliodide (13.1 mmol) were added at 50 °C, stirred for another 30 minutes and then at room temperature over night. Then 1.57 mL acetic acid were added, stirred 5 minutes and 190mL water were slowly added with stirring. The resulting suspension was stirred for another 30 minutes, filtered, washed with water and pentane and dried under vacuum at 75 °C to yield 2.33 g 2-(ethylthio)-6-hydroxy-3-phenylpyrimidin-4(3H)-one (9.4 mmol, 90%) as a white solid.

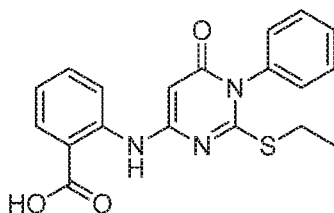
b) 6-chloro-2-(ethylthio)-3-phenylpyrimidin-4(3H)-one:

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To a suspension of 519 mg 2-(ethylthio)-6-hydroxy-3-phenylpyrimidin-4(3H)-one (2.09 mmol) and 0.264 mL N,N-dimethylaniline (253 mg, 2.09 mmol) 0.86 mL phosphoroxchloride (1.44 g, 9.4 mmol) were added at room temperature and the resulting solution was stirred for 10 minutes and then stirred at 95 °C for 35 minutes. The mixture was evaporated, hydrolyzed with 20 mL cold water, extracted with dichloromethane, the combined organic phases dried with sodium sulfate, and evaporated. The resulting red oil was suspended in 1 mL diethyl ether, 1 g silica gel added, stirred for 10 minutes, filtered over Hyflo, washed with diethyl ether and evaporated. 10 mL pentane was added and the resulting solid was filtered, washed with pentane and dried to result 376 mg 6-chloro-2-(ethylthio)-3-phenylpyrimidin-4(3H)-one (1.48 mmol, 71%) as an off-white solid.

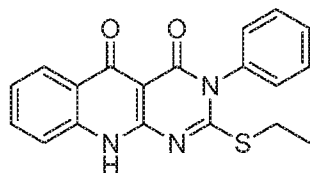
c) 2-((2-(ethylthio)-6-oxo-1-phenyl-1,6-dihydropyrimidin-4-yl)amino)benzoic acid:



To a solution of 969 mg 6-chloro-2-(ethylthio)-3-phenylpyrimidin-4(3H)-one (3.63 mmol) and 0.94 mL methyl anthranilate (1.1g, 7.27 mmol) in 18 mL DMA under Argon, 1 g potassium carbonate (7.27 mmol), 136 mg BINAP (0.22 mmol) and 67 mg Pd₂(dba)₃ (0.072 mmol) were added at room temperature and stirred at 100 °C for 17h. Another 33 mg Pd₂(dba)₃ (0.036 mmol) were added and stirred for 5 h at 100 °C. 4.5 mL water were added to the mixture and stirred for 3.25 h at 105 °C. To the cooled reaction mixture 180 mL water and 100 mL TBME were added, the aqueous phase extracted twice with TBME, combined organic phases washed with water, combined aqueous phases filtered over Hyflo, neutralized with 0.83 mL acetic acid, extracted three times with 100 mL DCM, combined DCM phases dried over sodium sulfate, filtered and evaporated. The resulting solid was stirred with 20 mL ethyl acetate, 20 mL pentane added, filtered, the solid washed with ethyl acetate / pentane 1:1 and pentane and dried to yield 474 mg 2-((2-(ethylthio)-6-oxo-1-phenyl-1,6-dihydropyrimidin-4-yl)amino)benzoic acid (1.29 mmol, 36%) as light yellow solid.

d) 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:

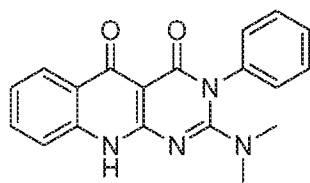
- 62 -



369 mg 2-((2-(ethylthio)-6-oxo-1-phenyl-1,6-dihydropyrimidin-4-yl)amino)benzoic acid (1 mmol) were stirred in 12 g polyphosphoric acid at 110 °C for 45 min, cooled to room temperature and poured on 40 g ice. The resulting solid was filtered, washed with water, 20 % aqueous potassium bicarbonate solution, water, and dried under vacuum at 50 °C for two days to yield 344 mg 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (0.99 mmol, 99%) as light yellow solid.

¹H-NMR (400 MHz, D₆-DMSO): δ(ppm) = 12.1 (bs, 1H), 8.08 (d, 1H, ³J = 8.0 Hz), 7.73-7.50 (m, 5H), 7.42-7.30 (m, 3H), 3.17 (q, 2H, ³J = 7.3 Hz), 1.31 (t, 3H, ³J = 7.3 Hz).

e) 2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione:

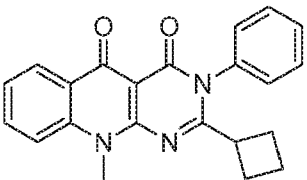
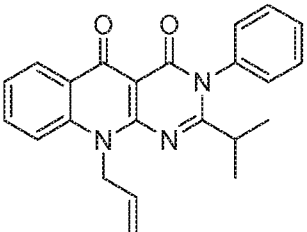
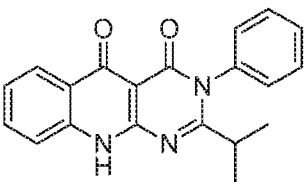
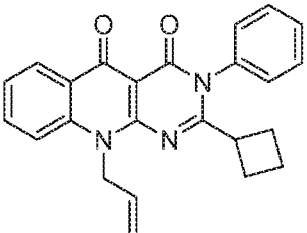
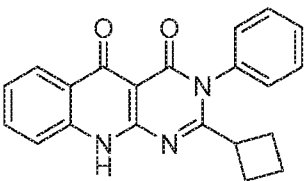


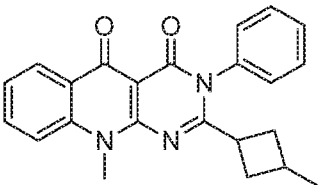
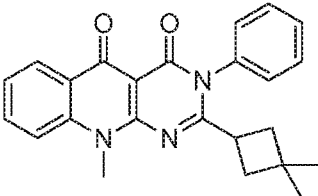
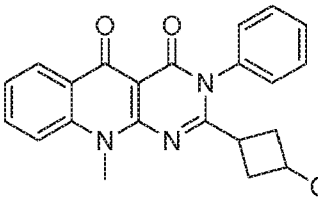
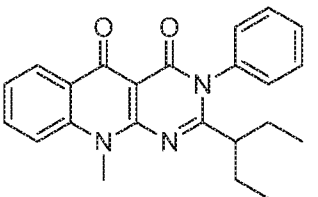
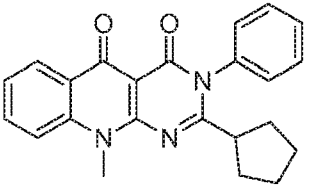
30 mg 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (0.086mmol) were added to 1 mL dimethylamin 33% in ethanol (333 mg, 7.39 mmol) in a sealed vial and heated to 90 °C for 18 h and to 110 °C for additional 3h. The mixture was evaporated, fractionated by RP-HPLC (C18, water / CAN 0.1% TFA), target fractions were pooled and freeze-dried to yield 12 mg 2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione (0.028 mmol, 33%) as a white powder.

