

**OXO-PYRIDINE DERIVATIVES AS INHIBITORS OF TRANSGLUTAMINASES
FOR USE IN THE TREATMENT OF PULMONARY FIBROSIS**

5 The invention relates to specifically selected inhibitors of transglutaminase 2 (TG2) useful for the treatment of pulmonary inflammation, pulmonary fibrosis, in particular idiopathic pulmonary fibrosis.

Background of the invention

10 Transglutaminases are part of the class of transferases and according to EC nomenclature they are correctly designated as "protein-glutamine: amine γ -glutamyl transferases" (EC 2.3.2.13). They link the ϵ -amino group of the amino acid lysine and the γ -glutamyl group of the amino acid glutamine forming an isopeptide bond while ammonia is released. In the absence of suitable amines and/or under certain conditions, deamidation of the glutamine may occur resulting in the corresponding glutamic acid.

15 Additionally, transglutaminases play an important role in many therapeutic areas such as the cardiovascular diseases (thrombosis and atherosclerosis), autoimmune diseases (celiac disease, Dühring-Brocq-disease, gluten ataxia), neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease), dermatological diseases (ichthyosis, psoriasis, acne) as well as in wound healing and inflammatory diseases (e.g. tissue fibrosis) (J.M. Wodzinska, Mini-Reviews in medical chemistry, 2005, 5, 279 - 292).

25 In the state of the art it was assumed that transglutaminase inhibitors might have a potential to treat fibrotic disorders. Fibrotic disorders are characterized by the accumulation of cross-linked extracellular matrix proteins. Diabetic nephropathy, cystic fibrosis, idiopathic pulmonary fibrosis, kidney fibrosis as well as liver fibrosis belong to the most important fibrotic disorders.

30 The objective of the present invention is to identify transglutaminase inhibitors which are suitable for the treatment of pulmonary inflammation and pulmonary fibrosis and in particular idiopathic pulmonary fibrosis (IPF).

35 Surprisingly, it was found that only a small group of transglutaminase inhibitors is actually suitable for the treatment of pulmonary inflammation and pulmonary fibrosis and in particular idiopathic pulmonary fibrosis.

Thus, the objective underlying the present invention is solved by the technical teachings of the independent claims. Further advantageous embodiments, aspects and details of

the invention are evident from the dependent claims, the description, the examples and the figures.

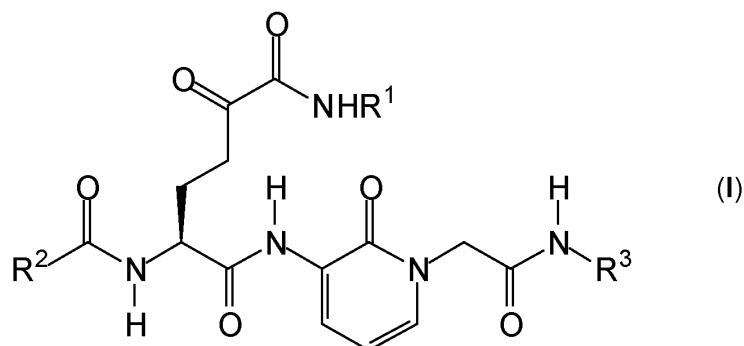
Surprisingly, it has been found that a small group of known reversible inhibitors of tissue transglutaminase 2 (TG2) with specific substitution pattern is effective in the treatment of pulmonary inflammation and pulmonary fibrosis and in particular IPF while other compounds of the same inhibitor family failed although they were expected to be highly active in the treatment of pulmonary inflammation and pulmonary fibrosis and in particular IPF.

This is actually a quite surprising result, since the chemical structures of the active compounds and the inactive compounds are considerable similar so that a skilled person could not expect that not all of the compounds of the patent publication WO 2023/275337 A1 would be suitable for the treatment of pulmonary inflammation and pulmonary fibrosis and in particular IPF.

Consequently, the group of TG inhibitors disclosed herein is a very specific selection of the compounds disclosed in WO 2023/275337 A1. This selected group of compounds is highly active in the treatment of treatment of pulmonary inflammation and pulmonary fibrosis and in particular IPF due to their specific substitution pattern and substituents while other substituents and substitution pattern disclosed in WO 2023/275337 A1 failed as demonstrated by comparative data.

The suitability of the selected compounds in the treatment of pulmonary inflammation and pulmonary fibrosis and in particular IPF was proven by a mouse model which is described in the experimental part in detail.

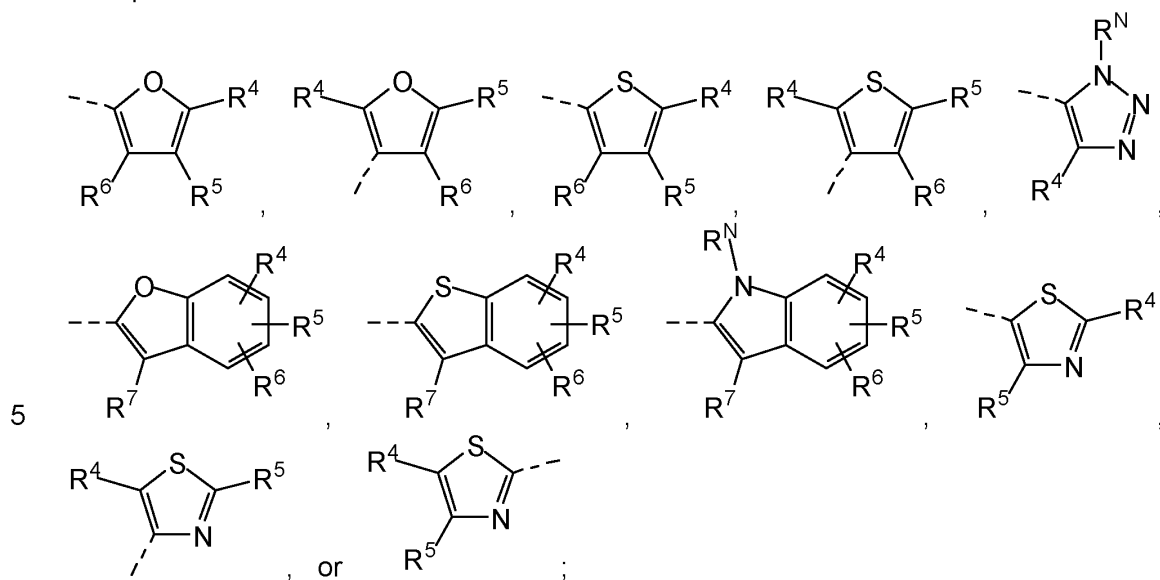
Thus, the present invention relates to the use of a group of selected compounds of the general formula (I):



wherein

R¹ represents $-H$ or $-CH_3$;

R² represents



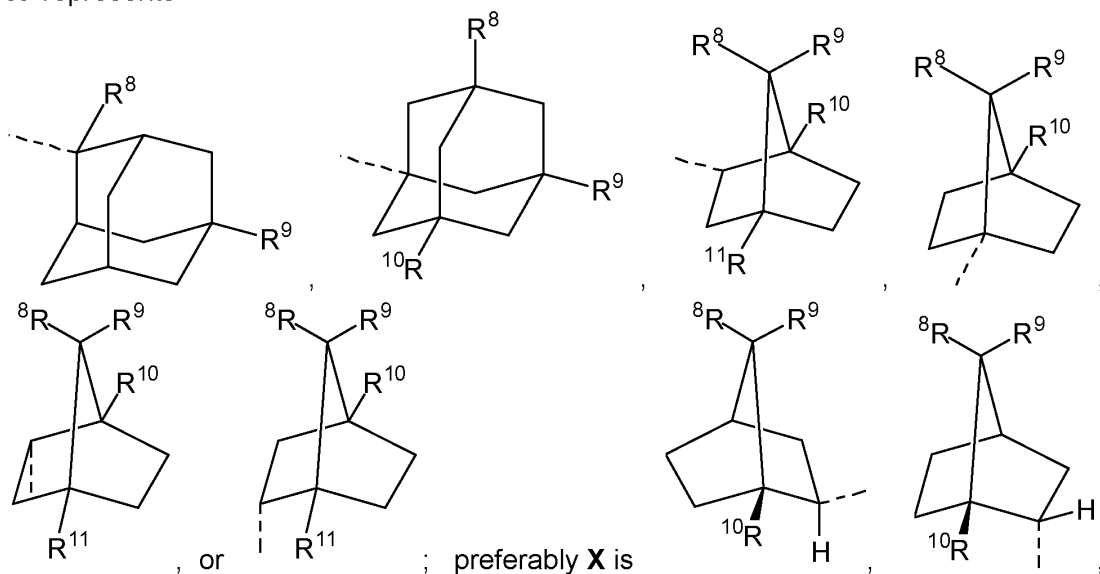
R³ represents $-X$ or $-CH_2-X$;

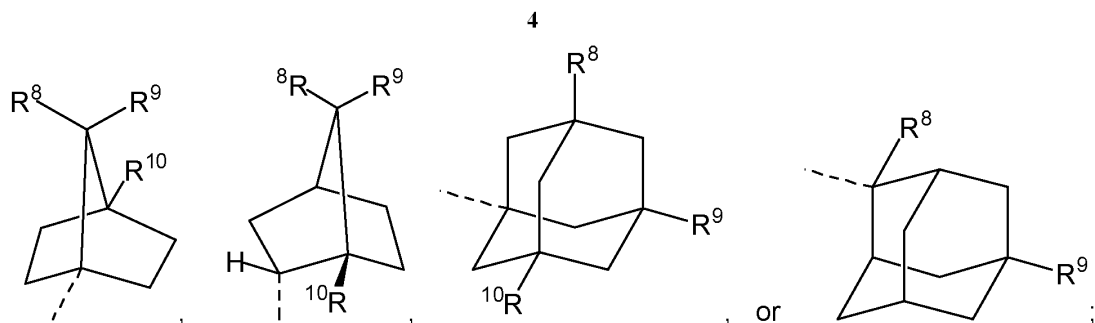
10 **R⁴**, **R⁵**, **R⁶** and **R⁷** represent independently of each other $-H$, $-F$, $-Cl$, $-Br$, $-CH_3$, or $-CF_3$;

R⁸, **R⁹**, **R¹⁰**, and **R¹¹** represent independently of each other $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-OH$, $-CH_3$, $-CF_3$, $-COCH_3$, $-CO_2CH_3$;

R^N represents $-H$ or $-CH_3$;

15 **X** represents

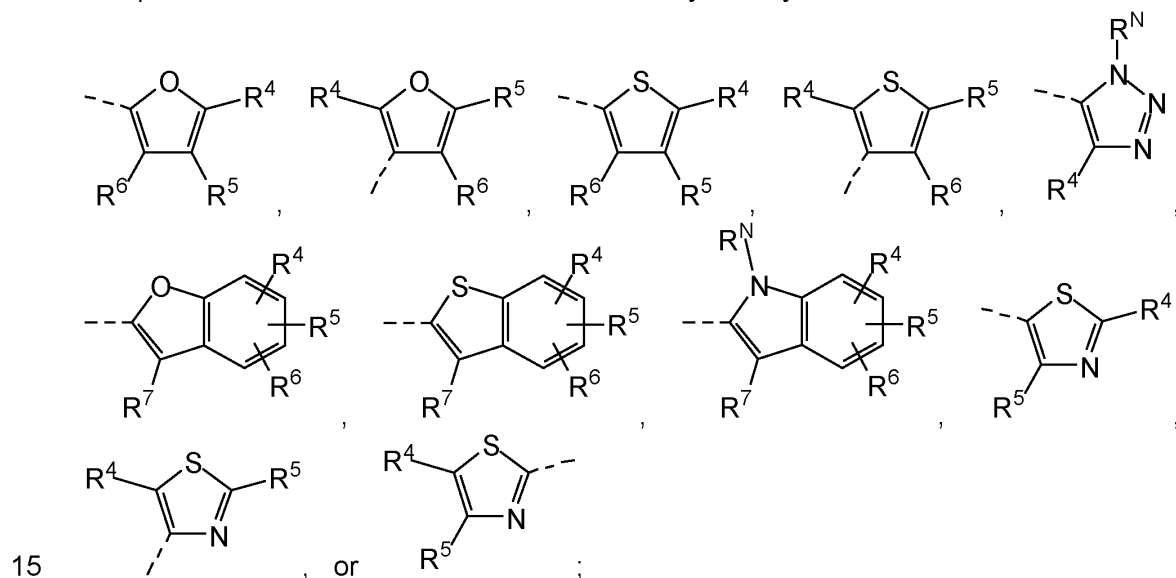




or a diastereomer, an enantiomer, a mixture of diastereomers, a mixture of enantiomers, a racemate, a solvate, a hydrate, or a pharmaceutically acceptable salt thereof in the treatment of pulmonary inflammation, pulmonary fibrosis, in particular idiopathic pulmonary fibrosis.

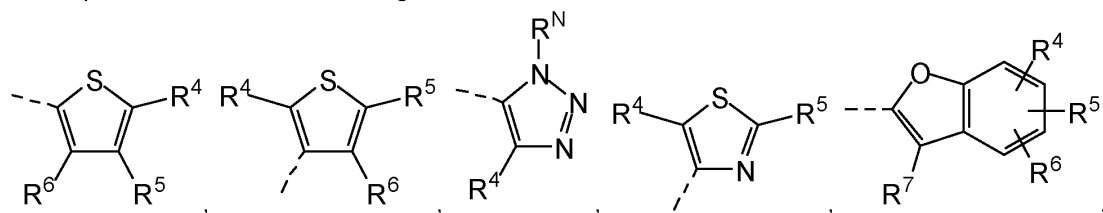
For the antifibrotic and anti-inflammatory activity especially the residue **R²** is highly important and the substituents on the residue **R²**.

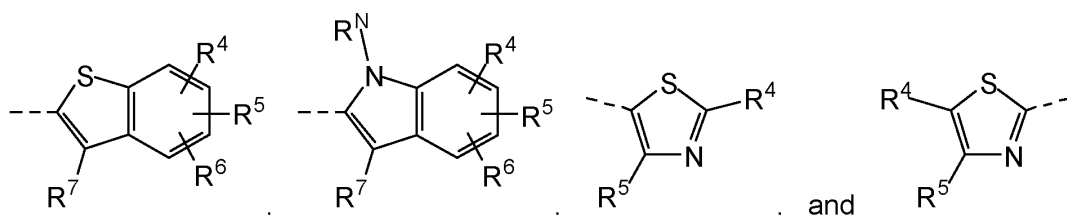
It was surprisingly found that of all the heterocyclic moieties disclose in WO 2023/275337 A1 only the following eleven moieties with specific substituents lead to compounds with antifibrotic and anti-inflammatory activity:



wherein **R⁴ – R⁷** and **R^N** have the meanings as disclosed herein.

More preferred are the following residues **R²**

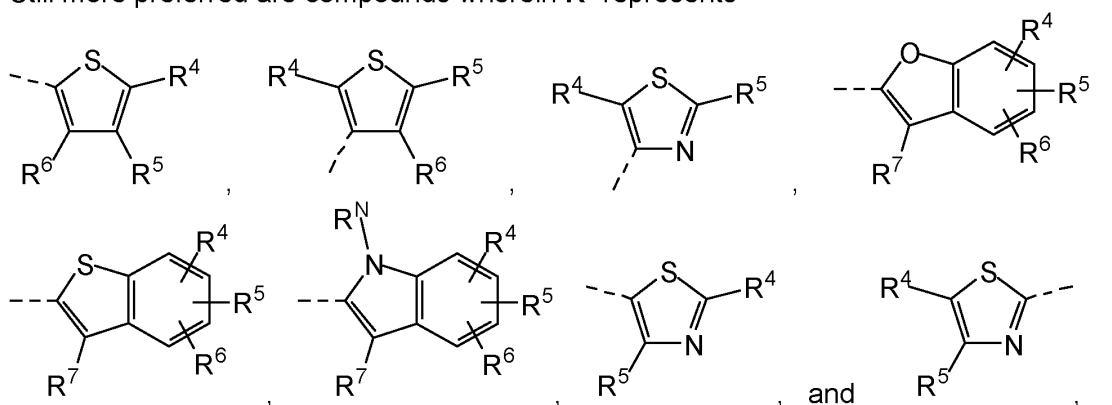




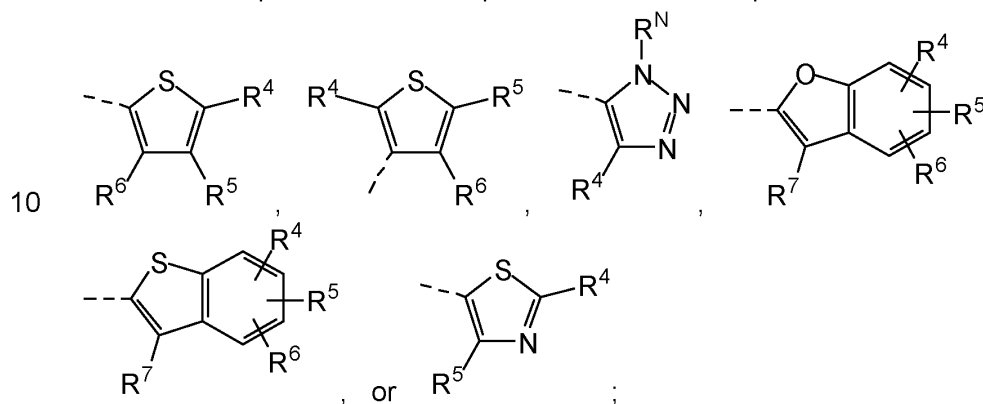
wherein $R^4 - R^7$ and R^N have the meanings as disclosed herein.

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Still more preferred are compounds wherein R^2 represents



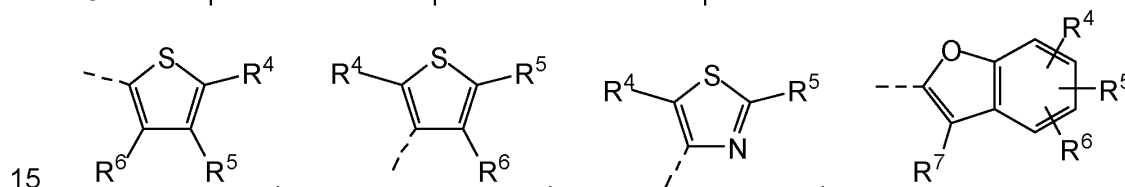
and still more preferred are compounds wherein R^2 represents



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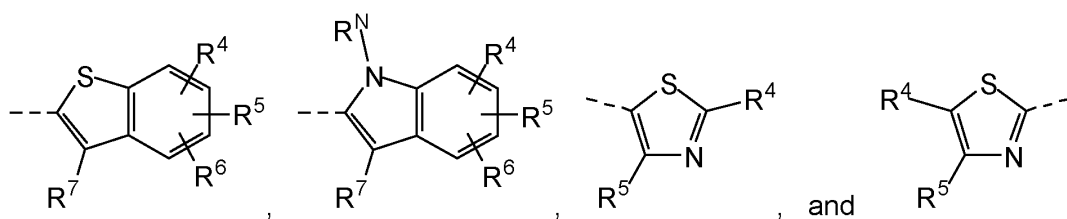
and $R^4 - R^7$ and R^N have the meanings as disclosed herein.

Still more preferred are compounds wherein R^2 represents

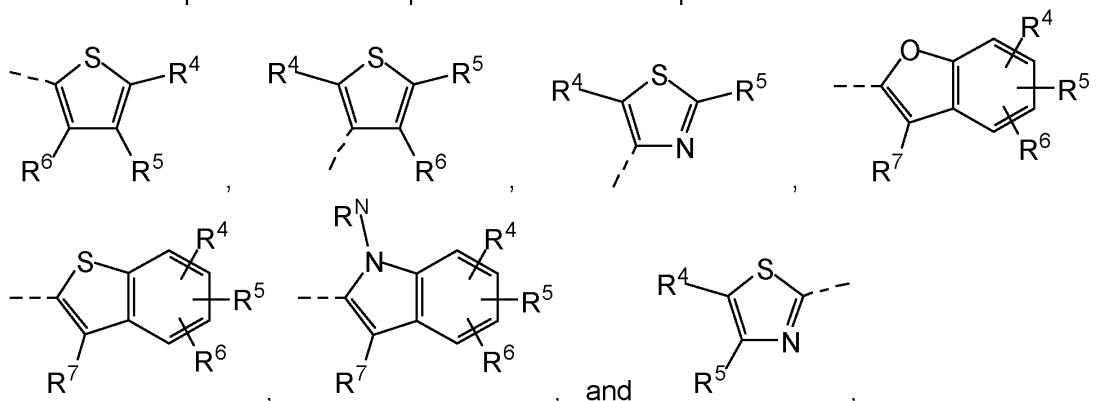


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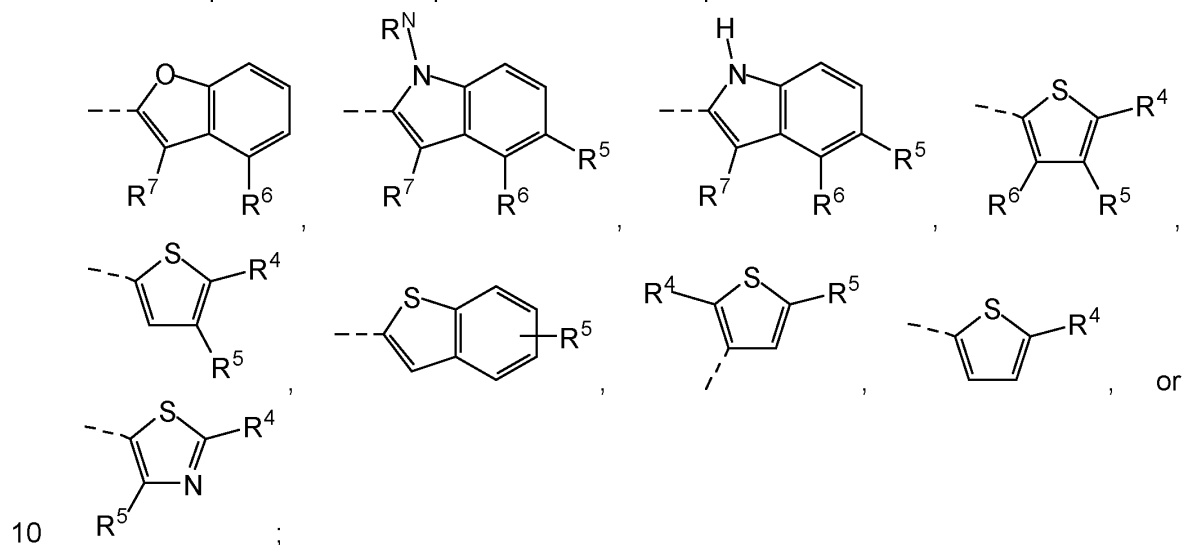


and still more preferred are compounds wherein R^2 represents



5 and $R^4 - R^7$ and R^N have the meanings as disclosed herein.

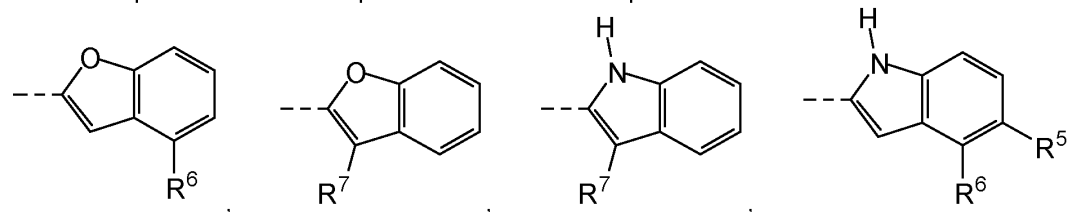
Still more preferred are compounds wherein R^2 represents



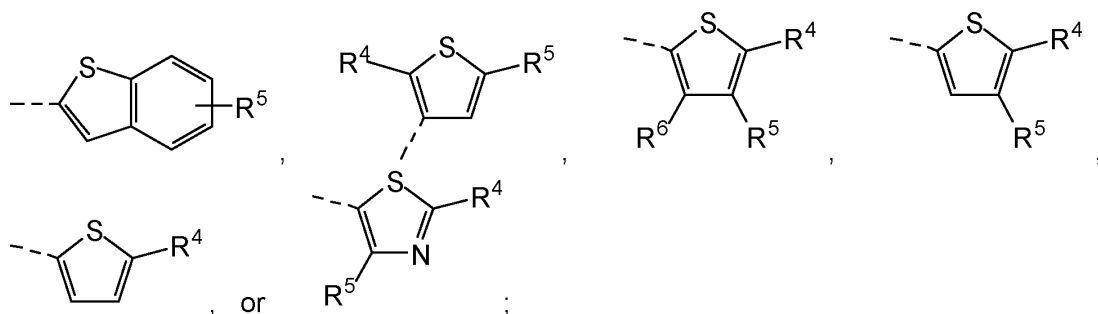
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and R^4 , R^5 , R^6 and R^7 have the meanings as disclosed herein and R^N is $-H$ or $-CH_3$.

