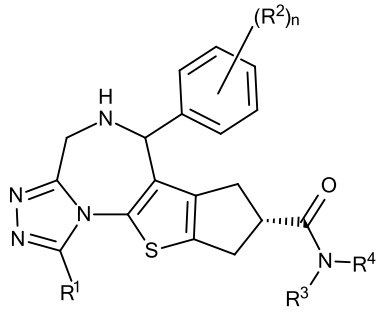
Low molecular weight PAFR antagonists are known in the art, for example, the compounds described in EP0194416A1 and EP0254245A1, by Weber et al. (Med. Res. Rev.1989, 9, 181-218) and Summers et al. (Curr. Pharm. Des. 1995, 1, 161-190). Compounds of the thienotriazolodiazepine class as disclosed therein have been reported to undergo hydrolytic degradation in acidic solution (e.g. Gallo et al. (J. Heterocyclic Chem. 1988, 25, 867-869), Legouin et al. (J. Heterocyclic Chem. 2000, 37, 127-129)). Some of these compounds have also been identified to act as inverse agonists of PAFR (Dupré et al. (J. Pharm. Exp. Ther. 2001, 299, 1, 358-365), Cellai et al. (Exp. Hematol. 2009, 37, 1176-1185)).

Further methods useful for the syntheses and separation of said and related compounds are disclosed in DE4132763A1, EP0388789A1, EP0450504A1, US7015213B1, WO2008/063667A1, Tahara et al. (Arzneimittel-forschung 1978, 28, 1153-1158), Sung et al. (Archiv der Pharmazie 1996, 329, 291-300), Fier et al. (Org. Lett. 2017, 19, 1454-1457), and Brenna et al. (Green Chem. 2017, 19, 5122-5130).

Summary

The present disclosure relates to a compound of formula (I.0)



(I.0)

,

wherein

R^1 is selected from the group R^1-G1 consisting of C_{1-4}-alkyl optionally substituted with 1 to 3 F and of C_{3-4}-cycloalkyl;

R^2 is selected from the group R^2-G1 consisting of F, Cl, Br, I, C_{1-4}-alkyl optionally substituted with 1 to 3 F or optionally substituted with 1 -CN, with 1 OH, or with 1 -O-C_{1-4}-alkyl, further consisting of C_{3-4}-cycloalkyl, -CN, -$CONH_2$, -CONH(C_{1-4}-alkyl), -CON(C_{1-4}-alkyl)$_2$, -COOH, -COO-C_{1-4}-alkyl, OH, -O-C_{1-4}-alkyl optionally substituted with 1 to 3 F, and consisting of -$S(O)_r$-C_{1-4}-alkyl with r = 0, 1, or 2;

n is selected from the group n-G1 consisting of 0, 1, 2, and 3;

R^3 is selected from the group R^3-G1 consisting of H and C_{1-4}-alkyl optionally substituted with 1 to 5 F; and

R^4 is selected from the group R^4-G1a consisting of C_{1-6}-alkyl

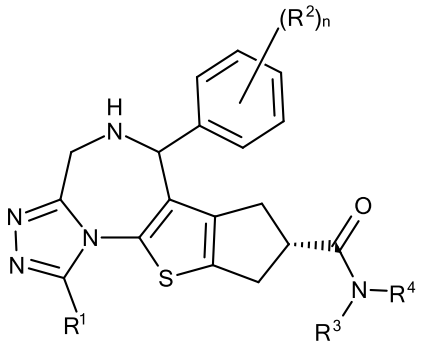
optionally substituted with 1 to 3 F and

optionally substituted with 1 to 2 substituents independently selected from -CN, -$CONH_2$, -CONH(C_{1-4}-alkyl), -CON(C_{1-4}-alkyl)$_2$, -COOH, -COO-C_{1-4}-alkyl, C_{1-3}-alkyl-CO-NH-, C_{1-3}-alkyl-$S(=O)_2$-NH-, OH, and -O-C_{1-3}-alkyl optionally substituted with 1 to 3 F;

wherein in any definition mentioned hereinbefore and if not specified otherwise, any alkyl or alkylene group may be straight-chained or branched,

the isomers, stereoisomers, tautomers, metabolites, prodrugs, solvates, hydrates, cocrystals, and the salts thereof, particularly the pharmaceutically acceptable salts thereof, or the combinations thereof.