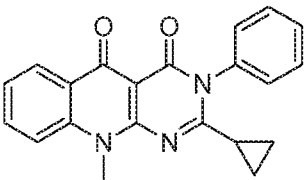
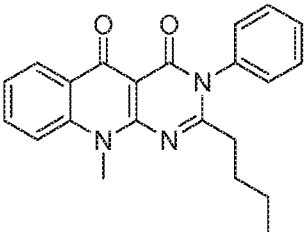
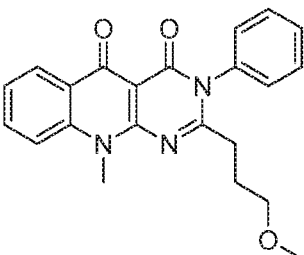
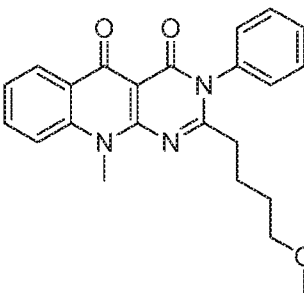
¹H-NMR (400 MHz, D₆-DMSO): δ(ppm) = 11.7 (bs, 1H), 8.02 (d, 1H, ³J = 8.1 Hz), 7.64-7.33 (m, 7H), 7.24 (t, 1H, ³J = 7.5 Hz), 2.71 (s, 6H).

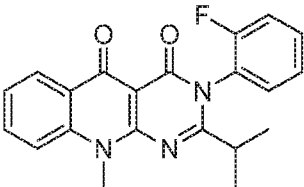
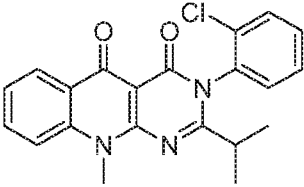
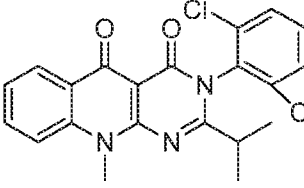
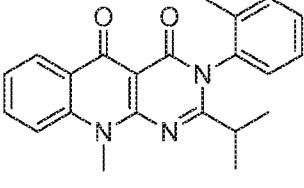
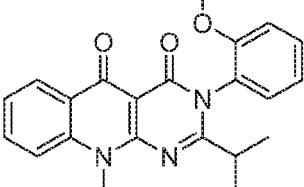
Table 1: Compounds of Formula (I)

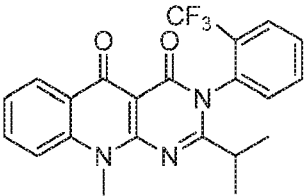
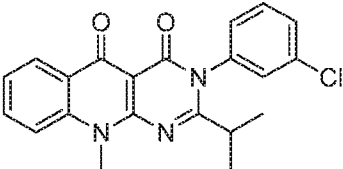
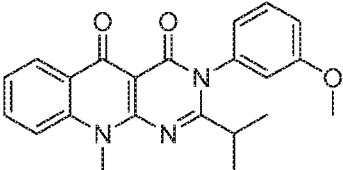
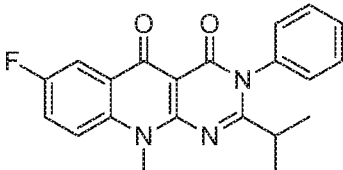
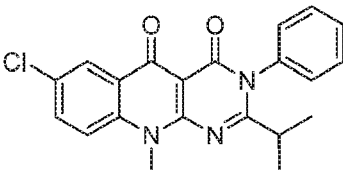
Examples (Ex) 1.1-1.48, 2.1-2.50 and 3.1-3.3 were synthesized according to/in analogy to Examples 1.1, 2.1 and 3.1 above. Examples 1.37, 1.39, 1.41 and 1.42 were prepared *via* alkylation of examples 1.3 or 1.5 with 2-iodoethanol or tert-butyl(2-bromoethyl) carbamate followed by deprotection, respectively. LCMS: LCMS Rt [min], method: method A, above.

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.1		2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	358.1
1.2		10-allyl-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	372.0
1.3		2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.62	332.1
1.4		10-allyl-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	384.1
1.5		2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.63	344.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.6		10-methyl-2-(3-methylcyclobutyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	372.1
1.7		2-(3,3-dimethylcyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	386.1
1.8		2-(3-methoxycyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.61	388.1
1.9		10-methyl-2-(pentan-3-yl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	374.1
1.10		2-cyclopentyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	372.1

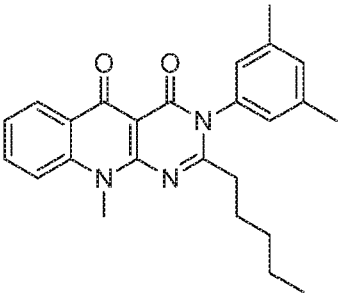
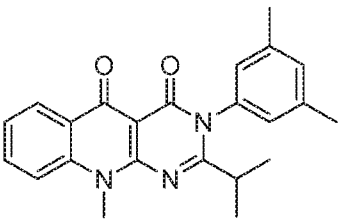
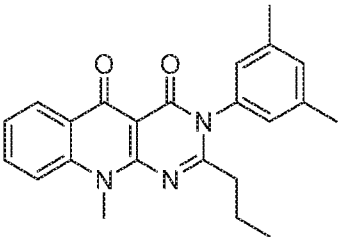
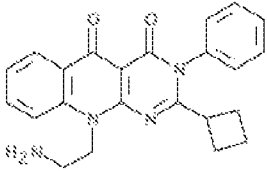
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.11		2-cyclopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.62	344.1
1.12		2-butyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	360.1
1.13		2-(3-methoxypropyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.60	376.1
1.14		2-(4-methoxybutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.62	390.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.15		3-(2-fluorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	364.1
1.16		3-(2-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	380.1
1.17		3-(2,6-dichlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	414.0
1.18		2-isopropyl-10-methyl-3-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	360.1
1.19		2-isopropyl-3-(2-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	376.1

