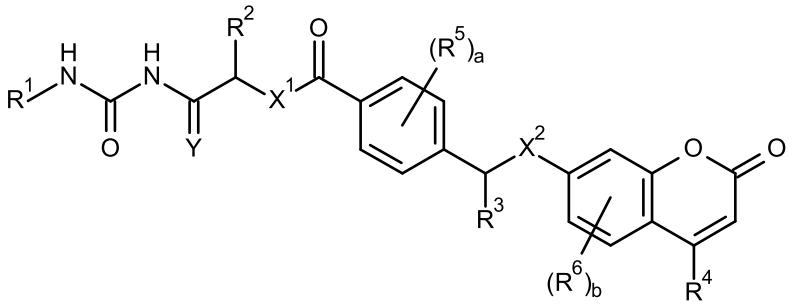
there is still a virtually unmet need in the art to provide compounds and methods for the treatment and/or the prophylaxis of muscle wasting conditions.

Brief Description of the Disclosure

The object of the present disclosure is to provide further small molecules that are suitable for use in the treatment and/or the prophylaxis of muscle wasting conditions or of conditions which can be attenuated by improving muscle conditions.

This object and further objects are achieved by the compounds of the general formula I described below and the pharmaceutically acceptable salts thereof:



(I)

wherein

R^1 is hydrogen or a group $-CH_2R^{1a}$, where R^{1a} is selected from the group consisting of hydrogen, C_1-C_3-alkyl, phenyl, where phenyl is unsubstituted or may carry 1, 2 or 3 radicals independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl and C_1-C_3-alkoxy; and a 5- to 10-membered heteroaromatic ring containing 1 to 4 heteroatoms or hetero-groups independently selected from the group consisting of N, NR^c, O and S as ring member(s), where the 5- to 10-membered heteroaromatic ring is unsubstituted or may carry 1, 2 or 3 radicals R^7;

R^2 is hydrogen, methyl or fluorinated methyl;

R^3 is hydrogen, methyl or fluorinated methyl;

R^4 is hydrogen or C_1-C_4-alkyl;

each R^5 is independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy and C_1-C_3-haloalkoxy;

each R^6 is independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy and C_1-C_3-haloalkoxy;

each R^7 is independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy and C_1-C_3-haloalkoxy;

X^1 is NR^a or O;

X^2 is NR^b, O or S;

Y represents an oxygen atom (so that C=Y is C=O) or two hydrogen atoms (so that C=Y is CH_2);

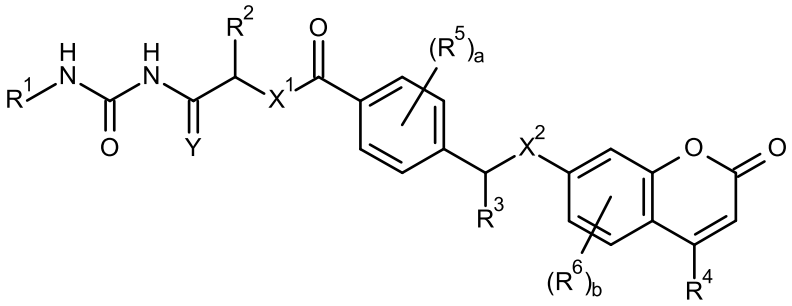
R^a, R^b, R^c are each independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;

a is 0, 1, 2, 3 or 4; and

b is 0, 1, 2 or 3.

The present disclosure therefore relates to the compounds of the general formula I and the pharmaceutically acceptable salts of the compounds of formula I.