In one aspect, the present disclosure relates to a compound of formula (I.0)



(I.0)

,

wherein

R^1 is selected from the group consisting of C_{1-4}-alkyl optionally substituted with 1 to 3 F and of C_{3-4}-cycloalkyl;

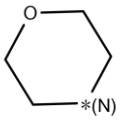
R^2 is selected from the group consisting of F, Cl, Br, I, C_{1-4}-alkyl, C_{3-4}-cycloalkyl, -CN, -$CONH_2$, -$CONH(C_{1-4}$-alkyl), -$CON(C_{1-4}$-alkyl)$_2$, -COOH, -COO-C_{1-4}-alkyl, OH, -O-C_{1-4}-alkyl, and -$S(O)_r$-C_{1-4}-alkyl with r = 0, 1, or 2,

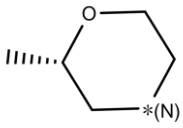
wherein the C_{1-4}-alkyl group of R^2 is optionally substituted with 1 to 3 F or optionally substituted with 1 -CN, with 1 OH, or with 1 -O-C_{1-4}-alkyl, and

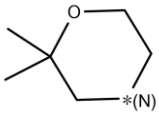
wherein the -O-C_{1-4}-alkyl group of R^2 is optionally substituted with 1 to 3 F;

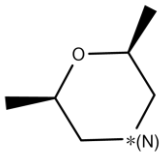
n is selected from the group consisting of 0, 1, 2, and 3; and

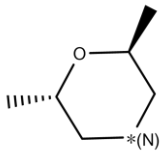
R^3 and R^4, together with the amide N atom they are attached to, form a heterocyclyl selected from the group consisting of

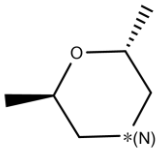


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, and


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or a salt thereof.

In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of the compound as described herein.

The present disclosure relates to a pharmaceutical composition comprising one or more compounds of formula (I.0), as defined hereinbefore or hereinafter, or pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising one or more compounds as described herein, or pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

The present disclosure relates to a pharmaceutical composition comprising one or more compounds of formula (I.0), as defined hereinbefore or hereinafter, or pharmaceutically acceptable salts thereof, and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising one or more compounds as described herein, or pharmaceutically acceptable salts thereof, and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

The present disclosure relates to a compound of formula (I.0), as defined hereinbefore or hereinafter, or a pharmaceutically acceptable salt thereof for use as a medicament.

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

The present disclosure relates to a method for the treatment of diseases or conditions which can be influenced by antagonizing the platelet activating factor receptor in a patient in need thereof, the method comprising administering to the patient one or more compounds of formula (I.0), as defined hereinbefore or hereinafter, or pharmaceutically acceptable salts thereof.

In addition, the present disclosure relates to the use of one or more compounds of formula (I.0), as defined hereinbefore or hereinafter, or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of diseases or conditions which can be influenced by antagonizing the platelet activating factor receptor.

In another aspect, the present disclosure relates to use of the compound as described herein or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of ocular diseases, preferably diabetic macular edema, dry and wet age-related macular degeneration, geographic atrophy and non-exudative choroidal neovascularization, and for the treatment of allergies and inflammation-related conditions and diseases, preferably urticaria and NASH.

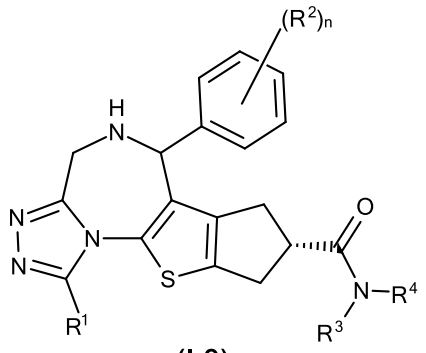
Furthermore, the present disclosure relates to a compound of formula (I.0), as defined hereinbefore or hereinafter, or a pharmaceutically acceptable salt thereof for use in a method for the treatment of diseases or conditions which can be influenced by antagonizing the platelet activating factor receptor, in a patient in need thereof.

