



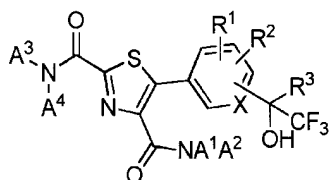
## (12) BREVET D'INVENTION

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- (74) Mandataire :  
**SABA&CO**
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- (54) Titre : **ALCOOLS TRIFLUOROMÉTHYLÉS UTILISÉS COMME MODULATEURS DE RORYT**
- (57) Abrégé : La présente invention concerne des composés de formule (I), dans laquelle X, A1, A2, A3, A4, R1, R2 et R3 sont tels que définis dans la description. L'invention concerne également un procédé pour traiter ou atténuer un syndrome, un trouble ou une maladie, ledit syndrome, ledit trouble ou ladite maladie étant la polyarthrite rhumatoïde ou le psoriasis. L'invention concerne également un procédé pour moduler l'activité de ROR? t chez un mammifère par administration d'une quantité thérapeutiquement efficace d'au moins un composé de la revendication 1.

## Revendications

1. Composé de Formule I,



Formule I

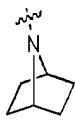
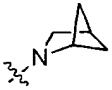
5 où

X représente CH, CR<sup>1</sup> ou N ;

A<sup>1</sup> représente un groupement alkyle en C<sub>(1-2)</sub> ;

A<sup>2</sup> représente un groupement cyclobutyle ou alkyle en C<sub>(1-4)</sub>,  
 10 où ledit groupement alkyle en C<sub>(1-4)</sub> est éventuellement substitué par OCH<sub>3</sub> ou jusqu'à trois atomes de fluor ;

ou A<sup>1</sup> et A<sup>2</sup> forment conjointement avec l'atome d'azote auquel ils sont liés un cycle choisi dans le groupe constitué par les groupements azétidinyle,

15 pipéridinyle, pyrrolidinyle , et  ;

où ledit cycle est éventuellement substitué par jusqu'à trois substituants indépendamment choisis dans le groupe constitué par F, CF<sub>3</sub>, CH<sub>3</sub>, -CN et CH<sub>2</sub>OH ;

20 R<sup>1</sup> représente un groupement Cl, C(CH<sub>3</sub>)<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, OCF<sub>3</sub>, CF<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>, CHF<sub>2</sub>, OCHF<sub>2</sub>, OCH<sub>3</sub>, F, CH<sub>3</sub> ou -CN ;

R<sup>2</sup> représente un atome H, F ou Cl ;

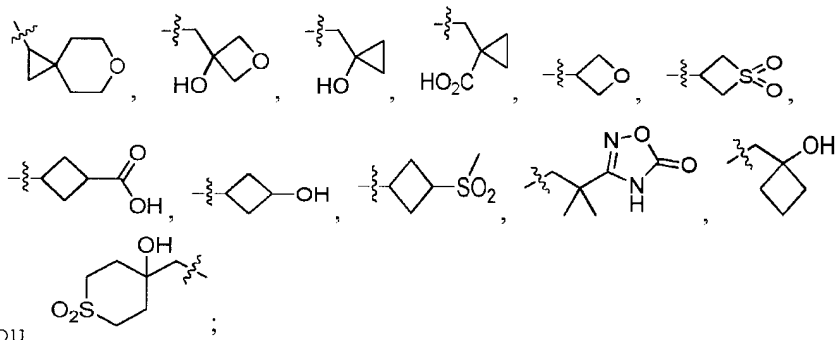
- 2 -

ou R<sup>1</sup> et R<sup>2</sup> peuvent former conjointement avec le groupement phényle auquel ils sont liés un groupement naphthalényle ou quinoléinyle ;

R<sup>3</sup> représente un groupement CF<sub>3</sub> ou CH<sub>2</sub>CH<sub>3</sub> ;

