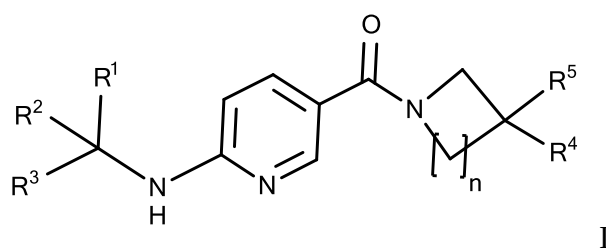


Moreover the compounds of the present invention exhibit further capacities, which are favorable for their pharmacokinetic and pharmacological profile, e.g. good solubility and good metabolic stability. Further advantages of the compounds of the present invention are good chemical stability and good permeability.

3. SUMMARY

In one aspect, the present disclosure provides a compound of the formula I,



wherein

n denotes 1 or 2;

R¹, R² and R³ are independently from each other selected from the group consisting of C₁₋₄-alkyl optionally substituted by hydroxy, CH₃-O-, CH₃-SO₂-, Phenyl-CH₂- optionally substituted by 1 to 3 halogen atoms and 5-6 membered heteroaryl-C₁₋₂-alkyl-;

or

R² and R³ together form a 3-6 membered carbocycle or 4-6 membered heterocyclyl containing one heteroatom selected from the group consisting of N and O;

or

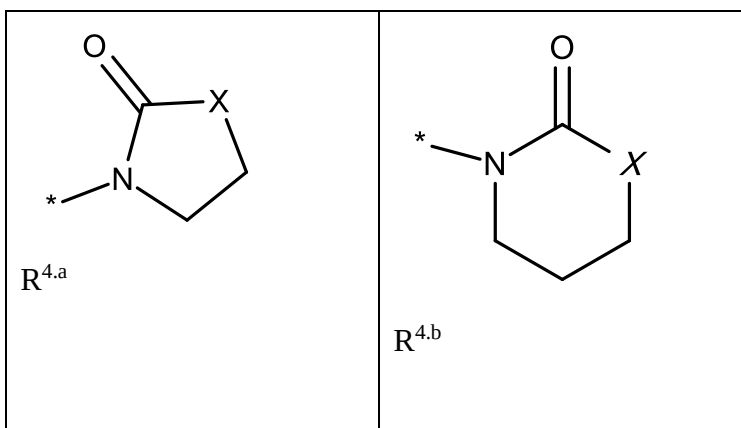
R^1 , R^2 and R^3 together form a bicyclic 5-8 membered carbocycle or a bicyclic 6-8 membered heterocyclyl containing one heteroatom selected from the group consisting of N and O;

wherein in the definition of R^1 , R^2 and R^3 mentioned alkyl, cycloalkyl, heteroaryl and heterocyclyl are optionally substituted by 1 to 3 halogen atoms;

R^4 denotes $R^{4.1}R^{4.2}N$ -, 5-6 membered heteroaryl, NC- or 5-6 membered heterocyclyl;

or

R^4 denotes a group of formula $R^{4.a}$ or $R^{4.b}$



wherein

X denotes CH_2 , $-NR^X$ or O;
wherein R^X denotes H or C_{1-3} -alkyl;

$R^{4.a}$ and $R^{4.b}$ independently from each other are optionally substituted by methyl ;

$R^{4.1}$ is selected from the group consisting of C_{1-4} -alkyl-CO- optionally substituted by 1-3 F-atoms, C_{3-4} -cycloalkyl or C_{1-2} -alkoxy, C_{3-5} -cycloalkyl-CO- substituted with $R^{4.1.1}$ and $R^{4.1.2}$, 4-6 membered heterocyclyl-CO- substituted with $R^{4.1.3}$ and $R^{4.1.4}$, 4-6 membered

heterocyclyl-CH₂-CO-, 5-6 membered heteroaryl-CO- optionally substituted by 1 halogen atom, H₃C-O- or 1 to 2 methyl, phenyl-CO- substituted with R^{4.1.5} and R^{4.1.6}, (C₁₋₃-alkyl)(C₁₋₃-alkyl)N-CO- and 5-6 membered heteroaryl;

wherein

R^{4.1.1}, R^{4.1.2} independently from each other are selected from the group consisting of H, -CH₃, F, CF₃ and -CN;