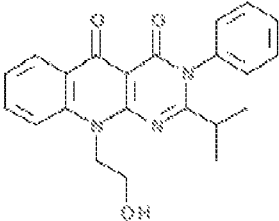
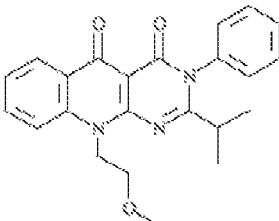
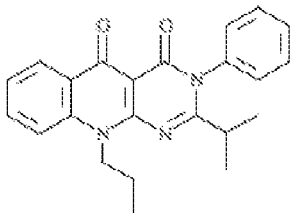
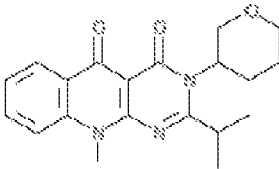
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.20		2-isopropyl-10-methyl-3-(2-(trifluoromethyl)phenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	414.1
1.21		3-(3-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	380.0
1.22		2-isopropyl-3-(3-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	376.1
1.23		7-fluoro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	364.1
1.24		7-chloro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	380.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.25		7-bromo-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	424.0
1.26		2-isopropyl-7,10-dimethyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	360.1
1.27		9-isopropyl-8-phenyl-1H-pyrimido[4,5-b]pyrrolo[3,2,1-ij]quinoline-6,7(2H,8H)-dione	0.64	358.1
1.28		2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.63	346.1
1.29		10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	374.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.30		10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	346.1
1.31		2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.62	332.0
1.32		2-cyclohexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.70	386.1
1.33		3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	360.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.34		3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.73	402.1
1.35		3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	374.1
1.36		3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.70	374.2
1.37		10-(2-aminoethyl)-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.45	387.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.38		2-isopropyl-3-(2-isopropylphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	388.1
1.39		2-cyclobutyl-10-(2-hydroxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.60	388.1
1.40		3-(2-bromophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	424.0
1.41		10-(2-aminoethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.44	375.1

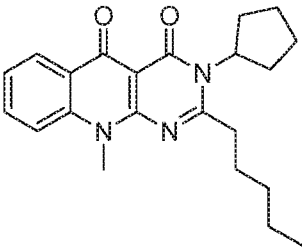
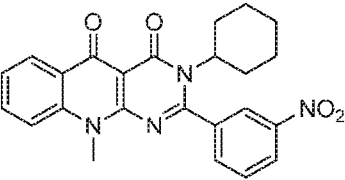
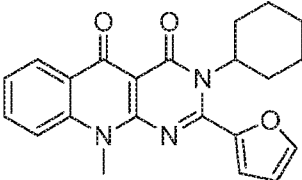
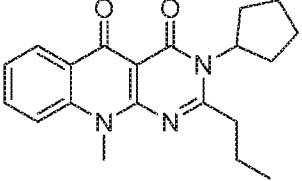
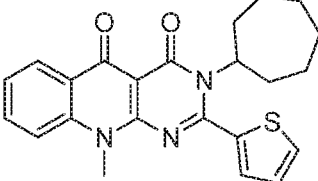
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.42		10-(2-hydroxyethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.59	376.1
1.43		2-isopropyl-10-(2-methoxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	390.0
1.44		2-isopropyl-3-phenyl-10-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	374.0
1.45		2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-3-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.62	354.0

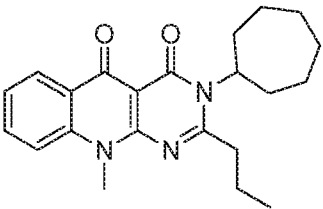
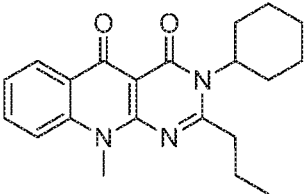
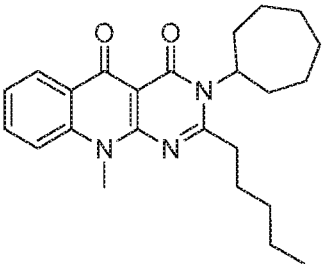
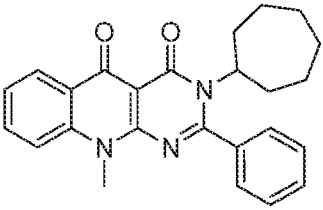
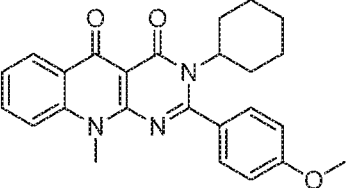
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
1.46		2-cyclobutyl-3-(2,6-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	426.1
1.47		2-hexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	388.1
1.48		2-heptyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	402.1
2.1		10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	364.1
2.2		3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.63	324.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.3		3-cyclopentyl-10-ethyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	352.1
2.4		2-(sec-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	352.1
2.5		3-cyclopentyl-2-isobutyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	352.1
2.6		2-(tert-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	352.1
2.7		2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-4-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.61	354.1

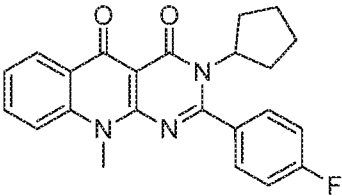
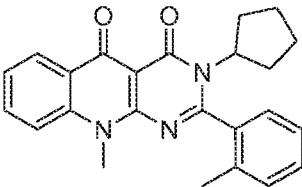
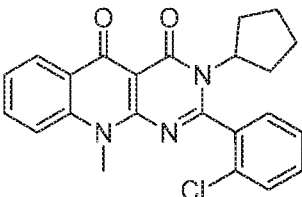
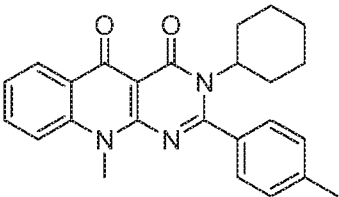
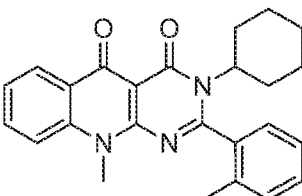
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.8		2-isopropyl-10-methyl-3-(piperidin-1-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	353.2
2.9		3-cyclopentyl-2-isopropyl-9-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	368.1
2.10		3-cyclopentyl-2-isopropyl-7-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	368.0
2.11		7-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	372.0
2.12		7-bromo-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione		