In an aspect, the present disclosure relates to a compound of the general formula I



(I)

wherein

R^1 is hydrogen or a group $-CH_2R^{1a}$, where R^{1a} is selected from the group consisting of hydrogen, C_1-C_3-alkyl, phenyl, where phenyl is unsubstituted

or may carry 1, 2 or 3 radicals independently selected from halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl and C_1-C_3-alkoxy; and a 5- to 10-membered heteroaromatic ring containing 1 to 4 heteroatoms or hetero-groups independently selected from the group consisting of N, NR^c, O and S as ring member, where the 5- to 10-membered heteroaromatic ring is unsubstituted or may carry 1, 2 or 3 radicals R^7;

R^2 is selected from the group consisting of hydrogen, methyl and fluorinated methyl;

R^3 is selected from the group consisting of hydrogen, methyl and fluorinated methyl;

R^4 is selected from the group consisting of hydrogen and C_1-C_4-alkyl;

each R^5 is independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy and C_1-C_3-haloalkoxy;

each R^6 is independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy and C_1-C_3-haloalkoxy;

each R^7 is independently selected from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy and C_1-C_3-haloalkoxy;

X^1 is NR^a or O;

X^2 is NR^b, O or S;

Y represents an oxygen atom or two hydrogen atoms;

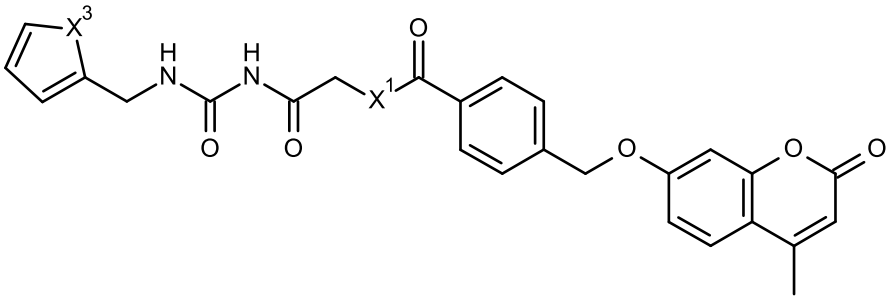
R^a, R^b, R^c are each independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;

a is 0, 1, 2, 3 or 4; and

b is 0, 1, 2 or 3;

and the pharmaceutically acceptable salts thereof.

In another aspect, the present disclosure relates to a compound of formula I as defined above, which corresponds to the formula I-A,



(I-A)

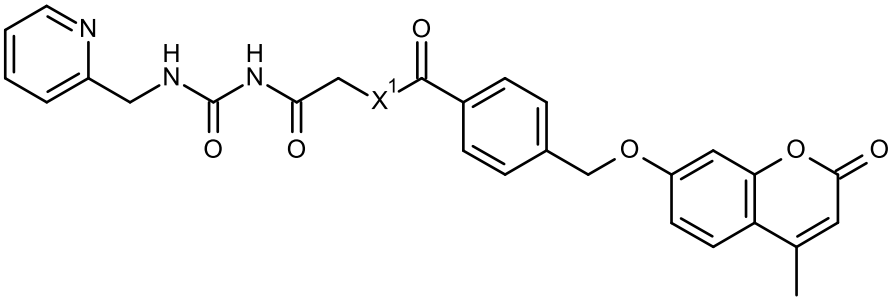
wherein

X^1 is NH or O; and

X^3 is O or S;

and the pharmaceutically acceptable salts thereof,

or to the formula I-B,



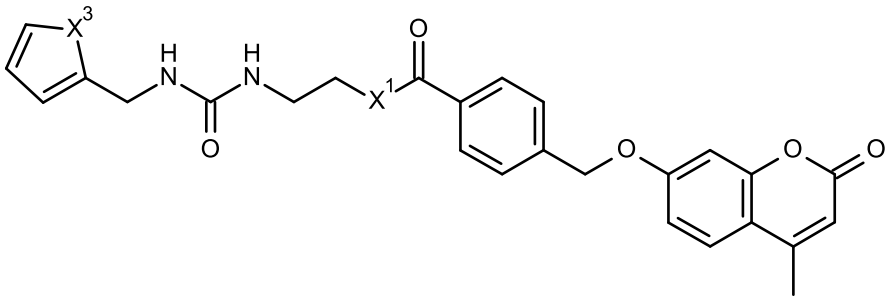
(I-B)

wherein

X^1 is NH or O;

and the pharmaceutically acceptable salts thereof,

or to the formula I-C,



(I-C)