5 A<sup>3</sup> représente H

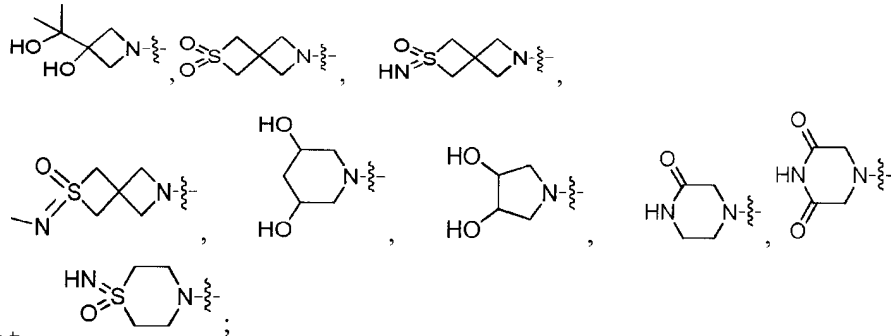
A<sup>4</sup> représente H ou un groupement alkyle en C<sub>(1-5)</sub>,



10 où ledit groupement alkyle en C<sub>(1-5)</sub> est éventuellement substitué par un à deux substituants indépendamment choisis parmi COOH, CONH<sub>2</sub>, -CN et OH ;

ou A<sup>3</sup> et A<sup>4</sup> peuvent former conjointement avec l'atome d'azote auquel ils sont liés un cycle choisi dans le

15 groupe constitué par les groupements

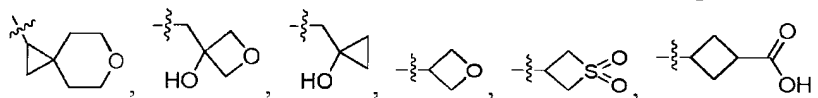


ainsi que les sels pharmaceutiquement acceptables de  
20 celui-ci.

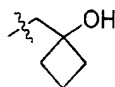
2. Composé selon la revendication 1, où :

R<sup>1</sup> représente un groupement Cl, C(CH<sub>3</sub>)<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, OCF<sub>3</sub>, CF<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>, CHF<sub>2</sub>, OCHF<sub>2</sub>, OCH<sub>3</sub>, F ou CH<sub>3</sub> ;

25 A<sup>4</sup> représente H ou un groupement alkyle en C<sub>(1-5)</sub>,



- 3 -

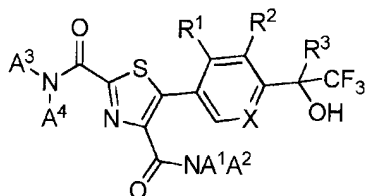


ou ;

où ledit groupement alkyle en C<sub>(1-5)</sub> est éventuellement substitué par un à deux substituants indépendamment choisis parmi CONH<sub>2</sub>, -CN et OH ;

5 et les sels pharmaceutiquement acceptables de ceux-ci.