Still more preferred are compounds wherein R^2 represents

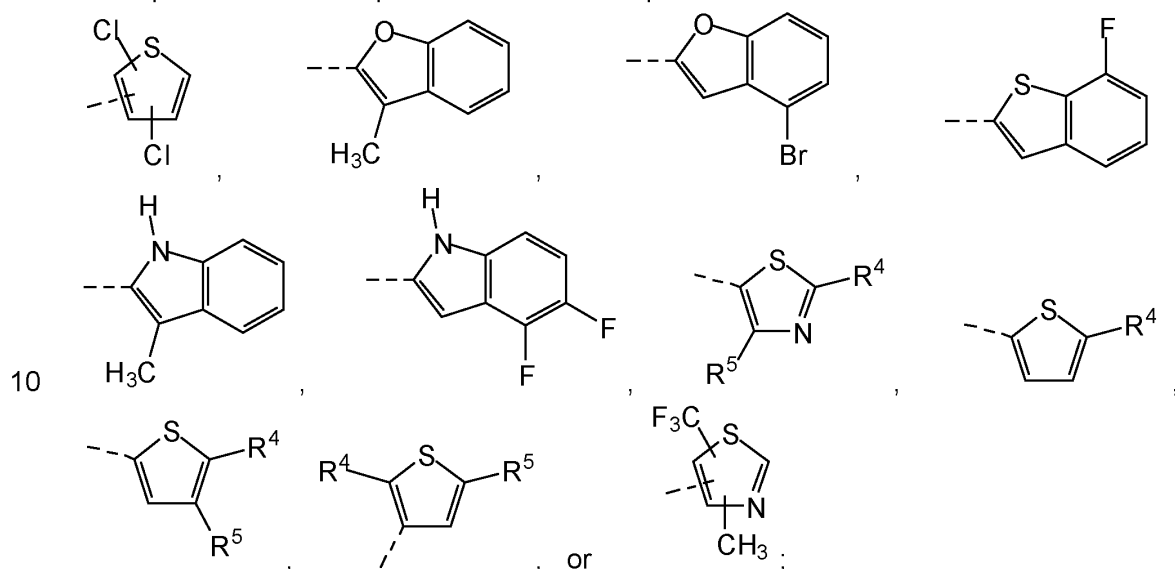


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- and R^4 , R^5 , R^6 and R^7 have the meanings as disclosed herein; and preferably R^4 , R^5 , R^6 represent independently of each other $-H$, $-F$, $-Cl$, $-Br$, $-CH_3$, or $-CF_3$, and most preferably $-H$, $-F$, $-Cl$, $-Br$, or $-CF_3$; and preferably R^7 represents $-H$, $-Cl$, or $-CH_3$, and most preferably R^7 represents $-H$ or $-CH_3$

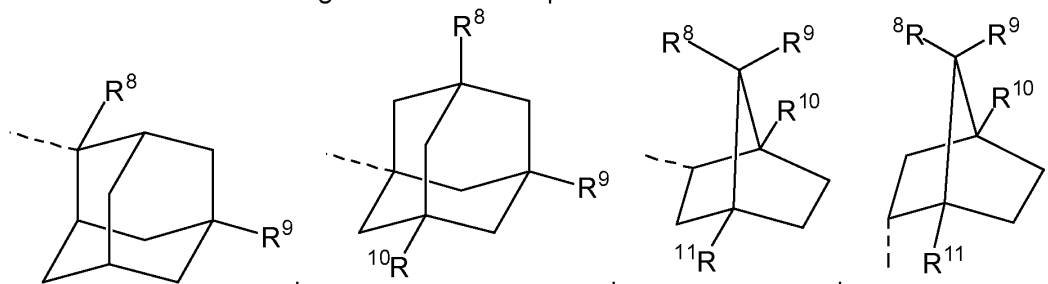
Most preferred are compounds wherein R^2 represents

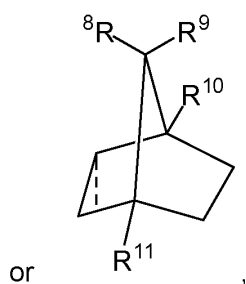


- and R^4 and R^5 represent independently of each other $-Cl$, $-Br$, $-CH_3$, or $-CF_3$, and most preferably $-Cl$, $-Br$, or $-CF_3$.

- 15 Residue R^3 represents $-X$ or $-CH_2-X$ and preferably $-X$.

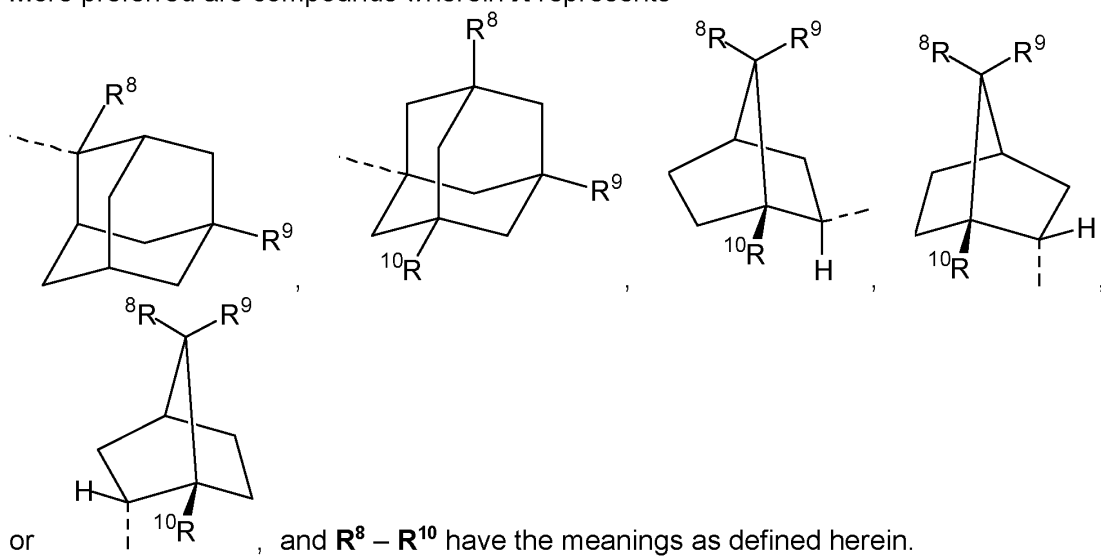
As residue X the following substituents are preferred:



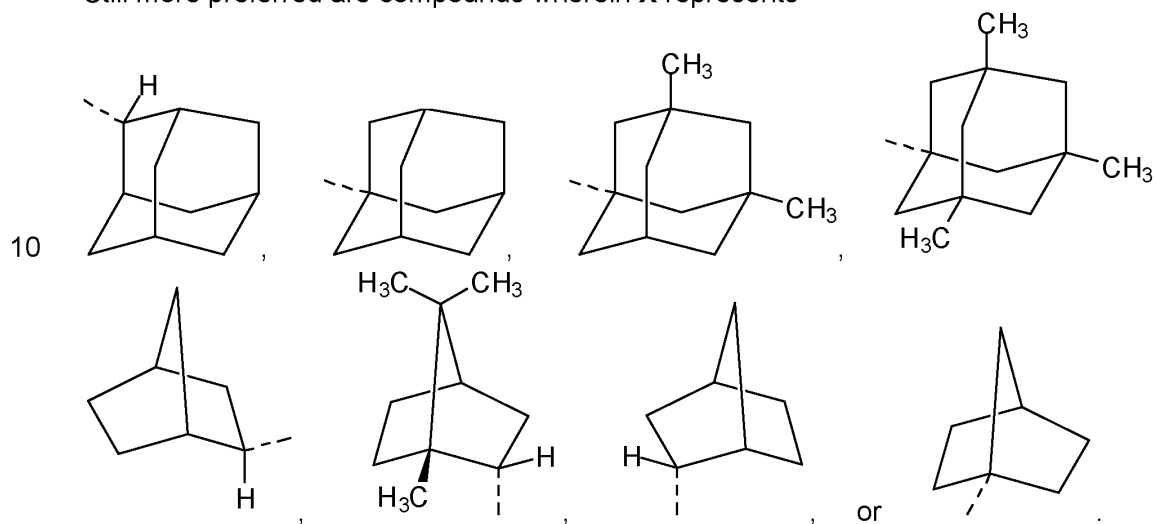


wherein $R^8 - R^{11}$ have the meanings as defined herein.

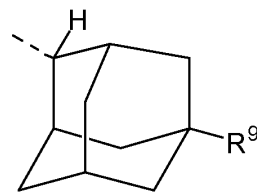
5 More preferred are compounds wherein **X** represents



Still more preferred are compounds wherein **X** represents



Most preferred are compounds wherein **X** represents



wherein **R⁹** has the meanings as defined herein and preferably represents $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-CH_3$, $-CF_3$; more preferably $-H$, $-Cl$, $-CH_3$, $-CF_3$; and still more preferably $-H$ or $-CH_3$, and most preferably $-H$.

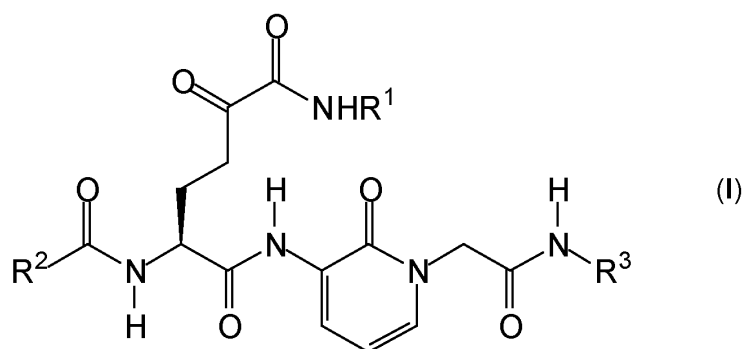
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Moreover, the substituents **R⁴**, **R⁵**, **R⁶** and **R⁷** represent most preferably independently of each other $-H$, $-Cl$, $-CH_3$, or $-CF_3$.

Furthermore, **R¹** represents preferably $-CH_3$.

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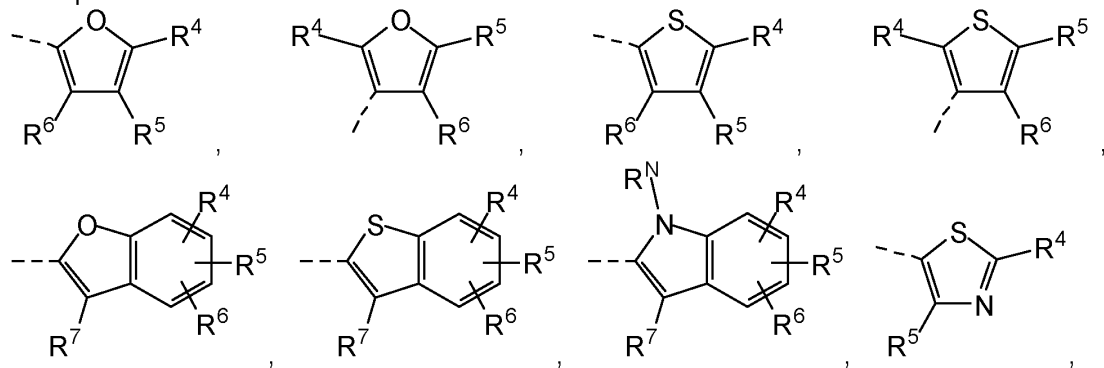
Especially preferred are for addressing the indications mentioned herein are the compounds of the general formula (I):



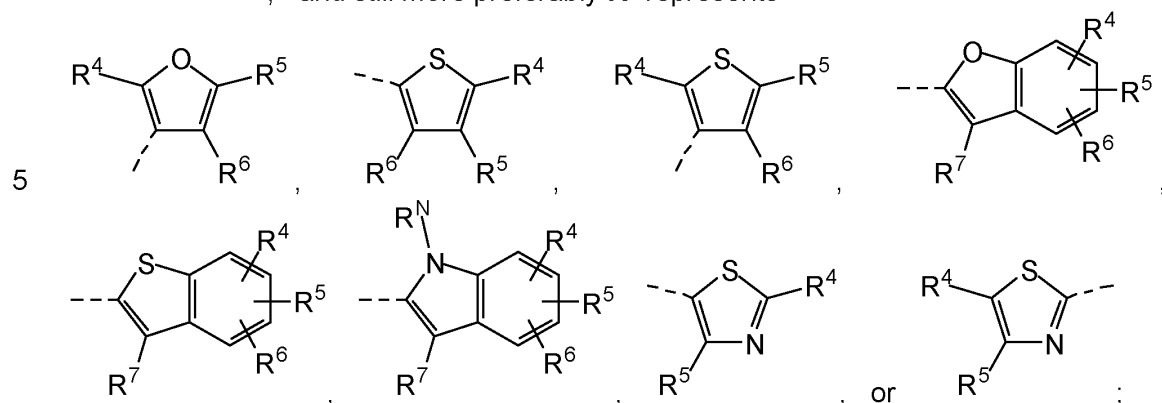
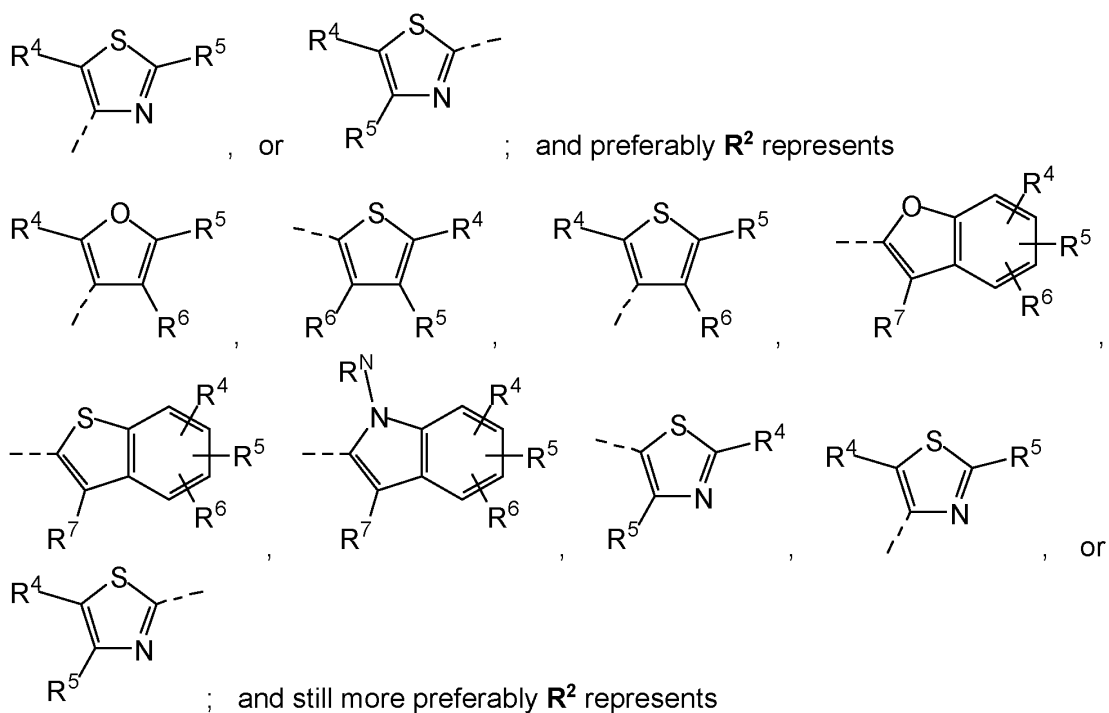
15 wherein

R¹ represents $-H$ or $-CH_3$;

R² represents



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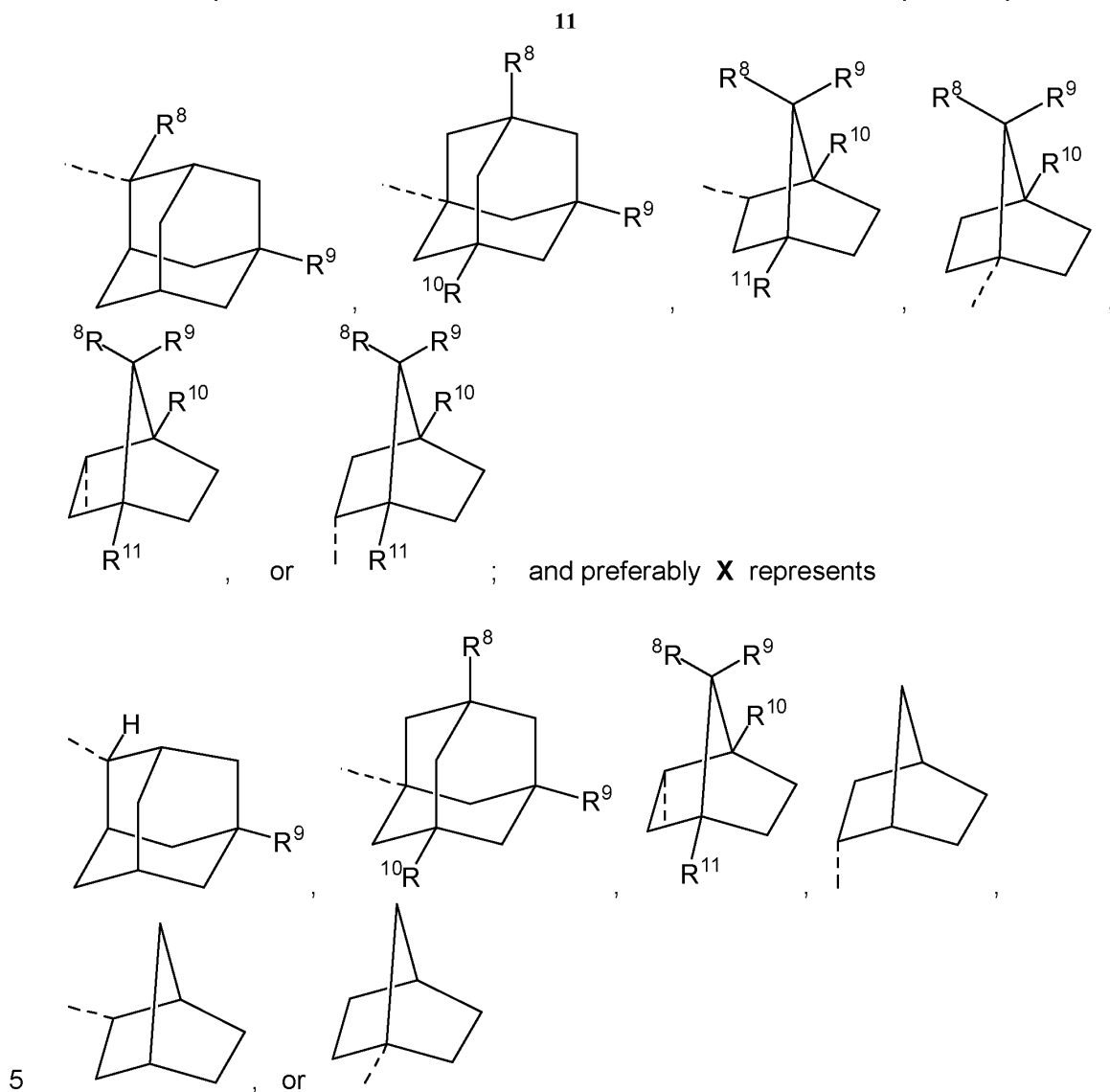
R³ represents **-X** ;

10 **R⁴**, **R⁵**, **R⁶** and **R⁷** represent independently of each other -H, -F, -Cl, -Br, -CH₃, or -CF₃;

R⁸, **R⁹**, **R¹⁰**, and **R¹¹** represent independently of each other -H or -CH₃;

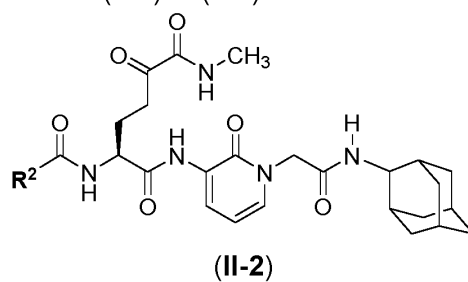
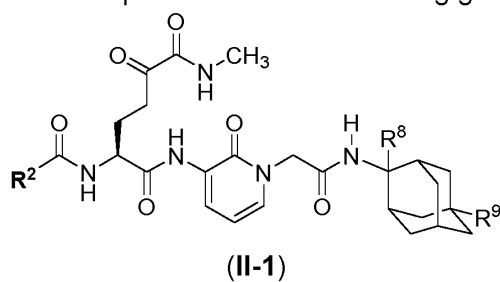
15 **R^N** represents -H or -CH₃;

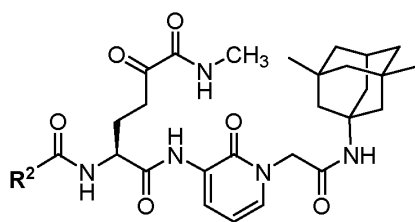
X represents



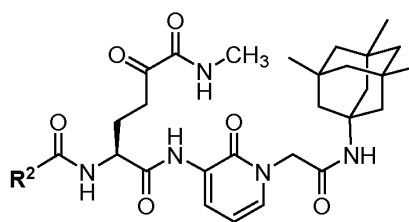
or a diastereomer, an enantiomer, a mixture of diastereomers, a mixture of enantiomers, a racemate, a solvate, a hydrate, or a pharmaceutically acceptable salt thereof in the treatment of pulmonary inflammation, pulmonary fibrosis, in particular idiopathic pulmonary fibrosis.

Also more preferred are the following general formulae (II-1) to (II-8):

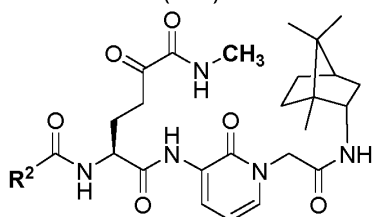




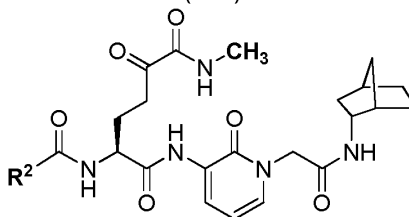
(II-3)



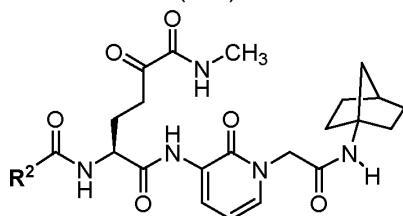
(II-4)



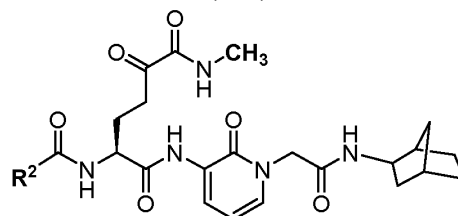
(II-5)



(II-6)



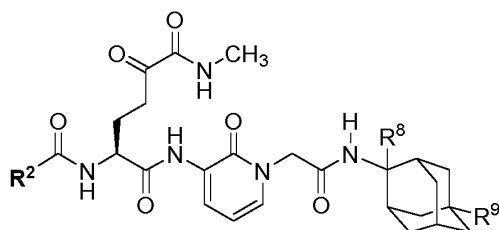
(II-7)



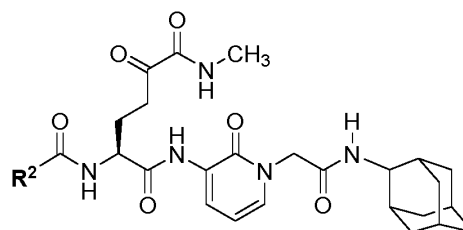
(II-8)

wherein the substituents **R²**, **R⁸** and **R⁹** have the meanings and the preferred meanings are disclosed herein.