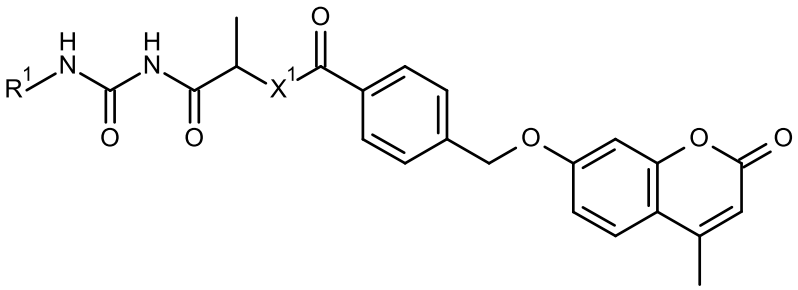
wherein

X^1 is NH or O; and

X^3 is O or S;

and the pharmaceutically acceptable salts thereof,

or to the formula I-D,



(I-D)

wherein

R^1 is hydrogen or methyl; and

X^1 is NH or O;

and the pharmaceutically acceptable salts thereof.

In yet another aspect, the present disclosure relates to the compound [2-(2-furylmethylcarbamoylamino)-2-oxo-ethyl] 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]benzoate and its pharmaceutically acceptable salts.

In yet another aspect, the present disclosure relates to the compound 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]-N-[2-(2-thienylmethylcarbamoylamino)ethyl]benzamide and its pharmaceutically acceptable salts.

In yet another aspect, the present disclosure relates to the compound [2-oxo-2-(2-pyridylmethylcarbamoylamino)ethyl] 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]benzoate and its pharmaceutically acceptable salts.

In yet another aspect, the present disclosure relates to a compound of formula I as defined above, which is selected from N-[2-(2-furylmethylcarbamoylamino)-2-oxo-ethyl]-4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]benzamide, [2-oxo-2-(2-thienylmethylcarbamoylamino)ethyl] 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]-benzoate, and 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]-N-[2-oxo-2-(2-thienylmethylcarbamoylamino)ethyl]-benzamide, and the pharmaceutically acceptable salts thereof.

In yet another aspect, the present disclosure relates to a compound of formula I as defined above, which is selected from (1-methyl-2-oxo-2-ureido-ethyl) 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]benzoate and [1-methyl-2-(methylcarbamoylamino)-2-oxo-ethyl] 4-[(4-methyl-2-oxo-chromen-7-yl)oxymethyl]benzoate, and the pharmaceutically acceptable salts thereof.

In yet another aspect, the present disclosure relates to a pharmaceutical composition comprising at least one compound of the general formula I as defined

above or at least one pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

Given the pharmacological properties of the compounds I, the present disclosure also relates to the compounds of the general formula I or the pharmaceutically acceptable salts thereof for use as a medicament.

In yet another aspect, the present disclosure relates to the compound as defined above or a pharmaceutically acceptable salt thereof, for use as a medicament.

It was found that the novel compounds are capable of attenuate muscle wasting and contractile dysfunction in cell tests as well as in clinically relevant animal models.

The present disclosure therefore relates to the compounds of the general formula I or the pharmaceutically acceptable salts of the compounds of formula I for use in the treatment or prophylaxis of muscle wasting conditions.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of muscle wasting conditions.