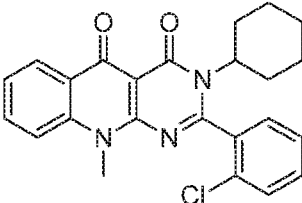
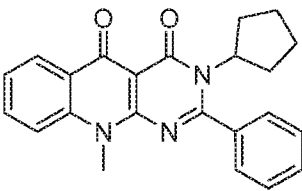
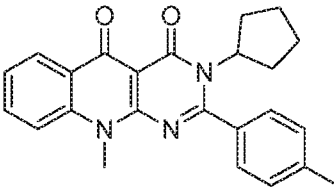
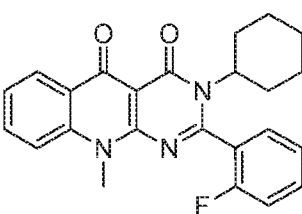
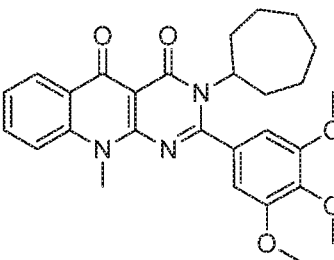
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.13		3-cyclopentyl-7-ethynyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	362.1
2.14		3-cyclopentyl-2-isopropyl-10-methyl-4,5-dioxo-3,4,5,10-tetrahydropyrimido[4,5-b]quinoline-7-carbonitrile	0.64	363.2
2.15		3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	338.1
2.16		3-cyclohexyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	386.1
2.17		3-cyclohexyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	392.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.18		3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	366.1
2.19		3-cyclohexyl-10-methyl-2-(3-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	431.1
2.20		3-cyclohexyl-2-(furan-2-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	376.1
2.21		3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	338.2
2.22		3-cycloheptyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	406.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.23		3-cycloheptyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.70	366.2
2.24		3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	352.1
2.25		3-cycloheptyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.73	394.2
2.26		3-cycloheptyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	400.1
2.27		3-cyclohexyl-2-(4-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	416.1

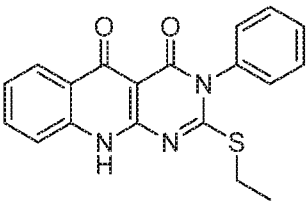
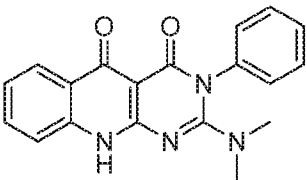
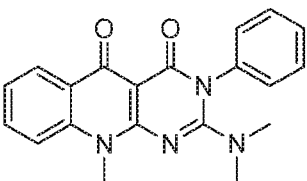
Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.28		2-cyclohexyl-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	378.1
2.29		3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	352.1
2.30		2-(3-bromophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.73	464.1
2.31		3-cycloheptyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	352.1
2.32		3-cyclopentyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	390.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.33		3-cyclopentyl-2-(4-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	390.0
2.34		3-cyclopentyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.66	386.2
2.35		2-(2-chlorophenyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	406.1
2.36		3-cyclohexyl-10-methyl-2-(p-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.71	400.1
2.37		3-cyclohexyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	400.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.38		2-(2-chlorophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	420.0
2.39		3-cyclopentyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.67	372.1
2.40		3-cyclopentyl-10-methyl-2-(p-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.71	386.1
2.41		3-cyclohexyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.70	404.2
2.42		3-cycloheptyl-10-methyl-2-(3,4,5-trimethoxyphenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	490.2

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.43		3-cyclopentyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.65	378.0
2.44		2-(4-chlorophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.70	420.1
2.45		3-cyclohexyl-10-methyl-2-(4-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.68	431.1
2.46		3-cycloheptyl-10-methyl-2-(3-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.74	445.1

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
2.47		3-cycloheptyl-2-(4-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.71	430.2
2.48		3-cycloheptyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.72	414.2
2.49		3-cyclopentyl-2-(furan-2-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.64	362.1
2.50		2-(3-bromophenyl)-3-cycloheptyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.74	478.1
2.51		9-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.69	372.0

Ex	Structure	Name	LCMS Rt [min], meth. A	[M+H] ⁺
3.1		2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.61	350.0
3.2		2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.58	333.0
3.3		2-(dimethylamino)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione	0.59	347.0

Biological Testing

1.1 In-vitro Testing: CFTR-Y122X assay

Activity of compounds of the present invention was examined in recombinant, dual reporter isogenic Hek293 cell lines ("CFTR-Y122X assay"). The engineered reporter constructs contained the 18 bp sequence stretch corresponding to a common Y122X PTC mutation in CFTR class I mutant patients (see Sermet-Gaudelus, BMC Medicine, 2007, 5(5)). Instead of a tyrosine (Y) in position 122 of the CFTR protein a TGA stop codon interrupts the open reading frame (Y122X) of the corresponding mRNA. This TGA stop codon triplet (followed by the pyrimidine base cytosine) is permissive to aminoglycoside mediated translational readthrough which served as positive control for high throughput screening. A corresponding TAA stop codon variant and a wildtype non mutated construct was used for confirmation and counter screening. The CFTR sequence was sandwiched between an eGFP reporter, and a triple myc tag sequence fused to a full length Renilla reporter. All sequences, including an intron containing one positioned pre-eGFP (b-globin intron) were cloned in frame. The

corresponding expression constructs were stably expressed in the isogenic HEK-R4 cell host (Invitrogen Incorp.) and selected by blasticidin resistance. The isogenic integration of the construct minimizes gene dose effects and improves assay reproducibility. Stably integrated single cell derived clones were selected and characterized for aminoglycoside mediated readthrough. A clone with optimal growth characteristics and strong response (EC_{50} of 1.5 mM) to paromomycin was pursued for HTS assay development. Readthrough of Y122X accumulates an intracellular localized fusion protein approximately 65.5 kDa in size as controlled by western blot analysis and immunofluorescence using an anti-renilla antibody. The eGFP reporter pre-PTC mutation serves as visual control for genetic stability of the screening clones and minimizes protein degradation of small fusion protein amounts. In the assay, compound concentration was 10 μ M. In miniaturized 1536 well format 2000 cells were dispensed in 4 μ l/well and incubated for 24 h at 37°C, 5% CO₂. 40 nl compounds were placed on the cells with control wells containing 1 μ l Paramomycin and 14.4 mM final concentration. Compounds were incubated for 24h. Renilla Glo substrate (2.5 μ l) was added and plates were centrifuged and processed for luminescence measurement using various readers. Activity calculation was done using the equation: $A1 (\%) = 100 \cdot (S - NC) / (AC - NC)$ where AC, NC and S correspond to active controls (injection of Stimulation buffer = 100% stimulation), neutral controls (buffer injection which Iloprost EC10) and screening samples (S). NC corresponds to 0% activity whereas AC is 100% activity (14 mM paromomycin). False positive artefacts were removed in confirmation and validation screening using the same assay format followed by counterscreening using the respective wildtype construct (w/o PTC mutation) cell model. Compounds were tested up to 100 μ M compound concentration.