In another aspect, the present disclosure relates to the compound as described herein or a pharmaceutically acceptable salt thereof for use in the treatment of ocular diseases, preferably diabetic macular edema, dry and wet age-related macular degeneration, geographic atrophy and non-exudative choroidal neovascularization, and for the treatment of allergies and inflammation-related conditions and diseases, preferably urticaria and NASH.

Further aspects of the present disclosure will become apparent to the person skilled in the art directly from the foregoing and following description and the examples.

Claims

1. A compound of formula (I.0)



(I.0)

,

wherein

R^1 is selected from the group consisting of C_{1-4}-alkyl optionally substituted with 1 to 3 F and of C_{3-4}-cycloalkyl;

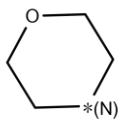
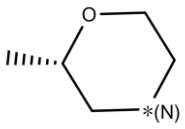
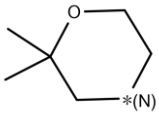
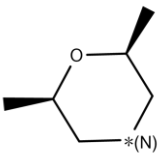
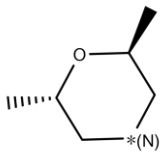
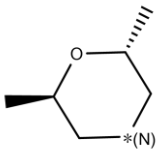
R^2 is selected from the group consisting of F, Cl, Br, I, C_{1-4}-alkyl, C_{3-4}-cycloalkyl, -CN, -$CONH_2$, -$CONH(C_{1-4}$-alkyl), -$CON(C_{1-4}$-alkyl$)_2$, -COOH, -COO-C_{1-4}-alkyl, OH, -O-C_{1-4}-alkyl, and -$S(O)_r$-C_{1-4}-alkyl with r = 0, 1, or 2,

wherein the C_{1-4}-alkyl group of R^2 is optionally substituted with 1 to 3 F or optionally substituted with 1 -CN, with 1 OH, or with 1 -O-C_{1-4}-alkyl, and

wherein the -O-C_{1-4}-alkyl group of R^2 is optionally substituted with 1 to 3 F;

n is selected from the group consisting of 0, 1, 2, and 3; and

R^3 and R^4, together with the amide N atom they are attached to, form a heterocyclyl selected from the group consisting of


,

,

,

,

, and

,

or a salt thereof.

2. The compound according to claim 1, wherein

R^1 is selected from the group consisting of CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CHF_2, CF_3, and cyclopropyl;

or a salt thereof.

3. The compound according to claim 1, wherein

R^1 is selected from the group consisting of CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and cyclopropyl;

or a salt thereof.

4. The compound according to claim 1, wherein

R^1 is CH_3;

or a salt thereof.

5. The compound according to any of claims 1 to 4, wherein

R^2 is selected from the group consisting of

F, Cl, Br, C_{1-3}-alkyl optionally substituted with 2 or 3 F, further consisting of cyclopropyl, -CN, -C_{1-3}-alkylene-OH, -C_{1-2}-alkylene-O-C_{1-2}-alkyl, OH, -O-C_{1-3}-alkyl optionally substituted with 2 or 3 F, and consisting of -S-C_{1-3}-alkyl; and

n is selected from the group consisting of 0, 1, and 2;

or a salt thereof.

6. The compound according to any of claims 1 to 4, wherein

R^2 is selected from the group consisting of

F, Cl, Br, CH_3, CH_2CH_3, cyclopropyl, CF_3, CH_2OH, OH, OCH_3, and S-CH_3; and

n is selected from the group consisting of 0, 1, and 2;

or a salt thereof.

7. The compound according to claim 1, wherein

R^1 is CH_3 ;

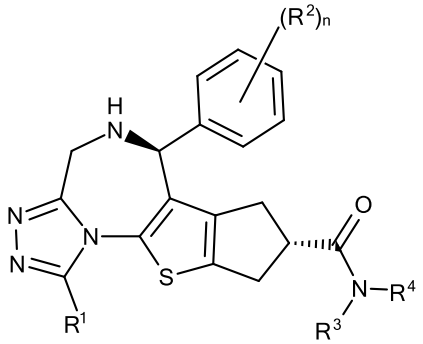
R^2 is Cl;

n is 1;

or a salt thereof.