- 5 Most preferred are the following general formulae (II-1) and (II-2):

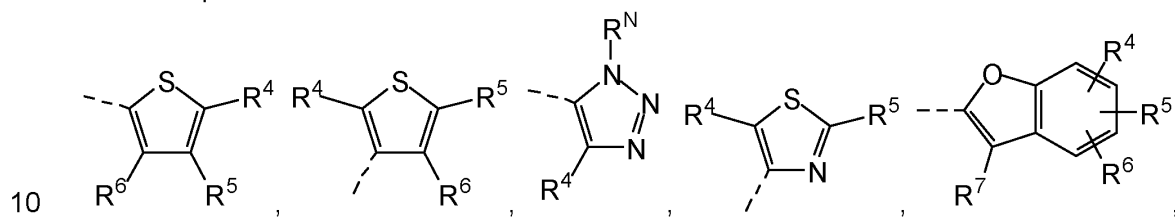


(II-1)

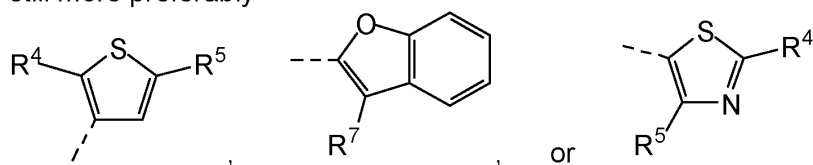
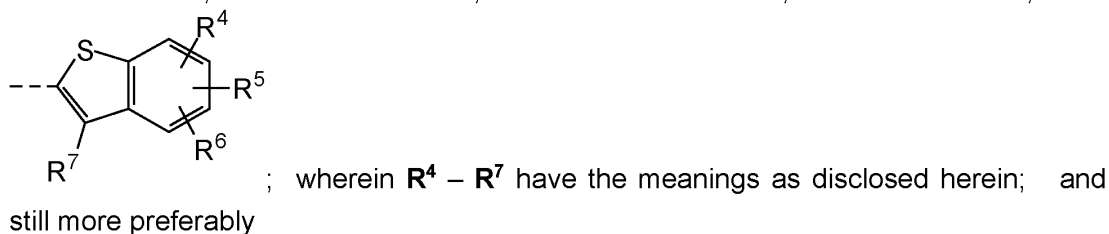
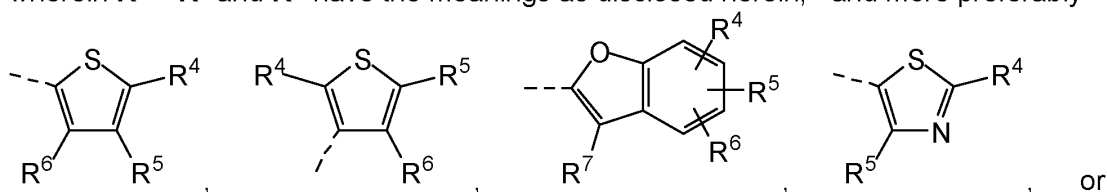
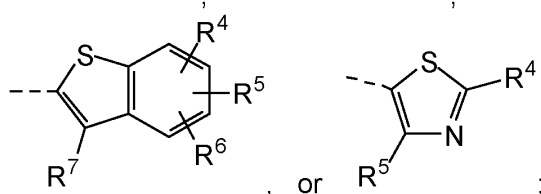
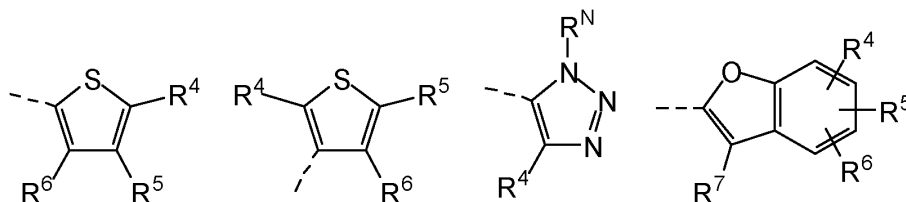
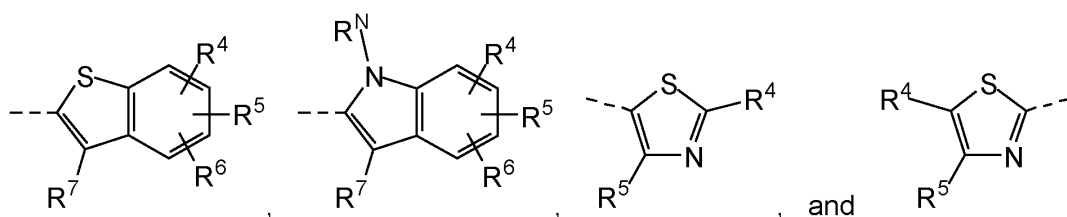


(II-2)

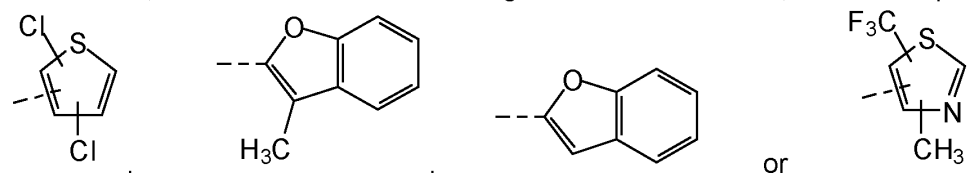
wherein **R⁸** and **R⁹** have the meanings and the preferred meanings are disclosed herein and **R²** represents



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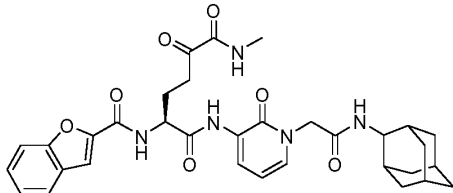
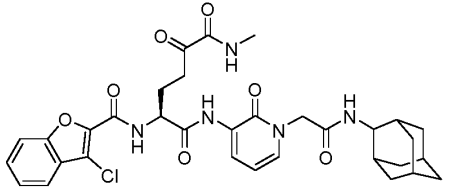
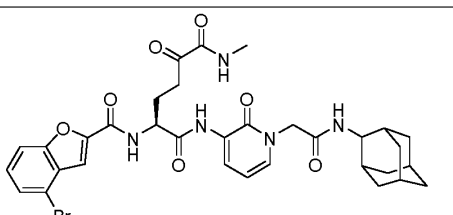
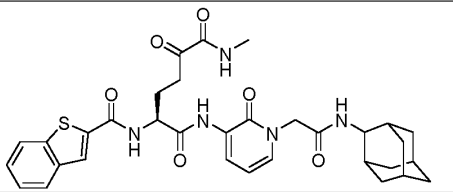
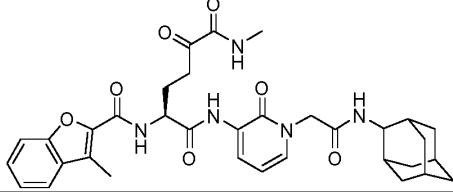
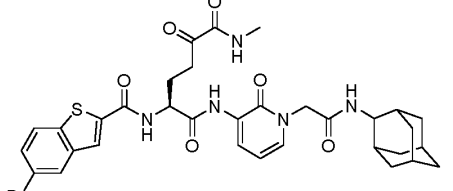
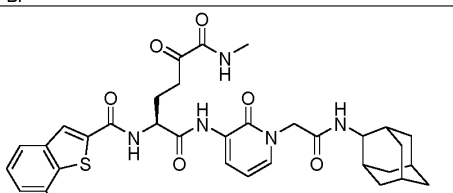
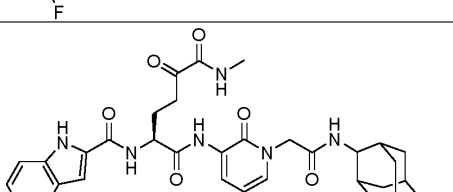


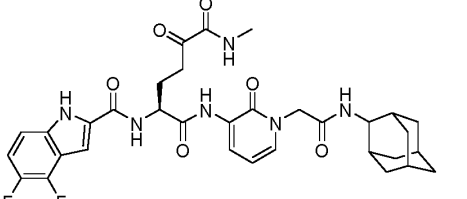
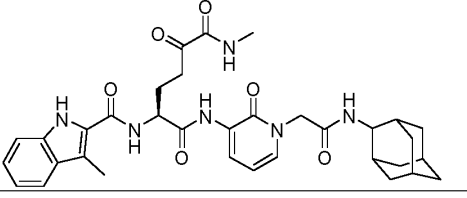
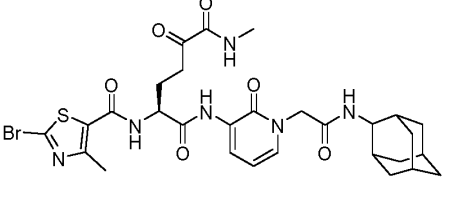
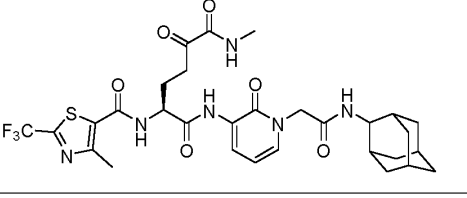
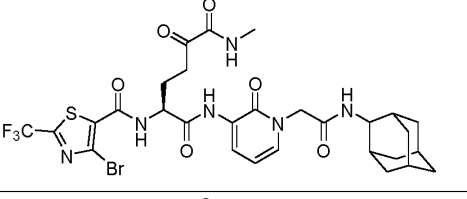
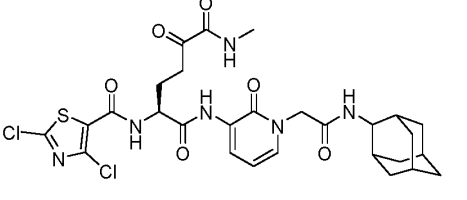
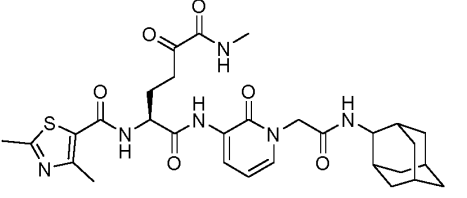
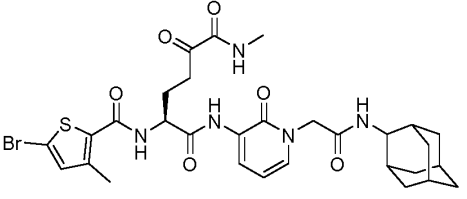
10 wherein R^4 , R^5 and R^7 have the meanings as disclosed herein; and most preferably



Especially preferred are the following compounds of general formula (I):

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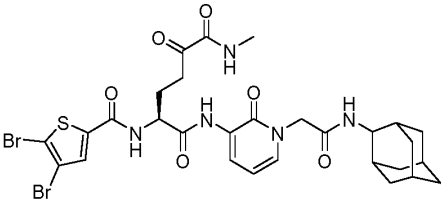
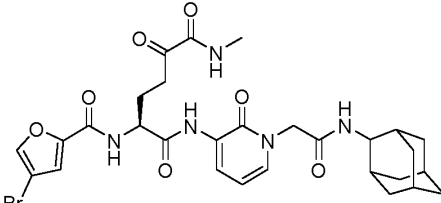
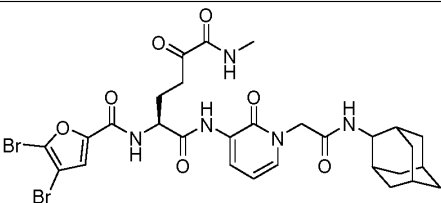
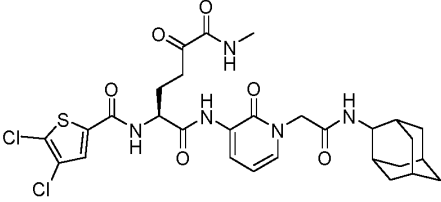
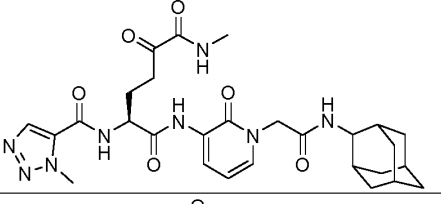
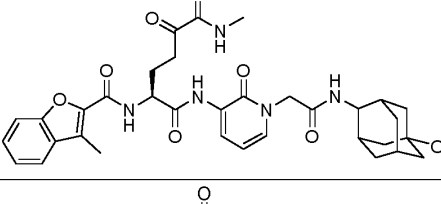
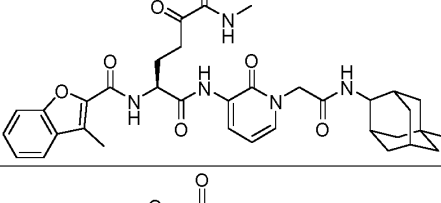
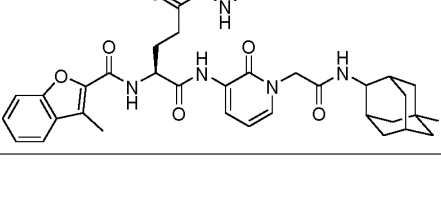
1		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
2		(S)-2-(3-chlorobenzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
3		(S)-2-(4-bromobenzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
4		(S)-2-(benzo[b]thiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
5		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanedi- amide
6		(S)-2-(5-bromobenzo[b]thiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
7		(S)-2-(7-fluorobenzo[b]thiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
8		(S)-2-(1H-indole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide

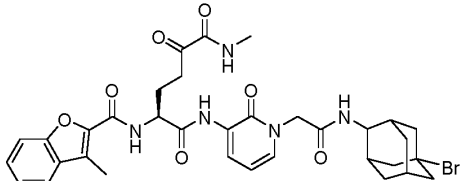
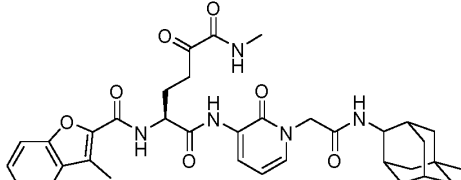
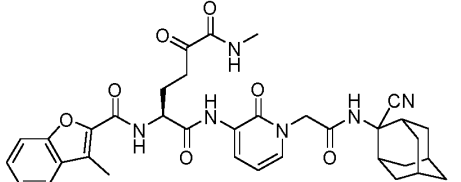
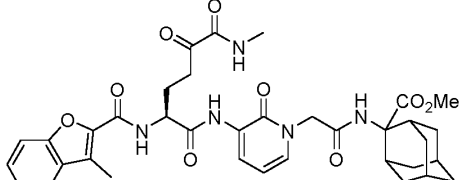
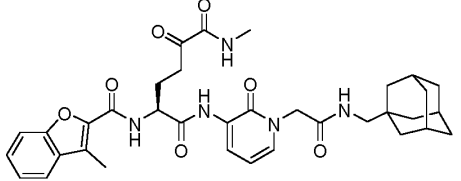
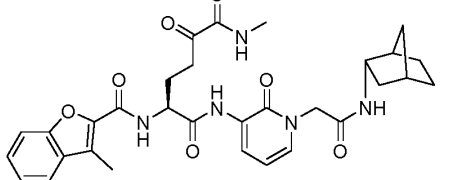
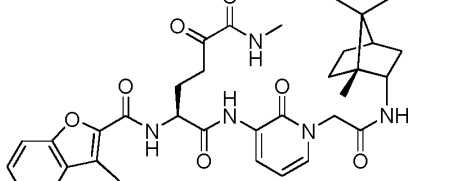
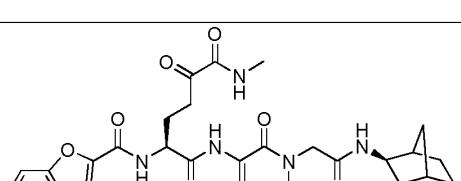
9		(S)-2-(4,5-difluoro-1H-indole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
10		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methyl-1H-indole-2-carboxamido)-5-oxohexanediamide
11		(S)-2-(2-bromo-4-methylthiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
12		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
13		(S)-2-(4-bromo-2-(trifluoromethyl)thiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
14		(S)-2-(2,4-dichlorothiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
15		(S)-2-(2,4-dimethylthiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
16		(S)-2-(5-bromo-3-methylthiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

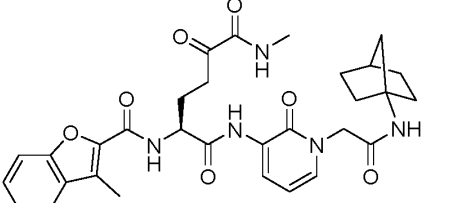
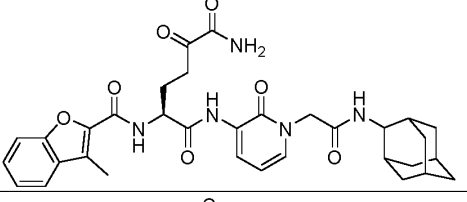
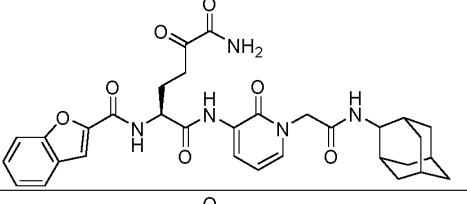
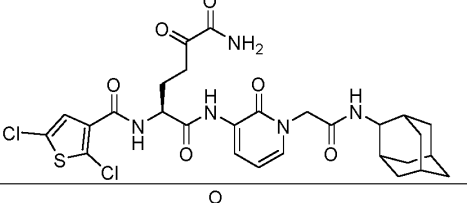
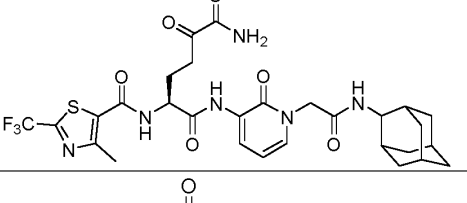
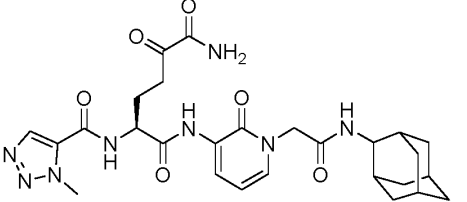
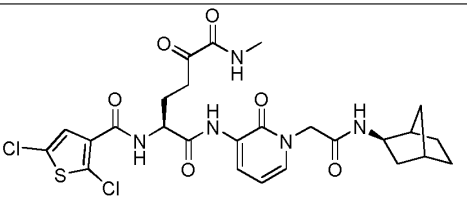
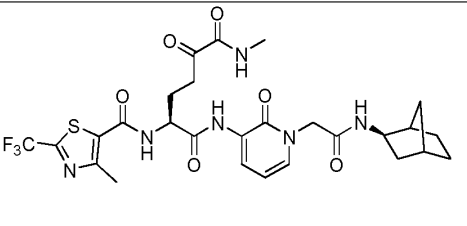
17		(S)-2-(3,5-dibromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
18		(S)-2-(5-bromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
19		(S)-2-(5-chlorothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
20		(S)-2-(5-bromo-3-methylfuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
21		(S)-2-(5-chlorofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
22		(S)-2-(5-chlorothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
23		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
24		(S)-2-(2,5-dibromothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide

25		(S)-2-(5-bromothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
26		(S)-2-(2-chloro-5-methylthiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
27		(S)-2-(2,5-dichlorothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
28		(S)-2-(2,5-dibromothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
29		(S)-2-(2-bromo-5-methylthiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
30		(S)-2-(2-bromothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
31		(S)-2-(2-chlorothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
32		(S)-2-(2,5-dimethylfuran-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

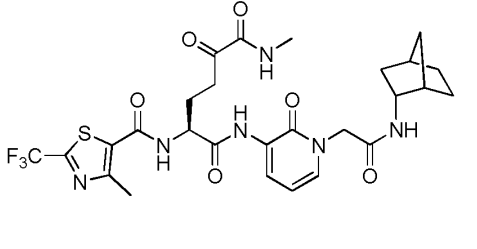
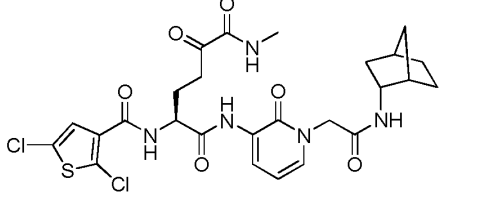
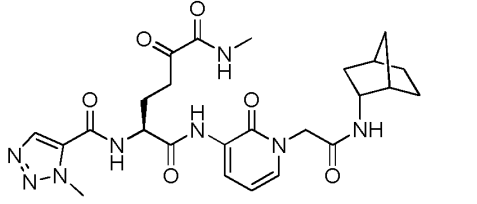
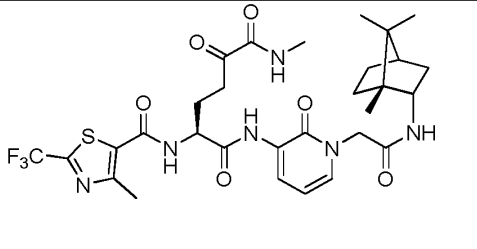
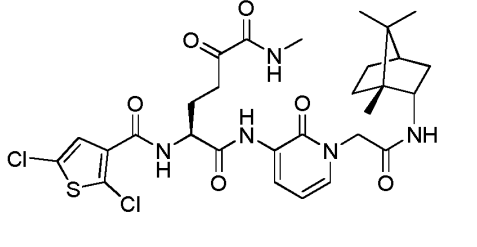
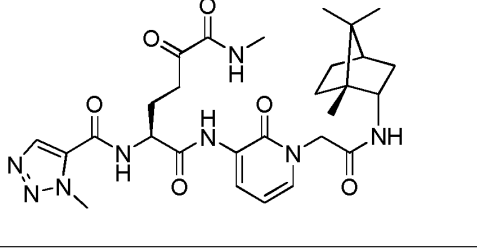
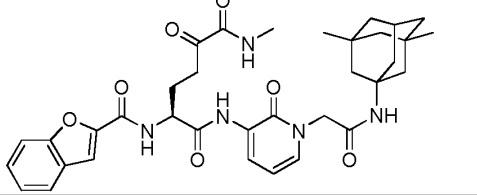
33		(S)-2-(4,5-dimethylthiazole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
34		(S)-2-(4-bromothiazole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
35		(S)-2-(4-bromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
36		(S)-2-(4-bromo-3-methylthiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
37		(S)-2-(3-bromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
38		(S)-2-(3-chloro-4-methylthiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
39		(S)-2-(4-bromo-5-chlorothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

40		(S)-2-(4,5-dibromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
41		(S)-2-(4-bromofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
42		(S)-2-(4,5-dibromofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
43		(S)-2-(4,5-dichlorothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
44		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
45		(S)-N1-(1-(2-(5-hydroxyadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
46		(S)-N1-(1-(2-(5-fluoroadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
47		(S)-N1-(1-(2-(5-chloroadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

48		(S)-N1-(1-(2-(5-bromoadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
49		(S)-N1-(1-(2-(5-methyladamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
50		(S)-N1-(1-(2-(2-carbonitrileadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
51		(S)-N1-(1-(2-(2-methyladamantane-2-carboxylate-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
52		(S)-N1-(1-(2-(1-adamantylmethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
53		(S)-N1-(1-(2-((1R,2S,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
54		(S)-N1-methyl-5-(3-methylbenzofuran-2-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
55		(S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

56:		(S)-N1-(1-(2-(bicyclo[2.2.1]heptan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
57		(S)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
58		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
59		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
60		(S)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
61		(S)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
62		(2S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(2,5-dichlorothiophene-3-carboxamido)-N6-methyl-5-oxohexanediamide
63		(2S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide

64		(2S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
65		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
66		(S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
67		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
68		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
69		(S)-2-(benzofuran-2-carboxamido)-5-oxo-N1-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
70		(S)-2-(3-methylbenzofuran-2-carboxamido)-5-oxo-N1-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide

71		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
72		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(2,5-dichlorothiophene-3-carboxamido)-N6-methyl-5-oxohexanediamide
73		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
74		(S)-N1-methyl-5-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
75		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N6-methyl-5-oxo-N1-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
76		(S)-N1-methyl-5-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
77		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

78		(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
79		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
80		(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
81		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
82		(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
83		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
84		(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide

or a pharmaceutically acceptable salt thereof.