Table 2: In-vitro activity in CFTR-Y122X assay:

Table 2 represents AC_{50} values for nonsense mutation suppression in the CFTR-Y122X assay.

Ex	A_{max} [%]	AC_{50} [μ M]		Ex	A_{max} [%]	AC_{50} [μ M]
1.1	258	1.3		2.6 ^a	127	-
1.2	63	-		2.7 ^a	151	-
1.3	279	6.1		2.8	264	10.6
1.4	279	4.0		2.9	73	18.4
1.5	170	1.1		2.10	25	25
1.6	165	6.1		2.11	192	10.7
1.7	7	3.8		2.12	23 ^a	-

Ex	A _{max} [%]	AC ₅₀ [μM]		Ex	A _{max} [%]	AC ₅₀ [μM]
1.8	18	11.8		2.13	11	-
1.9	200	11.7		2.14	9	6.6
1.10	277	11.0		2.15	275	3.8
1.11	188	9.1		2.16	312	8.6
1.12	391	4.8		2.17	293	5.8
1.13	13	-		2.18	222	9.9
1.14	18	-		2.19	248	11.6
1.15	169	7.8		2.20	201	2.3
1.16	200	9.3		2.21	214	7.6
1.17	230	8.8		2.22	197	11.0
1.18	248	6.9		2.23	181	5.0
1.19	16 ^b	-		2.24	170	2.3
1.20	65	13.8		2.25	149	6.4

Ex	A _{max} [%]	AC ₅₀ [μM]		Ex	A _{max} [%]	AC ₅₀ [μM]
1.21	167	10.2		2.26	97	11.1
1.22	23	1.9		2.27	97 ^a	-
1.23	139	13.4		2.28	89	15.1
1.24	140	11.5		2.29	73	14.3
1.25	68	19.5		2.30	71	22.2
1.26	254	9.6		2.31	67	2.5
1.27	271	6.8		2.32	43 ^d	-
1.28	361	7.6		2.33	18 ^d	-
1.29	336	7.1		2.34	33	8.4
1.30	262	6.5		2.35	31	9.4
1.31	177	10.6		2.36	29	3.5
1.32	38	-		2.37	28 ^d	-
1.33	16	0.7		2.38	21	10.0
1.34	16	3.2		2.39	31 ^e	-
1.35	13	1.5		2.40	20	6.7
1.36	9	1.0		2.41	18	4.9
1.37	348	0.9		2.42	18	10.7
1.38	15	-		2.43	17	14.7
1.39	250	3.2		2.44	16	-
1.40	112	12.1		2.45	14	11.0
1.41	198	19.5		2.46	12	4.2
1.42	117	15.7		2.47	10	3.1
1.43	9	-		2.48	7 ^d	-
1.44	118	15.2		2.49	7	1.8
1.45	389	4.7		2.50	6	4.4
1.46	25	-		2.51	6 ^a	-
1.47	210	11.3		3.1	65	5.8
1.48	235	11.7		3.2	294	11.6
2.1	102	21.0		3.3	18	3.5
2.2	235	2.1		3.3	18	3.5
2.3	101	21.6		3.3	18	3.5
2.4	258	6.1				

Ex	A _{max} [%]	AC ₅₀ [μM]		Ex	A _{max} [%]	AC ₅₀ [μM]
2.5	243	8.1				

^a % nonsense mutation suppression relative to paromomycin reference activity; measured at 25 μM compound concentration

^b % nonsense mutation suppression relative to paromomycin reference activity; measured at 12.5 μM compound concentration

^c % nonsense mutation suppression relative to paromomycin reference activity; measured at 31 μM compound concentration

^d % nonsense mutation suppression relative to paromomycin reference activity; measured at 100 μM compound concentration

^e % nonsense mutation suppression relative to paromomycin reference activity; measured at 50 μM compound concentration

The following compounds of formula (I) were tested in the above described CFTR-Y122X assay at the above dose ranges; suppression reaching only less than 5% of paromomycin reference activity was seen:

2-isopropyl-10-methyl-3-phenyl-7-(trifluoromethyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-cycloheptyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(4-chlorophenyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-cycloheptyl-10-methyl-2-(4-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-cycloheptyl-2-(4-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-cycloheptyl-2-(2,4-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(4-chlorophenyl)-3-cycloheptyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(4-(tert-butyl)phenyl)-3-cycloheptyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(4-(tert-butyl)phenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-cyclohexyl-2-(2,4-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-cycloheptyl-2-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2,3-dicyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(4-(tert-butyl)phenyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-cyclohexyl-3-(3,5-dimethylphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-(3-chlorophenyl)-2-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-isobutyl-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-isopropyl-10-methyl-3-(tetrahydrofuran-3-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
and
3-cyclopentyl-2-(1-cyclopentylpiperidin-3-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione.

5

1.2 In-vitro Testing: Coagulation factor 9-R29X assay

Activity of compounds of the present invention was examined using reporter constructs of full length human coagulation factor F9 containing the R29X (TAG) mutation known from hemophilia B patients ("F9-R29X assay"). Full length F9 cDNA was stably expressed in the
10 above isogenic HekR4 cell background. Stop codon readthrough and full length F9 expression was determined with a miniaturized confocal high throughput imaging assay. In paraformaldehyd fixed and permeabilized cells (10 uM compound; 24h incubation) F9 expression was identified with a commercial F9 antibody raised against the F9 C-terminus. The antibody does not detect the truncated F9 protein (R29X) from solvent control treated
15 cells. F9 staining intensity (Alexa-Fluor 488) and Draq5 nuclear staining served as readout for data calculation. Percent activity was measured in comparison to high (active control) and low controls (DMSO solvent). A dose-response analysis for compound induced F9 expression for the PTC mutant (R29X) was determined using a F9 ELISA assay.