R^{4.1.3}, R^{4.1.4} independently from each other are selected from the group consisting of H, -CH₃, F, CF₃ and -CN;

R^{4.1.5}, R^{4.1.6} independently from each other are selected from the group consisting of H, -CH₃, F, CF₃ and -CN;

R^{4.2} is selected from the group consisting of H, C₁₋₄-alkyl, C₃₋₄-cycloalkyl, C₃₋₄-cycloalkyl-C₁₋₂-alkyl- and phenyl-C₁₋₂-alkyl-;

wherein in the definition of R^{4.2} mentioned alkyl, cycloalkyl and phenyl are optionally substituted by 1-3 F-atoms or one C₁₋₂-alkyl-O-;

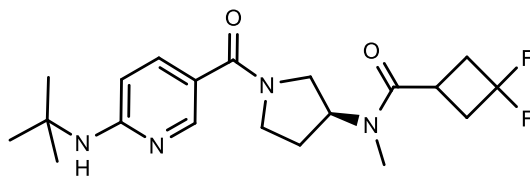
R⁵ denotes H or C₁₋₂-alkyl;

or

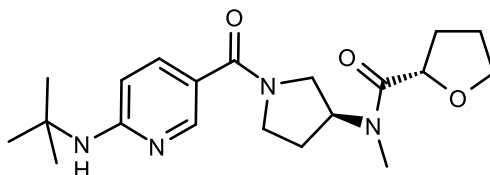
R⁴ and R⁵ together form 4-6 membered heterocyclyl containing 1 heteroatom selected from the group consisting of N and O;

or a pharmaceutically acceptable salt thereof.

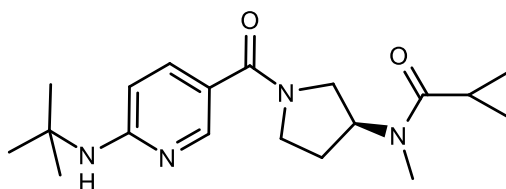
In another aspect, the present disclosure provides a compound of formula:



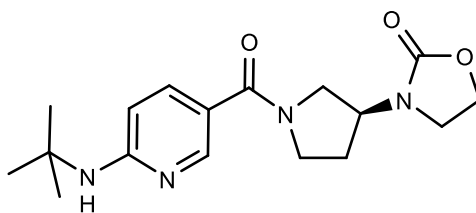
In another aspect, the present disclosure provides a compound of formula:



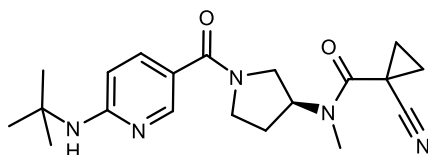
In another aspect, the present disclosure provides a compound of formula:



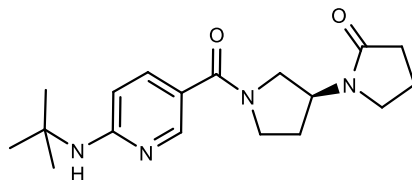
In another aspect, the present disclosure provides a compound of formula:



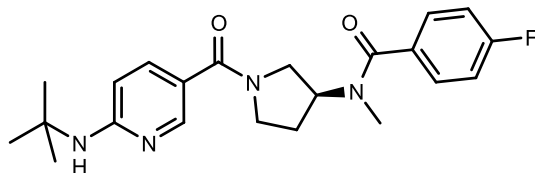
In another aspect, the present disclosure provides a compound of formula:



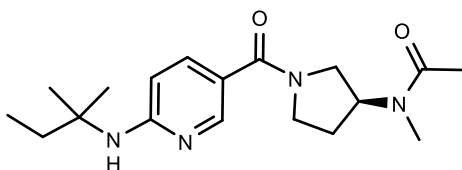
In another aspect, the present disclosure provides a compound of formula:



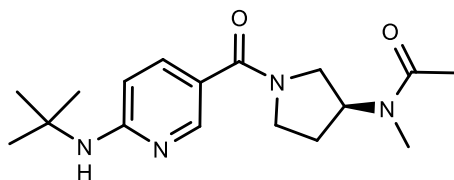
In another aspect, the present disclosure provides a compound of formula:



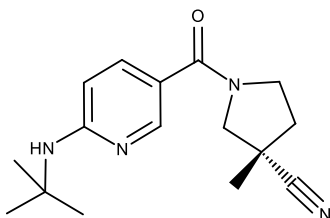
In another aspect, the present disclosure provides a compound of formula:



In another aspect, the present disclosure provides a compound of formula:



In another aspect, the present disclosure provides a compound of formula:



In another aspect, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of at least one compound as described herein or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure provides a compound as described herein, or a pharmaceutically acceptable salt thereof for use as a medicament.

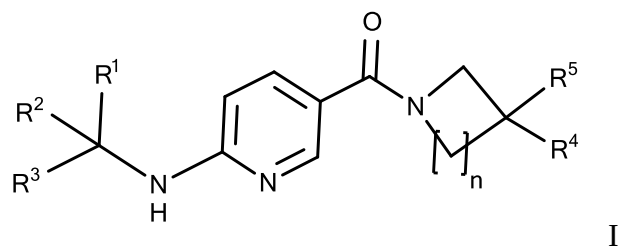
In another aspect, the present disclosure provides use of the compound as described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient suffering from Crohn's disease, ulcerative colitis, atopic dermatitis, systemic sclerosis, Non-Alcoholic Steatohepatitis (NASH), psoriasis, chronic kidney disease, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, rheumatoid arthritis, scleroderma, asthma, allergic rhinitis, allergic eczema, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, graft versus host disease, psoriatic arthritis, Hyperlipidemia, colorectal cancer or pancreatic cancer related new onset diabetes.

In another aspect, the present disclosure provides a pharmaceutical composition comprising additionally to a compound as described herein, a pharmaceutically active compound selected from the group consisting of an immunomodulatory agent, anti-inflammatory agent or a chemotherapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that the problem mentioned above is solved by compounds of formula I of the present invention.

The present invention therefore relates to a compound of formula I



wherein

n denotes 1 or 2;

R^1 , R^2 and R^3 are independently from each other selected from the group consisting of C_{1-4} -alkyl optionally substituted by hydroxy, CH_3-O- , CH_3-SO_2- , Phenyl- CH_2- optionally substituted by 1 to 3 halogen atoms and 5-6 membered heteroaryl- C_{1-2} -alkyl- ;

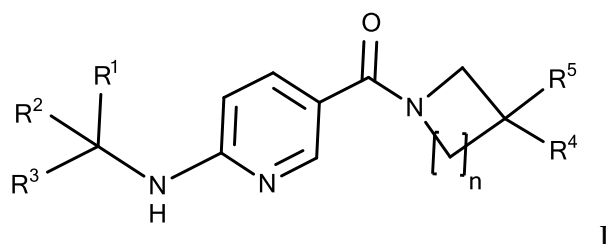
or

R^2 and R^3 together form a 3-6 membered carbocycle or 4-6 membered heterocyclyl containing one heteroatom selected from the group consisting of N and O;

or

CLAIMS

1. A compound of the formula I,



wherein

n denotes 1 or 2;

R^1 , R^2 and R^3 are independently from each other selected from the group consisting of C_{1-4} -alkyl optionally substituted by hydroxy, CH_3-O- , CH_3-SO_2- , Phenyl- CH_2- optionally substituted by 1 to 3 halogen atoms and 5-6 membered heteroaryl- C_{1-2} -alkyl-;

or

R^2 and R^3 together form a 3-6 membered carbocycle or 4-6 membered heterocyclyl containing one heteroatom selected from the group consisting of N and O;