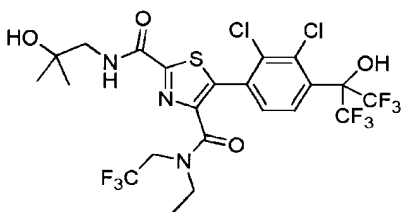
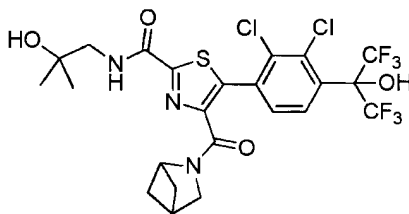
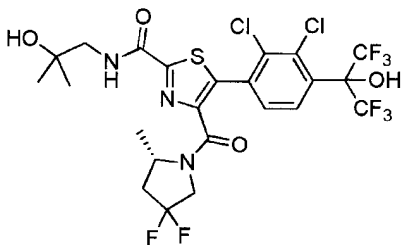
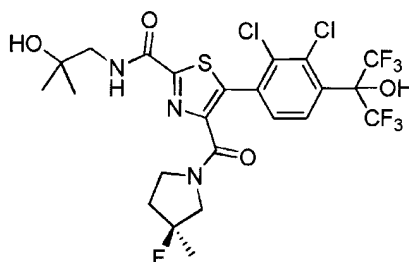
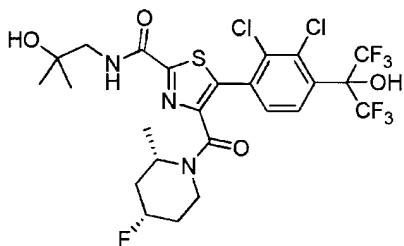
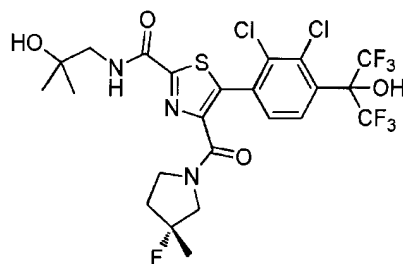
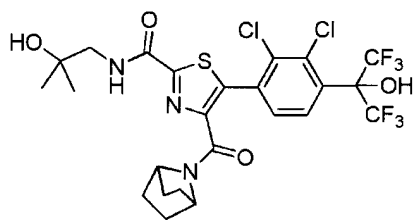
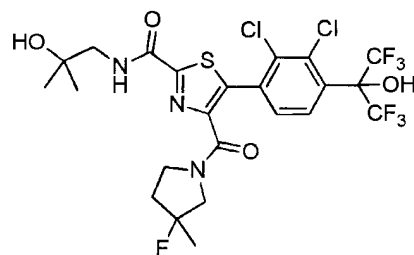
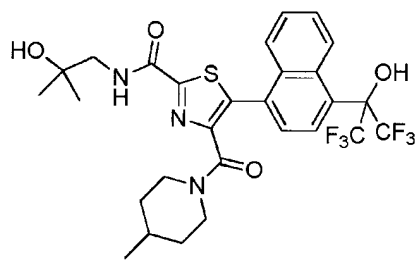
3. Composé selon la revendication 2 de Formule **II** :

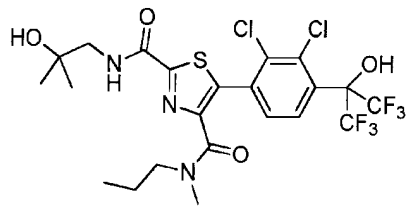


10 Formule **II**

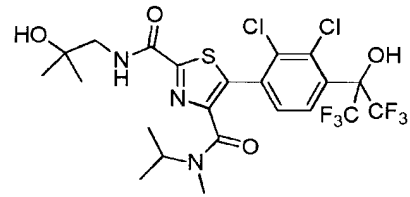
et les sels pharmaceutiquement acceptables de ceux-ci.