8. The compound according to any of claims 1 to 7, wherein

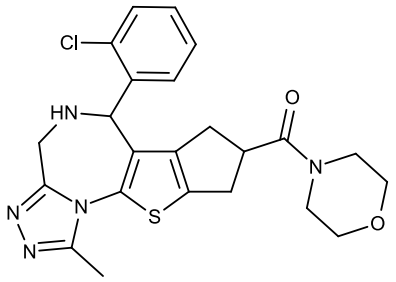
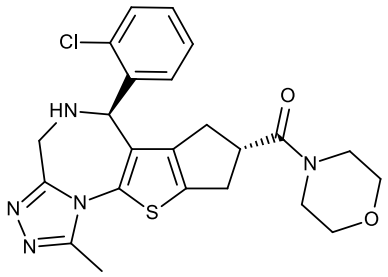
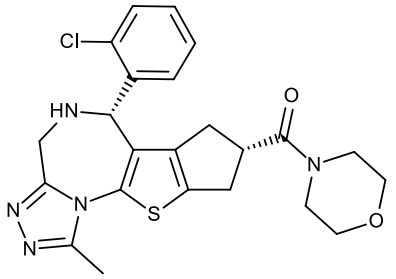
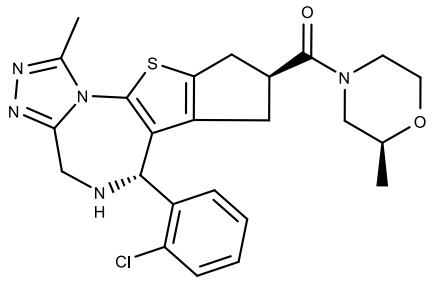
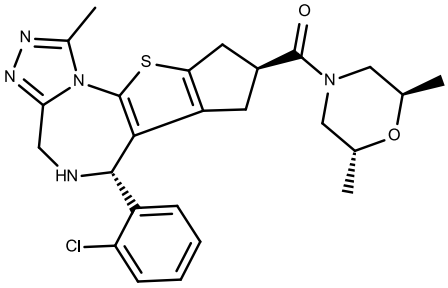
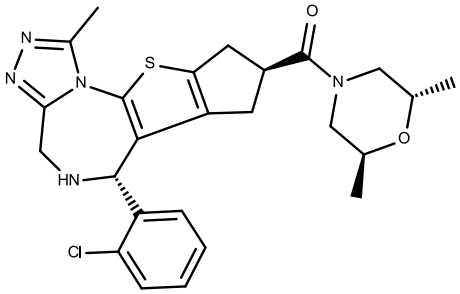
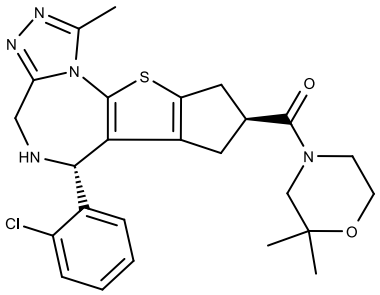
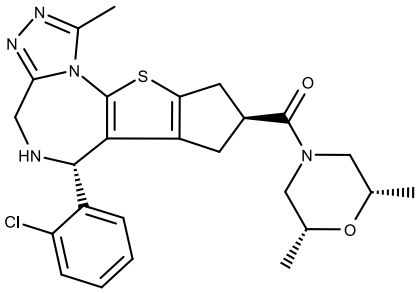
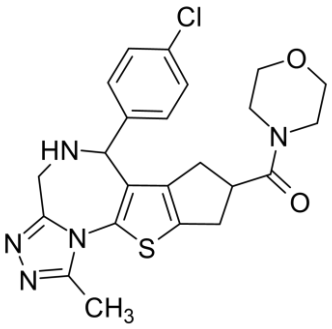
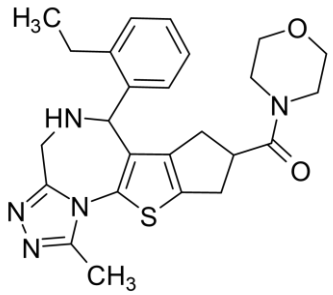
the stereochemistry of the compound is according to formula (I.1)

