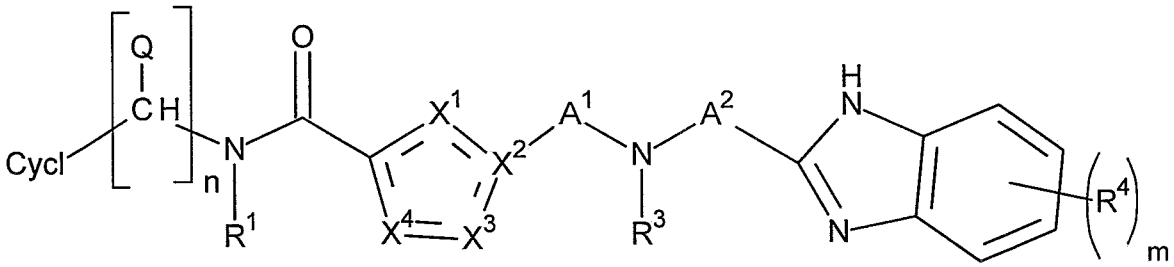
hepcidin, diseases related to or caused by increased iron levels or iron overload and diseases associated with ineffective erythropoiesis.

SUMMARY OF INVENTION

In one aspect, there is provided compounds according to formula (A-II)



(A-II)

wherein

m is 0, 1, 2 or 3 and

R^4 indicates 1, 2 or 3 optional substituents, which may independently be selected from the group consisting of

- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted alkoxy, and
- a carboxyl group;

X^1 is C, N, S or O;

X^2 is C or N;

X^3 is C, N, S or O; and

X^4 is C, N, or S

with the proviso that 1 to 3 heteroatoms X^{1-4} are present,

and wherein X^1, X^3 and X^4, when having the meaning of C or N, may carry a hydrogen atom or a further substituent;

R^1 is selected from the group consisting of

- hydrogen and
- optionally substituted alkyl;

Cycl is selected from the group consisting of

- substituted aryl and
- substituted or unsubstituted heteroaryl;

Q is

- hydrogen or

-

- C_1-C_4-alkyl, which may form a fused 5- or 6-membered ring with Cycl;

n is 0 or an integer of 1 to 8, preferably n is 0 or 1 to 4, preferably n is 0, 1, 2 or 3;

A^1 is
- unsubstituted linear or branched C_1-C_4-alkanediyl;

A^2 is
- linear or branched C_1-C_4-alkanediyl, which may be substituted with 1 or 2 substituents selected from halogen, hydroxy, an oxo group and an amino group or

- a direct bond;

R^3 is
- hydrogen, or
- optionally substituted alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered mono- or bicyclic ring; or

R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring;
or pharmaceutically acceptable salts thereof.

In another aspect of the present disclosure, there is provided compounds as described herein for use as a medicament.

In another aspect, there is provided the use of the compounds in the manufacture of a medicament for the inhibition of iron transport mediated by ferroportin, wherein the medicament is ferroportin inhibitor.

In another aspect, there is provided the use of the compounds in the manufacture of a medicament for the prophylaxis and/or treatment of iron metabolism disorders leading to increased iron levels or increased iron absorption, and/or iron overload.

In another aspect, there is provided the use of the compounds in the manufacture of a medicament for the prophylaxis and/or treatment of diseases related to or caused by increased iron levels, increased iron absorption or iron overload, wherein said diseases are selected from thalassemia, including alpha-thalassemia, beta-thalassemia and delta-thalassemia, hemoglobinopathy, hemoglobin E disease, hemoglobin H disease, haemochromatosis, hemolytic anemia, including in particular sickle cell anemia or congenital dyserythropoietic anemia.

In another aspect, there is provided the use of the compounds in the manufacture of a medicament for the prophylaxis and/or treatment of diseases associated with ineffective erythropoiesis, wherein said diseases are selected from myelodysplastic syndromes (MDS, myelodysplasia), polycythemia vera and congenital dyserythropoietic anemia; and/or infections caused by the pathogenic bacterium *Vibrio vulnificus*, in an adjunctive therapy by limiting the amount of iron available to said pathogenic bacterium

Vibrio vulnificus; and/or neurodegenerative diseases selected from Alzheimer's disease and Parkinson's disease by limiting the deposition or increase of iron in tissue or cells.

In another aspect, there is provided the use of the compounds in the manufacture of a medicament for the prophylaxis and/or treatment of formation of radicals, reactive oxygen species (ROS) and oxidative stress; and/or cardiac, liver and endocrine damage caused by iron overload; and/or inflammation triggered by excess iron.

In another aspect, there is provided a medicament containing one or more of the compounds, which may further contain

one or more pharmaceutical carriers; and/or

auxiliaries; and/or

solvents; and/or

at least one additional pharmaceutically active compound, which is preferably selected from active compounds for the prophylaxis and treatment of iron overload, thalassemia, or haemochromatosis, active compounds for the prophylaxis and treatment of neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, and the associated symptoms, and iron-chelating compounds.

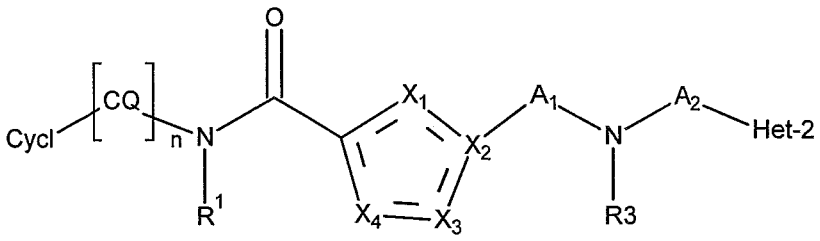
In another aspect, there is provided a medicament containing one or more of the compounds as defined herein and at least one additional pharmaceutically active compound in a combination therapy composition for co-administration in the form of a fixed-dose formulation or in the form of a free dose combination of the respective components,

wherein the one or more other pharmaceutically active compounds are preferably active compounds for reducing iron overload, which are selected from Tmprss6-ASO, iron chelators, curcumin, SSP-004184, Deferitrin, deferasirox, deferoxamine and/or deferiprone; and/or pharmaceutically active compounds which are selected from antioxidants, such as n-acetyl cysteine; anti-diabetics, such as GLP-1 receptor agonists; antibiotics, such as vancomycin (Van) or tobramycin; drugs for the treatment of malaria; anticancer agents; antifungal drugs; drugs for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, comprising dopamine agonists such as Levodopa; anti-viral drugs, such as interferon-α or ribavirin; immunosuppressents, such as cyclosporine A or cyclosporine A derivatives; iron supplements; vitamin supplements; red cell production stimulators; anti-inflammatory biologies; anti-thrombolytics; statins; vasopressors; and inotropic compounds.

DESCRIPTION OF THE INVENTION

The inventors have surprisingly found that specific compounds having the general structural formula (A-I) as defined herein, act as ferroportin inhibitors, thus effectively inhibiting iron transport and accordingly being particularly suitable for the use as medicaments, in particular for the use in the treatment and/or prophylaxis of diseases caused by a lack of hepcidin, diseases associated with ineffective erythropoiesis or iron metabolism disorders leading to increased iron levels, such as particularly iron overload states such as in particular thalassemia and hemochromatosis. Very particularly the new compounds turned out to be suitable for treating thalassemia and hemochromatosis. The new compounds are also suitable for the treatment of diseases caused by pathologically low hepcidin-levels and for the use in the inhibition of iron transport.

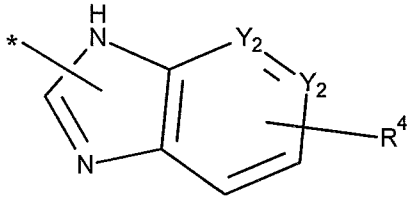
Accordingly, the invention relates to novel compounds of general formula (A-I)



(A-I)

wherein

Het-2 is an optionally substituted bicyclic heteroaryl of the formula



wherein * indicates the binding site to A^2 and

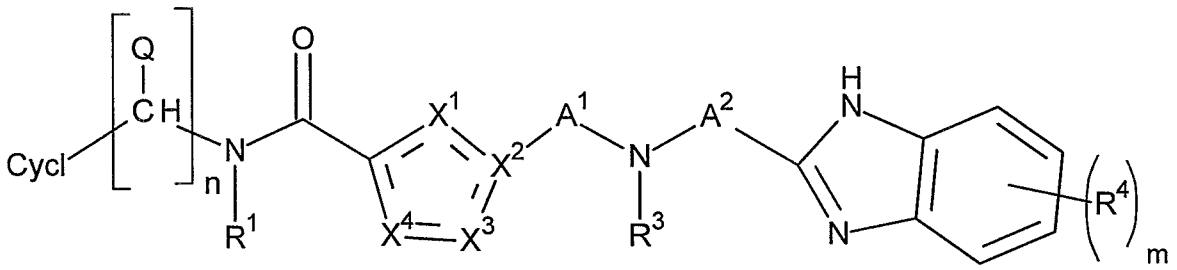
R^4 indicates 1, 2 or 3 optional substituents, which may independently be selected from the group consisting of

- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted alkoxy, and
- a carboxyl group;

X^1 is C, N, S or O;
X^2 is C or N;
X^3 is C, N, S or O; and
X^4 is C, N, or S
with the proviso that 1 to 3 heteroatoms X are present,

CLAIMS:

1. Compounds according to formula (A-II)



(A-II)

wherein
m is 0, 1, 2 or 3 and
R^4 indicates 1, 2 or 3 optional substituents, which may independently be selected from the group consisting of

- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted alkoxy, and
- a carboxyl group;

X^1 is C, N, S or O;
X^2 is C or N;
X^3 is C, N, S or O; and
X^4 is C, N, or S
with the proviso that 1 to 3 heteroatoms X^{1-4} are present,
and wherein X^1, X^3 and X^4, when having the meaning of C or N, may carry a hydrogen atom or a further substituent;

R^1 is selected from the group consisting of
- hydrogen and
- optionally substituted alkyl;

Cycl is selected from the group consisting of
- substituted aryl and
- substituted or unsubstituted heteroaryl;

Q is

- hydrogen or
- C_1-C_4-alkyl, which may form a fused 5- or 6-membered ring with Cycl;

n is 0 or an integer of 1 to 8, preferably n is 0 or 1 to 4, preferably n is 0, 1, 2 or 3;

A^1 is
- unsubstituted linear or branched C_1-C_4-alkanediyl;

A^2 is
- linear or branched C_1-C_4-alkanediyl, which may be substituted with 1 or 2 substituents selected from halogen, hydroxy, an oxo group and an amino group or
- a direct bond;

R^3 is
- hydrogen, or
- optionally substituted alkyl; or

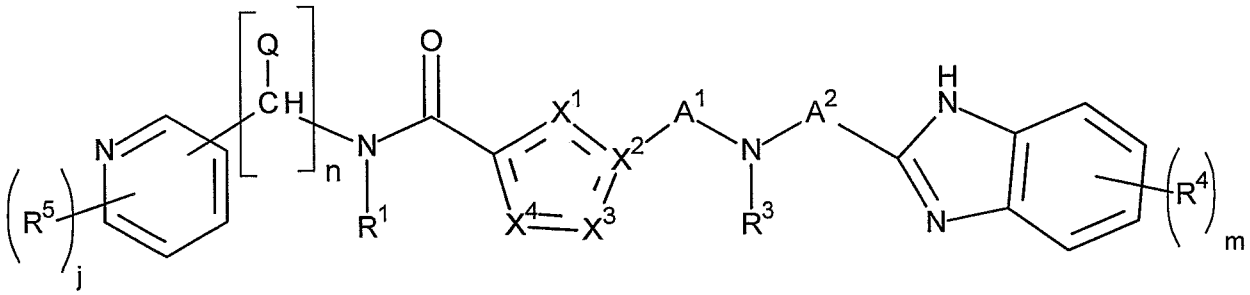
A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered mono- or bicyclic ring; or

R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring;

or pharmaceutically acceptable salts thereof.

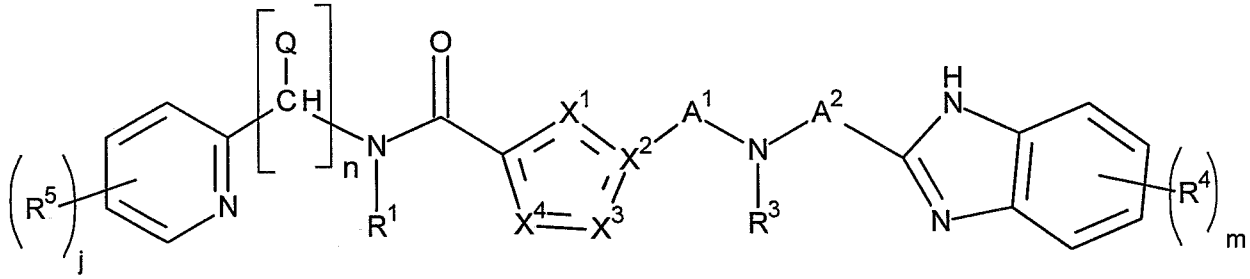
2. Compounds according to claim 1, wherein Cycl is substituted or unsubstituted heteroaryl,

such as preferably a substituted or unsubstituted pyridinyl, forming compounds according to formula (A-IIIb)



(A-IIIb)

preferably according to formula (A-IVb)



(A-IVb)

wherein
j is 0, 1, 2, 3 or 4 and

R^5 indicates 1 to 4 optional substituents, which may independently be selected from the group consisting of

- halogen, preferably F and Cl,
- optionally substituted alkyl, preferably methyl, trifluoromethyl, hydroxymethyl,
- hydroxy,
- alkoxy, preferably methoxy,
- an oxo group (=O), forming a substituted pyridinyl-group of the formula



or

- an amino group, such as $-NH_2$, mono- or dialkylamino, preferably dialkylamino
- an aminocarbonyl group, preferably NH_2-(C=O)-,
- cyano, and
- a heterocyclyl group, preferably a morpholinyl-group,

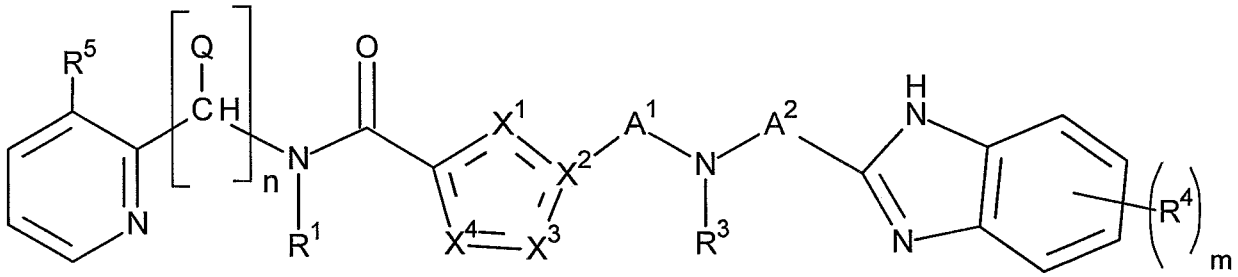
preferably

R^5 indicates 1 to 3 substituents, more preferably 1 substituent, which may independently be selected from the group consisting of

- halogen
- optionally substituted alkyl,
- hydroxy, and
- alkoxy,

or pharmaceutically acceptable salts thereof.

3. Compounds according to claim 2, having the formula (A-IVd)



(A-IVd)

or pharmaceutically acceptable salts thereof.

4. Compounds according to any one of claims 2 or 3, wherein R^5 is selected from the group consisting of

- halogen and
- optionally substituted alkyl,

preferably R^5 is halogen,

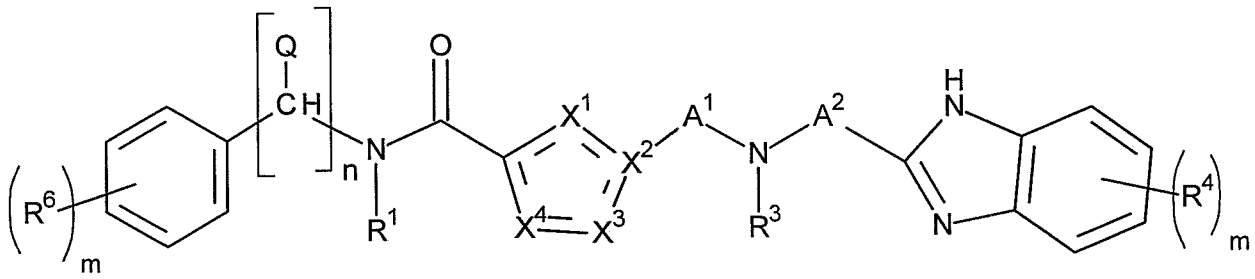
more preferably R^5 is selected from Cl and F, even more preferably R^5 is F,

or pharmaceutically acceptable salts thereof.

5. Compounds according to claim 1, wherein Cycl is an aryl group, which is substituted with 1 to 3 substituents selected from the group consisting of

- hydroxy,
- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino,
- optionally substituted acyl,
- optionally substituted alkoxy,
- optionally substituted aryloxy,
- optionally substituted heterocyclyloxy,
- optionally substituted aryl, and
- optionally substituted heterocyclylyl;

preferably Cycl is a substituted phenyl group, forming compounds according to formula (A-Vb)



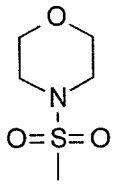
(A-Vb)

wherein

m is 0, 1, 2 or 3 and

R^6 indicates 1, 2 or 3 substitutens which are independently selected from the group consisting of

- hydroxy,
- halogen, preferably F and Cl,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino, such as ($-NH_2$) or mono- or dialkylamino, preferably dimethylamino,
- optionally substituted acyl,
- optionally substituted alkoxy, preferably methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted aryloxy,
- optionally substituted heterocyclyloxy,
- optionally substituted aryl,
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl,
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula



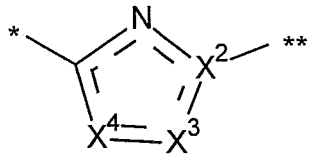
- ;

or pharmaceutically acceptable salts thereof.