4. Composé selon la revendication 2, choisi dans  
15 le groupe constitué par les suivants :

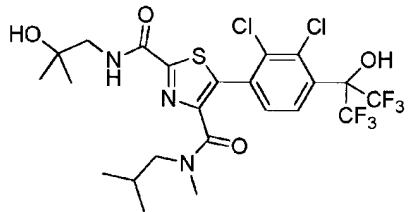




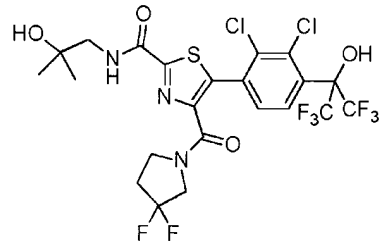
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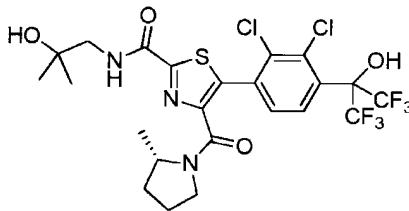
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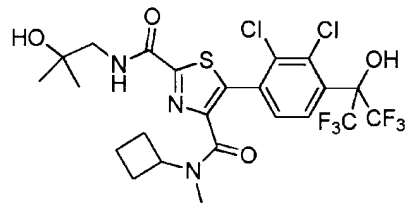
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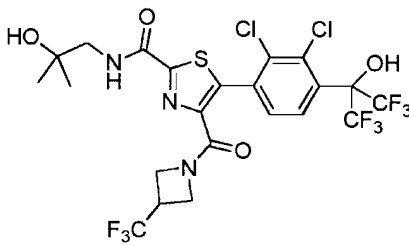
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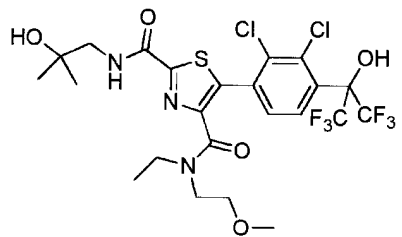
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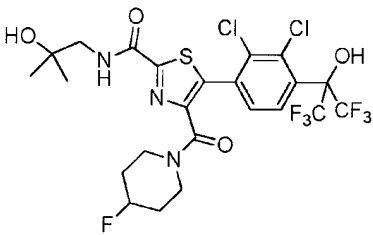