or

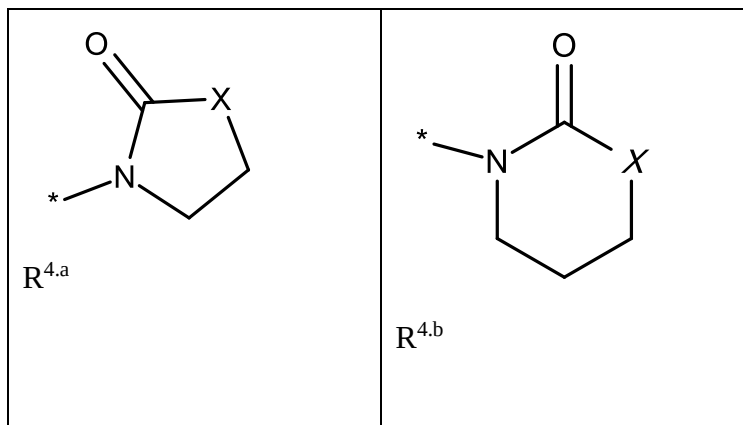
R^1 , R^2 and R^3 together form a bicyclic 5-8 membered carbocycle or a bicyclic 6-8 membered heterocyclyl containing one heteroatom selected from the group consisting of N and O;

wherein in the definition of R^1 , R^2 and R^3 mentioned alkyl, cycloalkyl, heteroaryl and heterocyclyl are optionally substituted by 1 to 3 halogen atoms;

R^4 denotes $R^{4.1}R^{4.2}N-$, 5-6 membered heteroaryl, NC- or 5-6 membered heterocyclyl;

or

R^4 denotes a group of formula $R^{4.a}$ or $R^{4.b}$



wherein

X denotes CH_2 , $-\text{NR}^X$ or O;

wherein R^X denotes H or C_{1-3} -alkyl;

$R^{4.a}$ and $R^{4.b}$ independently from each other are optionally substituted by methyl ;

$R^{4.1}$ is selected from the group consisting of C_{1-4} -alkyl-CO- optionally substituted by 1-3 F-atoms, C_{3-4} -cycloalkyl or C_{1-2} -alkoxy, C_{3-5} -cycloalkyl-CO- substituted with $R^{4.1.1}$ and $R^{4.1.2}$, 4-6 membered heterocyclyl-CO- substituted with $R^{4.1.3}$ and $R^{4.1.4}$, 4-6 membered heterocyclyl- CH_2 -CO-, 5-6 membered heteroaryl-CO- optionally substituted by 1 halogen atom, H_3C -O- or 1 to 2 methyl, phenyl-CO- substituted with $R^{4.1.5}$ and $R^{4.1.6}$, $(\text{C}_{1-3}\text{-alkyl})(\text{C}_{1-3}\text{-alkyl})\text{N-CO-}$ and 5-6 membered heteroaryl;

wherein

$R^{4.1.1}$, $R^{4.1.2}$ independently from each other are selected from the group consisting of H, $-\text{CH}_3$, F, CF_3 and $-\text{CN}$;

$R^{4.1.3}$, $R^{4.1.4}$ independently from each other are selected from the group consisting of H, $-\text{CH}_3$, F, CF_3 and $-\text{CN}$;

$R^{4.1.5}$, $R^{4.1.6}$ independently from each other are selected from the group consisting of H, $-CH_3$, F, CF_3 and $-CN$;

$R^{4.2}$ is selected from the group consisting of H, C_{1-4} -alkyl, C_{3-4} -cycloalkyl, C_{3-4} -cycloalkyl- C_{1-2} -alkyl- and phenyl- C_{1-2} -alkyl-;

wherein in the definition of $R^{4.2}$ mentioned alkyl, cycloalkyl and phenyl are optionally substituted by 1-3 F-atoms or one C_{1-2} -alkyl-O-;