6. Compounds according to any one of the preceding claims, wherein

X^1 is N

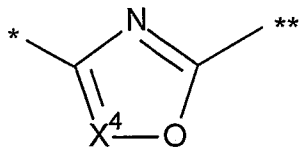
and wherein one or two further heteroatoms X (X^2, X^3, X^4) are present, and wherein
X^2 is C or N;
X^3 is C, N, S or O; and
X^4 is C or N,
forming a group



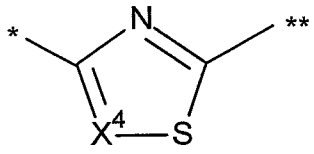
wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
with the proviso that in case of two further heteroatoms X^{2-4} both are selected to be N or one is N and one (except X^2) is O;
and wherein X^3 and X^4, when having the meaning of C or N, may carry a hydrogen atom or a further substituent,
or pharmaceutically acceptable salts thereof.

7. Compounds according to claim 6, wherein

X^2 is C;
X^3 is O or S; and
X^4 is N or C, preferably C,
forming a group



or

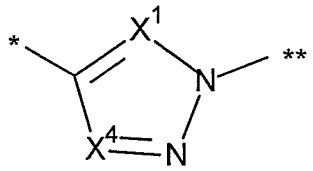


, respectively

wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^4 may carry a hydrogen atom or a further substituent;
or pharmaceutically acceptable salts thereof.

8. Compounds according to any one of claims 1 to 5, wherein

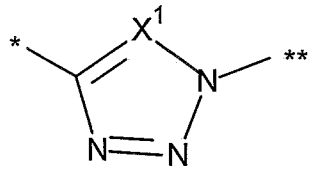
X^2 and X^3 are both N,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^1 and X^4 are C;
and wherein X^1 and/or X^4 may carry a hydrogen atom or a further substituent;

or

wherein also X^4 is N,
forming a group

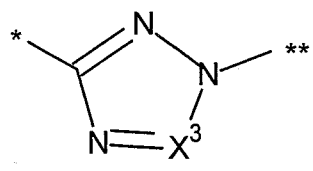


wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^1 may carry a hydrogen atom or a further substituent;

or pharmaceutically acceptable salts thereof.

9. Compounds according to any one of claims 1 to 5, wherein

X^1, X^2 and X^4 are N, and
X^3 is C,
forming a group



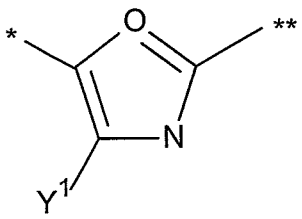
wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;

and wherein
X^3 may carry a hydrogen atom or a further substituent,
or pharmaceutically acceptable salts thereof.

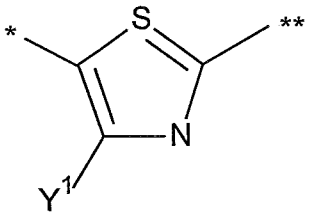
10. Compounds according to any one of claims 1 to 5, wherein

X^1 is O or S,
X^2 is C,
X^3 is N, and
X^4 is C, and wherein
Y^1 indicates
- hydrogen or
- an optional subsitutent to X^4;

forming a group



or



, respectively,

wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
or pharmaceutically acceptable salts thereof.

11. Compounds according to any one of the preceding claims, wherein the further substituents of X^1, X^3 and X^4 are selected from the group consisting of
- halogen, preferably Cl, and
- optionally substituted alkyl, preferably linear or branched C_1-C_3-alkyl, which may be substituted with 1 to 3 halogens or with a methylene-group; such as preferably a methyl-group, an iso-propyl-group, a CF_3-group or a methylene-substituted ethyl-group

or pharmaceutically acceptable salts thereof.

12. Compounds according to any one of the preceding claims, wherein
n is 1, and/or
Q is H, and/or
R^1 is H,
or pharmaceutically acceptable salts thereof.

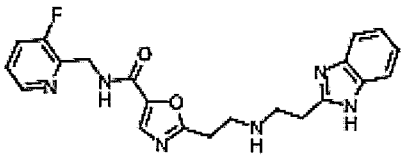
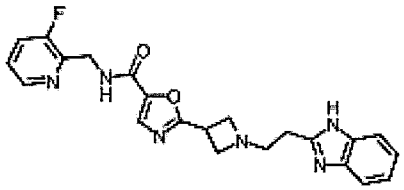
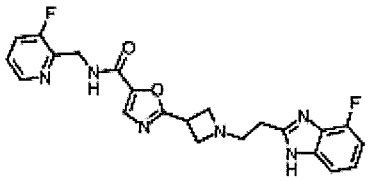
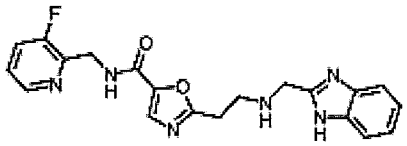
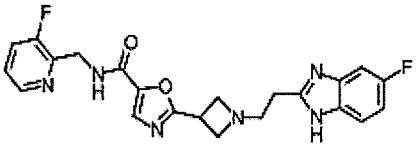
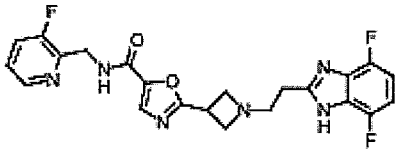
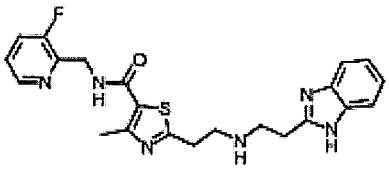
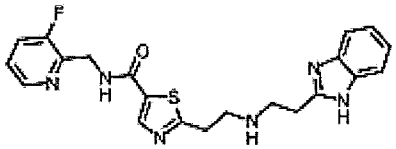
13. Compounds according to any one of the preceding claims, wherein
A^1 and A^2 are optionally substituted alkanediyl and are the same or different and are independently selected from optionally substituted

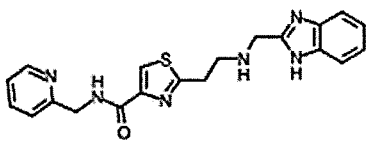
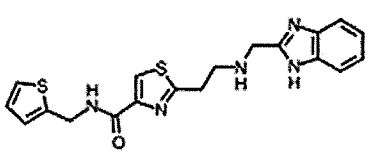
- methylene and
- ethane-1,2-diyl, or wherein

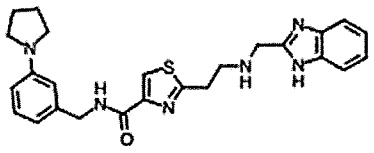
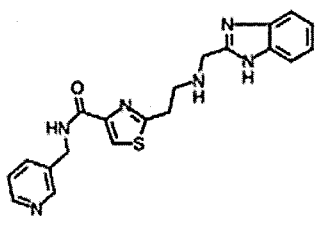
A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered aliphatic monocyclic ring;

or pharmaceutically acceptable salts thereof.

14. Compounds according to any one of the preceding claims, which are selected from

Exp. No.	Structure	Exp. No.	Structure
1		2	
3		4	
5		6	
7		8	

Exp No.	Compound
12	
16	

Exp No.	Compound
21	
35	

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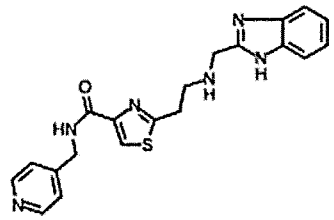
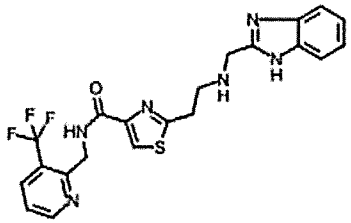
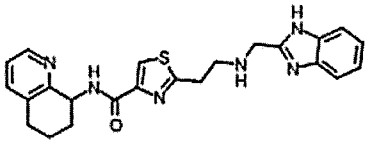
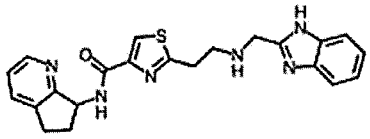
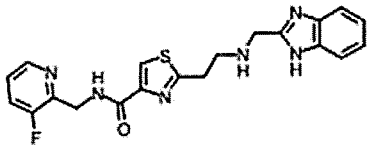
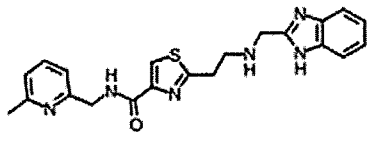
36	
37	
38	
39	
40	
42	