The present disclosure relates in particular to the compounds of the general formula I or the pharmaceutically acceptable salts of the compounds of formula I for use in the treatment or prophylaxis of skeletal or cardiac muscle atrophy resulting from one of the following diseases or conditions: congestive heart failure, chronic heart failure, cancer, cancer treatment with myotoxic substances, congenital myopathy, AIDS, chronic obstructive pulmonary disease (COPD), chronic renal diseases, renal failure, diabetes, severe burns, sarcopenia during aging, reduction in blood supply, temporary or long term immobilization, long term mechanical ventilation, denervation, prolonged weightlessness and malnutrition.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of skeletal or cardiac muscle atrophy resulting from one of the following diseases or conditions: congestive heart failure, chronic heart failure, cancer, cancer treatment with myotoxic and/or cardiotoxic substances such as doxorubicin, congenital myopathy, AIDS, chronic obstructive pulmonary disease (COPD), chronic renal diseases, renal failure, diabetes, severe burns, sarcopenia during aging, reduction in blood supply, temporary or long term immobilization, long term mechanical ventilation, denervation, prolonged weightlessness and malnutrition.

Furthermore, the compounds of the present disclosure are potent inhibitors of MuRF1 function by inhibiting the ubiquitin E3 ligase activity of MuRF1 and the binding of MuRF1 to target muscle proteins, such as titin. Thus, the present disclosure further relates to the compounds of the general formula I or the pharmaceutically acceptable salts of the compounds of formula I for use in the treatment or prophylaxis of conditions which are associated with an increased Muscle RING Finger 1 (MuRF1) expression, in particular of myopathies which are associated with an increased MuRF1 expression.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of conditions which are associated with an

increased Muscle RING Finger 1 (MuRF1) expression, in particular of myopathies which are associated with an increased Muscle RING Finger 1 (MuRF1) expression.

It was also found that the compounds of the general formula I have a beneficial effect in cardiac conditions associated with systolic or diastolic dysfunction which is not directly related to their effect on muscle conditions. The disclosure therefore also relates to the compound of the general formula I or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of cardiac conditions associated with systolic or diastolic dysfunction.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of cardiac conditions associated with systolic or diastolic dysfunction.

It was also found that the compounds of the general formula I have a beneficial effect in diabetes. The disclosure therefore also relates to the compound of the general formula I or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of diabetes, especially diabetes type II.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diabetes.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of

- skeletal or cardiac muscle atrophy resulting from or associated with heart failure with reduced ejection fraction (HF-rEF), heart failure with preserved ejection fraction (HF-pEF), hypertension or tumor cachexia;
- muscle atrophy and/or cardiac toxicity induced by Doxorubicin;
- sarcopenia and/or cardiomyopathy due to aging;
- muscle atrophy due to chronic renal disease;

- diaphragm weakness due to mechanical ventilation or congestive heart failure;
- congenital myopathy, in particular congenetic muscle atrophy;
- diabetes-induced muscle atrophy; and/or
- diabetes.

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The disclosure further relates to a medicament, comprising at least one compound of the formula I, as described herein, or at least one pharmaceutically acceptable salt of the compound of the formula I.

The disclosure further relates to a pharmaceutical composition comprising a compound selected from compounds of the general formula I, as described herein, or at least one pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

The disclosure further relates to the use of compounds selected from compounds of the general formula I, as defined herein, or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment or prophylaxis of muscle-wasting conditions; or for treatment or prophylaxis of the above-listed conditions or disorders.

The disclosure further relates to a method for treating or preventing one of the above-listed conditions or disorders, said method comprising the step of administering a compound selected from compounds of the general formula I, as defined herein, or a pharmaceutically acceptable salts thereof to a subject in need thereof.

In yet another aspect, the present disclosure relates to a use of a compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a condition, as defined above.

Detailed Description of the Invention

The terms "compound of the formula I" and "compounds I" are used as synonyms.

The term "pharmaceutically acceptable salts" refers to cationic or anionic salts compounds, wherein the counter ion is derived from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids.

It will be understood that, as used herein, references to the compounds of formula I are meant to also include the pharmaceutically acceptable salts.

If the compounds of formula I are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such