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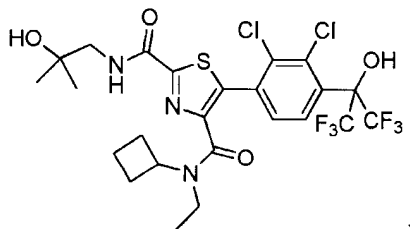
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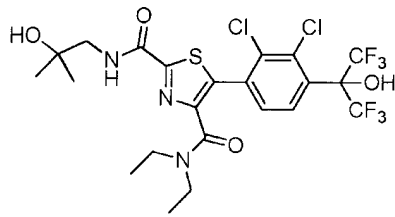
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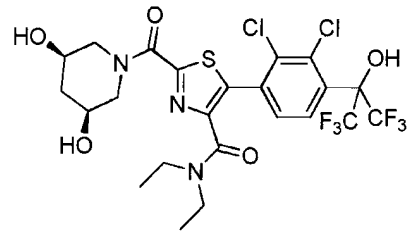
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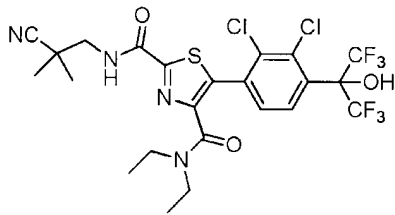
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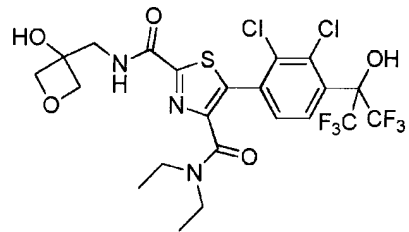
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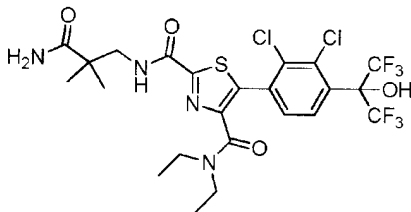
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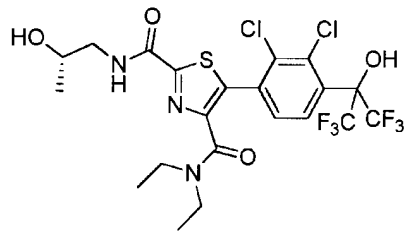
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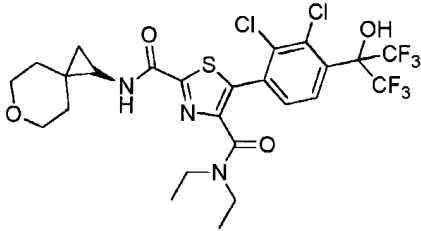