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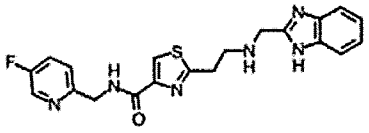
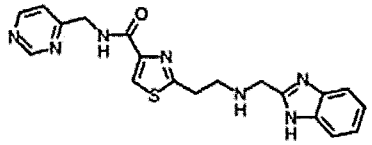
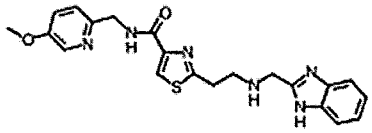
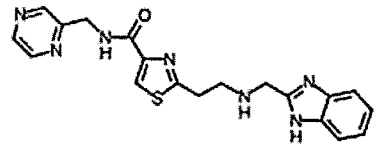
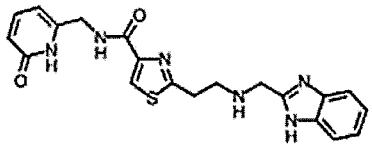
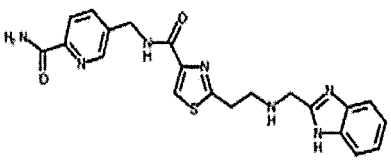
43	
44	
45	
46	
47	
54	

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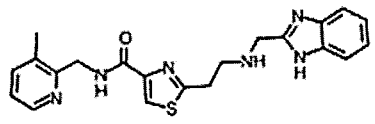
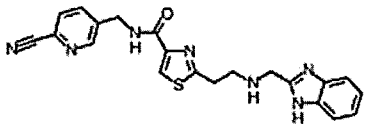
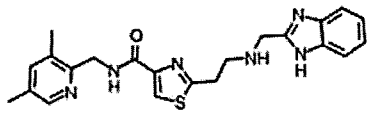
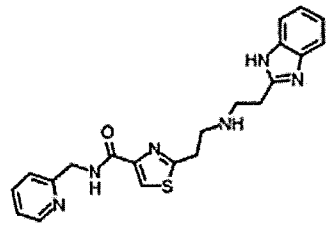
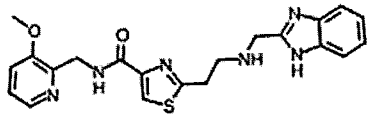
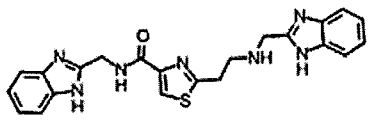
55	
56	
57	
58	
59	
60	

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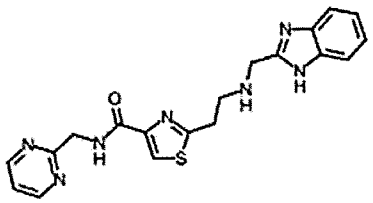
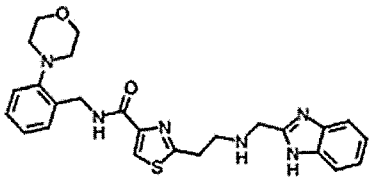
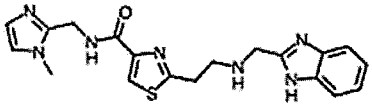
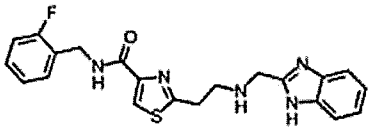
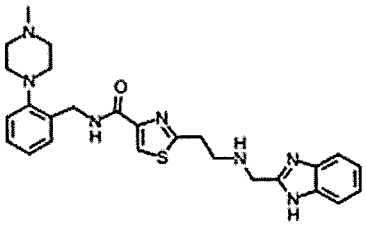
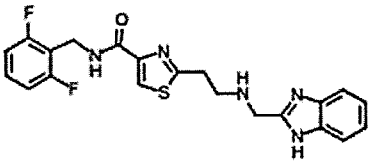
61	
63	
64	
65	
68	
69	

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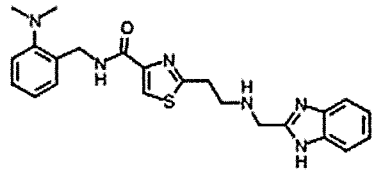
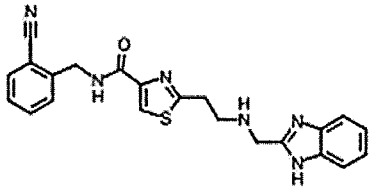
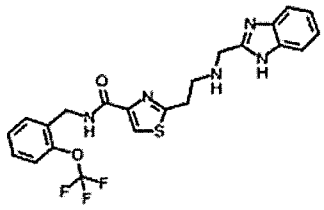
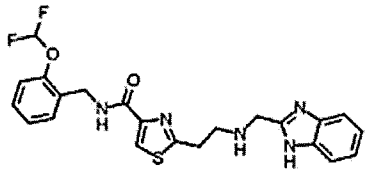
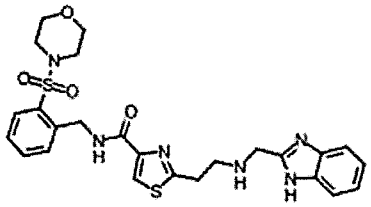
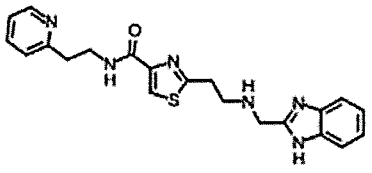
70	
71	
72	
74	
75	
76	

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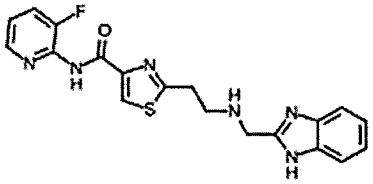
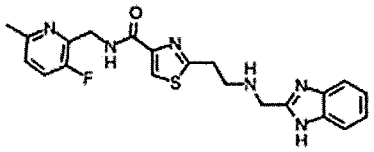
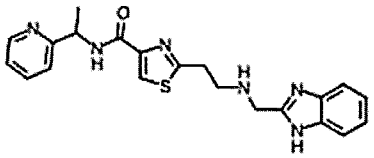
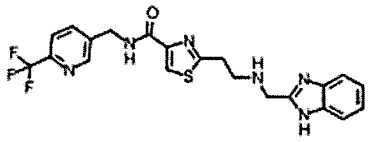
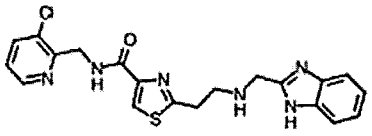
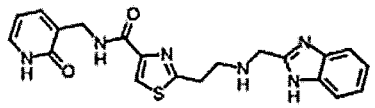
77	
79	
80	
81	
82	
83	

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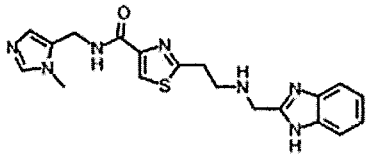
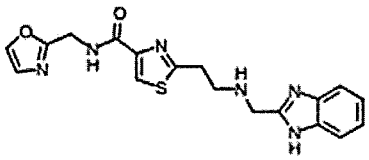
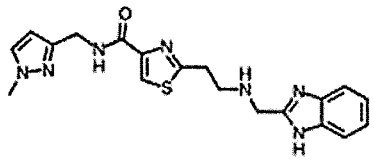
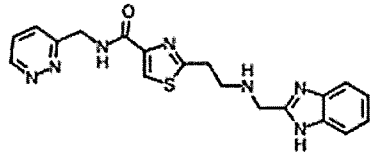
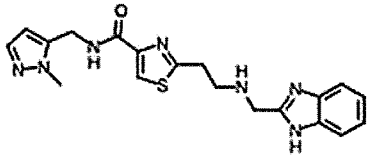
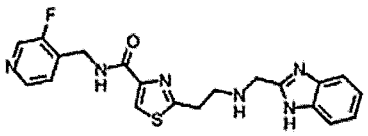
84	
85	
86	
87	
88	
89	

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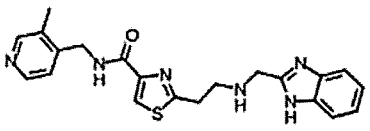
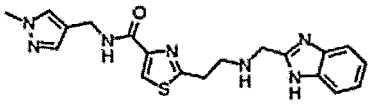
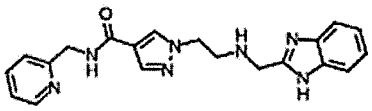
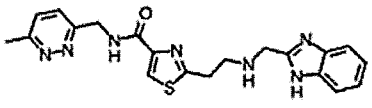
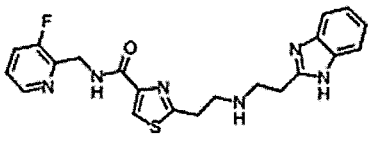
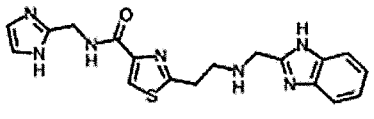
90	
91	
92	
93	
94	
95	