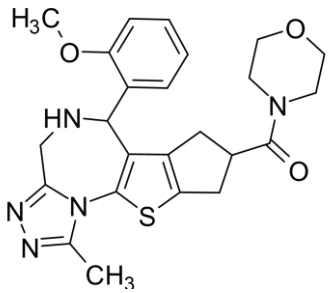
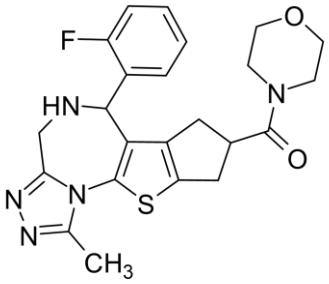
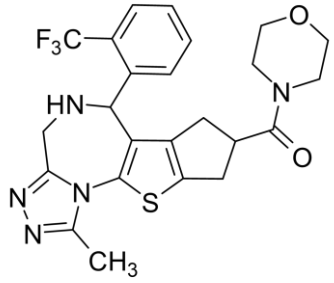
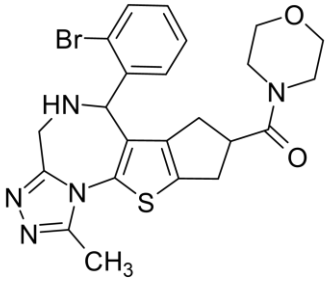
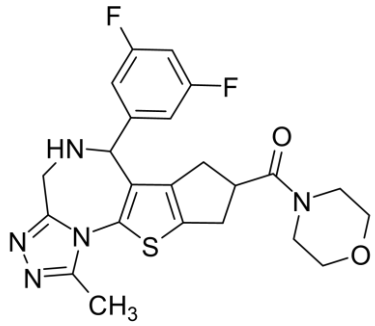
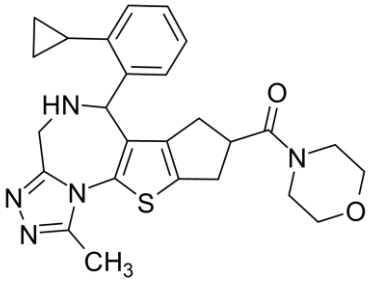
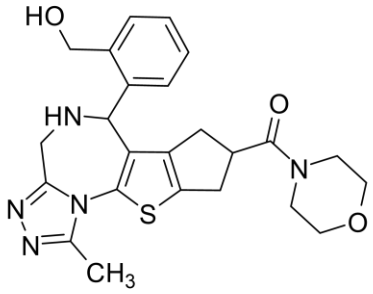
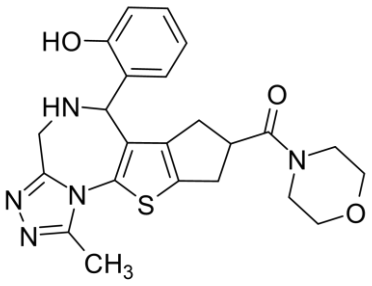
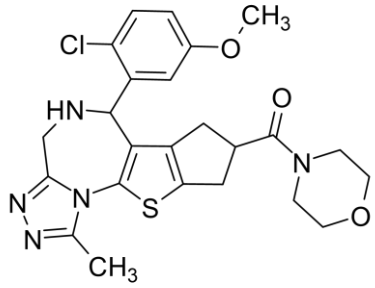
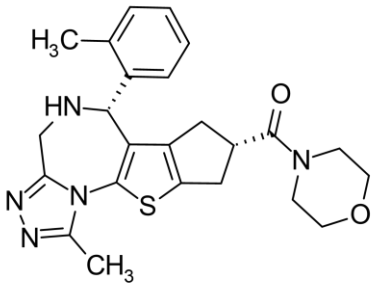