R^5 denotes H or C_{1-2} -alkyl;

or

R^4 and R^5 together form 4-6 membered heterocyclyl containing 1 heteroatom selected from the group consisting of N and O;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1,

wherein

n denotes 1,

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1,

wherein

n denotes 2,

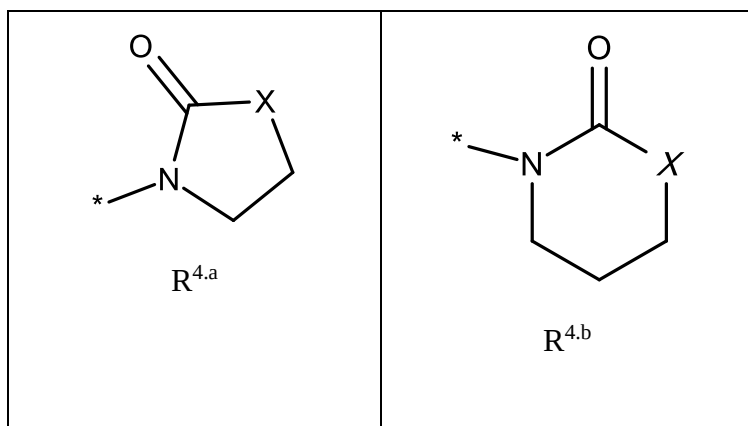
or a pharmaceutically acceptable salt thereof.

4. The compound according to one or more of claims 1 to 3, wherein

R^1 denotes methyl,

or a pharmaceutically acceptable salt thereof.

5. The compound according to one or more of claims 1 to 4, wherein R^2 denotes methyl,
or a pharmaceutically acceptable salt thereof.
6. The compound according to one or more of claims 1 to 5, wherein R^3 denotes C_{1-3} -alkyl optionally substituted by hydroxy
or a pharmaceutically acceptable salt thereof.
7. The compound according to one or more of claims 1 to 4, wherein R^2 and R^3 together form a 4-6 membered carbocycle or 6-membered heterocyclyl containing one oxygen atom,
or a pharmaceutically acceptable salt thereof.
8. The compound according to one or more of claims 1 to 7, wherein R^4 is selected from the group consisting of $R^{4.1}R^{4.2}N-$, pyridinyl and $NC-$;
or
 R^4 denotes a group of formula $R^{4.a}$ or $R^{4.b}$



wherein

X denotes CH_2 or O;

$R^{4.a}$ and $R^{4.b}$ independently from each other are optionally substituted by methyl ,

$R^{4.1}$ is selected from the group consisting of C_{1-4} -alkyl-CO-, C_{3-4} -cycloalkyl-CO- substituted with $R^{4.1.1}$ and $R^{4.1.2}$, 5-6 membered heterocyclyl-CO- substituted with $R^{4.1.3}$ and $R^{4.1.4}$, 6 membered heterocyclyl-CH₂-CO-, 5 membered heteroaryl-CO- optionally substituted by 1 halogen atom, phenyl-CO- substituted with $R^{4.1.5}$ and $R^{4.1.6}$ and 6 membered heteroaryl;

wherein

$R^{4.1.1}$, $R^{4.1.2}$ independently from each other are selected from the group consisting of H, -CH₃, F, CF₃ and -CN;

$R^{4.1.3}$, $R^{4.1.4}$ independently from each other are selected from the group consisting of H, -CH₃, F, CF₃ and -CN;

$R^{4.1.5}$, $R^{4.1.6}$ independently from each other are selected from the group consisting of H, -CH₃, F, CF₃ and -CN;

$R^{4.2}$ denotes methyl;

or a pharmaceutically acceptable salt thereof.

9. The compound according to one or more of claims 1 to 8, wherein

R^5 denotes H or methyl;

or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 1, wherein

n denotes 1 or 2;

R^1 denotes methyl;

R^2 denotes methyl;

R^3 denotes C_{1-3} -alkyl optionally substituted by hydroxyl;