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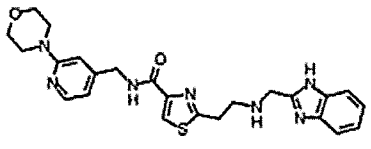
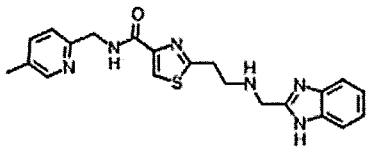
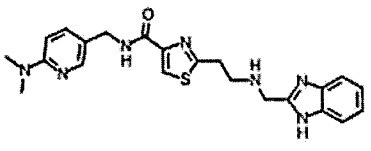
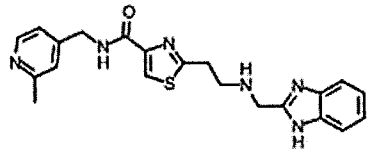
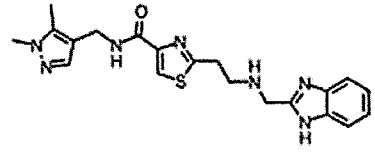
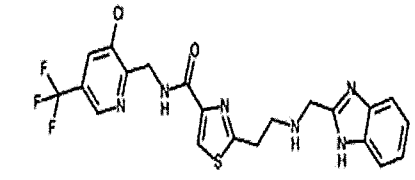
96	
97	
98	
99	
100	
101	

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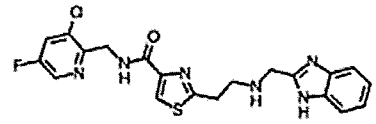
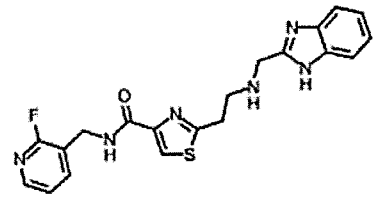
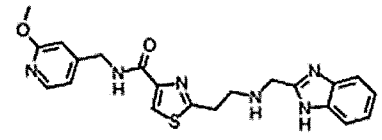
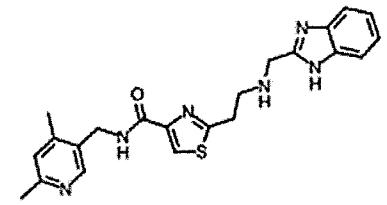
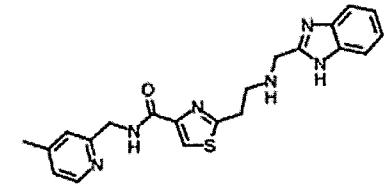
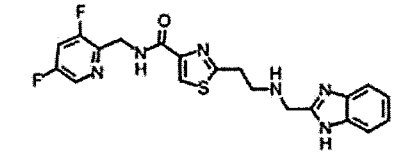
102	
103	
104	
105	
106	
108	

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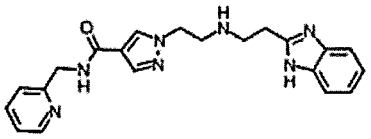
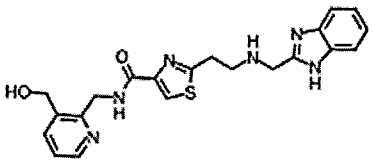
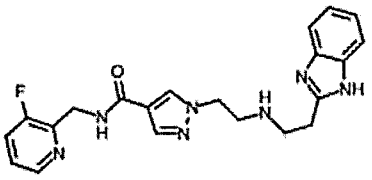
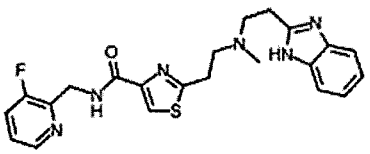
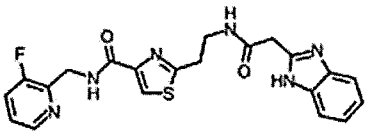
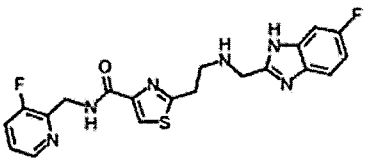
109	
110	
111	
112	
113	
114	

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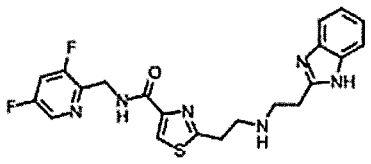
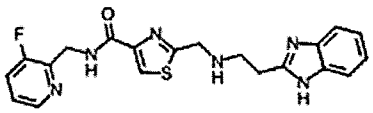
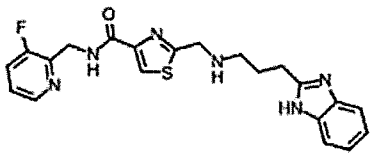
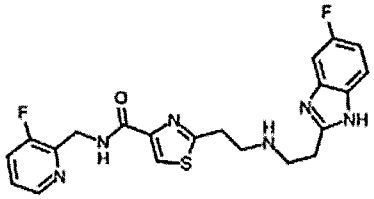
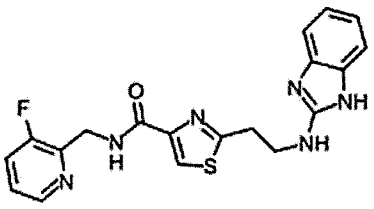
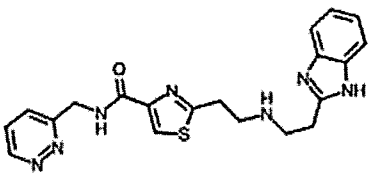
116	
118	
119	
120	
121	
122	

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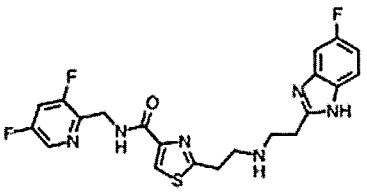
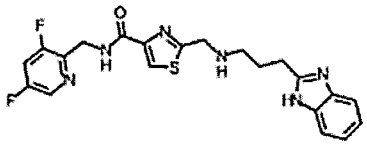
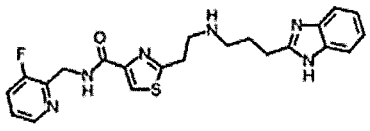
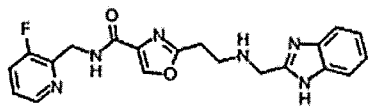
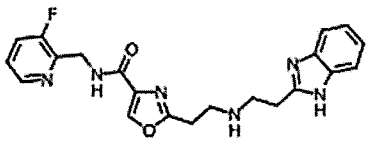
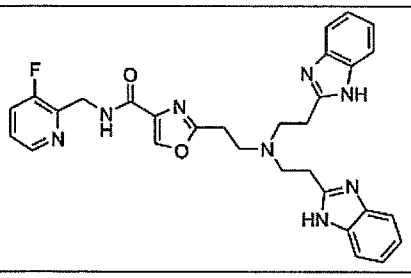
123	
124	
125	
126	
127	
128	

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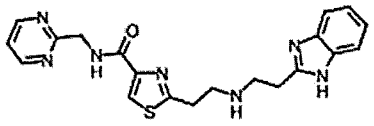
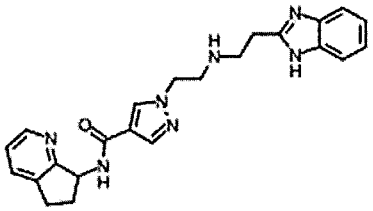
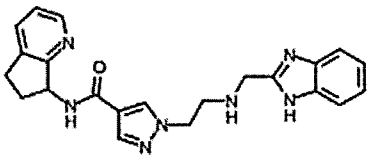
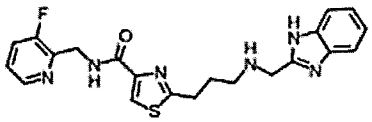
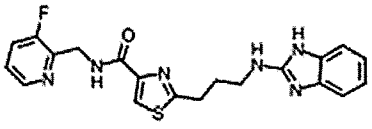
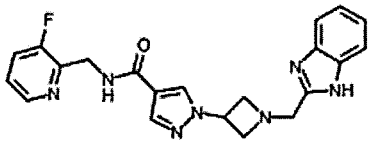
129	
131	
132	
134	
135	
136	

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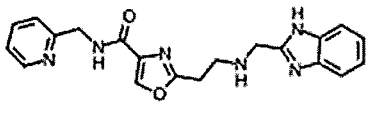
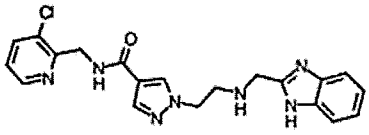
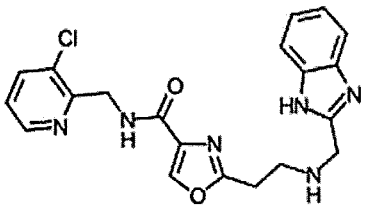
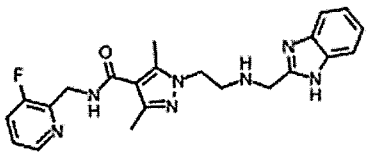
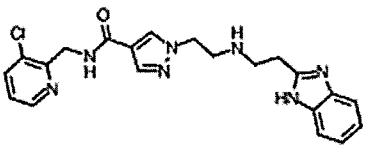
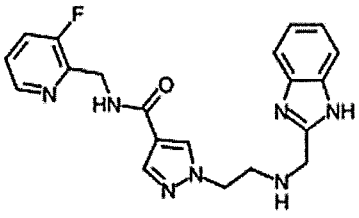
137	
138	
141	
142	
144	
145	