Table 3: In-vitro activity in F9-R29X assay:

20 Table 3 represents AC₅₀ values for nonsense mutation suppression in the F9-R29X assay.

Ex	A _{max} [%]	AC ₅₀ [μM]
2.17	157	5.4
2.20	158	5.5
2.31	167	1.9

1.3 In-vitro Testing: α-L-iduronidase –Q70X/-W402X assay

Activity of compounds of the present invention was examined using a functional readout for two clinically common stop codon (TAG) mutants (Q70X, W402X) of the lysosomal enzyme
25 α-L-iduronidase. Lack of α-L-iduronidase expression in such stop codon patients leads to the lysosomal storage disorder Mucopolysaccharidosis I (MPSI) also called Hurler syndrome. Reporter constructs analogous to constructs above were expressed. In the assay, 2500 cells/well were treated for 48h with compound, washed with PBS and lysed (0.4 M Sodiumformate, 0.1 % NaN₃, 0.9 % NaCl, 0.2 % Triton, pH 3.5). Restored α-L-iduronidase
30 activity in cell lysates was measured with the fluorescent 4-MU iduronide substrate (4

Methylumbelliferyl α -L-iduronide) after 45 min incubation. Again, paromomycin was used as reference control (14 mM).

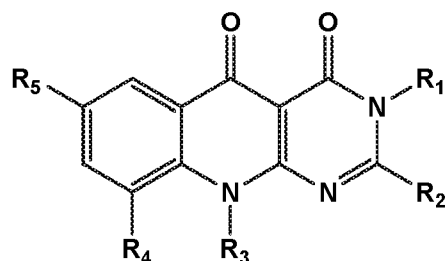
Table 4: In-vitro activity in α -L-iduronidase –Q70X/-W402X assay:

Table 3 represents AC₅₀ values for nonsense mutation suppression in the α -L-iduronidase –
5 Q70X/-W402X assay.

Ex	Q70X A _{max} [%]	Q70X AC ₅₀ [μ M]	W402X A _{max} [%]	W402X AC ₅₀ [μ M]
2.17	265	2.1	211	2.9
2.20	386	1.0	189	0.9
2.31	438	1.7	300	2.9

Claims:

1. A compound of formula (I) in free form or in pharmaceutically acceptable salt form which is



(I);

5 wherein

R₁ is a five- to seven-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

10 and

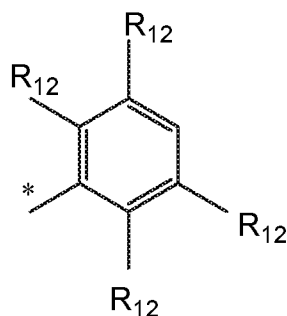
R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;
or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl which may be substituted once or more than once by R₁₀;

15 or R₂ is a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₁;

or

20

R₁ is



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;

and

R_2 is C_{2-7} alkyl which may be substituted once or more than once by R_{13} ;

or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ;

or R_2 is a three- to seven-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ;

R_3 is hydrogen or $-CH_2R_{18}$;

R_{18} is hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy- C_{1-3} alkyl, hydroxy- C_{1-3} alkyl, or amino- C_{1-3} alkyl;

and

R_4 is hydrogen, halogen, hydroxyl, amino, cyano, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C_{1-2} alkylene, and wherein said ring system may be substituted once or more than once by R_{19} ;

or

R_3 and R_4 taken together are $-CH_2-CH_2-$;

R_5 is hydrogen, halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkinyl, C_{1-4} alkoxy or C_{1-4} halogenalkoxy; or C_{3-4} cycloalkyl, wherein one carbon

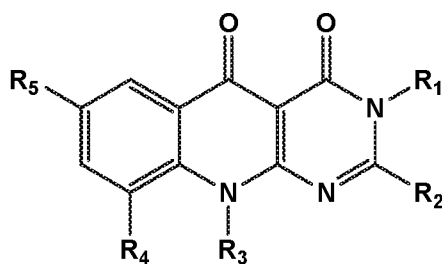
atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₄cycloalkyl may be substituted once or more than once by halogen;

- 5 R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the
10 C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;
or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;
or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

- 15
R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl
20 may be substituted once or more than once by halogen;
or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;
or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

- 25 for use as a medicament for the treatment of a disease caused by a nonsense mutation.

2. A compound of formula (I) in free form or in pharmaceutically acceptable salt form which is



(I);

wherein

R_1 is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_6 ;

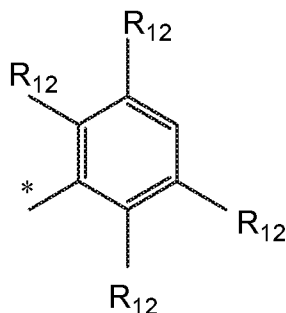
and

R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 ; or R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} ;

or

R_1 is



wherein the phenyl ring is attached via the bond marked with an asterisk; each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein the C_{3-6} cycloalkyl may be substituted once or more than once by halogen; and

R_2 is C_{2-7} alkyl which may be substituted once or more than once by R_{13} ;

or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ;

or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

5 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ;

R_3 is hydrogen or $-CH_2R_{18}$;

10 R_{18} is hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy C_{1-3} alkyl, hydroxy C_{1-3} alkyl, or amino C_{1-3} alkyl;

and

R_4 is hydrogen, halogen, hydroxyl, amino, cyano, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-

amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino;

15 or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C_{1-2} alkylene, and wherein said ring system may be substituted once or more than once by R_{19} ;

20 or

R_3 and R_4 taken together are $-CH_2-CH_2-$;

R_5 is hydrogen, halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkinyl or C_{1-4} alkoxy; or

25 C_{3-4} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-4} cycloalkyl may be attached directly or via a C_{1-2} alkylene;

R_6 , R_{11} , R_{17} and R_{19} each independently is halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino;

30 C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;

or two R_6 , R_{11} , R_{17} or R_{19} at the same ring atom together are oxo;

35 or two R_6 , R_{11} , R_{17} or R_{19} at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

for use as a medicament for the treatment of a disease caused by a nonsense mutation.