Suitability of Use

As mentioned above, the present invention is directed to a small group of compounds selected from WO 2023/275337 A1 which have proven suitability for the treatment of pulmonary inflammation, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis.

This suitability was proven by the bleomycin mouse model, the standard model for testing if a compound has a pulmonary anti-inflammatory and anti-fibrotic effect and thus could be developed for the treatment of IPF.

Although expected, far not all compounds disclosed in WO 2023/275337 A1 do show a pulmonary anti-inflammatory and anti-fibrotic effect as evident from the data obtained by the inventors.

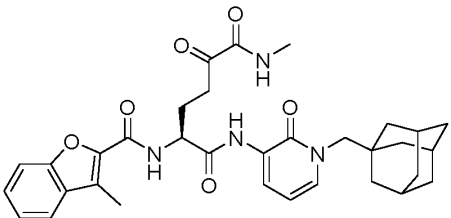
Representative compounds of the formula (I) were tested. In this regard, the term >>representative compound(s) of the formula (I)<< refers to the following compounds or in case the singular is used, to one of the following compounds:

Compound 4, Compound 5, Compound 12, Compound 23, Compound 33,
Compound 53, Compound 54, Compound 77 and Compound 83.

The representative compounds of the formula (I) were tested together with a considerable number of further compounds selected from WO 2023/275337 A1. These further compounds were expected to also show a considerable anti-inflammatory and anti-fibrotic effect in regard to the lung, but surprisingly they failed. The data generated by the inventors did not prove a considerable anti-inflammatory and anti-fibrotic effect in regard to the lung of these further compounds disclosed in WO 2023/275337 A1, so that these further tested compounds are now negative reference compounds.

Consequently, the term >> reference compounds << refers to the following compounds of WO 2023/275337 A1 which do not show an anti-inflammatory and anti-fibrotic effect:

Reference compounds R-1 – R-111

R-1		(S)-N1-(1-(1-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediarnide
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R-2		(2S)-N1-(1-((3-hydroxy-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-3		(2S)-N1-(1-((3-bromo-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-4		(S)-N1-(1-(2-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-5		(2S)-2-(4-tert-butyl-1H-pyrrole-3-carboxamido)-N6-methyl-N1-(1-(2-(1-adamantyl)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
R-6		(2S)-2-(4-cyano-1-methyl-1H-pyrrole-2-carboxamido)-N6-methyl-N1-(1-(3-(1-adamantyl)propyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide

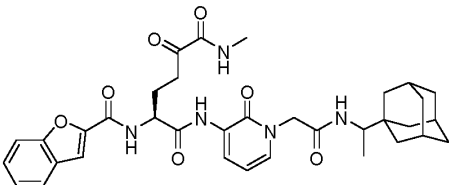
Reference compounds **R-1** to **R-6** comprise one of the preferred substituents R^3 and in addition reference compounds **R-1** to **R-4** comprise also one of the preferred substituents R^2 , but due to the missing amide group through which the substituent R^3 is

5 connected to the pyridinone moiety, **R-1** to **R-6** did not have a distinct anti-inflammatory and/or anti-fibrotic effect.

R-7		(S)-N1-(1-(2-(2-adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
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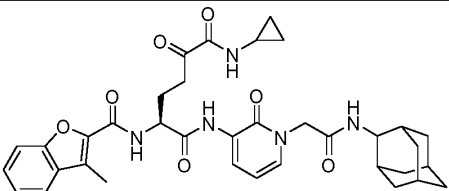
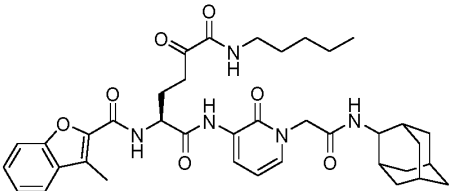
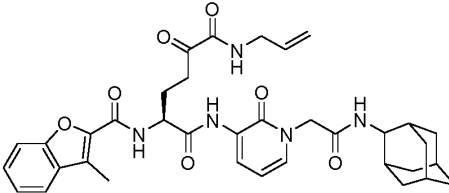
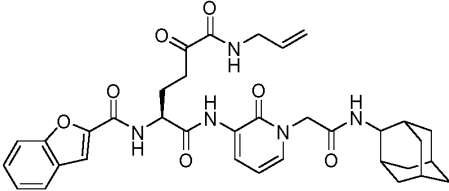
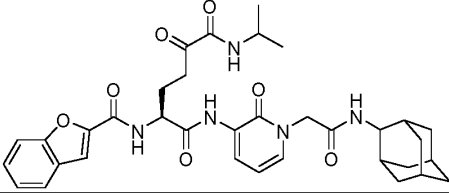
Reference compound **R-7** does actually have the amide group between the substituent R^3 and the pyridinone moiety. However, this amide group is methylated and this seems to destroy the anti-inflammatory and anti-fibrotic effect. Thus, reference compound **R-7** does not have a distinct anti-inflammatory and/or anti-fibrotic effect.

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R-8		(S)-N1-(1-(2-(1-(1-adamantyl)ethanamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
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Reference compound **R-8** has a methyl substituted methylenyl linker between the amide group and the substituent R^3 which seems to destroy the anti-inflammatory and anti-fibrotic effect. Thus, reference compound **R-8** does not have a distinct anti-inflammatory and/or anti-fibrotic effect.

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R-9		(S)-N1-cyclopropyl-N6-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-(3-methylbenzofuran-2-carboxamido)-2-oxohexanediamide
R-10		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxo-N6-pentylhexanediamide
R-11		(S)-N1-allyl-N6-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-(3-methylbenzofuran-2-carboxamido)-2-oxohexanediamide
R-12		(S)-N1-allyl-5-(benzofuran-2-carboxamido)-N6-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxohexanediamide
R-13		(S)-2-(benzofuran-2-carboxamido)-N6-isopropyl-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide

R-14		(S)-2-(benzofuran-2-carboxamido)-N6-cyclopropyl-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanedi- amide
R-15		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxo-N6-phenylhexanedi- amide
R-16		(S)-2-(benzofuran-2-carboxamido)-N6-benzyl-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanedi- amide
R-17		(S)-2-((S)-1,4-diazabicyclo[2.2.2]octane-2-carboxamido)-N6-tert-butyl-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanedi- amide
R-18		(S)-N1-tert-butyl-5-(1H-indole-3-carboxamido)-N6-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxohexanedi- amide
R-19		(S)-N1-tert-butyl-N6-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-(6-methylimidazo[2,1-b]thiazole-3-carboxamido)-2-oxohexanedi- amide
R-20		(S)-2-(benzo[d]thiazole-2-carboxamido)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-cyclopentyl-5-oxohexanedi- amide
R-21		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-cyclopentyl-2-(imidazo[2,1-b]thiazole-6-carboxamido)-5-oxohexanedi- amide

R-22		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-cyclopentyl-2-(4-hydroxy-6-(trifluoromethoxy)quinoline-3-carboxamido)-5-oxohexanediamide
R-23		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(cinnoline-3-carboxamido)-N6-cyclohexyl-5-oxohexanediamide
R-24		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-cyclohexyl-2-(3-ethylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-25		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-cyclohexyl-2-(1-ethyl-1H-indole-2-carboxamido)-5-oxohexanediamide
R-26		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-cyclohexyl-2-(2-methyl-1,8-naphthyridine-3-carboxamido)-5-oxohexanediamide

Reference compounds **R-17** to **R-26** do neither have a suitable substituent R^1 , nor any suitable substituents R^2 or R^3 . These compounds do not show any noticeable anti-inflammatory or anti-fibrotic effect.

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However, the reference compounds **R-9** to **R-16** do actually have one of the preferred substituents R^2 and also one of the preferred substituents R^3 . Thus, from the reference compounds **R-9** to **R-16** it can be concluded that the substituent R^1 is also of mayor importance and that only compounds, wherein substituent R^1 represents hydrogen ($-H$) or methyl ($-CH_3$) have a distinct anti-inflammatory and anti-fibrotic effect. Any longer alkyl chains such as cyclopropyl, cyclopentyl, pentyl, allyl, iso-propyl or larger substituents such as phenyl and benzyl seem to lead to compounds without any distinct anti-inflammatory or anti-fibrotic effect.

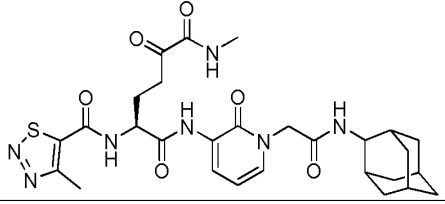
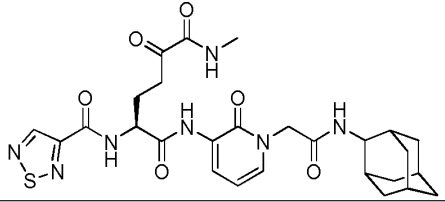
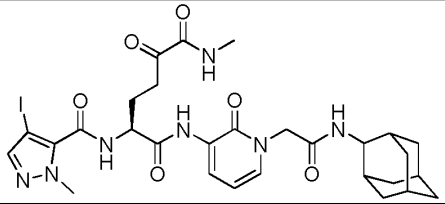
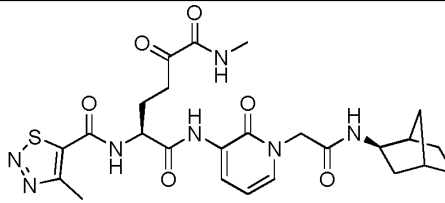
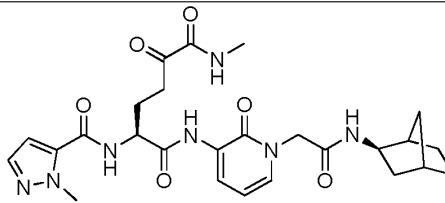
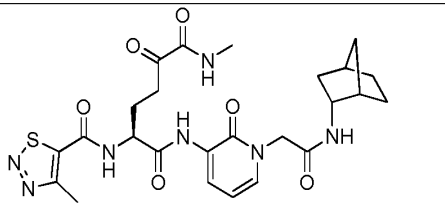
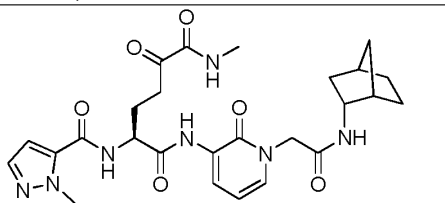
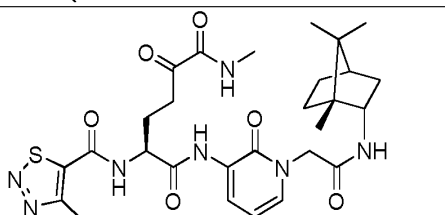
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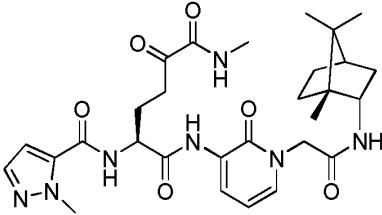
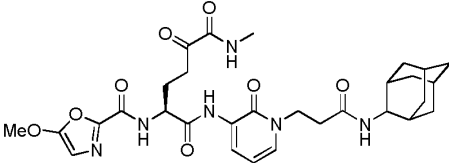
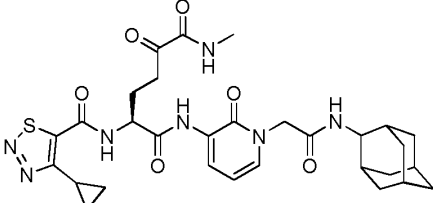
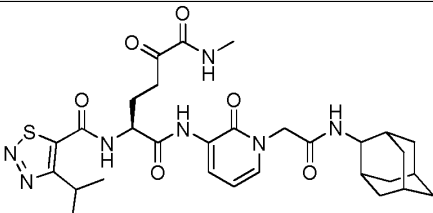
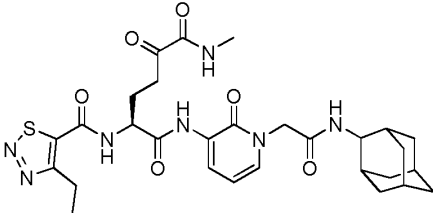
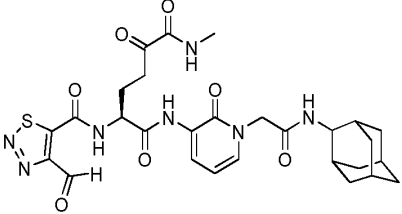
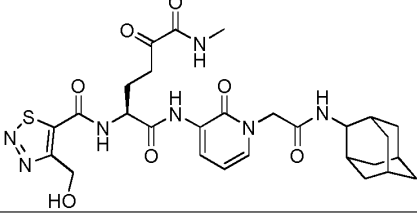
R-27		(S)-2-(1H-benzo[d]imidazole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-28		(S)-2-(2,3-dihydro-1H-indene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-29		(S)-2-((S)-1-acetylpyrrolidine-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-30		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(2H-tetrazole-5-carboxamido)hexanediamide
R-31		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(pyrazine-2-carboxamido)hexanediamide
R-32		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-((S)-1-methylpyrrolidine-2-carboxamido)-5-oxohexanediamide
R-33		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-((S)-pyrrolidine-3-carboxamido)hexanediamide

R-34		(S)-2-((2S,4S)-4-bromopyrrolidine-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
R-35		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-((S)-piperidine-2-carboxamido)hexanedi- amide
R-36		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-((R)-piperidine-3-carboxamido)hexanedi- amide
R-37		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-((R)-morpholine-3-carboxamido)-5-oxohexanedi- amide
R-38		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(quinuclidine-3-carboxamido)hexanedi- amide
R-39		(S)-methyl 3-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylamino)-1,5,6-trioxohexan-2-ylcarbonyl)-5-nitrobenzoate
R-40		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(5-nitronicotinamido)-5-oxohexanedi- amide
R-41		(S)-5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylamino)-1,5,6-trioxohexan-2-ylcarbonyl)nicotinic acid

R-42		(S)-methyl 5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylamino)-1,5,6-trioxohexan-2-ylcarbamoyl)nicotinate
R-43		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(6-methylimidazo[2,1-b]thiazole-5-carboxamido)-5-oxohexanediamide
R-44		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(nicotinamido)-5-oxohexanediamide
R-45		(S)-2-(isonicotinamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-46		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(pyridazine-4-carboxamido)hexanediamide
R-47		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(pyridazine-3-carboxamido)hexanediamide
R-48		(S)-N1-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-imidazole-5-carboxamido)-5-oxohexanediamide
R-49		(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-imidazole-5-carboxamido)-5-oxohexanediamide

R-50		(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-imidazole-5-carboxamido)-5-oxohexanediamide
R-51		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1H-1,2,4-triazole-3-carboxamido)hexanediamide
R-52		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,4-triazole-3-carboxamido)-5-oxohexanediamide
R-53		(S)-2-(benzofuran-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-54		(S)-2-(benzo[b]thiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-55		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-pyrazole-3-carboxamido)-5-oxohexanediamide
R-56		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-pyrazole-4-carboxamido)-5-oxohexanediamide
R-57		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-pyrazole-5-carboxamido)-5-oxohexanediamide

R-58		(S)-N1-(1-(2-(2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-5-oxohexanediamide
R-59		(S)-N1-(1-(2-(2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1,2,5-thiadiazole-3-carboxamido)hexanediamide
R-60		(S)-2-(4-iodo-1-methyl-1H-pyrazole-5-carboxamido)-N1-(1-(2-(2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-61		(S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-5-oxohexanediamide
R-62		(S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-pyrazole-5-carboxamido)-5-oxohexanediamide
R-63		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-5-oxohexanediamide
R-64		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-pyrazole-5-carboxamido)-5-oxohexanediamide
R-65		(S)-N1-methyl-5-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide

R-66		(S)-N1-methyl-5-(1-methyl-1H-pyrazole-5-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
R-67		(S)-N1-(1-(3-(2-adamantylamino)-3-oxopropyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(5-methoxyoxazole-2-carboxamido)-N6-methyl-5-oxohexanediamide
R-68		(S)-2-(4-cyclopropyl-1,2,3-thiadiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-69		(S)-2-(4-isopropyl-1,2,3-thiadiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-70		(S)-2-(4-ethyl-1,2,3-thiadiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-71		(S)-2-(4-formyl-1,2,3-thiadiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-72		(S)-2-(4-(hydroxymethyl)-1,2,3-thiadiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

Reference compounds **R-27** to **R-72** have actually one of the preferred substituents R¹ and one of the preferred substituents R³. However, the substituent R² seems to play

an incredibly important role in regard to the anti-inflammatory and anti-fibrotic activity which is not understood yet. However, by empirical trials the inventors could generate data which show that reference compounds **R-27** to **R-72** do not exhibit a distinct anti-inflammatory and anti-fibrotic pulmonary effect which must be tightly connected to the chemical structure of the substituent R^2 . Some substituents R^2 of the inactive reference compounds are quite similar to the preferred claimed substituents R^2 . For example, inactive reference compounds **R-51** and **R-52** have a 1,2,4-triazole moiety as substituent R^2 , while in contrast the active representative compounds **44**, **61**, **64**, **73** and **76** have a 1,2,3-triazole moiety. This is an absolutely unexpected result.

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Similarly, inactive reference compounds **R-27** and **R-28** have a benzoimidazole or respectively an indene moiety as substituent R^2 . These moieties are quite similar to the preferred benzofuran and benzothiophene moieties of the representative compounds of formula (I) as well as to the representative compounds **8** – **10**, which comprise an indole moiety instead of the benzoimidazole moiety.

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Even more surprising was that reference compounds **R-53** and **R-54** have a benzofuran or a benzothiophene moiety as substituent R^2 which are bound at position 3 to the amide group, while in contrast the preferred representative compounds **1** – **3** and **5** comprise a benzofuran moiety connected at position 2 and preferred representative compounds **4**, **6** and **7** comprise a benzothiophene moiety connected at position 2 to the amide group. Such results could not be foreseen by any skilled person.

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R-73		(S)-2-(2-acetyloxazole-4-carboxamido)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
R-74		(S)-N1-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(2-isopropylloxazole-5-carboxamido)-N6-methyl-5-oxohexanediamide
R-75		(2S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

R-76		(2S)-N1-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3,5-dimethylisoxazole-4-carboxamido)-N6-methyl-5-oxohexanediamide
R-77		(S)-N1-(1-(2-(5-carboxy-2-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methylpyrimidine-5-carboxamido)-5-oxohexanediamide
R-78		(2S)-N1-(1-(2-(4-aminoadamantane-N,N-dimethyl-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1,2,3,4-tetrahydronaphthalene-2-carboxamido)hexanediamide
R-79		(S)-N1-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1,2,3,4-tetrahydroquinoline-6-carboxamido)hexanediamide
R-80		(S)-N1-(1-(2-(2-carboxy-2-amino-5-(trifluoromethyl)adamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(3-oxo-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)hexanediamide
R-81		(S)-N1-(1-(2-(5-ethyladamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1,6-naphthyridine-2-carboxamido)-5-oxohexanediamide
R-82		(S)-N1-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(2,6-naphthyridine-1-carboxamido)-5-oxohexanediamide

R-83		(S)-2-(4-amino-1,2,5-oxadiazole-3-carboxamido)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
R-84		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(6-(dimethylamino)benzofuran-2-carboxamido)-N6-methyl-5-oxohexanedi- amide
R-85		(S)-2-(2-acetamidothiazole-5-carboxamido)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
R-86		(S)-N4-(1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylamino)-1,5,6-trioxohexan-2-yl)-1H-pyrrole-2,4-dicarboxamide
R-87		(S)-N1-(1-(2-(1-acetylamino-4-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(5-sulfamoylfuran-3-carboxamido)hexanedi- amide
R-88		(S)-2-(benzofuran-5-carboxamido)-N1-(1-(2-(1-acetylamino-4-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
R-89		(S)-2-(benzofuran-6-carboxamido)-N1-(1-(2-(4-aminoadamantane-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
R-90		(S)-N1-(1-(2-(4-aminoadamantane-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-(1-methylcyclopropyl)-1,2,4-oxadiazole-5-carboxamido)-5-oxohexanedi- amide

R-91		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(5-methyl-1,2,4-oxadiazole-3-carboxamido)-5-oxohexanediamide
R-92		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1,2,3-thiadiazole-4-carboxamido)hexanediamide
R-93		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1,2,4-thiadiazole-5-carboxamido)hexanediamide
R-94		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxo-2-(1,3,4-thiadiazole-2-carboxamido)hexanediamide
R-95		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-cyclopropyl-1,2,3-thiadiazole-5-carboxamido)-N6-methyl-5-oxohexanediamide
R-96		(S)-N1-(1-(2-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-imidazole-2-carboxamido)-5-oxohexanediamide
R-97		(S)-N1-(1-(2-(((1R,2R,5R)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(1H-imidazole-4-carboxamido)-N6-methyl-5-oxohexanediamide

Reference compounds **R-73** to **R-97** do neither have a suitable substituent R^2 , nor any suitable substituent R^3 . These compounds do not show any noticeable anti-inflammatory or anti-fibrotic effect.

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R-98		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(2-methoxy-4-methylthiazole-5-carboxamido)-N6-methyl-5-oxohexanediamide
R-99		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-phenylthiazole-5-carboxamido)-5-oxohexanediamide
R-100		(S)-2-(4,5-dibromo-3-methoxythiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

Especially interesting are the reference compounds **R-98** to **R-100**, because these compounds have suitable substituents R^1 and R^3 . Moreover, it seems that also substituent R^2 belongs to the list of preferred substituents. However, here also the substituents connected to the residue R^2 have to be considered and the conclusion has to be drawn that a phenyl substituent ($-\text{Ph}$) as well as a methoxy substituent ($-\text{OCH}_3$) on residue R^2 destroy any anti-inflammatory and anti-fibrotic effect.

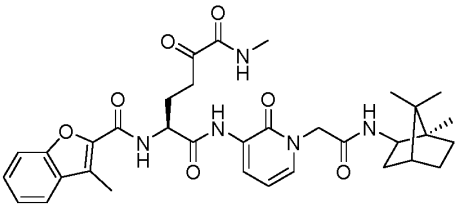
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R-101		(S)-N1-(1-(2-(bicyclo[2.2.1]heptan-7-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-102		(S)-N1-(1-(2-(bicyclo[2.2.1]hept-5-en-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

R-103		(2S)-N1-(1-(2-(bicyclo[2.2.2]octan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-104		(S)-N1-methyl-5-(3-methylbenzofuran-2-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
R-105		(S)-N1-methyl-5-(3-methylbenzofuran-2-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
R-106		(S)-N1-(1-(2-(4-homoisotwistane-3-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-107		(S)-N1-(1-(2-(diamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-108		(S)-N1-(1-(2-(diamantane-4-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-109		(S)-N1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
R-110		(S)-N1-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

A further quite surprising result is that reference compounds **R-101** to **R-110** do not show any distinct pulmonary anti-inflammatory and anti-fibrotic activity. Although the substituents R^1 and R^2 are selected from the preferred list of suitable substituents, the residue R^3 seems to destroy any distinct pulmonary anti-inflammatory and anti-fibrotic activity. Consequently, only very specific substituents R^3 are suitable to provide compounds showing a distinct pulmonary anti-inflammatory and anti-fibrotic effect.

Moreover, not only the chemical structure of the carbobicyclic ring systems is important, also important is the stereochemistry as evident from reference compound **R-111**.

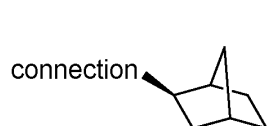
R-111		(S)-N1-methyl-5-(3-methylbenzofuran-2-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediarnide
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Although the trimethylbicyclo[2.2.1]heptan-2-yl residue as such belongs to the preferred list of substituents R^3 , the stereochemistry of reference compound **R-111** seems to be not suitable to provide compounds showing an anti-inflammatory and anti-fibrotic activity.

The 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl residue of reference compound **R-111** has (1R,2R,4R) stereochemistry which seems to be not suitable.