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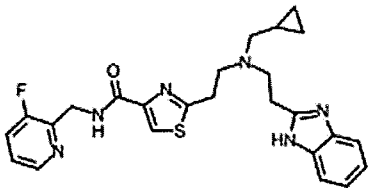
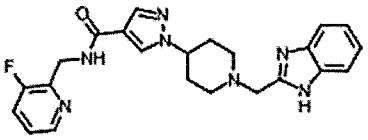
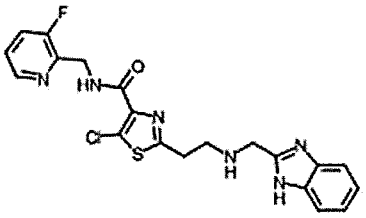
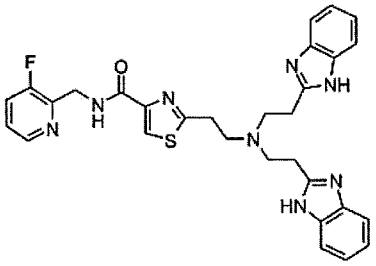
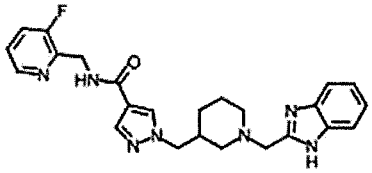
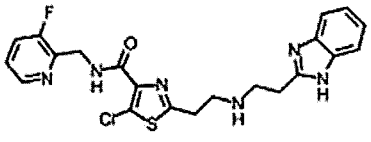
148	
150	
151	
152	
153	
154	

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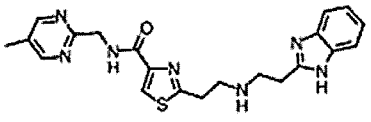
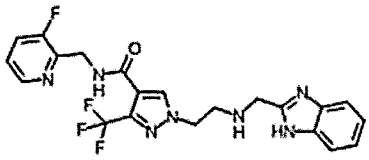
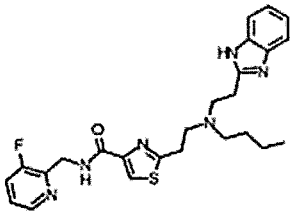
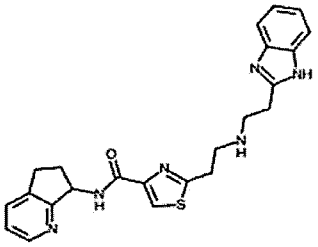
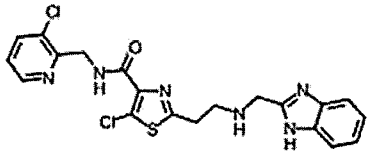
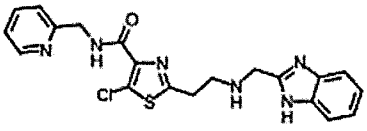
155	
156	
157	
158	
159	
160	

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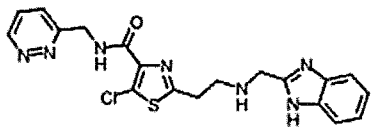
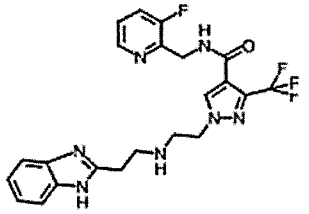
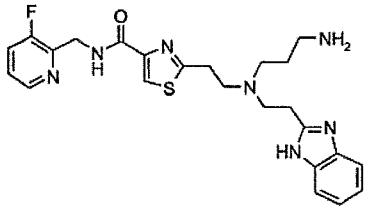
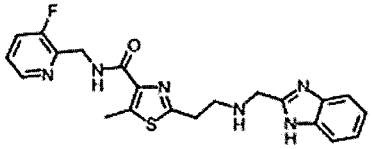
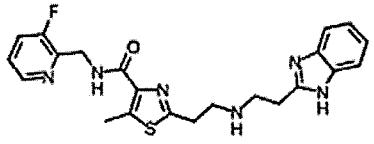
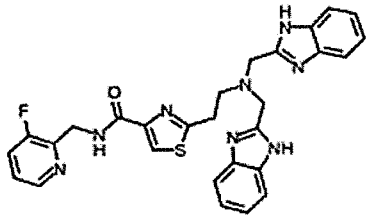
161	
162	
163	
164	
165	
166	

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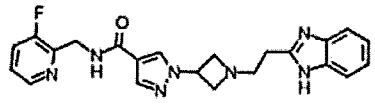
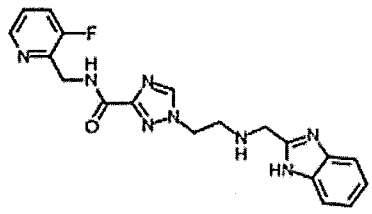
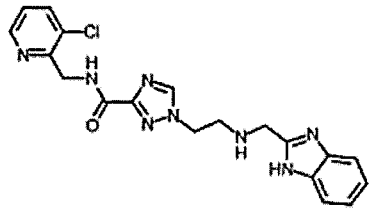
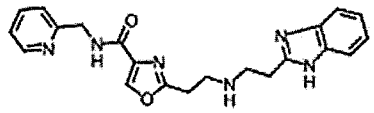
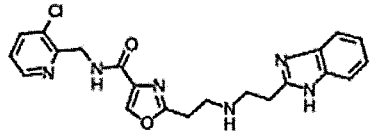
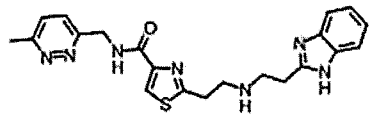
167	
169	
170	
171	
173	
174	

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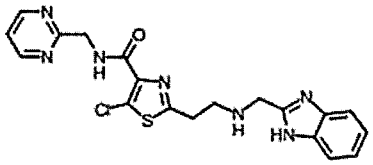
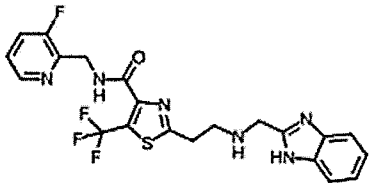
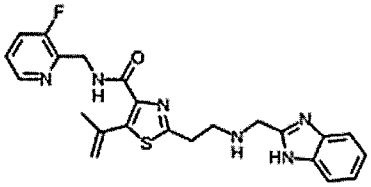
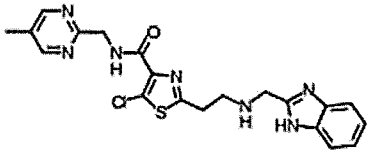
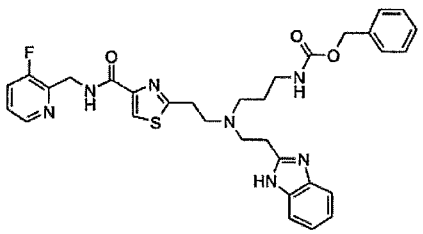
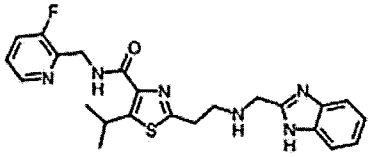
175	
176	
177	
178	
179	
180	

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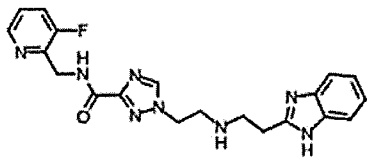
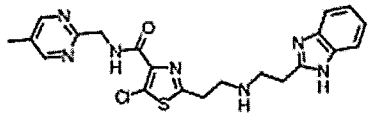
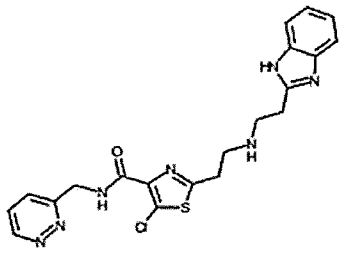
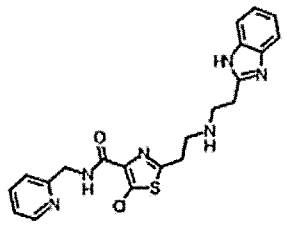
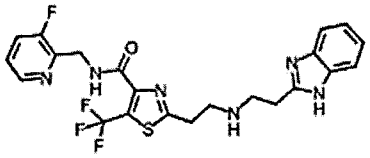
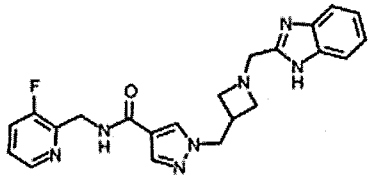
181	
182	
183	
184	
186	
187	