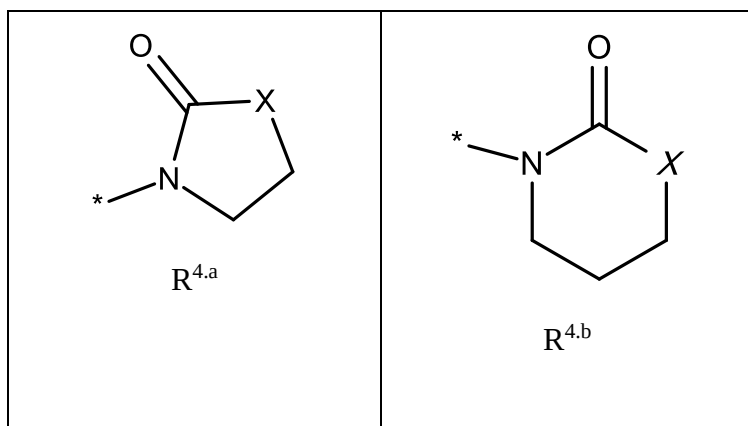
or

R^2 and R^3 together form a 4-6 membered carbocycle or a 6-membered heterocyclyl containing one oxygen atom;

R^4 is selected from the group consisting of $R^{4.1}R^{4.2}N$ -, pyridinyl and NC -;

or

R^4 denotes a group of formula $R^{4.a}$ or $R^{4.b}$;



wherein

X denotes CH_2 or O;

$R^{4.a}$ and $R^{4.b}$ independently from each other are optionally substituted by methyl ,

$R^{4.1}$ is selected from the group consisting of C_{1-4} -alkyl-CO-, C_{3-5} -cycloalkyl-CO- substituted with $R^{4.1.1}$ and $R^{4.1.2}$, 4-6 membered heterocyclyl-CO- substituted with $R^{4.1.3}$ and $R^{4.1.4}$, 6 membered heterocyclyl- CH_2 -CO-, 5-6 membered heteroaryl-CO- optionally substituted by 1 halogen atom, phenyl-CO- substituted with $R^{4.1.5}$ and $R^{4.1.6}$ and 6 membered heteroaryl containing 1 or 2 N-atoms;

wherein

$R^{4.1.1}$, $R^{4.1.2}$ independently from each other are selected from the group consisting of H, F and $-CN$;

$R^{4.1.3}$, $R^{4.1.4}$ independently from each other are selected from the group consisting of H, $-CH_3$ and CF_3 ;

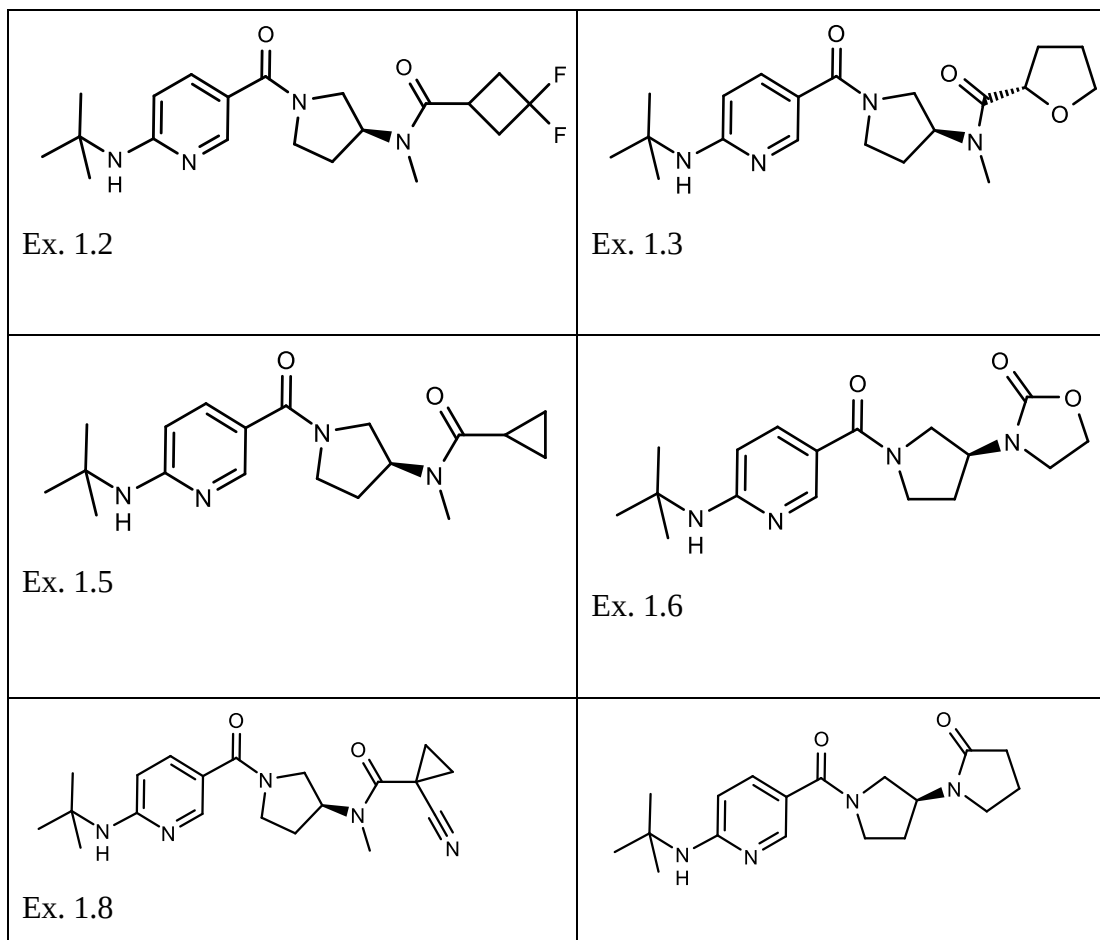
$R^{4.1.5}$, $R^{4.1.6}$ independently from each other are selected from the group consisting of H and F;