The inventors found that the bicyclo[2.2.1]heptan-2-yl residues must have one of the following stereochemistries: **(1R,2R,4S)** or **(1S,2R,4R)** or **(1R,2S,4R)**

Preferably, the unsubstituted bicyclo[2.2.1]heptan-2-yl residue must have the stereochemistry **(1R,2R,4S)** or **(1S,2R,4R)** and the 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl residue must have the stereochemistry **(1R,2S,4R)** as shown below:



(1R,2R,4S)-
bicyclo[2.2.1]heptan-2-yl



(1S,2R,4R)-
bicyclo[2.2.1]heptan-2-yl



(1R,2S,4R)-1,7,7-
trimethylbicyclo[2.2.1]heptan-2-yl

Conclusion

WO 2023/275337 A1 discloses a considerably number of TG2 inhibitors assuming that these TG2 inhibitors would also have anti-inflammatory and anti-fibrotic properties in regard to the lung. Such compounds have certain alkyl and phenyl substituents as residue R¹ and in addition certain specific carbobicyclic groups as residue R³ in combination with certain heterocyclic groups, preferably aromatic heterocyclic groups as residue R². Although these three residues R¹ – R³ stand for quite similar substituents, only very specific substituents for R¹ together with selected substituents for R² in combination with further selected specific substituents for R³ provide finally compounds which exhibit a distinct pulmonary anti-inflammatory and anti-fibrotic activity. In case only one of these carefully selected substituents R¹ and R² and R³ is not selected in accordance with the selection rules disclosed herein, no noticeable anti-inflammatory and anti-fibrotic effect could be detected.

Therefore, the present application adds to the teachings of WO 2023/275337 A1 the selection rules which are surprising and could not be foreseen by any person skilled in the art in order to obtain compounds which actually have a considerable anti-inflammatory and anti-fibrotic effect in the lung.

These selection rules teach which of all the substituents R¹ and R² and R³ as disclosed in WO 2023/275337 A1 are able to provide compounds with an anti-inflammatory and anti-fibrotic effect in the lung. Moreover, these selection rules also teach, which substituents have to and which have not to be present on the residues R² and R³ and still in addition to these teachings outline which stereochemistry the residues R³ must have and which not.

These finding are derived from over 100 reference compounds and enable a skilled person to identify compounds of WO 2023/275337 A1 which have an anti-inflammatory and anti-fibrotic effect in the lung and which do not have such an effect.

Medical Use of Pharmaceutical Compositions

Another aspect of the present invention relates to the use of a pharmaceutical composition for the treatment of pulmonary inflammation, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis (IPF).

This pharmaceutical composition contains as active ingredient a representative compound of general formula (I) together with at least one pharmaceutically acceptable

carrier, excipient and/or diluent. Such pharmaceutical compositions were tested in the mouse model as disclosed in the experimental part herein.

Within these pharmaceutical compositions the representative compound of general formula (I) might be contained in the form of a hydrate, solvate or salt.

Methods of Use

The present invention relates also to a method for treatment of pulmonary inflammation, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis, said method comprises administering to a patient in need thereof a pharmaceutically active amount of a representative compound of general formula (I) or a pharmaceutical composition thereof sufficient to treat the pulmonary inflammation, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis in that patient.

Pneumonia is a common acute respiratory infection that affects alveoli as well as distal bronchial tree of the lungs. It is difficult to define a general mechanism for infection of the lower airways. Many different strains of bacteria, various viruses and also fungal infection can cause pneumonia and these do typically not share common features, but pathogen-specific virulence factors/mechanisms do contribute to development of the condition in the context of a specific pathogen. This suggests that the host immune response to a specific pathogen in the airway plays a determinant role in the development of pneumonia. Infection typically spreads to the lower respiratory tract from the nasopharynx following immune escape (seeding through the circulatory system can occur but is uncommon). Once a lower respiratory tract infection has occurred two opposing processes ultimately determine the subsequent sequence of events and fate of the organ. Firstly, immune resistance that seeks to eliminate the pathogen, and secondly, tissue resilience that attempts to control or prevent, and ultimately resolve, tissue damage caused by the immune response, the pathogen, or most likely both. In general, an inadequate or unbalanced immune response can result in adverse outcomes which can present as an acute crisis, failed resolution or late pulmonary complications. Tissue resident innate immune cells (macrophages, effector cytokine production by innate lymphoid cells) and also circulation derived neutrophils and monocytes/macrophages constitute a critical line of defence against invading pathogens. Specifically, alveolar macrophages have essential roles in both immune resistance and tissue resilience.

Viral pneumonia is often associated with interstitial inflammation and diffuse alveolar damage, and interstitial fibrosis can be a late sequelae following an episode of pneumonia, with e.g. 35% of patients reported to present with moderate to severe

fibrosis following SARS-Cov2 infection. The intensity (CRP, LDH) and duration of lung involvement plays an important role in the development of persistent inflammatory processes. Anti-fibrotic therapy can be administered during the acute phase of pneumonia and has been reported to ameliorate lung fibrosis. It is also important to note that patients hospitalized for pneumonia have higher risk for subsequent all-cause hospitalization and an increased 10-year mortality risk, with COPD/pulmonary disease being a significant driver of hospital readmission following an episode of community acquired pneumonia. Increased risk for sepsis, cardiovascular disease and other extra-pulmonary complications has been reported, and is likely related to an aberrant state of the immune system after a bout of severe infection (pneumonia). Indeed, impaired host defence (i.e. defects in alveolar macrophage effector functions) to a secondary infection of the lower airways has been demonstrated in experimental models. Alveolar macrophages are differentiated tissue-resident cells that are continually replaced in the steady state by self-renewal; only in conditions that cause a major depletion of these cells, do blood monocytes contribute to the replenishment of the respective "empty" immune niches in the organ. A circulation-derived IL-1 β ⁺ / SPP1⁺ population of macrophages may constitute the link for the risk of development of fibrotic disease. In support of this, recent single cell transcriptomic analysis identified two populations of macrophages linked to human interstitial pulmonary fibrosis, characterized by high levels of SPP1 and CHI3L1 expression, respectively.

Mouse models have significantly contributed to our understanding of pulmonary fibrosis, for example showing that overexpression of either IL-13 or TGF- β 1 results in organ fibrosis, and highlighting how IL-13 signalling links to maturation and TGF- β 1 production in macrophages which ultimately drives fibrogenic reactions. However, neither the bleomycin model nor endogenous factor overexpression models faithfully reproduce or provide insights into the early events leading to idiopathic pulmonary fibrosis. Interestingly, a serendipic recent observation in a mouse model has provided some important clue as to how aberrant cellular interplay may ultimately lead to pulmonary fibrosis. Ifngr1^{-/-}Rag2^{-/-} mice (Rag2^{-/-} mice lack adaptive immune cells) were generated to investigate the role of IFN γ in regulating activation of specific innate lymphoid cell (ILC) subsets. IFN γ is a crucial factor in controlling ILC2 activity in the lung. Importantly it was observed that these mice spontaneously and predictably developed lung fibrosis, including many of the hallmark features associated with human idiopathic fibrosis. The predictive disease course in these mice allowed for molecular analysis of different phases of the disease. Furthermore, it was shown that immune-suppressive treatment during the early inflammatory phase but not later phases stopped fibrosis development, demonstrating that dysregulated innate immune cell activity ultimately links to fibrosis. scRNAseq analysis identified three expanding/contributing

cell populations: i. pro-fibrogenic fibroblasts, ii. a Siglec-Flow macrophage population, and iii. an ILC2 subset. ILC2 cells are activated by IL-33, an epithelially produced signal of injury/infection. Knocking-out IL-33 blocked both ILC2 infiltration into lung fluid and fibrosis development. Unsurprisingly, it has been reported that defects in IL-33 receptor ameliorate disease in the bleomycin mouse model of fibrosis, given that bleomycin-induced damage to epithelial cells will drive IL-33 production. However, in the spontaneous fibrosis model epithelial injury is not a feature but fibrosis development is nevertheless stopped in the absence of this cytokine. Interestingly, in the context of spontaneous fibrosis onset, IL-33 was not just produced by epithelial cells but also by pro-fibrogenic fibroblasts providing a positive feedback cellular crosstalk that may contribute to disease development. ILC2 are known to affect macrophage maturation by producing IL-13 and IL-4, and macrophages produce TGF- β 1 that promote myofibroblast differentiation and fibrosis. Interestingly, ILC2 isolated from idiopathic pulmonary fibrosis patients overexpress IL-13 and IL-1RL1 (IL-33 receptor chain) and display downregulation of IFNGR1 expression (IFN γ receptor) compared to healthy volunteers, features reflecting cell activation and resistance to suppressive signalling. Furthermore, these findings are consistent with the IFN γ being a key negative regulator of fibrogenic fibroblast activity.

Accordingly, organ damage can be seen as an injury due to unbalanced opposing immune resistance and tissue resilience activities as a consequence of an infection. TG2 has been shown to be a critical regulator of inflammatory and repair responses that provide a crucial link between initial inflammation, subsequent tissue injury and late-stage fibrosis. Targeting TG2 may directly reduce fibrogenic activities regardless of the presence or absence of active inflammation. This is supported by the recent demonstration that both macrophage infiltration and fibrosis in the lung are drastically reduced in the absence of TG2 in a tissue-specific TGF- β 1 transgenic mouse model. TG2 therefore constitutes a viable target even in the context of an active infection in terms of controlling acute inflammation (e.g. pneumonia) and modulating long-term outcome. The fact that TG2 contributes to the pro-fibrotic signalling pathways at multiple levels, namely 1. TGF- β activation (see bleomycin model), 2. NF- κ B signalling (see bleomycin model) and 3. TGF- β -activated Smad-independent signalling (cAbl-MRTF-A axis) (see in-vitro assay data) makes it an excellent target. Blocking TG2 is likely to primarily target fibroblast responses, but it will thereby also block the self-perpetuating cellular crosstalk between innate lymphoid cells, macrophages and fibrogenic fibroblasts that is ultimately at the heart of chronic deleterious condition. Macrophages also play a crucial role in the development of sepsis, - the extreme version of an unbalanced response - contributing to proinflammatory reactions through cytokine secretion. It is worth noting that several studies have implicated TG2 in the

pathogenesis of sepsis, despite the fact that the enzyme can demonstrably adopt opposing roles in inflammatory processes.

Thus, it has been found that the compound of general formula (I) or a pharmaceutical composition according to the present invention are particularly useful for treatment of pulmonary inflammation / pneumonia, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis.

Thus, in view of the above, the present invention relates also to a method for treatment of pulmonary inflammation / pneumonia, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis, said method comprises administering to a patient in need thereof a pharmaceutically active amount of a representative compound of general formula (I) or a pharmaceutical composition thereof sufficient to treat the pulmonary inflammation, pulmonary fibrosis, and in particular idiopathic pulmonary fibrosis in that patient.

Description of the Figures

Fig. 1 shows the body weight change results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

Fig. 2 shows the survival results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

Fig. 3 shows the mouse lung weight results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

Fig. 4 shows the inspiratory capacity results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

Fig. 5 shows the vital capacity results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

Fig. 6 shows the vital chord compliance results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

Fig. 7 shows the forced vital capacity results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).

- Fig. 8** shows the forced expiratory volume at 100 ms results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Comp. 5 (Example 2).
- 5 **Fig. 9** shows the dynamic compliance results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).
- Fig. 10** shows the Ashcroft score results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).
- 10 **Fig. 11** shows the COL1A1 positive surface (%) results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).
- Fig. 12** shows the Inflammation score: Lymphocytes results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Comp. 5 (Example 2).
- 15 **Fig. 13** shows the Inflammation score: Eosinophiles results of efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 (Example 2).
- 20 **Fig. 14** shows graphs obtained by testing the effect of representative compounds (**A** Compound 5; **B** Compound 7; **C** Compound 9; **D** Compound 10; **E** Compound 43) of the present application on TGF β -stimulated collagen 1 expression in normal human lung fibroblasts (NHLF).

25

Examples

30

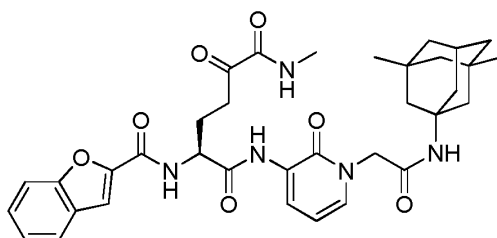
Chemical Examples:

The compounds 1 – 76 were synthesized and characterized as disclosed in WO 2023/275337 A1.

35 The compounds 77 – 84 are not explicitly disclosed in WO 2023/275337 A1, but were synthesized in analogy to the compounds 1 – 76 as disclosed in WO 2023/275337 A1.

Thus, the synthesis of compounds 77 – 84 is not described in detail again so that in the following reference is made to the reaction procedures described in WO 2023/275337 A1 in detail.

Compound **77**:



(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

Chemical Formula: $C_{35}H_{41}N_5O_7$

Exact Mass: 643.30

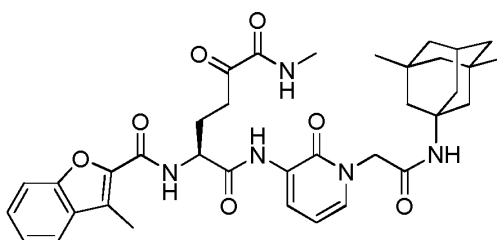
Molecular Weight: 643.73

The synthesis of compound **77** was performed according to compound **II-210** of WO 2023/275337 A1, using benzofuran-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

Yield: 25 mg, 74% (last step)

ESI-MS: 644.5 $[M+H]^+$

Compound **78**:



(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

Chemical Formula: $C_{36}H_{43}N_5O_7$

Exact Mass: 657.32

Molecular Weight: 657.76

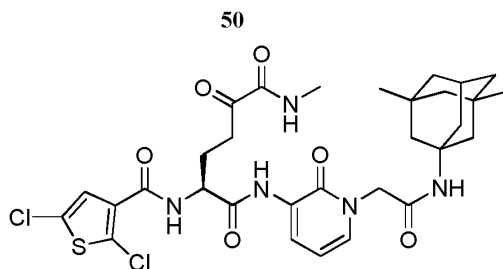
15

The synthesis of compound **78** was performed according to compound **II-210** of WO 2023/275337 A1, using 3-methylbenzo[b]furan-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

Yield: 47 mg, 80% (last step)

20 ESI-MS: 658.5 $[M+H]^+$

Compound **79**:



(S)-2-(2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

Chemical Formula: $C_{31}H_{37}Cl_2N_5O_6S$

Exact Mass: 677.18

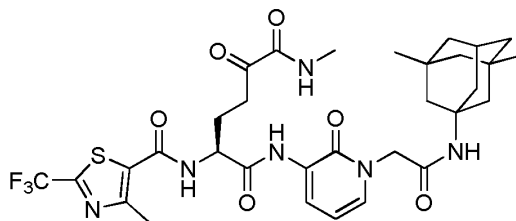
Molecular Weight: 678.63

The synthesis of compound **79** was performed according to compound **II-210** of WO 2023/275337 A1, using 2,5-dichlorothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

Yield: 39 mg, 71% (last step)

ESI-MS: 678.3 / 680.3 $[M+H]^+$

Compound **80**:



(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide

Chemical Formula: $C_{32}H_{39}F_3N_6O_6S$

Exact Mass: 692.26

Molecular Weight: 692.75

10

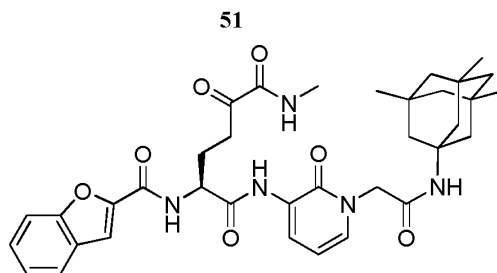
The synthesis of compound **80** was performed according to compound **II-210** of WO 2023/275337 A1, using 4-methyl-2-(trifluoromethyl)thiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

Yield: 29 mg, 68% (last step)

ESI-MS: 693.4 $[M+H]^+$

Compound **81**:

15

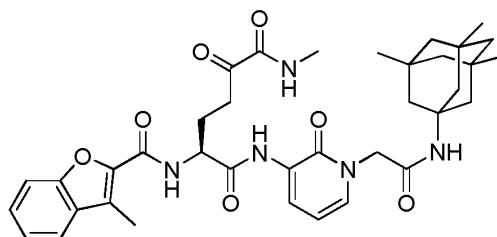


(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
 Chemical Formula: $C_{36}H_{43}N_5O_7$
 Exact Mass: 657.32
 Molecular Weight: 657.76

The synthesis of compound **81** was performed according to compound **II-211** of WO 2023/275337 A1, using benzofuran-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

- 5 Yield: 32 mg, 70% (last step)
 ESI-MS: 658.5 $[M+H]^+$

Compound **82**:



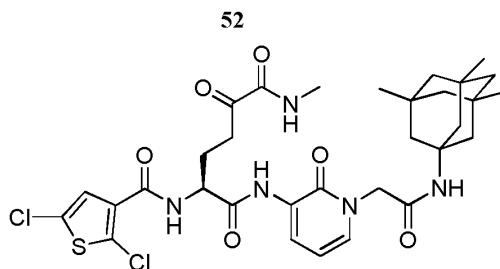
(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
 Chemical Formula: $C_{37}H_{45}N_5O_7$
 Exact Mass: 671.33
 Molecular Weight: 671.78

- 10 The synthesis of compound **82** was performed according to compound **II-211** of WO 2023/275337 A1, using 3-methylbenzo[b]furan-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

Yield: 41 mg, 73% (last step)
 ESI-MS: 672.5 $[M+H]^+$

15

Compound **83**:



(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide

Chemical Formula: C₃₂H₃₉Cl₂N₅O₆S

Exact Mass: 691.20

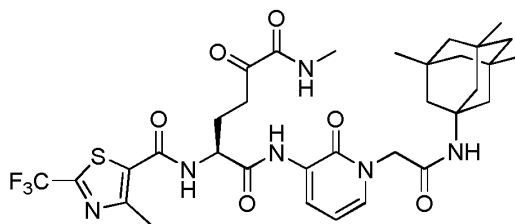
Molecular Weight: 692.65

The synthesis of compound **83** was performed according to compound **II-211** of WO 2023/275337 A1, using 2,5-dichlorothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6.

5 Yield: 54 mg, 82% (last step)

ESI-MS: 692.3 / 694.3 [M+H]⁺

Compound **84**:



(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanedi- amide

Chemical Formula: C₃₃H₄₁F₃N₆O₆S

Exact Mass: 706.28

Molecular Weight: 706.78

10 The synthesis of compound **84** was performed according to compound **II-211** of WO 2023/275337 A1, using 4-methyl-2-(trifluoromethyl)thiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in step 6 (according to ZED3264).

Yield: 20 mg, 62% (last step)

ESI-MS: 707.4 [M+H]⁺

15

The following examples are intended to illustrate the invention with selected compounds without limiting the protecting scope of the present intellectual property right on these concrete examples. It is clear for a person skilled in the art that analogous compounds and compounds produced according to analogous synthetic ways fall under the protecting scope of the present intellectual property right.

20

Biological *in-vivo* Examples:

5 **Example 1**
Efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis

10 The efficacy of representative compounds of formula (I) was tested in a 21-day mouse model on 8 – 9 weeks old male mice by administration of 30 and 65 mg/kg via *per oral* (PO) administration 2 x per day (BID/q12h) following bleomycin (BLM) challenge in the mouse model of BLM-induced pulmonary fibrosis vs. positive control Nintedanib. Mice were allocated into groups as indicated in the tables below.

Table 1 Groups, challenge, treatment

Group	N	Challenge IN (Day 0)	Treatment (Day 7 – Day 21)	Dose and Frequency
1	5	Saline	-	-
2	14	Bleomycin ~1 mg/kg (~ 0,9 U/mL)	0.1% HEC	10 mL/kg <i>per oral</i> / 2x/day
3	14		Nintedanib	60 mg/kg <i>per oral</i> / 2x/day

15

Table 2 Groups, challenge, treatment

Group	N	Challenge IN (Day 0)	Treatment (Day 7 – Day 21)	Dose and Frequency
4	15	Bleomycin ~1 mg/kg (~ 0,9 U/mL)	Vehicle (low dose 250 mg/kg) (500 mg/kg/day)	10 mL/kg <i>per oral</i> 2x/day
5	15		Representative com- pound of formula (I)	30 mg/kg 10 mL/kg <i>per oral</i> / BID/q12h

6	15		Vehicle (high dose 500 mg/kg) (1000 mg/kg/day)	10 mL/kg <i>per oral</i> / BID/q12h
7	15		Representative com- pound of formula (I)	65 mg/kg 10 mL/kg <i>per oral</i> / BID/q12h

Body weight was measured on days 0, 1, 4, and 6 – 21. Mice were generally weighed directly before administration of treatment solutions. Body weight was measured on days 0, 1 and 4 twice per day and on days 6 to 21 once a day. Mann-Whitney test was employed for lung weights and histopathological assessment, while ANOVA was employed for body weight data processing. Differences between groups are considered statistically significant when $p < 0.05$.

Blood-plasma concentration of the representative compounds of formula (I) was determined either 0.5 hours or 1 hour after administration on days 7 and 21. Plasma was prepared by centrifugation of blood samples. Then, the plasma was removed and collected.

Anaesthesia was generally performed with a combination of ketamine and xylazine in saline.

On day 21, lung function measurements were performed on mice from group 1 – 7, followed by lung weighing and tissue sampling. Mice were anaesthetized with a combination of ketamine and xylazine. Pulmonary function test (PFT) measurements were conducted on a suitable Pulmonary function testing system. Parameters measured using this technique include airway pressure, pulmonary resistance and dynamic lung compliance. Mice were anaesthetized and tracheotomised. Three semiautomatic manoeuvres were performed: Boyle's law functional residual capacity (FRC), quasistatic Pressure Volume test (PV) and fast flow volume manoeuvre, Resistance and Compliance test was performed using automated ventilation. Data calculation was performed using automated data acquisition software. Setup, procedures, software etc. have been performed according the manufacturers manual.

For lung sampling, lungs were removed and weighed. Cranial right lobe was removed for compound concentration analysis by LC-MS/MS (groups 5 and 7). Remaining lung tissue was stored in 10% formalin and processed for histopathological analysis.

Crossman's Trichrome staining for Ashcroft/Matsuse score and Col1A1 Immunohistochemistry with quantitative digital imaging was performed. Inflammation score was performed on haematoxylin-eosin (H&E) stained slides. Ashcroft Matsuse score was determined.

5

For intranasal (IN) challenge saline solution of bleomycin was administered.

Hydroxyethylcellulose (HEC) (0.1%) was used as vehicle for Nintedanib formulation and was administered from day 7 - 21 to mice in group 2 in two daily (BID) administrations (60 mg/kg). Application volume: 10 mL/kg/dose.

10

The Nintedanib formulation is 0.1% Hydroxyethylcellulose with a 6 mg/mL Nintedanib. Formulation was administered orally from days 7 to 21 to mice in group 3 in two daily (BID) administrations. Application volume: 10 mL/kg/dose.

15

Vehicle used for the formulation of the representative compounds of formula (I) was administered either in low dose or high dose orally from days 7 to 21 to animals in group 4 and 6 in two daily (BID) administrations. Application volume: 10 mL/kg/dose.

Formulation of a representative compound of formula (I) was administered orally from days 7 to 21 to animals in group 5 (30 mg/kg) and in group 7 (65 mg/kg) in two daily (BID) administrations. Application volume: 10 mL/kg.

20

For histopathological evaluation, lungs without cranial right lung lobe were embedded in paraffin and stained on H&E for inflammation evaluation. Samples were stained according to Crossman's Trichrome (Gray P. The Microtometist's Formulary and Guide. Published by Robert E. Krieger Publishing Co.). Pulmonary histological changes were assessed using Matsuse modification of Ashcroft score (Ashcroft H et al. J Clin Pathol (1988) 41 :467-70; Matsuse T et al. Eur Respir J (1999) 13 :71-77). Immunohistochemistry for collagen was performed using the anti-collagen 1A1 (COL1A1) antibody. Slides were incubated with primary rabbit monoclonal anti-COL1A1 antibody. Level of de novo collagen 1A1 (COL1A1) deposition was evaluated using digital image analysis software. Statistical analysis and graphical presentation will be performed using GraphPad Prism software.

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For each representative compound of formula (I) concentration analysis, an anti-protease cocktail was added to the homogenization solvent. Lung samples (about 50 mg) were homogenized using Milli-Q water (1/1, w/w). The mixture was vortex mixed for 60 seconds. To homogenate acetonitrile containing internal standard was added.