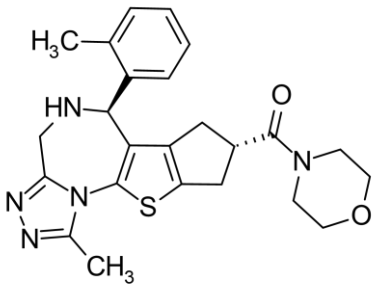
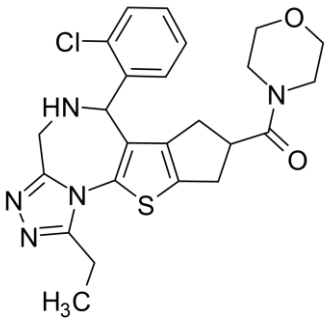
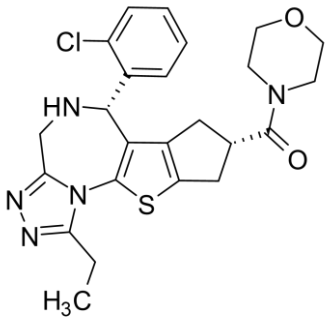
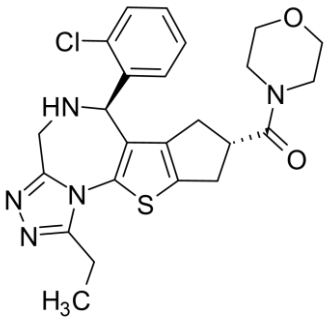
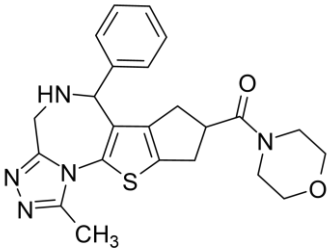
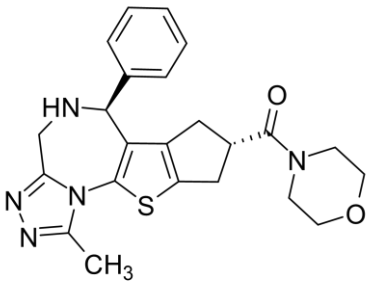
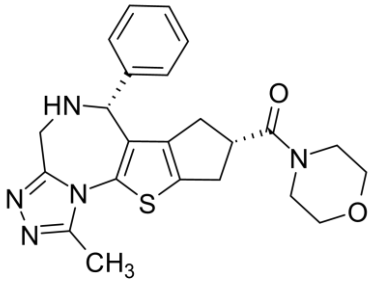
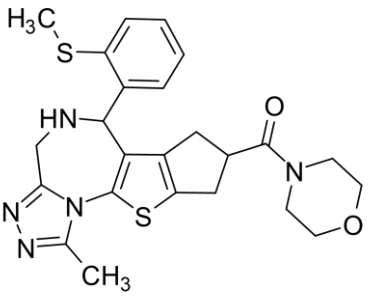
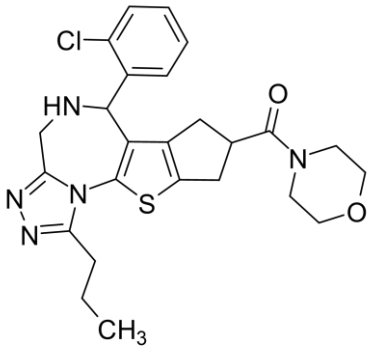
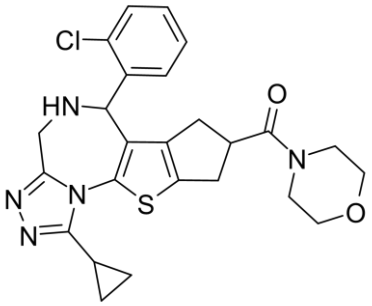
(I.1)

or a salt thereof.