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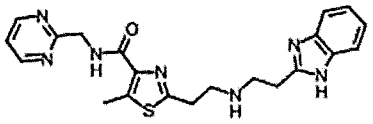
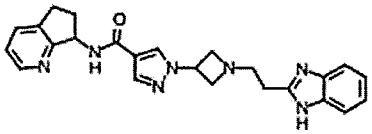
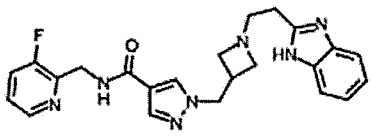
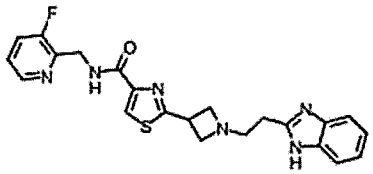
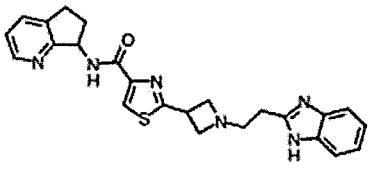
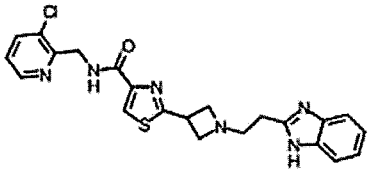
188	
191	
192	
193	
194	
195	

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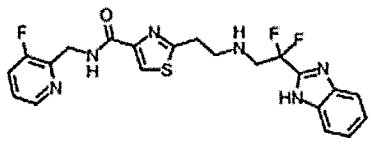
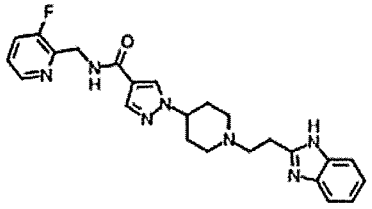
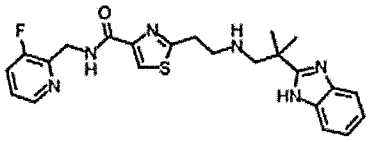
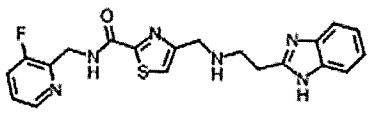
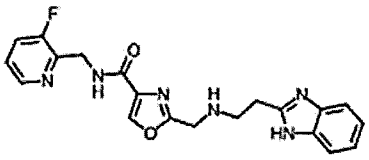
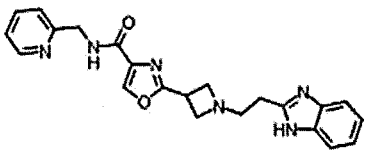
196	
198	
199	
205	
206	
207	

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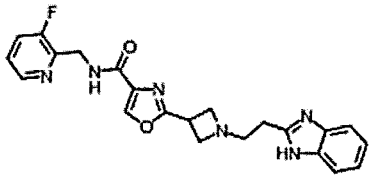
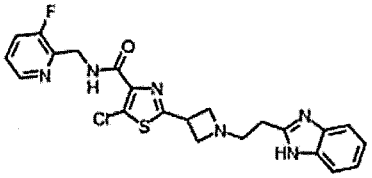
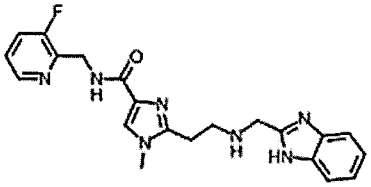
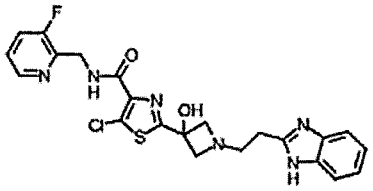
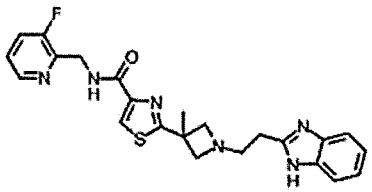
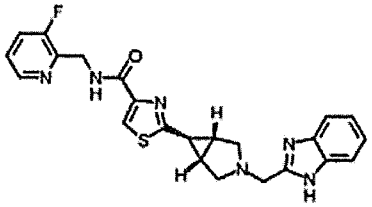
208	
209	
210	
211	
212	
213	

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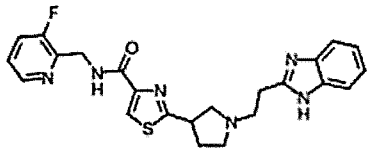
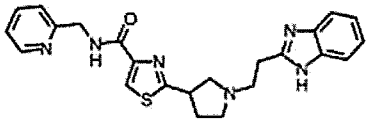
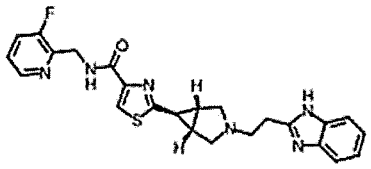
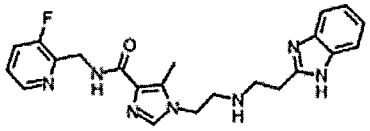
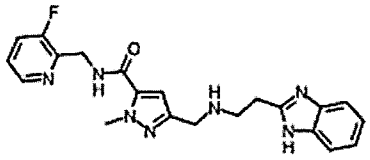
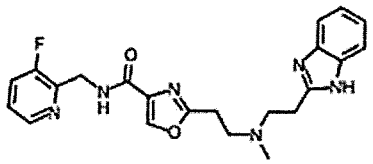
214	
215	
218	
219	
220	
223	

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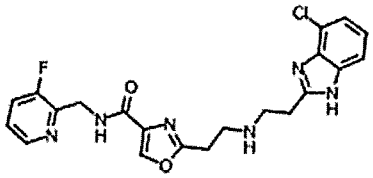
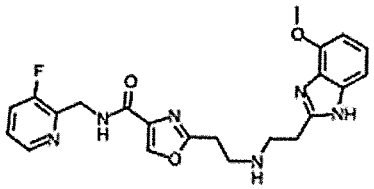
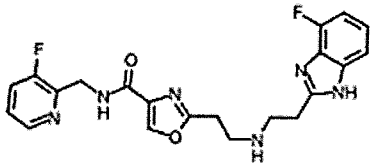
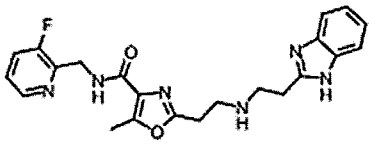
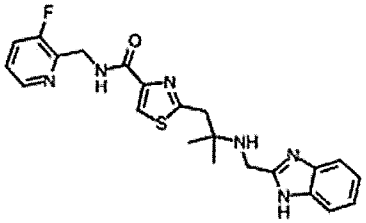
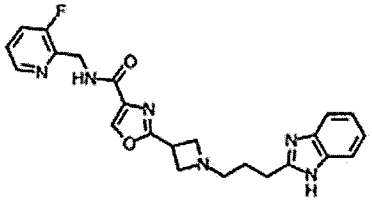
226	
227	
228	
230	
231	
233	

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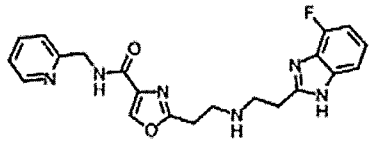
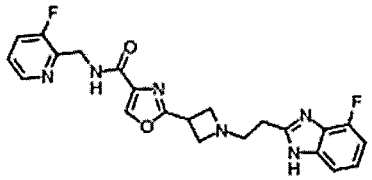
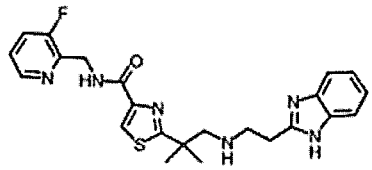
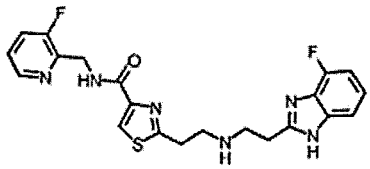
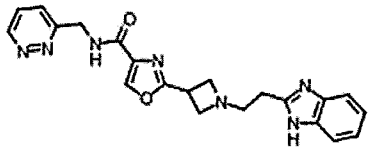
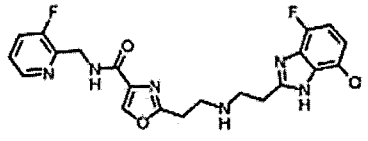
236	
239	
242	
243	
244	
247	