3. A compound selected from

2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-allyl-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-allyl-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-methyl-2-(3-methylcyclobutyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(3,3-dimethylcyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(3-methoxycyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-methyl-2-(pentan-3-yl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-cyclopentyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-cyclopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-butyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(3-methoxypropyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-(4-methoxybutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-(2-fluorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-(2-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-(2,6-dichlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

2-isopropyl-10-methyl-3-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

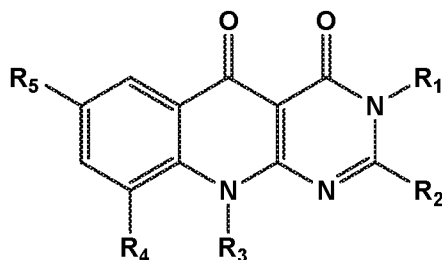
2-isopropyl-3-(2-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 2-isopropyl-10-methyl-3-(2-(trifluoromethyl)phenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-3-(3-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 5 7-fluoro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 7-chloro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 7-bromo-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-7,10-dimethyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 9-isopropyl-8-phenyl-1H-pyrimido[4,5-b]pyrrolo[3,2,1-ij]quinoline-6,7(2H,8H)-dione;
- 10 2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-cyclohexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 15 3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-(2-aminoethyl)-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 20 2-isopropyl-3-(2-isopropylphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-cyclobutyl-10-(2-hydroxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-(2-bromophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-(2-aminoethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-(2-hydroxyethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 25 2-isopropyl-10-(2-methoxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-3-phenyl-10-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-3-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-cyclobutyl-3-(2,6-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione
- 30 2-hexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 2-heptyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 3-cyclopentyl-10-ethyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 35 2-(sec-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 3-cyclopentyl-2-isobutyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(tert-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-4-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 5 2-isopropyl-10-methyl-3-(piperidin-1-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-9-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-7-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
7-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
7-bromo-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10 3-cyclopentyl-7-ethynyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-10-methyl-4,5-dioxo-3,4,5,10-tetrahydropyrimido[4,5-b]quinoline-7-carbonitrile;
3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 15 3-cyclohexyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(3-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-2-(furan-2-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 20 3-cycloheptyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 25 3-cyclohexyl-2-(4-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-cyclohexyl-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(3-bromophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cycloheptyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 30 3-cyclopentyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-(4-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(2-chlorophenyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclohexyl-10-methyl-2-(p-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 35 3-cyclohexyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 2-(2-chlorophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-10-methyl-2-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-10-methyl-2-(p-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclohexyl-2-(2-fluorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 5 3-cycloheptyl-10-methyl-2-(3,4,5-trimethoxyphenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
 dione;
 3-cyclopentyl-10-methyl-2-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(4-chlorophenyl)-3-cyclohexyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclohexyl-10-methyl-2-(4-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10 3-cycloheptyl-10-methyl-2-(3-nitrophenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cycloheptyl-2-(4-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cycloheptyl-10-methyl-2-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-2-(furan-2-yl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(3-bromophenyl)-3-cycloheptyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 15 9-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; and
 2-(dimethylamino)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 or salts of these compounds;
 20 for use as a medicament for the treatment of a disease caused by a nonsense mutation.

4. A compound of formula (I) in free form or in pharmaceutically acceptable salt form which is



(I);

wherein

25

R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

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and

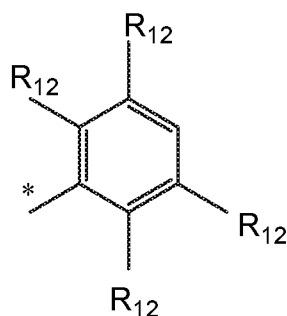
R_2 is C_{2-6} alkyl which may be substituted once or more than once by R_7 ;

or R_2 is $-X_1-R_8$; $-X_1-$ is $-O-$, $-S-$ or $-N(R_9)-$; R_9 is hydrogen or C_{1-4} alkyl; and R_8 is C_{1-6} alkyl which may be substituted once or more than once by R_{10} ;

- 5 or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{11} ;

10 or

R_1 is



wherein the phenyl ring is attached via the bond marked with an asterisk;

- 15 each R_{12} independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C_{1-4} alkyl, C_{1-4} halogenalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, di(C_{1-4} alkyl)-amino- C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} halogenalkoxy, C_{1-4} alkylamino or di(C_{1-4} alkyl)amino; or C_{3-6} cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C_{3-6} cycloalkyl may be attached directly or via a C_{1-2} alkylene, and wherein
- 20 the C_{3-6} cycloalkyl may be substituted once or more than once by halogen;
- and

R_2 is C_{2-7} alkyl which may be substituted once or more than once by R_{13} ;

or R_2 is $-X_2-R_{14}$; $-X_2-$ is $-O-$, $-S-$ or $-N(R_{15})-$; R_{15} is hydrogen or C_{1-4} alkyl; and R_{14} is C_{1-6} alkyl which may be substituted once or more than once by R_{16} ;

- 25 or R_2 is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R_{17} ;

R₃ is hydrogen or -CH₂R₁₈;

R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or aminoC₁₋₃alkyl;

5 and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic
10 ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

15

R₃ and R₄ taken together are -CH₂-CH₂-;

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the
20 C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
25

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

30 or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

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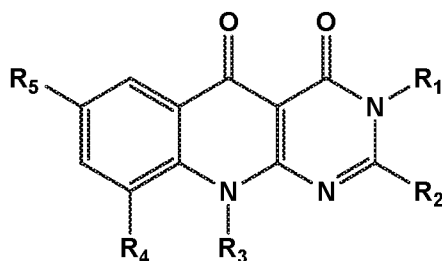
or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

- 5 or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

for use as a medicament.

- 10 5. A compound of formula (I) in free form or in pharmaceutically acceptable salt form which is



(I);

wherein

- 15 R₁ is a five- to six-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₆;

and

R₂ is C₂₋₆alkyl which may be substituted once or more than once by R₇;

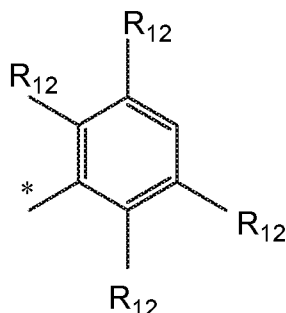
- 20 or R₂ is -X₁-R₈; -X₁- is -O-, -S- or -N(R₉)-; R₉ is hydrogen or C₁₋₄alkyl; and R₈ is C₁₋₆alkyl which may be substituted once or more than once by R₁₀;

- or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₁;
- 25

or

R₁ is

- 103 -



wherein the phenyl ring is attached via the bond marked with an asterisk;

each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋

5 4alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

and

10 R₂ is C₂₋₇alkyl which may be substituted once or more than once by R₁₃;

or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl which may be substituted once or more than once by R₁₆;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from

15 nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or

20 aminoC₁₋₃alkyl;

and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

25 or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

R₃ and R₄ taken together are -CH₂-CH₂-;

5

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

10 R₆, R₁₁, R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the

15 C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring atom together are oxo;

or two R₆, R₁₁, R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

20

R₇, R₁₀, R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl

25 may be substituted once or more than once by halogen;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together are oxo;

or two R₇, R₁₀, R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

30 provided the compound is not

2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

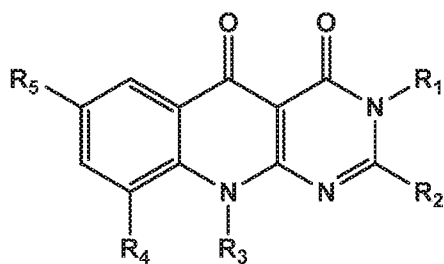
2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

35 3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 5 3-cyclopentyl-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclohexyl-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclohexyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
 3-cyclopentyl-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione.