9. The compound according to claim 1, wherein said compound is selected from:

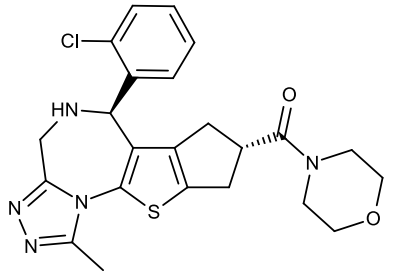
1		2	
3		4	
5		6	
26		27	
52		53	

54		55	
56		57	
58		59	
60		61	
62		63	

64		67	
68		69	
74		76	
78		79	
80		81	

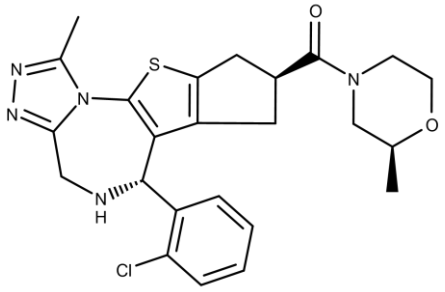
or a salt thereof.

10. The compound according to claim 9, wherein said compound is



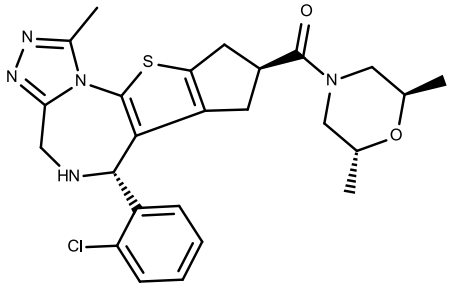
.

11. The compound according to claim 9, wherein said compound is



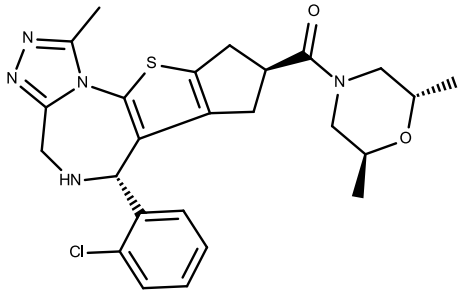
.

12. The compound according to claim 9, wherein said compound is



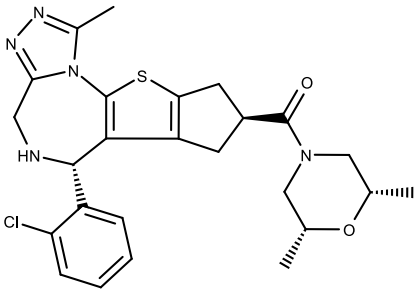
.

13. The compound according to claim 9, wherein said compound is



.

14. The compound according to claim 9, wherein said compound is



15. A pharmaceutically acceptable salt of the compound according to one or more of claims 1 to 14.

16. A pharmaceutical composition comprising one or more compounds according to one or more of claims 1 to 14, or pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

17. A pharmaceutical composition comprising one or more compounds according to one or more of claims 1 to 14, or pharmaceutically acceptable salts thereof, and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

18. The pharmaceutical composition according to claim 17,
wherein the one or more additional therapeutic agents are selected from the group consisting of antidiabetic agents, agents for the treatment of overweight and/or obesity, agents for the treatment of high blood pressure, heart failure and/or atherosclerosis, agents for the treatment of ocular diseases, and agents for the treatment of allergies and inflammation-related conditions and diseases.

19. The compound according to one or more of claims 1 to 14 or a pharmaceutically acceptable salt thereof, for use as a medicament.

20. The compound according to one or more of claims 1 to 14 or a pharmaceutically acceptable salt thereof for use in the treatment of ocular diseases, preferably diabetic macular edema, dry and wet age-related macular degeneration, geographic atrophy and non-exudative choroidal neovascularization, and for the treatment of allergies and inflammation-related conditions and diseases, preferably urticaria and NASH.

21. Use of the compound according to one or more of claims 1 to 14 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of ocular diseases, preferably diabetic macular edema, dry and wet age-related macular degeneration, geographic atrophy and non-exudative choroidal neovascularization, and for the treatment of allergies and inflammation-related conditions and diseases, preferably urticaria and NASH.