The mixture was vortex mixed and centrifuged. Compound concentration was determined from lung homogenate supernatant by LC-MS/MS.

Plasma samples were analyzed by LC-MS/MS. Each representative compound of formula (I) was extracted via protein precipitation with acetonitrile containing internal standard. The LC-MS/MS method was based on reverse-phase chromatography and samples were quantified against a min. 6-point matrix-matched calibration standard curve including QCs, blank and double blank samples.

10 Body weight monitoring:

In comparison to the saline-challenged mice, all three positive control groups (BLM HEC 10mL/kg/PO/BID, BLM Vehicle 250mg/kg/ PO/BID, and BLM Vehicle 500mg/kg/ PO/BID) showed significantly lower body weight on the various time points during the course of the 21-day mouse model. Three positive control groups (BLM HEC 10mL/kg/ PO/BID, BLM Vehicle 250mg/kg/ PO/BID, and BLM Vehicle 500mg/kg/ PO/BID) showed significantly higher body weight loss in comparison to the saline-challenged mice during the course of the study.

20 The body weight capture data were as expected. Saline-challenged mice gained weight over time, all Bleomycin induced mice showed a drop in body weight. No unusual survival rate of all mice during the study was observed.

Lung weight

25 When compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500mg/kg/PO/BID) exhibited significantly increased lung weight. Lung weight capture showed an expected increase in lung weight upon Bleomycin induction.

30 Mice treated with Nintedanib showed a significant decrease of lung weight to its respective vehicle group (HEC 10 mL/kg/PO/BID).

Groups treated with a representative compound of formula (I) (both 30 and 65 mg/kg/PO/BID) showed significant decrease in lung weight with lower dose (30 mg/kg/PO/BID) when compared to their respective Vehicles (250 mg/kg/PO/BID and 35 500 mg/kg/PO/BID).

All treatment groups with Nintedanib and a representative compound of formula (I) showed a significant decrease in lung weight.

Boyle's law functional residual capacity

Boyle's law describes the relationship between pressure and volume of a gas, while functional residual capacity (FRC) measures the volume of air remaining in the lungs after a normal exhalation.

When compared to the mice from the saline-challenged group, BLM-challenged mice treated with Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly decreased total lung capacity.

Mice treated with Nintedanib showed a slight decreased in total lung capacity, however, change was not significant as compared to vehicles HEC (10mL/kg/PO/BID).

Groups treated with a representative compound of formula (I) (both 30 and 65 mg/kg/PO/BID) showed no significant change in lung capacity when compared to their respective Vehicles (250 mg/kg/PO/BID and 500 mg/kg/PO/BID).

Based on the described data the BLM-challenge resulted in known and well-characterized change in lung tissue which is widely used as animal model to investigate pulmonary fibrogenesis [Chua F, Gauldie J, Laurent GJ. Pulmonary fbrosis: searching for model answers. Am J Respir Cell Mol Biol. 2005; 33:9–13]. Bleomycin is an anti-neoplastic drug which increases reactive oxygen species, leading to apoptosis of alveolar epithelial cells and pulmonary fibrosis [Drakopanagiotakis F, Xifteri A, Polychronopoulos V, Bouros D. Apoptosis in lung injury and fbrosis. Eur Respir J. 2008; 32:1631–8]. The bleomycin model has histological characteristics similar to human disease; however, there are differences in chronicity and pathogenesis, which means the bleomycin model does not mimic all features of human pulmonary fibrosis.

Experimental observations such as increase of lung weight and decreased functional lung parameters (reduced functional residual capacity) underline the technical proof of organ remodeling upon BLM-challenge leading to impaired organ function. The positive control Nintedanib resulted in improved parameters based on lung weight and functional parameters validating the model outcome and assay window compared to vehicle groups. Groups treated with a representative compound of general formula (I) (both 30 and 65 mg/kg/PO/BID) showed significant decrease in lung weight although lung capacity was not significantly changed. Overall, this data support that a representative compound of general formula (I) results in similar model outcome as compared to the positive control Nintedanib.

Quasistatic Pressure Volume test

Measures the relationship between pressure and volume in the lungs. By plotting the pressure and volume data, a pressure-volume curve is obtained. This curve provides valuable information about lung compliance and elastic properties. Lung compliance refers to the ability of the lungs to expand and contract. It is influenced by factors such as the elasticity of lung tissue, the presence of any lung diseases, and the overall health of the respiratory system. It helps in assessing lung mechanics and determining lung compliance.

10

When compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly reduced chord compliance (Cchord), inspiratory capacity (IC) and vital capacity (VC).

15

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in a significant increase of Cchord, IC and VC when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

20

Groups treated with a representative compound of formula (I) (30 mg/kg/PO/BID) showed a slight, non-significant increase in Cchord, IC and VC when compared to its respective Vehicle (250 mg/kg/PO/BID).

25

In this comprehensive lung function analyses additional data related to fibrogenesis induction and organ function impairment were recorded. The pressure-volume curve underlined the induction of disease with BLM-challenge which is demonstrated by a shift of animal towards the right and down relative to sham animals. All vehicle treated groups showed this pronounced lung function impairment induced by BLM-challenge. This is also reflected in a number of additional pulmonary function tests to assess lung compliance and elastic properties. Overall, the positive control Nintedanib demonstrated a significant increase of pulmonary function tests when compared to respective vehicle group. The low dose group treated with a representative compound of general formula (I) was able to demonstrate a non-significant trend in those pulmonary function tests pointing towards a benefit.

30

Fast Flow Volume maneuver

During the fast flow volume maneuver, the spirometer measures the flow of air (in milliliters per second) against the volume of air (in milliliters) during both inhalation and exhalation. This data is then plotted on a graph known as the flow-volume curve.

When compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly reduced forced vital capacity (FVC) and forced expiratory volume (FEV₁₀₀).

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in a significant increase of FVC and FEV₁₀₀ when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

Groups treated with a representative compound of formula (I) (both 30 and 65 mg/kg/PO/BID) showed similar response in FVC and FEV₁₀₀ when compared to their respective vehicles (250 and 500 mg/kg/PO/BID).

When compared to the animals from the saline-challenged group, BLM-challenged animals treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited similar response in max mid expiratory flow (MMEF) and peak expiratory flow (PEF).

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in no significant change of MMEF and PEF when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

Groups treated with a representative compound of formula (I) (both 30 and 65 mg/kg/PO/BID) showed similar response in MMEF and PEF when compared to their respective vehicles (250 and 500 mg/kg/PO/BID).

The data generated in the fast flow volume maneuver allowed an estimation of fibrotic remodeling of the lung tissue translated into impaired organ function. During this study we observed a stronger decrease in FVC and FVC_{100ms} in the HEC vehicle groups compared to both HPbCD vehicle groups. As a result of this, Nintedanib demonstrated a statistically significant effect which is not demonstrated for a representative compound of general formula (I). However, the accomplished improvement with either Nintedanib or a representative compound of general formula (I) was comparable to each other and close to Sham animals tested in this study.

BLM-challenge does not primarily induce an obstructive pulmonary disease which explains a less pronounced effect on MMEF and PEF across groups studied in this study.

Resistance and Compliance

When compared to the animals from saline-challenged group, BLM-challenged animals treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significant reduction in dynamic compliance.

5

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in significant increase of dynamic compliance when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

- 10 Groups treated with a representative compounds of formula (I) (30 mg/kg/PO/BID) showed slight increase in response of dynamic compliance when compared to their respective control (Vehicle 250 mg/kg/PO/BID).

- 15 In all BLM-challenged animals, measurement of resistance was observed to have similar response as in saline-challenged group, regardless if vehicle or treatment was administered.

- BLM-challenge primarily induced a non-obstructive pulmonary disease which is illustrated in the lack of change across treatment groups for resistance measurement.
- 20 Hence, the almost not changed parameter "lung resistance" is not surprising considering the nature of the BLM-challenge model. The more relevant parameter to assess fibrotic remodeling is "dynamic compliance". It refers to the ability of the lungs to expand and contract during the breathing process. Hence, lung tissue challenged by BLM becomes less flexible due to fibrotic remodeling of the extracellular matrix. As a
- 25 result, we observed a decrease in dynamic compliance upon BLM-challenge. Similar to other functional parameters the effect was most pronounced with HEC vehicle control and less pronounced with HPbCD used as vehicle for a representative compound of general formula (I). Nintedanib demonstrated a statistically significant effect, a representative compound of general formula (I) could show a trend towards a benefit.

30

Ashcroft score

- In comparison to the saline-challenged group, Ashcroft score was significantly increased in BLM-challenged mice treated with vehicles HEC (10mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID). This indicates that the Bleomycin challenge
- 35 clearly impacted the lung tissue architecture and induced tissue remodeling including fibrotic changes.

Treatment with Nintedanib (60mg/kg/PO/BID) significantly reduced Ashcroft score compared to the respective vehicle group (HEC10mL/kg/PO/BID). Technically, this

data supports that the in vivo model has been successfully conducted. The effect of Nintedanib defines the expected assay window / in vivo effect size.

5 Treatment with a representative compound of formula (I) (30mg/kg/PO/BID) significantly reduced Ashcroft score, compared to the respective control (Vehicle 250mg/kg/PO/BID).

10 Treatment with a representative compound of formula (I) (65mg/kg/PO/BID) significantly reduced Ashcroft score compared to the respective control (Vehicle 500mg/kg/PO/BID). The range of effect is comparable to Nintedanib and confirmed that transglutaminase inhibition has a structural benefit in the bleomycin mouse model.

Collagen 1A1 positive surface (%)

15 In comparison to the saline-challenged group, COL1A1 positive surface was significantly increased in BLM- challenged mice treated with vehicles HEC (10mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID).

20 Treatment with Nintedanib (60mg/kg/PO/BID) significantly decreased COL1A1 positive surface compared to the respective vehicle group (HEC10mL/kg/PO/BID).

25 Treatment with a representative compound of formula (I) (30mg/kg/PO/BID) significantly decreased COL1A1 positive surface compared to the respective control (Vehicle 250mg/kg/PO/BID).

Observation in Col1A1 positive surface confirming the treatment effect of Nintedanib and a representative compound of formula (I) at lower dose tested with a link to anti-fibrotic effect.

30 These morphological data demonstrated a clear BLM-challenge effect in the lung and underlined the success of the model conducted. The observed effect across all vehicle groups can be significantly improved by Nintedanib and with a representative compound of general formula (I). Treatment effects with a representative compound of general formula (I) might be considered less variable compared to Nintedanib at the lower dose tested which underlined a clear morphological benefit upon transglutaminase inhibition.

35 In combination with the Col1A1 staining a beneficial treatment effect of a representative compound of general formula (I) compared with Nintedanib was underlined on top of the Ashcroft fibrosis scoring.

Inflammation score

In comparison to the saline-challenged group, inflammation score (lymphocytes & eosinophils) was significantly increased in BLM-challenged animals treated with vehicles HEC (10mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID).

Treatment with Nintedanib (60mg/kg/PO/BID) significantly reduced the accumulation of eosinophils compared to the respective vehicle group (HEC 10mL/kg/PO/BID).

10 Treatment with representative compound of formula (I) (30mg/kg/PO/BID) significantly reduced the accumulation of lymphocytes and eosinophils compared to the respective control (Vehicle 250mg/kg/PO/BID).

15 Treatment with a representative compound of formula (I) (65mg/kg/PO/BID) did not influence the accumulation of lymphocytes and eosinophils compared to the respective control (Vehicle 500mg/kg/PO/BID).

20 With regards to inflammation score bleomycin clearly induced an increase in inflammatory cell infiltration in all vehicle treated groups compared to saline challenged mice. Nintedanib reduced eosinophiles and no statistically significant effect was observed on lymphocytes, whereas compounds of general formula (I) reduced lymphocytes and eosinophiles and the lower dose tested.

25 Conclusion

Overall, various readouts in the study confirmed the positive anti-fibrotic and anti-inflammatory effect of the compounds of general formula (I) compared to Nintedanib in the bleomycin-induced mouse lung model.

30 Groups treated with a compound of general formula (I) showed significant decrease in Ashcroft score and Col1A1 with the administration of lower dose. The observed effect is comparable to the pos. control Nintedanib confirming that transglutaminase inhibition in the model showed an in vivo effect in bleomycin induced lung fibrosis. Overall, the data provides evidence for PoP/PoC targeting transglutaminases (specifically TG2) in
35 mouse bleomycin model and together with the PFT the morphological effect translates into a functional pulmonary organ improvement.

Example 2

5 **Efficacy study in a 21-day mouse model of bleomycin induced pulmonary fibrosis with Compound 5 vs. positive control Nintedanib**

Table 3 Groups, challenge, treatment

Group	N	Challenge IN (Day 0)	Treatment (Day 7 – Day 21)	Dose and Frequency
1	5	Saline	-	-
2	14	Bleomycin ~1 mg/kg (~ 0,9 U/mL)	0.1% HEC	10 mL/kg <i>per oral</i> / 2x/day
3	14		Nintedanib	60 mg/kg <i>per oral</i> / 2x/day

Table 4 Groups, challenge, treatment

Group	N	Challenge IN (Day 0)	Treatment (Day 7 – Day 21)	Dose and Frequency
4	15	Bleomycin ~1 mg/kg (~ 0,9 U/mL)	Vehicle (low dose 250 mg/kg) (500 mg/kg/day)	10 mL/kg <i>per oral</i> 2x/day
5	15		Compound 5	30 mg/kg 10 mL/kg <i>per oral</i> / BID/q12h
6	15		Vehicle (high dose 500 mg/kg) (1000 mg/kg/day)	10 mL/kg <i>per oral</i> / BID/q12h
7	15		Compound 5	65 mg/kg 10 mL/kg <i>per oral</i> / BID/q12h

The bleomycin mouse model is now described again with reference to the specific representative compound 5 and with reference to the figures obtained with comp. 5.

As shown in **Fig. 1**, in comparison to the saline-challenged mice, all three positive control groups (BLM HEC 10mL/kg/PO/BID, BLM Vehicle 250mg/kg/ PO/BID, and BLM Vehicle 500mg/kg/ PO/BID) showed significantly lower body weight on the various time points during the course of the 21-day mouse model. Three positive control groups (BLM HEC 10mL/kg/ PO/BID, BLM Vehicle 250mg/kg/ PO/BID, and BLM Vehicle 500mg/kg/ PO/BID) showed significantly higher body weight loss in comparison to the saline-challenged mice during the course of the study.

The body weight capture data were as expected. Saline-challenged mice gained weight over time, all Bleomycin induced mice showed a drop in body weight.

As shown in **Fig. 2** no unusual survival rate of all mice during the study was observed.

As shown in **Fig. 3**, when compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500mg/kg/PO/BID) exhibited significantly increased lung weight.

Mice treated with Nintedanib (60 mg/kg) showed a significant decrease of lung weight, compared to its respective vehicle group (HEC 10 mL/kg/PO/BID).

Groups treated with Compound 5 (both 30 and 65 mg/kg/PO/BID) showed significant decrease in lung weight with lower dose (30 mg/kg/PO/BID) when compared to their respective Vehicles (250 mg/kg/PO/BID and 500 mg/kg/PO/BID).

All treatment groups with Nintedanib and Compound 5 showed a significant decrease in lung weight.

Overall, these observations are in line with published data on the BLM-challenge model [Jean-Claude Gilhodes, Yvon Julé, Sebastian Kreuz, Birgit Stierstorfer, Detlef Stiller, Lutz Wollin. Quantification of Pulmonary Fibrosis in a Bleomycin Mouse Model Using Automated Histological Image Analysis. PLoS One. 2017; 12(1): e0170561]. Upon disease induction animals loose weight and recover over time. The observed drop out rate was low. Changes in lung weight are expected to increase due to the BLM-challenge and subsequent fibro-inflammatory tissue remodeling and excessive extra-cellular matrix generation and remodeling.

As shown in **Fig. 4**, when compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly reduced inspiratory capacity (IC).

5

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in a significant increase of IC when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

Groups treated with Compound 5 (30 mg/kg/PO/BID) showed a slight, non-significant increase in IC when compared to its respective Vehicle (250 mg/kg/PO/BID).

The observed reduced IC is a result of BLM-challenge reducing the overall organ capacity to take in as much air as it should during inhalation. Usually, this is caused by factors that restrict lung expansion. This change is typically induced with the BLM-challenge. Nintedanib and the group treated with compound 5 at lower dose demonstrated a beneficial effect.

As shown in **Fig. 5**, when compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly reduced vital capacity (VC).

20

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in a significant increase of VC when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

Groups treated with Compound 5 (30 mg/kg/PO/BID) showed a slight, non-significant increase VC when compared to its respective Vehicle (250 mg/kg/PO/BID).

25

The observed change in VC is a result of BLM-challenge indicating a reduction in overall lung volume which can be caused by conditions that affect lung elasticity or restrict lung expansion. Both are typically induced with the BLM-challenge. Nintedanib and the group treated with compound 5 at lower dose demonstrated a beneficial effect.

30

As shown in **Fig. 6**, when compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly reduced chord compliance (Cchord).

35

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in a significant increase of Cchord when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

40

Groups treated with Compound 5 (30 mg/kg/PO/BID) showed a slight, non-significant increase in Cchord when compared to its respective Vehicle (250 mg/kg/PO/BID).

5 The BLM-challenge has reduced Cchord which means that the lungs have lost some of their elasticity and flexibility, making it more difficult to expand and contract effectively. Usually, this is observed in lung diseases related to fibrosis or emphysema. We intentionally induced this with the BLM-challenge and both Nintedanib and compound 5 at lower dose demonstrated a beneficial effect.

10

As shown in **Fig. 7** and **Fig. 8**, when compared to the mice from the saline-challenged group, BLM-challenged mice treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significantly reduced forced vital capacity (FVC) and FEV100.

15

Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in a significant increase of FVC and FEV100 when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

20 Groups treated with Compound 5 (both 30 and 65 mg/kg/PO/BID) showed similar response in FVC and FEV100 when compared to their respective Vehicle (250 and 500 mg/kg/PO/BID).

25

The reduced FVC and FEV100 is due to various factors such as lung tissue scarring, inflammation, and stiffness. Commonly it is seen in conditions like pulmonary fibrosis and in this model induced by BLM-challenge. During this study we observed a stronger decrease in FVC and FEV100 in the HEC vehicle groups compared to both HPbCD vehicle groups. As a result of this, Nintedanib demonstrated a statistically significant effect which is not demonstrated for the representative compound 5.

30 As shown in **Fig. 9**, when compared to the animals from saline-challenged group, BLM-challenged animals treated with vehicles HEC (10 mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID) exhibited significant reduction in dynamic compliance.

35 Treatment with Nintedanib (60 mg/kg/PO/BID) resulted in significant increase of dynamic compliance when compared to respective vehicle group (HEC 10 mL/kg/PO/BID).

40 Groups treated with Compound 5 (30 mg/kg/PO/BID) showed slight increase in response of dynamic compliance when compared to their respective control (Vehicle 250 mg/kg/PO/BID).

- Dynamic compliance refers to the ability of the lungs to expand and contract during the breathing process. Hence, lung tissue challenged by BLM becomes less flexible due to fibrotic remodeling of the extracellular matrix. As a result, we observed a decrease in dynamic compliance upon BLM-challenge. Similar to other functional parameters the effect was most pronounced with HEC vehicle control and less pronounced with HPbCD used as vehicle for a representative compound 5. Nintedanib demonstrated a statistically significant effect, compound 5 could show a trend towards a benefit.
- As shown in **Fig. 10**, in comparison to the saline-challenged group, Ashcroft score was significantly increased in BLM-challenged mice treated with vehicles HEC (10mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID). This indicates that the Bleomycin challenge clearly impacted the lung tissue architecture and induced tissue remodeling including fibrotic changes.
- Treatment with Nintedanib (60mg/kg/PO/BID) significantly reduced Ashcroft score compared to the respective vehicle group (HEC10mL/kg/PO/BID). Technically, this data supports that the in vivo model has been successfully conducted. The effect of Nintedanib defines the expected assay window / in vivo effect size.
- Treatment with Compound 5 (30mg/kg/PO/BID) significantly reduced Ashcroft score, compared to the respective control (Vehicle 250mg/kg/PO/BID).
- Treatment with Compound 5 (65mg/kg/PO/BID) significantly reduced Ashcroft score compared to the respective control (Vehicle 500mg/kg/PO/BID). The range of effect is comparable to Nintedanib and confirm that TG2 inhibition has a structural benefit in the bleomycin mouse model.
- As shown in **Fig. 11**, in comparison to the saline-challenged group, COL1A1 positive surface was significantly increased in BLM- challenged mice treated with vehicles HEC (10mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID).
- Treatment with Nintedanib (60mg/kg/PO/BID) significantly decreased COL1A1 positive surface compared to the respective vehicle group (HEC10mL/kg/PO/BID).
- Treatment with Compound 5 (30mg/kg/PO/BID) significantly decreased COL1A1 positive surface compared to the respective control (Vehicle 250mg/kg/PO/BID).
- Observation in Col1A1 positive surface confirming the treatment effect of Nintedanib and Compound 5 at lower dose tested with a link to anti-fibrotic effect.

These morphological data reflected in the Ashcroft Score and Col1A1 positive surface staining demonstrate a significantly improved organ structure by Nintedanib treatment and to a comparable level with compound 5. In particular for the Ashcroft Score the observed treatment effects with compound 5 might be considered less variable compared to Nintedanib at the lower dose tested which underlined a clear morphological benefit upon transglutaminase inhibition. In combination with the Col1A1 staining a beneficial treatment effect of compound 5 compared with Nintedanib was underlined on top of the Ashcroft fibrosis scoring.

As shown in **Fig. 12** and **Fig. 13**, in comparison to the saline-challenged group, inflammation score (lymphocytes & eosinophils) was significantly increased in BLM-challenged animals treated with vehicles HEC (10mL/kg/PO/BID) and Vehicle (250 and 500 mg/kg/PO/BID).

Treatment with Nintedanib (60mg/kg/PO/BID) resulted in no statistically significant effect on lymphocytes compared to the respective vehicle group (HEC10mL/kg/PO/BID). Eosinophilic cell infiltrates were reduced by Nintedanib.

Treatment with Compound 5 (30mg/kg/PO/BID) significantly reduced the accumulation of lymphocytes and eosinophiles compared to the respective control (Vehicle 250mg/kg/PO/BID).

Treatment with Compound 5 (65mg/kg/PO/BID) did not influence the accumulation of lymphocytes and eosinophiles compared to the respective control (Vehicle 500mg/kg/PO/BID).

With regards to inflammation score bleomycin clearly induced an increase in inflammatory cell infiltration in all vehicle treated groups compared to saline challenged mice. With Nintedanib no statistically significant effect was observed on lymphocytes, whereas Compound 5 reduced lymphocytes and eosinophilic cell infiltrates and the lower dose tested. With this observation a pleiotropic mode of action as described for Nintedanib might have a less pronounced effect on immune-cell infiltration compared to transglutaminase inhibition which has been discussed in the literature to impact resolution of inflammation and function as marker for inflammation [Su, T; Qin, X.-Y.; Furutani, Y. Transglutaminase 2 as a Marker for Inflammation and Therapeutic Target in Sepsis. *Int. J. Mol. Sci.* 2021, 22, 1897].

Conclusion

- 5 The results of the study clearly demonstrate beneficial effect with Compound 5 on pulmonary fibrosis, inflammation, and morphology as well as a certain improvement in pulmonary function tests. BLM-challenge model induced lung tissue and function impairment: Vehicle animals showed increase lung weight, increased Ashcroft score, increased Col 1A1 staining, lymphocyte infiltration, and impaired functional parameters.
- 10 Treatment with Nintedanib resulted in improved lung function parameters indicating improved elasticity of the lung. Compound 5 showed comparable effect to Nintedanib on morphological changes: Improved Ashcroft score and improved Col1A1 stain indicating less fibrotic ECM remodeling. The observed morphological improvement
- 15 with Compound 5 are most important and for the lower dose tested less variable compared to Nintedanib pointing in the direction of a more pronounced organ tissue benefit. Compound 5 demonstrated reduced inflammatory score which could be used to explain the less variable data compared to a pleiotropic mode of action associated with Nintedanib which is less linked to anti-inflammation compared to transglutaminase
- 20 2 inhibition. For some functional parameters we observed more pronounced effects with the HEC vehicle group compared to the HPbCD vehicle groups. As a result of this, Nintedanib demonstrated a broader statistically significant effect which is not demonstrated for Compound 5 as strongly. However, Compound 5 at lower dose showed a tendency, non-significant improvement of functional parameters compared to
- 25 its vehicle indicating that morphological improvement translated into improved lung function in the conducted BLM-challenge model.