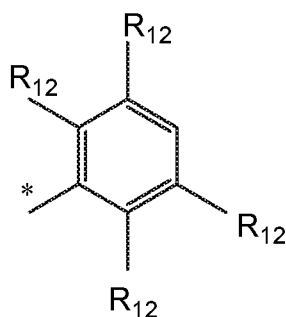
10

6. A compound of formula (I) in free form or in pharmaceutically acceptable salt form which is



(I);

wherein

15 R₁ is

wherein the phenyl ring is attached via the bond marked with an asterisk;

each R₁₂ independently is hydrogen, halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino; or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen

20

atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

and

R₂ is C₂₋₇alkyl which may be substituted once or more than once by R₁₃;

5 or R₂ is -X₂-R₁₄; -X₂- is -O-, -S- or -N(R₁₅)-; R₁₅ is hydrogen or C₁₋₄alkyl; and R₁₄ is C₁₋₆alkyl which may be substituted once or more than once by R₁₆;

or R₂ is a three- to five-membered monocyclic saturated or unsaturated non-aromatic ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and wherein said ring system may be substituted once or more
10 than once by R₁₇;

R₃ is hydrogen or -CH₂R₁₈;

R₁₈ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₁₋₃alkoxyC₁₋₃alkyl, hydroxyC₁₋₃alkyl, or aminoC₁₋₃alkyl;

15 and

R₄ is hydrogen, halogen, hydroxyl, amino, cyano, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;
or a three- to seven-membered monocyclic aromatic, saturated or unsaturated non-aromatic
20 ring system, wherein said ring system may contain from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, wherein said ring system may be attached directly or via a C₁₋₂alkylene, and wherein said ring system may be substituted once or more than once by R₁₉;

or

25

R₃ and R₄ taken together are -CH₂-CH₂-;

R₅ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkinyl or C₁₋₄alkoxy; or C₃₋₄cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the
30 C₃₋₄cycloalkyl may be attached directly or via a C₁₋₂alkylene;

R₁₃ and R₁₆ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

or two R₁₃ or R₁₆ at the same carbon atom together are oxo;

- 5 or two R₁₃ or R₁₆ at the same carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

R₁₇ and R₁₉ each independently is halogen, hydroxyl, amino, cyano, nitro, C₁₋₄alkyl, C₁₋₄halogenalkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy-C₁₋₄alkyl, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, di(C₁₋₄alkyl)-amino-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄halogenalkoxy, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

or C₃₋₆cycloalkyl, wherein one carbon atom may be replaced by an oxygen atom, wherein the C₃₋₆cycloalkyl may be attached directly or via a C₁₋₂alkylene, and wherein the C₃₋₆cycloalkyl may be substituted once or more than once by halogen;

- 15 or two R₁₇ or R₁₉ at the same ring atom together are oxo;
or two R₁₇ or R₁₉ at the same ring carbon atom together with said carbon atom form a C₃₋₆cycloalkyl;

provided the compound is not

- 20 2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-methyl-2-pentyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-methyl-3-phenyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-ethyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(3,5-dimethylphenyl)-2-ethyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
25 3-(3,5-dimethylphenyl)-10-methyl-2-pentylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(3,5-dimethylphenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; or
3-(3,5-dimethylphenyl)-10-methyl-2-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione.

7. A compound of formula I according to claim 1, wherein said compound is selected from the group consisting of

- 30 2-cyclobutyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-allyl-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-allyl-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
35 2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 10-methyl-2-(3-methylcyclobutyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(3,3-dimethylcyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(3-methoxycyclobutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10-methyl-2-(pentan-3-yl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
5 2-cyclopentyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-cyclopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-butyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(3-methoxypropyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(4-methoxybutyl)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
10 3-(2-fluorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(2-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-(2,6-dichlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-10-methyl-3-(o-tolyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-3-(2-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
15 2-isopropyl-10-methyl-3-(2-(trifluoromethyl)phenyl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione;
3-(3-chlorophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-3-(3-methoxyphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
7-fluoro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
20 7-chloro-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
7-bromo-2-isopropyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-isopropyl-7,10-dimethyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
9-isopropyl-8-phenyl-1H-pyrimido[4,5-b]pyrrolo[3,2,1-ij]quinoline-6,7(2H,8H)-dione;
10-allyl-3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
25 3-cyclopentyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-10-ethyl-2-isopropylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(sec-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isobutyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
2-(tert-butyl)-3-cyclopentyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
30 2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-4-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
dione;
2-isopropyl-10-methyl-3-(piperidin-1-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-9-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
3-cyclopentyl-2-isopropyl-7-methoxy-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
35 7-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;

- 7-bromo-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-7-ethynyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-cyclopentyl-2-isopropyl-10-methyl-4,5-dioxo-3,4,5,10-tetrahydropyrimido[4,5-b]quinoline-7-carbonitrile;
- 5 9-chloro-3-cyclopentyl-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(ethylthio)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-(dimethylamino)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione; and
 2-(dimethylamino)-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-(2-aminoethyl)-2-cyclobutyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 10 2-isopropyl-3-(2-isopropylphenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-cyclobutyl-10-(2-hydroxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 3-(2-bromophenyl)-2-isopropyl-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-(2-aminoethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 10-(2-hydroxyethyl)-2-isopropyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 15 2-isopropyl-10-(2-methoxyethyl)-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-isopropyl-3-phenyl-10-propylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-isopropyl-10-methyl-3-(tetrahydro-2H-pyran-3-yl)pyrimido[4,5-b]quinoline-4,5(3H,10H)-
 dione;
 2-cyclobutyl-3-(2,6-dichlorophenyl)-10-methylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
- 20 2-hexyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 2-heptyl-10-methyl-3-phenylpyrimido[4,5-b]quinoline-4,5(3H,10H)-dione;
 or salts of these compounds.
8. A pharmaceutical composition comprising a therapeutically effective amount of a
- 25 compound according to any one of claims 1 to 7 and one or more pharmaceutically acceptable carriers.
9. A combination comprising a therapeutically effective amount of the compound according to any one of claims 1 to 7 and one or more therapeutically active agents.
- 30 10. A method of suppressing the effect of nonsense mutations in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 7.

11. A method of treating a disease caused by nonsense mutations in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 7.