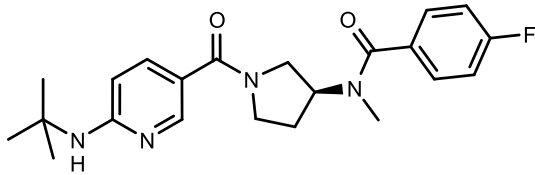
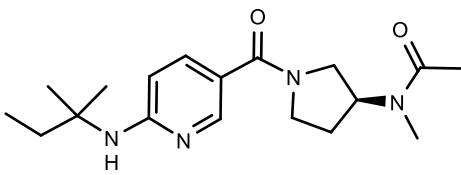
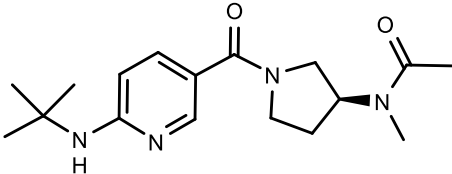
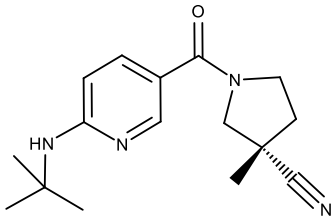
$R^{4.2}$ denotes methyl;

R^5 denotes H or methyl;

or a pharmaceutically acceptable salt thereof.

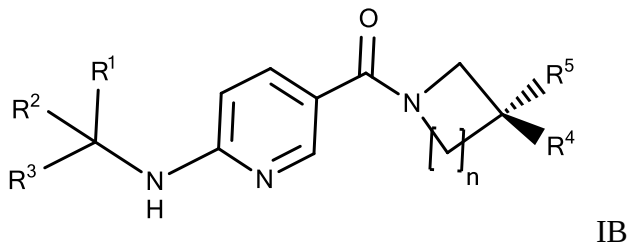
11. The compound according to claim 1 or 10 selected from the group consisting of examples 1.2, 1.3, 1.5, 1.6, 1.8, 1.9, 1.11, 3.2, 5.1 and 7.1;



	Ex. 1.9
 Ex. 1.11	 Ex. 3.2
 Ex. 5.1	 Ex. 7.1

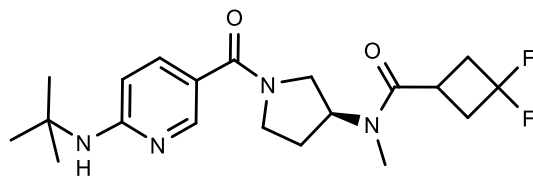
or a pharmaceutically acceptable salt thereof.