Biological *in-vitro* Examples:

Example 3

Testing the effect of compounds according to the invention on TGF β -stimulated α SMA and collagen 1 expression in normal human lung fibroblasts (NHLF)

Experiment setup α SMA immunostaining

Normal human lung fibroblasts (NHLF) (Lonza #CC2512) were seeded as 2000 cells/well in Pure-Col (Advanced Biomatrix #5005) coated 384-well plates in FGM medium supplemented with FBS, FGF, insulin, GA (Lonza #CC3132) and incubated overnight at 37°C, 5% CO₂, 95% humidity.

The next day, cell medium was replaced with starvation medium (FGM w/o FBS) and cells were incubated overnight.

After an overnight incubation, cells were treated with compounds or vehicle (0.1% DMSO).

- 5 Test compounds were tested at 9 consecutive 3-fold dilutions starting from 10 μ M. SB525334 (ALK5 inhibitor; BioVision #2880-5) was tested at 9 consecutive 3-fold dilutions starting from 10 μ M. Nintedanib (Santa Cruz #sc-364433) was tested at 9 consecutive 3-fold dilutions starting from 10 μ M.

- 10 Following 1 hour pre-incubation with compounds, cells were stimulated with TGF β (R&D Systems #240-B) at final concentration 1 ng/mL and incubated for 48 h at 37°C, 5% CO₂, 95% humidity.

Each compound was tested in duplicate, while TGF β stimulated and unstimulated controls were tested in 12 replicas each.

At the end of 48 h of incubation, α SMA immunostaining was performed.

- 15 Cell medium was discarded, cells were washed with PBS and then fixed with 4% formaldehyde (Ultra-Pure Polysciences #18814-10) for 20 min.

Cells were then washed and blocked with 3% BSA (Sigma #A2153), 2% FBS (BioWest #S1810-500), 0.2% Triton X-100 (Sigma #T9284) in PBS for 2 h.

- 20 After blocking step, anti- α SMA antibody (AbCam #ab7817) was added diluted 500x in blocking buffer and incubated for 1 h.

Cells were then washed, followed by addition of secondary anti-mouse antibody conjugated to AF488 (ThermoFisher #A11029) diluted 500x in blocking buffer + Hoechst stain (Molecular Probes #H21492) diluted 2000x and incubated for 1 h.

- 25 Imaging was performed using High Content ImageXpress instrument (Molecular Devices):

- 10X objective, 2 sites imaged per each well;
- α SMA was detected using FITC channel, cell nuclei (Hoechst) was detected using DAPI channel.

30 **Experiment setup Collagen 1 immunostaining**

Normal human lung fibroblasts (NHLF) (Lonza #CC2512) were seeded as 2000 cells/well in Pure-Col (Advanced Biomatrix #5005) coated 384-well plates in FGM medium supplemented with FBS, FGF, insulin, GA (Lonza #CC3132) and incubated overnight at 37°C, 5% CO₂, 95% humidity.

- 35 The next day, cell medium was replaced with starvation medium (FGM w/o FBS) with addition of L-ascorbic acid (Sigma #A8960), Ficoll 70 (Sigma #F2878) and Ficoll 400 (Sigma #F4375) and cells were then treated with compounds or vehicle (0.1% DMSO). Test compounds were tested at 9 consecutive 3-fold dilutions starting from 10 μ M.

- SB525334 (ALK5 inhibitor; BioVision #2880-5) was tested at 9 consecutive 3-fold dilutions starting from 10 μ M. Nintedanib (Santa Cruz #sc-364433) was tested at 9 consecutive 3-fold dilutions starting from 10 μ M. Reference compounds showed inhibition of collagen expression.
- 5 Following 1 hour pre-incubation with compounds, cells were stimulated with TGF β (R&D Systems #240-B) at final concentration 1 ng/mL and incubated for 72 h at 37°C, 5% CO₂, 95% humidity.
- Each compound was tested in duplicate, while TGF β stimulated and unstimulated controls were tested in 12 replicas each.
- 10 At end of 72 h of incubation, Collagen 1 immunostaining was performed.
- Cell medium was discarded, cells were washed with PBS and then fixed with methanol (Sigma #154903) for 2 min.
- Cells were then washed and anti-collagen 1 antibody (Sigma #C2456) was added diluted 1000x in PBS and incubated for 1 h.
- 15 Cells were then washed, followed by addition of secondary anti-mouse antibody conjugated to AF488 (ThermoFisher #A11029) diluted 500x in blocking buffer + Hoechst stain (Molecular Probes #H21492) diluted 2000x and incubated for 1 h.
- Imaging was performed using High Content ImageXpress instrument (Molecular Devices):
- 20 - 10X objective, 2 sites imaged per each well;
- Collagen 1 was detected using FITC channel, cell nuclei (Hoechst) was detected using DAPI channel.

Data analysis

- 25 Percentage of α SMA positive cells, collagen positive cells and total cell number (Hoechst nuclear dye) was quantified using MetaXpress software (Molecular Devices). Inhibition of α SMA and collagen 1 was calculated by subtracting the unstimulated control from all other data and then using the equation: $(1 - (\text{mean compound treatment} / \text{mean TGF}\beta \text{ vehicle})) \times 100$.
- 30 IC₅₀ values were determined by plotting % inhibition against the Log10 compound test concentration using a four-parametric sigmoidal curve fit with a variable slope using GraphPad Prism software.
- If no concentration achieved more than 50% inhibition, IC₅₀ was expressed as > 10,000 nM (highest concentration tested, categorized "D" or "no potency", compare to table 5).
- 35 If IC₅₀ was found to be between 6,666 nM [extrapolated] and 10,0000 nM, compound was categorized "C" or "weak". More potent compounds (IC₅₀ between 3,333 nM and 6,666 nM [extrapolated]) were categorized "B" or "medium". Most potent compounds (IC₅₀ below 3,333 nM were ranked "A" / "strong", compared to table 5).

Influence of compounds on cell number was expressed relative to vehicle (mean compound treatment / mean vehicle) × 100.

Results

5 αSMA immunostaining

The FMT assay goal was testing the effect of compounds on TGFβ-stimulated αSMA and collagen 1 expression in NHLF (normal human lung fibroblasts). As positive controls the Alk5 inhibitor SB525334 and Nintedanib (unspecific pan-kinase inhibitor) were included.

10 TGF-β1 induces αSMA synthesis, and this was dose-dependently inhibited by Alk5 kinase inhibitor and nitedanib;

The compounds of the present invention did not display any meaningful inhibitory activity towards TGF-β1 induced αSMA synthesis therefore suggesting a novel mode-of-action compared to the Alk5 inhibitor and the pan-kinase blocker.

15

Results

Collagen 1 immunostaining

For FMT intracellular α-smooth muscle actin (αSMA) expression was assessed by high content imaging. In parallel samples were analyzed for extracellular collagen I A1 expression by high content imaging. Collagen deposits produced by stimulated fibroblasts / myofibroblasts are the hallmark of fibrosis. Cell viability (number of nuclei) was determined in all samples.

25 All of compounds 1 – 84 of the present invention showed a dose-dependent effect in the assay (either strong, medium, or weak), whereas the reference compounds R-1 – R-11 not according to the present invention showed no activity (see also table 5 below). Fig. 14 A – E shows the results for inventive compounds 5, 7, 9, 10, and 43 (showing all strong dose-dependent effect in the assay, see table 5). The results clearly demonstrate the effectiveness of the compounds of the present invention.

30

Table 5. Effect of compounds on reducing TGFβ-stimulated collagen 1 expression in NHLF (normal human lung fibroblasts).

A: strong (IC₅₀ < 3,333 nM), **B:** medium (3,333 nM ≤ IC₅₀ < 6,666 nM),
C: weak (6,666 nM ≤ IC₅₀ ≤ 10,000 nM), **D:** no potency (IC₅₀ > 10,000 nM)

35

Compound	Effect	Compound	Effect
1	C	R-1	D
2	B	R-2	D
3	A	R-3	D

4	B	R-4	D
5	A	R-5	D
6	B	R-6	D
7	A	R-7	D
8	B	R-8	D
9	A	R-9	D
10	A	R-10	D
11	A	R-11	D
12	B	R-12	D
13	A	R-13	D
14	A	R-14	D
15	B	R-15	D
16	B	R-16	D
17	B	R-17	D
18	A	R-18	D
19	B	R-19	D
20	B	R-20	D
21	C	R-21	D
22	B	R-22	D
23	C	R-23	D
24	A	R-24	D
25	B	R-25	D
26	C	R-26	D
27	B	R-27	D
28	B	R-28	D
29	C	R-29	D
30	C	R-30	D
31	C	R-31	D
32	C	R-32	D
33	B	R-33	D
34	C	R-34	D
35	B	R-35	D
36	B	R-36	D
37	B	R-37	D
38	B	R-38	D

39	B	R-39	D
40	B	R-40	D
41	C	R-41	D
42	B	R-42	D
43	A	R-43	D
44	C	R-44	D
45	C	R-45	D
46	C	R-46	D
47	C	R-47	D
48	C	R-48	D
49	C	R-49	D
50	C	R-50	D
51	C	R-51	D
52	C	R-52	D
53	A	R-53	D
54	B	R-54	D
55	A	R-55	D
56	B	R-56	D
57	B	R-57	D
58	B	R-58	D
59	A	R-59	D
60	B	R-60	D
61	C	R-61	D
62	B	R-62	D
63	B	R-63	D
64	C	R-64	D
65	B	R-65	D
66	B	R-66	D
67	B	R-67	D
68	B	R-68	D
69	B	R-69	D
70	B	R-70	D
71	B	R-71	D
72	C	R-72	D
73	C	R-73	D

74	B	R-74	D
75	B	R-75	D
76	C	R-76	D
77	B	R-77	D
78	B	R-78	D
79	A	R-79	D
80	B	R-80	D
81	B	R-81	D
82	B	R-82	D
83	B	R-83	D
84	B	R-84	D
		R-85	D
		R-86	D
		R-87	D
		R-88	D
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		R-90	D
		R-91	D
		R-92	D
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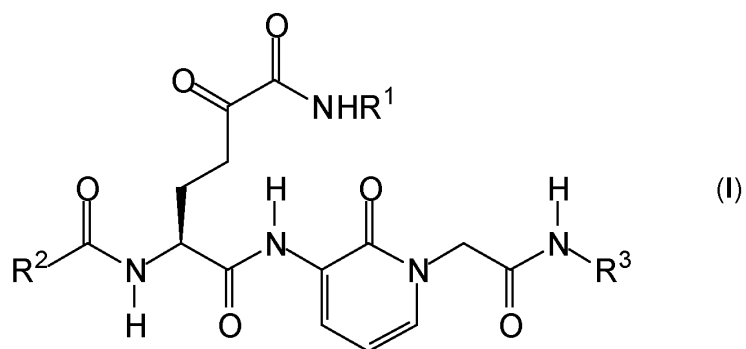
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		R-110	D
		R-111	D

Conclusion

Targeting TGF- β s at ligand or receptor level ameliorates lung fibrosis in various animal models. However, broad inhibition of TGF- β activity/signalling is associated with unacceptable side effects both in animal models and human clinical trials. Therefore, more selective intervention that specifically targets downstream fibrotic reactions but leaves other critical functions of TGF- β such as in resolution of inflammatory processes intact, offers critical advantages. Several compounds of the present invention are apparently strong potent inhibitors of TGF- β 1 induced collagen I synthesis while apparently not altering canonical Smad signalling (indicated by functional α SMA expression). Moreover, compound 5 has been tested in the bleomycin mouse model and has been shown to have a potent anti-fibrotic and anti-inflammatory activity. Taken together, this suggest that not only are the respective drug candidates potent blocker of fibrosis in the in vivo model but that the mode of action may primarily be targeting Smad-independent TGF- β signalling and therefore potentially preserve anti-inflammatory functions of TGF- β 1, beyond others.

CLAIMS

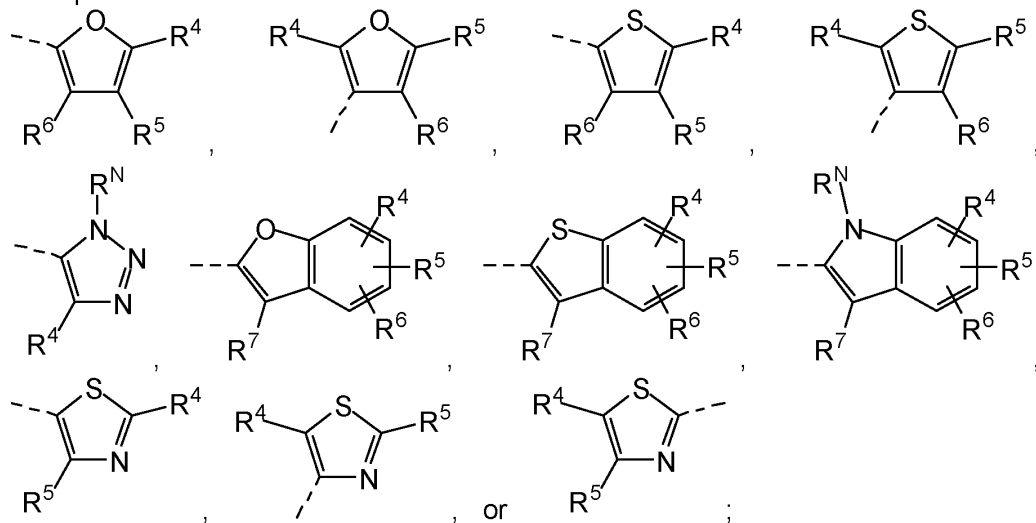
- 5 1. A compound of the general formula (I):



wherein

R¹ represents -H or -CH₃;

R² represents



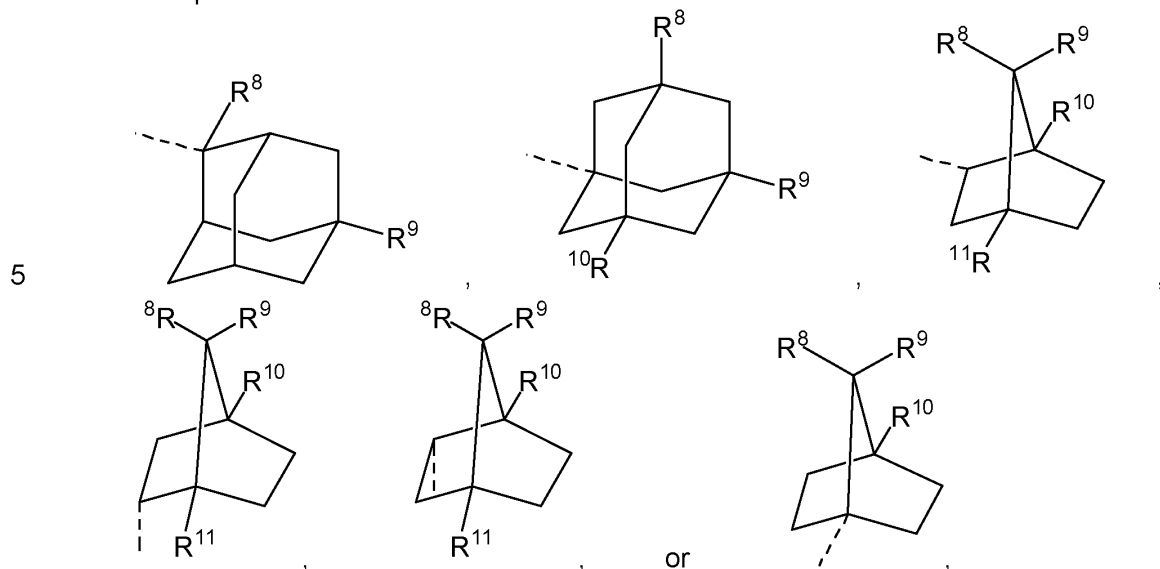
R³ represents **-X** or **-CH₂-X**;

R⁴, R⁵, R⁶ and R⁷ represent independently of each other -H, -F, -Cl, -Br, -CH₃, or -CF₃;

R⁸, R⁹, R¹⁰, and R¹¹ represent independently of each other -H, -F, -Cl, -Br, -CN, -OH, -CH₃, -CF₃, -COCH₃, -CO₂CH₃;

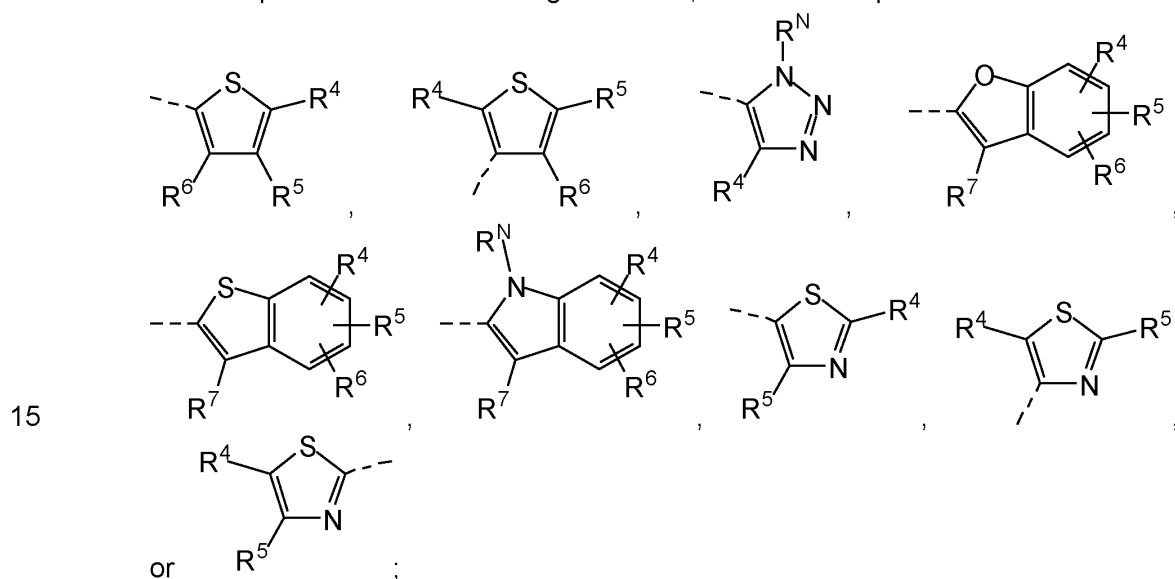
R^N represents $-H$ or $-CH_3$;

X represents



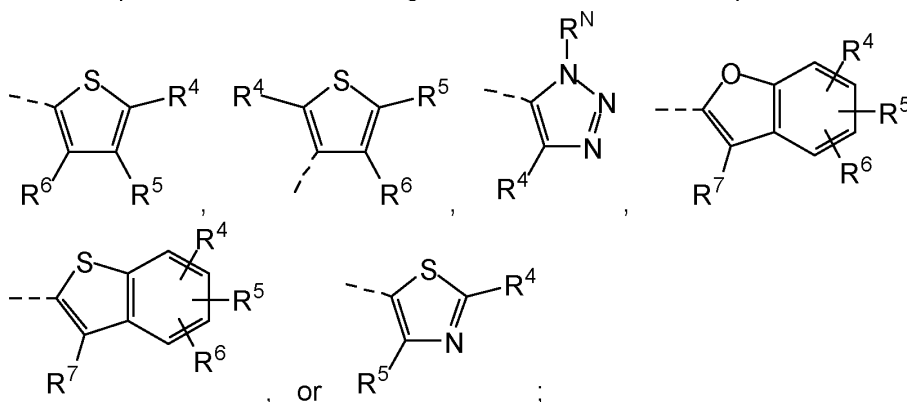
or a diastereomer, an enantiomer, a mixture of diastereomers, a mixture of enantiomers, a racemate, a solvate, a hydrate, or a pharmaceutically acceptable salt thereof for use in the treatment of pulmonary inflammation, pulmonary fibrosis, in particular **idiopathic pulmonary fibrosis**.

2. The compound for use according to claim 1, wherein R^2 represents



and $R^4 - R^7$ and R^N have the meanings as defined in claim 1.

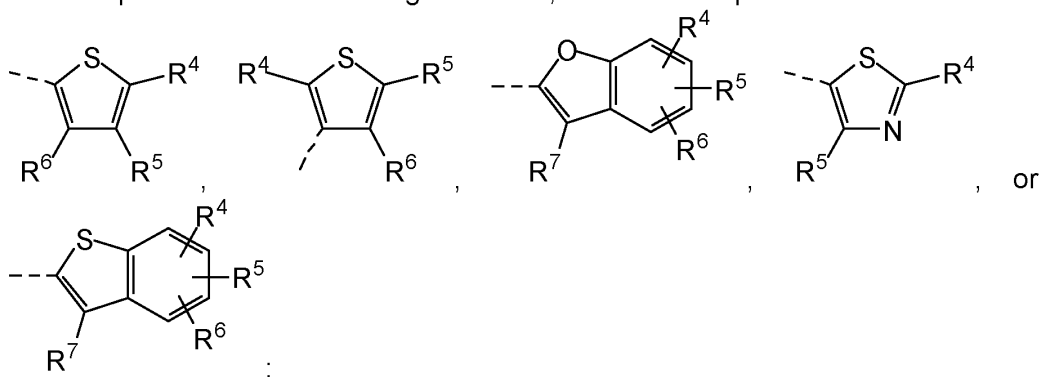
3. The compound for use according to claim 1, wherein **R²** represents



5

and **R⁴ – R⁷** and **R^N** have the meanings as defined in claim 1.

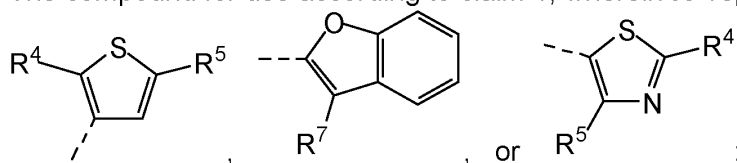
4. The compound for use according to claim 1, wherein **R²** represents



10

and **R⁴ – R⁷** have the meanings as defined in claim 1.

5. The compound for use according to claim 1, wherein **R²** represents

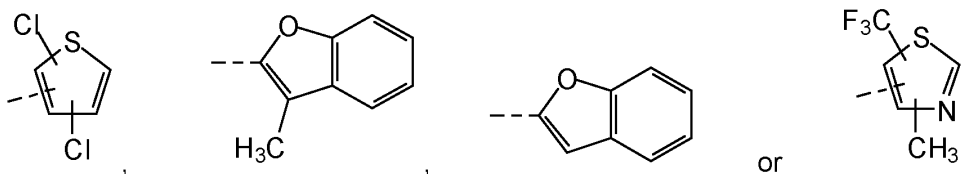


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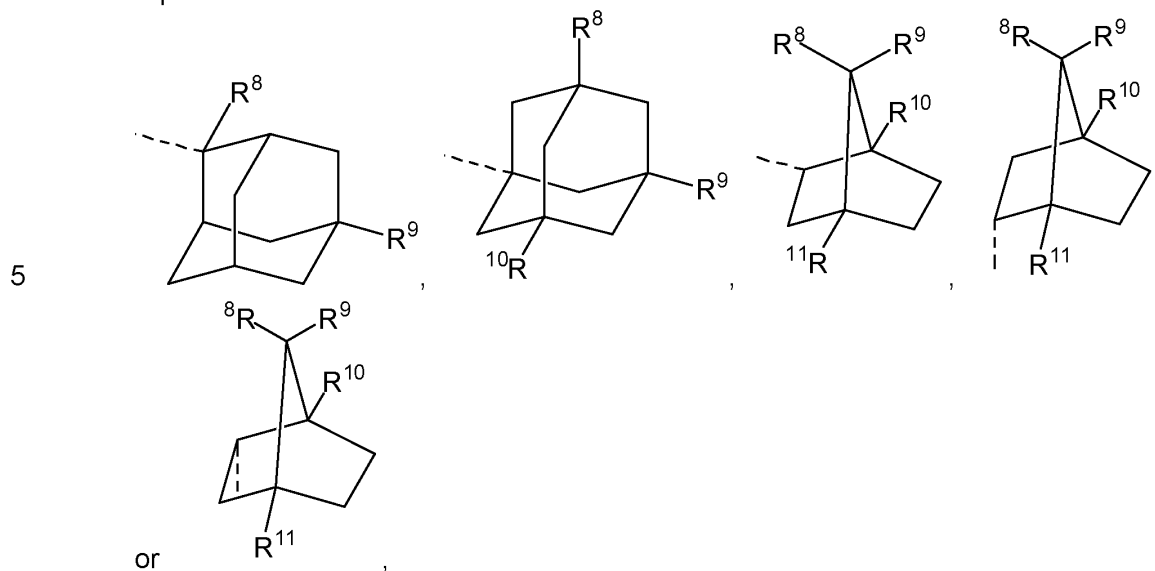
and **R⁴ – R⁷** have the meanings as defined in claim 1.