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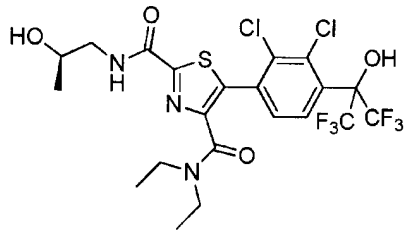
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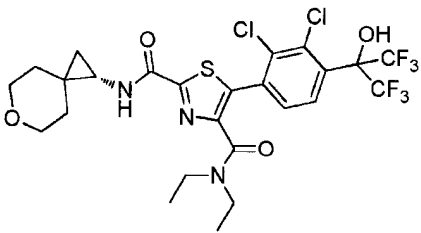
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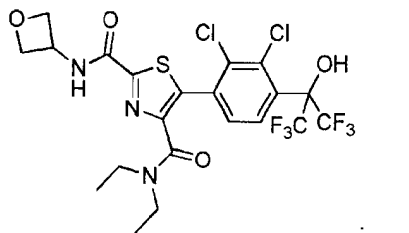
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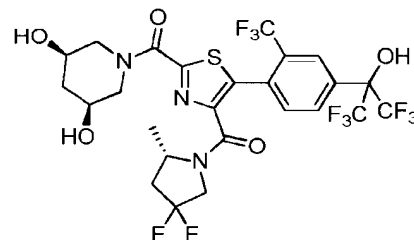
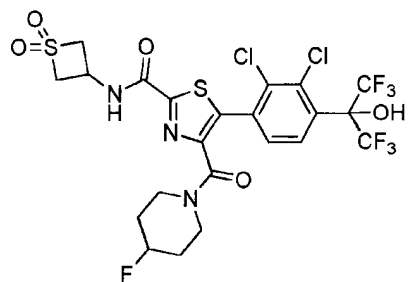
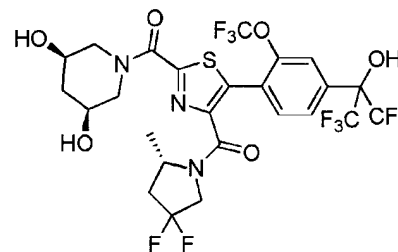
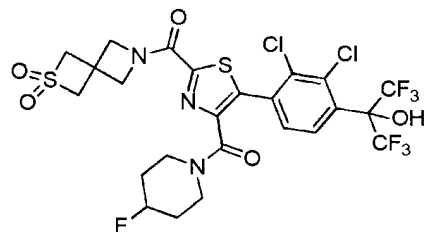
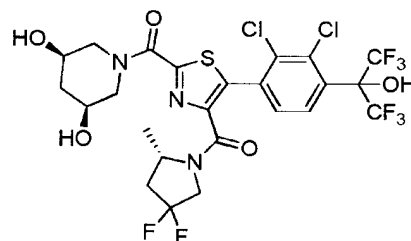
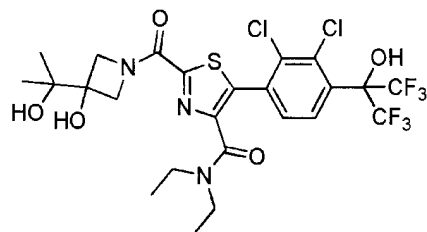
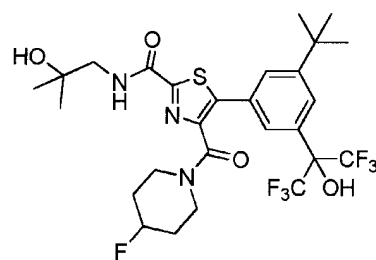
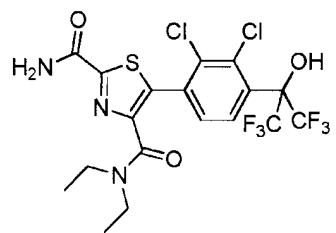