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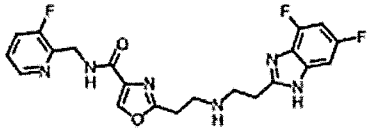
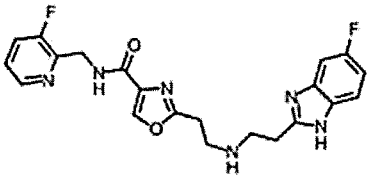
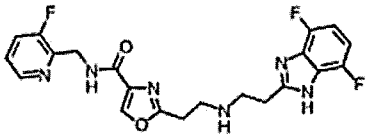
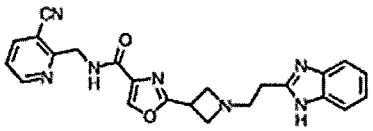
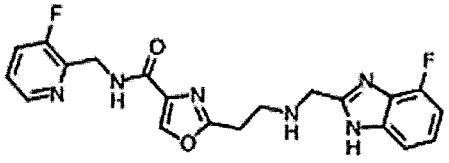
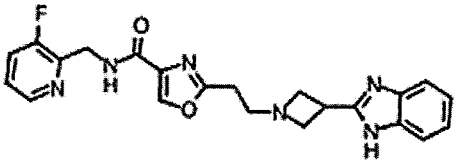
249	
250	
251	
252	
253	
255	

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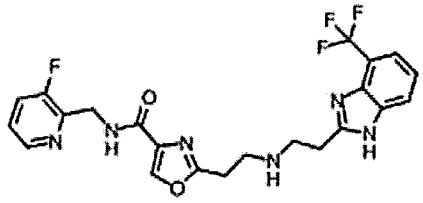
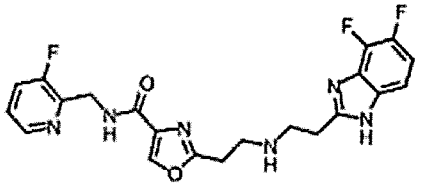
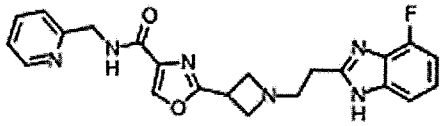
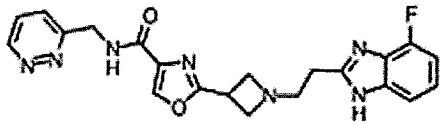
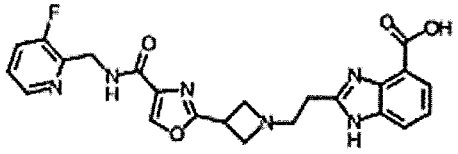
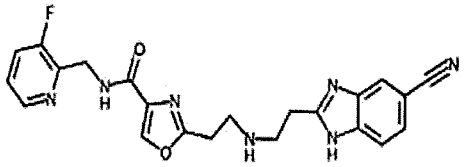
256	
257	
258	
261	
264	
265	

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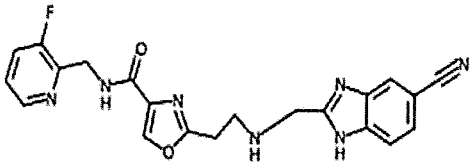
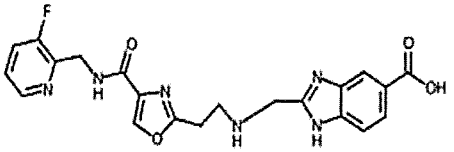
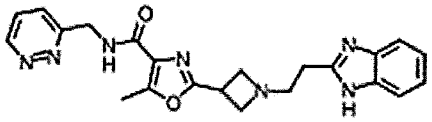
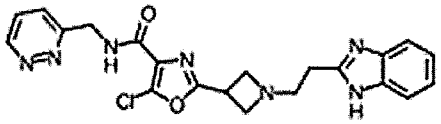
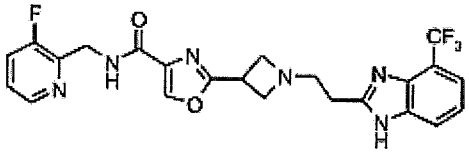
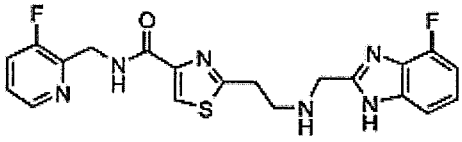
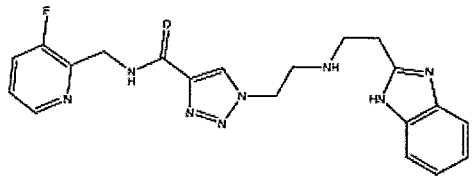
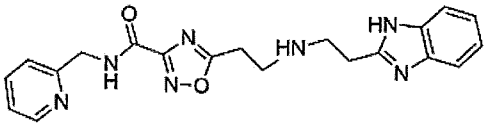
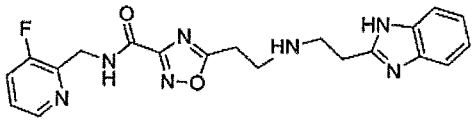
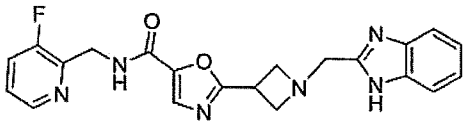
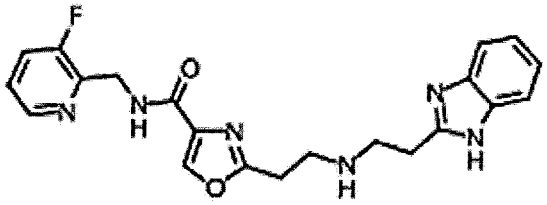
266	
267	
270	
271	
273	
274	

Exp No.	Compound
277	
278	

Exp No.	Compound
279	
280	

or pharmaceutically acceptable salts thereof.

15. Compounds according to any one of the preceding claims, having the formula



or pharmaceutically acceptable salts thereof.

16. Compounds according to any one of the preceding claims for use as a medicament.

17. Use of compounds according to any one of claims 1-15 in the manufacture of a medicament acting as ferroportin inhibitor.

18. Use of compounds according to any one of claims 1-15 in the manufacture of a medicament for the prophylaxis and/or treatment of iron metabolism disorders leading to increased iron levels or increased iron absorption, and/or iron overload.

19. Use of compounds according to any one of claims 1-15 in the manufacture of a medicament for the prophylaxis and/or treatment of diseases related to or caused by increased iron levels, increased iron absorption or iron overload, wherein said diseases are selected from thalassemia, including alpha-thalassemia, beta-thalassemia and delta-thalassemia, hemoglobinopathy, hemoglobin E disease, hemoglobin H disease, haemochromatosis, hemolytic anemia, including in particular sickle cell anemia or congenital dyserythropoietic anemia.

20. Use of compounds according to any one of claims 1-15 in the manufacture of a medicament for the prophylaxis and/or treatment of
diseases associated with ineffective erythropoiesis, wherein said diseases are selected from myelodysplastic syndromes (MDS, myelodysplasia), polycythemia vera and congenital dyserythropoietic anemia; and/or
infections caused by the pathogenic bacterium *Vibrio vulnificus*, in an adjunctive therapy by limiting the amount of iron available to said pathogenic bacterium *Vibrio vulnificus*; and/or
neurodegenerative diseases selected from Alzheimer's disease and Parkinson's disease by limiting the deposition or increase of iron in tissue or cells.

21. Use of compounds according to any one of claims 1-15 in the manufacture of a medicament for the prophylaxis and/or treatment of
diseases, cell, tissue and/or organ damage caused by formation of radicals, reactive oxygen species (ROS) and oxidative stress; and/or
cardiac, liver and endocrine damage caused by iron overload; and/or
inflammation triggered by excess iron.

22. A medicament containing one or more of the compounds according to any one of claims 1-15, which may further contain
one or more pharmaceutical carriers; and/or
auxiliaries; and/or
solvents; and/or
at least one additional pharmaceutically active compound, which is preferably selected from active compounds for the prophylaxis and treatment of iron overload, thalassemia, or haemochromatosis, active compounds for the prophylaxis and treatment of neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, and the associated symptoms, and iron-chelating compounds.

23. The medicament according to claim 22, wherein said medicament is to be administered orally or parenterally in the form of a formulation.

24. A medicament containing one or more of the compounds as defined in any one of claims 1-15 and at least one additional pharmaceutically active compound in a combination therapy composition for co-administration in the form of a fixed-dose formulation or in the form of a free dose combination of the respective components;
wherein the one or more other pharmaceutically active compounds are preferably active compounds for reducing iron overload, which are selected from Tmprss6-ASO, iron chelators, curcumin, SSP-004184, Deferitrin, deferasirox, deferoxamine and/or deferiprone; and/or pharmaceutically active compounds which are selected from antioxidants, such as n-acetyl cysteine; anti-diabetics, such as GLP-1 receptor agonists; antibiotics, such as vancomycin (Van) or tobramycin; drugs for the treatment of malaria; anticancer agents; antifungal drugs; drugs for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, comprising dopamine agonists such as Levodopa; anti-viral drugs, such as interferon-α or ribavirin; immunosuppressents, such as cyclosporine A or cyclosporine A derivatives; iron supplements; vitamin supplements; red cell production stimulators; anti-inflammatory biologies; anti-thrombolytics; statins; vasopressors; and inotropic compounds.