12. The compound according to one or more of claims 1 to 11, wherein the compound is of formula IB

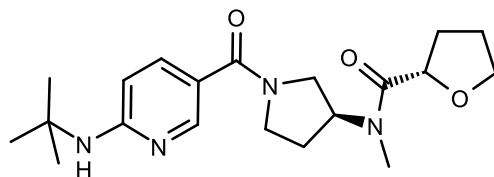


or a pharmaceutically acceptable salt thereof.

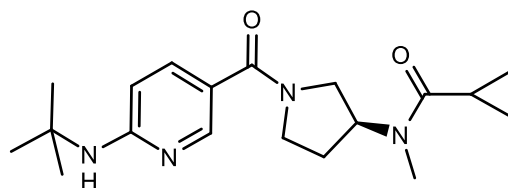
13. A compound of formula:



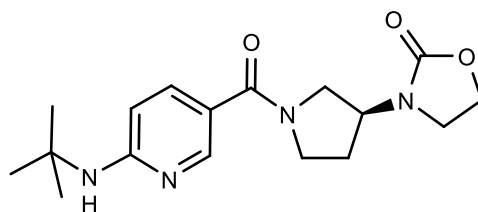
14. A compound of formula:



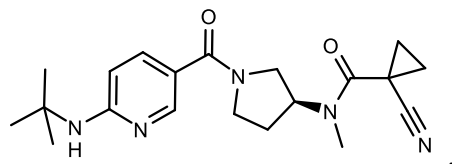
15. A compound of formula:



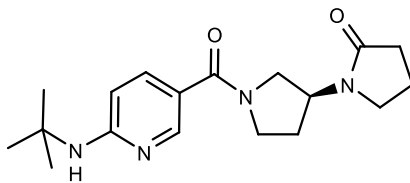
16. A compound of formula:



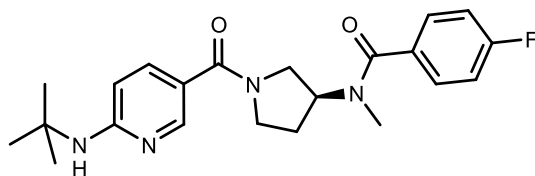
17. A compound of formula:



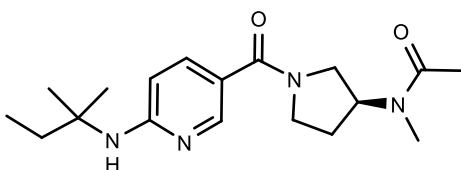
18. A compound of formula:



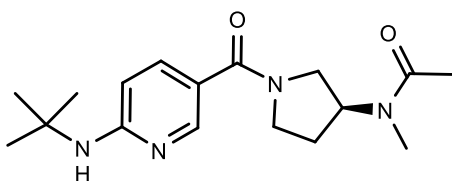
19. A compound of formula:



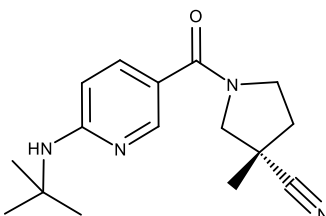
20. A compound of formula:



21. A compound of formula:



22. A compound of formula:



23. A pharmaceutically acceptable salt of the compound of any one of claims 13 to 22.

24. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.
25. A compound according to one or more of claims 1 to 22, or a pharmaceutically acceptable salt thereof for use as a medicament.
26. Use of the compound according to one or more of claims 1 to 22, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient suffering from Crohn's disease, ulcerative colitis, atopic dermatitis, systemic sclerosis, Non-Alcoholic Steatohepatitis (NASH), psoriasis, chronic kidney disease, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, rheumatoid arthritis, scleroderma, asthma, allergic rhinitis, allergic eczema, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, graft versus host disease, psoriatic arthritis, Hyperlipidemia, colorectal cancer or pancreatic cancer related new onset diabetes.
27. A pharmaceutical composition comprising additionally to a compound according to any one or more of claims 1 to 22, a pharmaceutically active compound selected from the group consisting of an immunomodulatory agent, anti-inflammatory agent or a chemotherapeutic agent.