6. The compound for use according to claim 1, wherein **R²** represents

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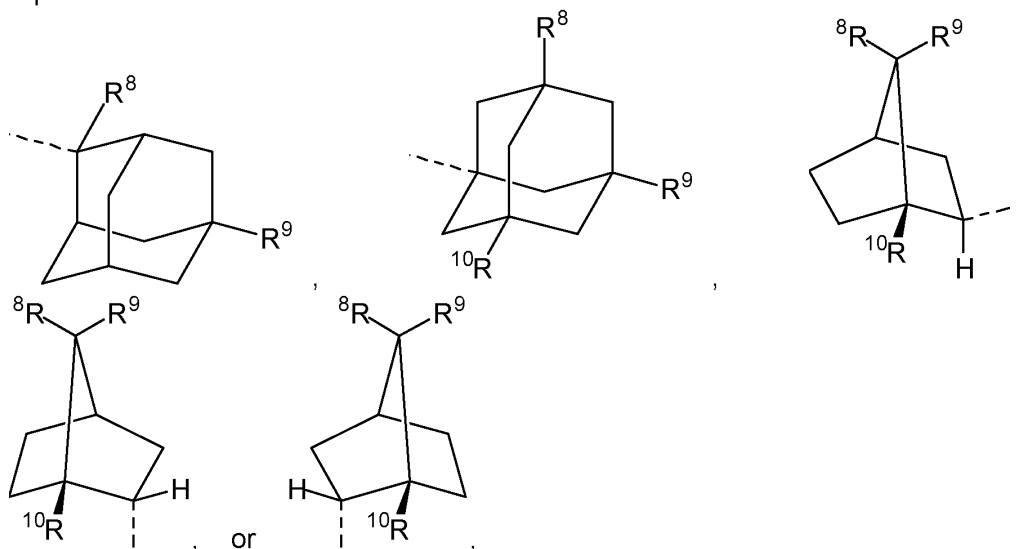


7. The compound for use according to any one of the claims 1 – 6, wherein **X** represents



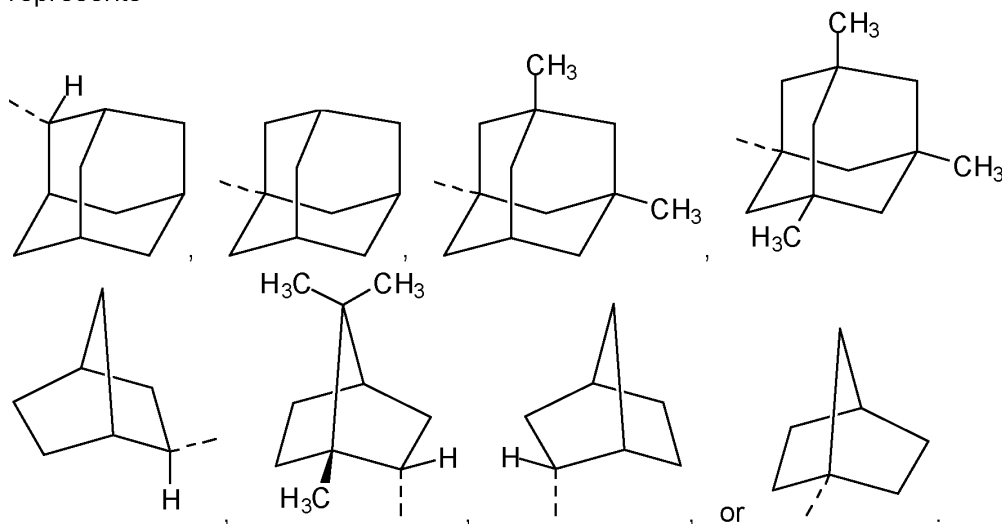
and **R⁸ – R¹¹** have the meanings as defined in claim 1.

- 10 8. The compound for use according to any one of the claims 1 – 6, wherein **X** represents

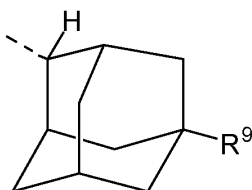


and $R^8 - R^{10}$ have the meanings as defined in claim 1.

9. The compound for use according to any one of the claims 1 – 6, wherein **X** represents

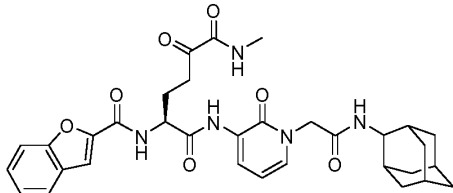
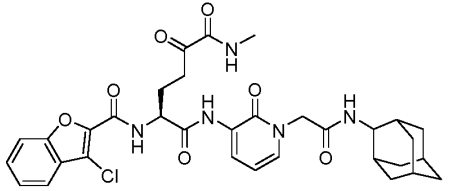
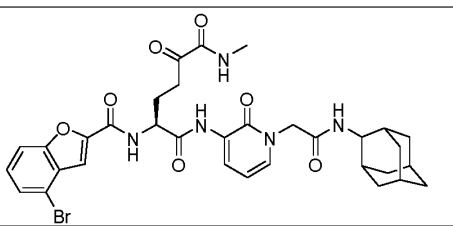
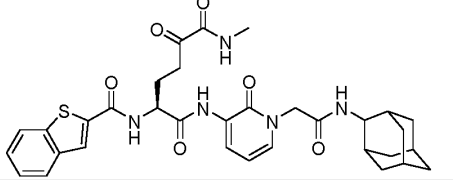
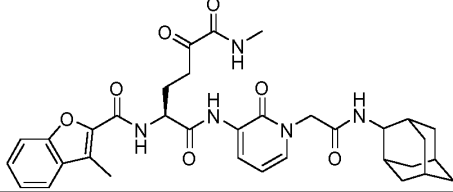
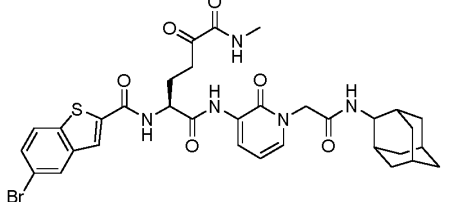
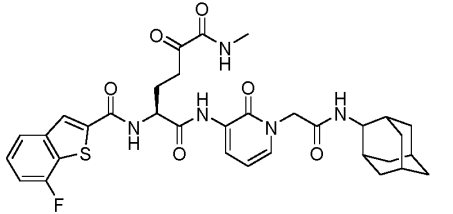
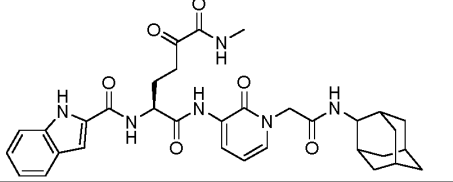


10. The compound for use according to any one of the claims 1 – 6, wherein **X** represents



and R^9 has the meanings as defined in claim 1.

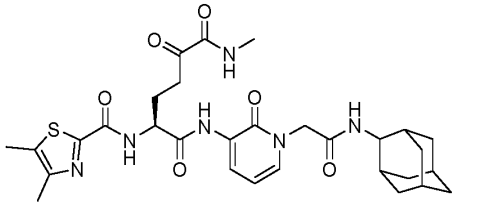
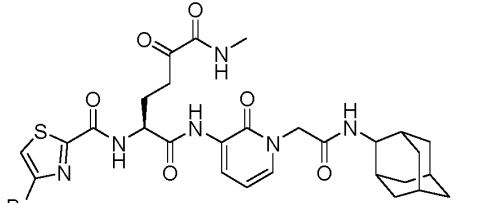
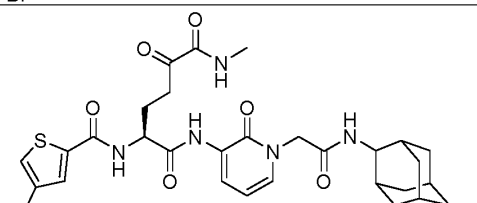
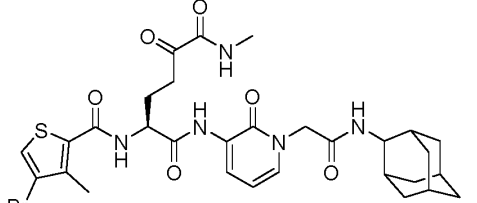
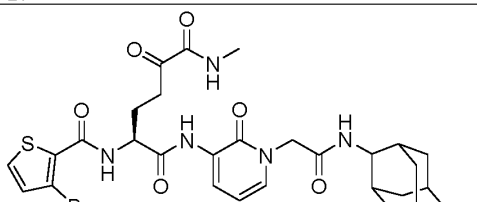
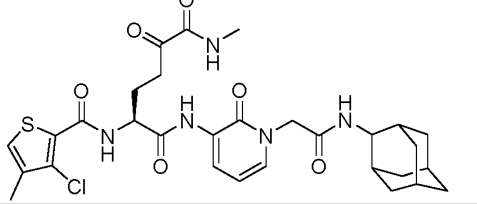
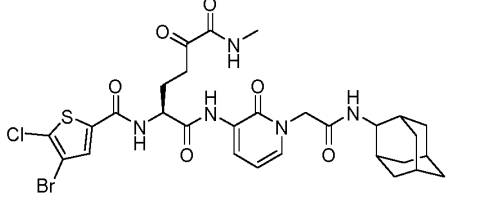
11. The compound for use according to any one of the claims 1 – 10, wherein R^4 , R^5 , R^6 and R^7 represent independently of each other $-H$, $-Cl$, $-CH_3$, or $-CF_3$.
12. The compound for use according to any one of the claims 1 – 11, wherein R^3 represents $-X$.
13. The compound for use according to any one of the claims 1 – 12, wherein R^1 represents $-CH_3$.
14. The compound for use according to claim 1 selected from the group consisting of:

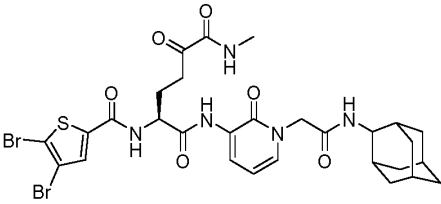
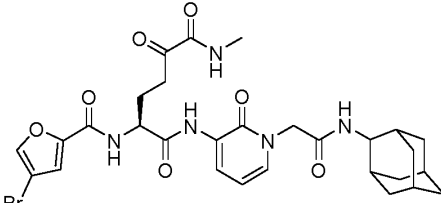
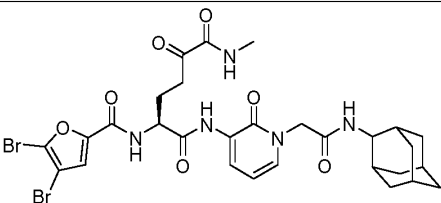
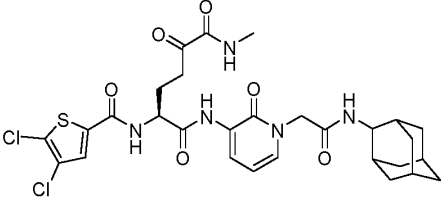
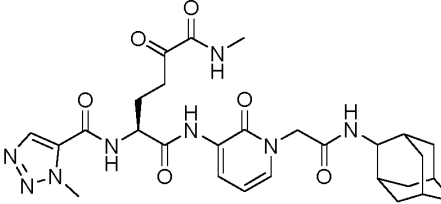
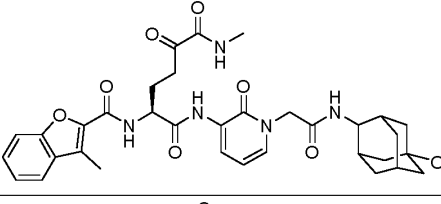
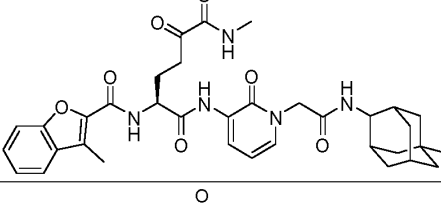
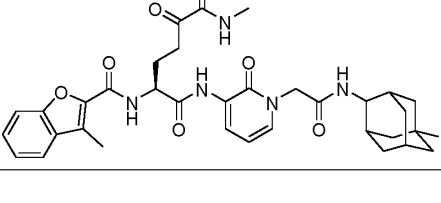
1		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
2		(S)-2-(3-chlorobenzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
3		(S)-2-(4-bromobenzofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
4		(S)-2-(benzo[b]thiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
5		S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanedi- amide
6		(S)-2-(5-bromobenzo[b]thiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
7		(S)-2-(7-fluorobenzo[b]thiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
8		(S)-2-(1H-indole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide

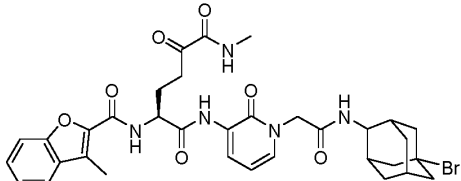
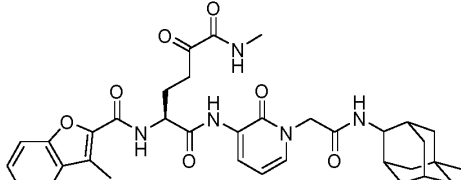
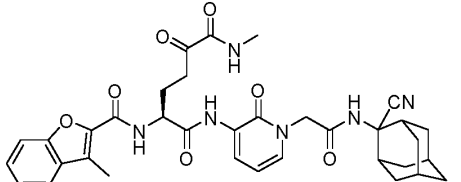
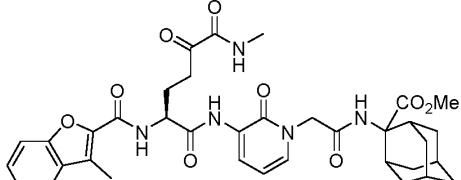
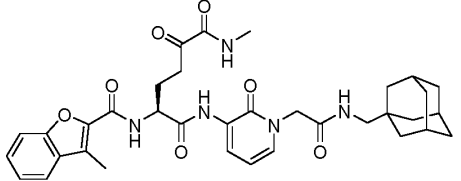
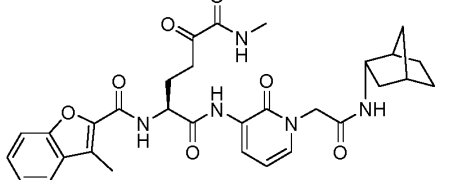
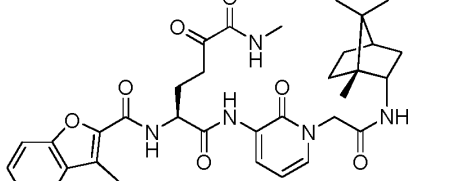
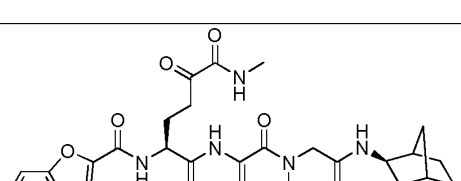
9		(S)-2-(4,5-difluoro-1H-indole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
10		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methyl-1H-indole-2-carboxamido)-5-oxohexanediamide
11		(S)-2-(2-bromo-4-methylthiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
12		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
13		(S)-2-(4-bromo-2-(trifluoromethyl)thiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
14		(S)-2-(2,4-dichlorothiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
15		(S)-2-(2,4-dimethylthiazole-5-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
16		(S)-2-(5-bromo-3-methylthiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

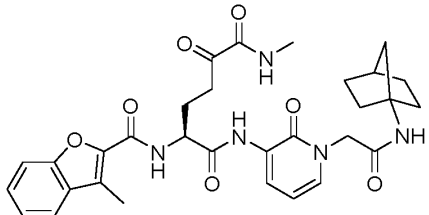
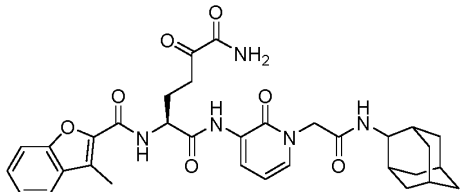
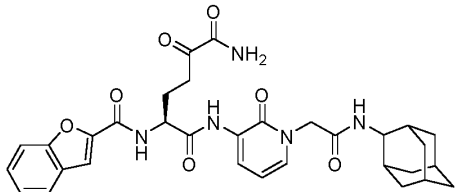
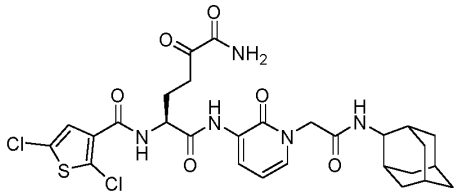
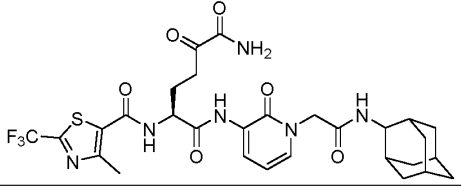
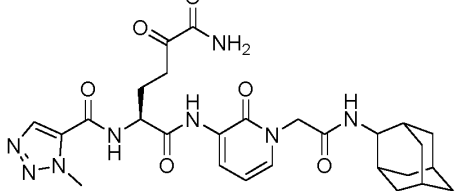
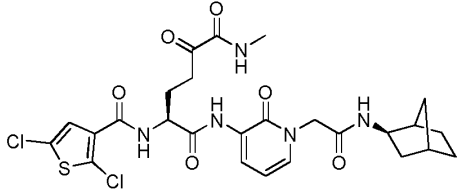
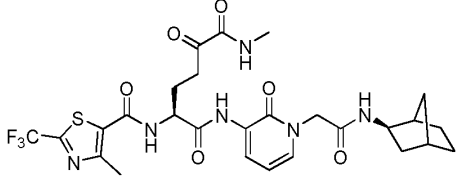
17		(S)-2-(3,5-dibromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
18		(S)-2-(5-bromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
19		(S)-2-(5-chlorothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
20		(S)-2-(5-bromo-3-methylfuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
21		(S)-2-(5-chlorofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
22		(S)-2-(5-chlorothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
23		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide
24		(S)-2-(2,5-dibromothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanedi- amide

25		(S)-2-(5-bromothiophene-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
26		(S)-2-(2-chloro-5-methylthiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
27		(S)-2-(2,5-dichlorothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
28		(S)-2-(2,5-dibromothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
29		(S)-2-(2-bromo-5-methylthiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
30		(S)-2-(2-bromothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
31		(S)-2-(2-chlorothiazole-4-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
32		(S)-2-(2,5-dimethylfuran-3-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

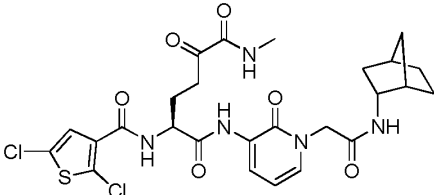
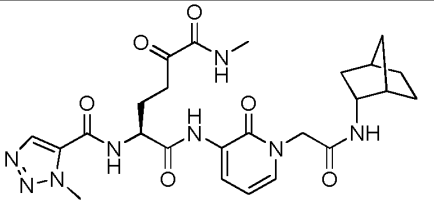
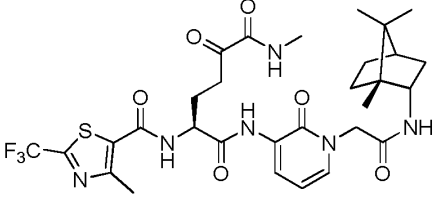
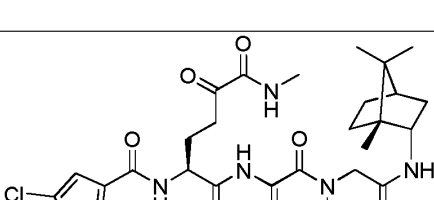
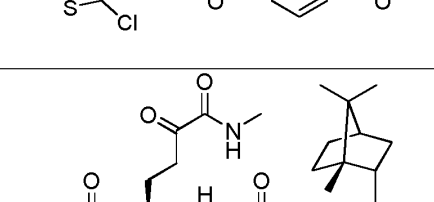
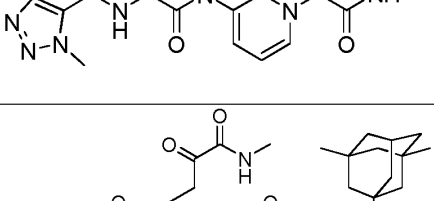
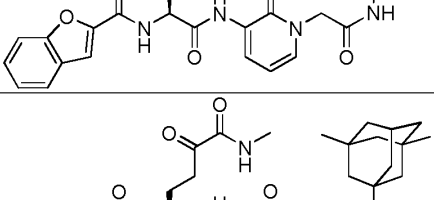
33		(S)-2-(4,5-dimethylthiazole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
34		(S)-2-(4-bromothiazole-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
35		(S)-2-(4-bromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
36		(S)-2-(4-bromo-3-methylthiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
37		(S)-2-(3-bromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
38		(S)-2-(3-chloro-4-methylthiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
39		(S)-2-(4-bromo-5-chlorothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide

40		(S)-2-(4,5-dibromothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
41		(S)-2-(4-bromofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
42		(S)-2-(4,5-dibromofuran-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
43		(S)-2-(4,5-dichlorothiophene-2-carboxamido)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
44		(S)-N1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
45		(S)-N1-(1-(2-(5-hydroxyadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
46		(S)-N1-(1-(2-(5-fluoroadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
47		(S)-N1-(1-(2-(5-chloroadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

48		(S)-N1-(1-(2-(5-bromoadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
49		(S)-N1-(1-(2-(5-methyladamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
50		(S)-N1-(1-(2-(2-carbonitrileadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
51		(S)-N1-(1-(2-(2-methyladamantane-2-carboxylate-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
52		(S)-N1-(1-(2-(1-adamantylmethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
53		(S)-N1-(1-(2-((1R,2S,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
54		(S)-N1-methyl-5-(3-methylbenzofuran-2-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
55		(S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

56:		(S)-N1-(1-(2-(bicyclo[2.2.1]heptan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
57		(S)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
58		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
59		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
60		(S)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
61		(S)-N1-(1-(2-(2-Adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
62		(2S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(2,5-dichlorothiophene-3-carboxamido)-N6-methyl-5-oxohexanediamide
63		(2S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide

64		(2S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
65		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
66		(S)-N1-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
67		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-oxohexanediamide
68		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
69		(S)-2-(benzofuran-2-carboxamido)-5-oxo-N1-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
70		(S)-2-(3-methylbenzofuran-2-carboxamido)-5-oxo-N1-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
71		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide

72		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(2,5-dichlorothiophene-3-carboxamido)-N6-methyl-5-oxohexanediamide
73		(S)-N1-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-5-oxohexanediamide
74		(S)-N1-methyl-5-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
75		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N6-methyl-5-oxo-N1-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
76		(S)-N1-methyl-5-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-2-oxo-N6-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-yl)hexanediamide
77		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
78		(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide

79		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
80		(S)-N1-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide
81		(S)-2-(benzofuran-2-carboxamido)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
82		(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(3-methylbenzofuran-2-carboxamido)-5-oxohexanediamide
83		(S)-2-(2,5-dichlorothiophene-3-carboxamido)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-5-oxohexanediamide
84		(S)-N1-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N6-methyl-2-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-5-oxohexanediamide

or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound of any one of the claims 1 – 12 as an active ingredient, together with at least one pharmaceutically acceptable carrier, excipient and/or diluent for use in the treatment of pulmonary inflammation, pulmonary fibrosis, in particular idiopathic pulmonary fibrosis.