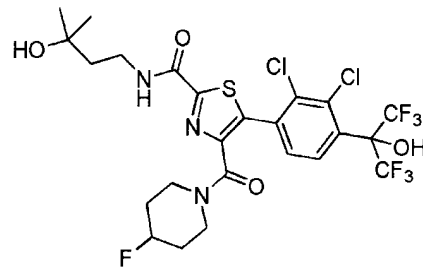
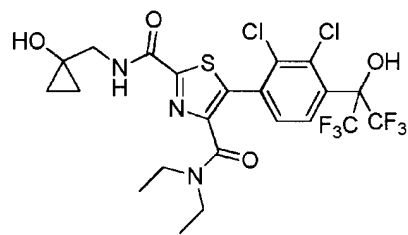
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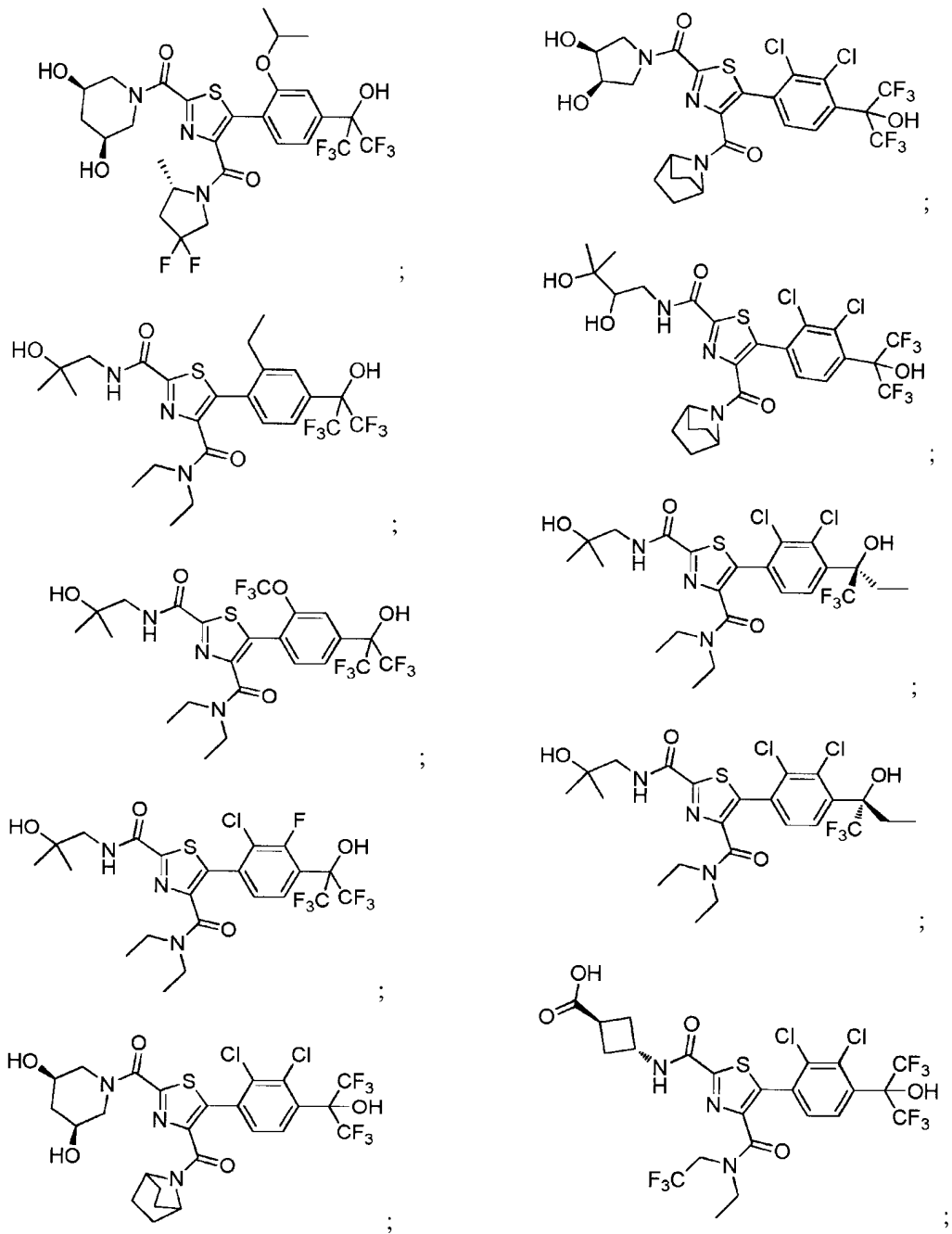
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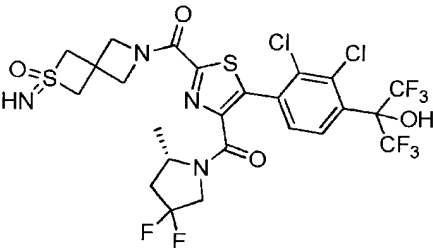
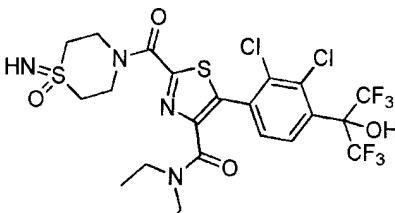
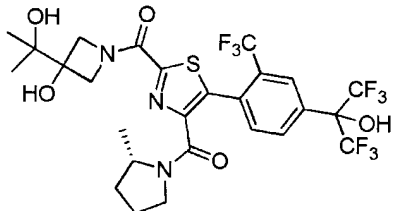
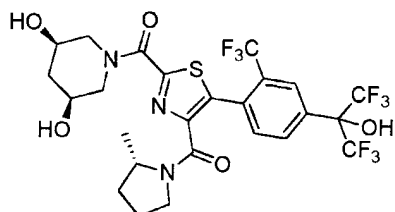
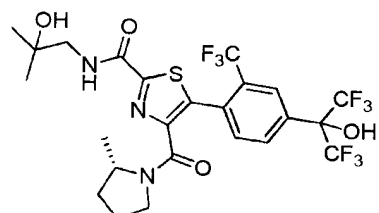
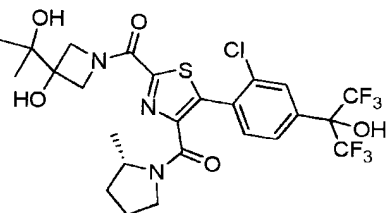
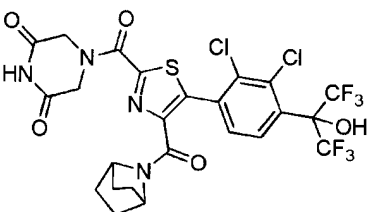
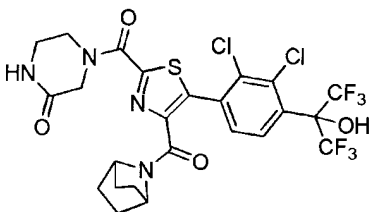
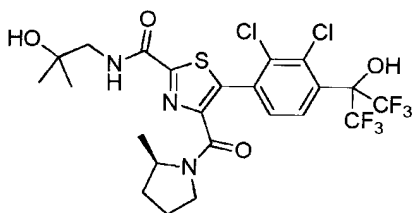
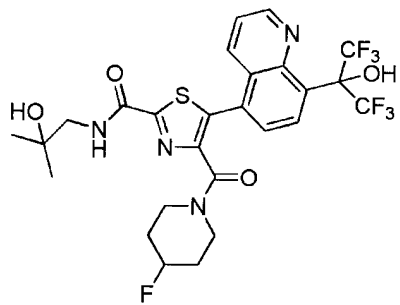


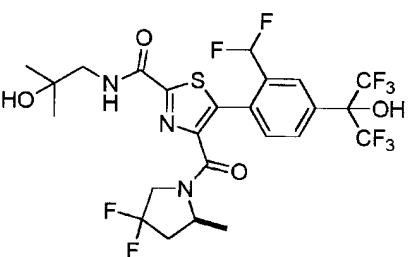
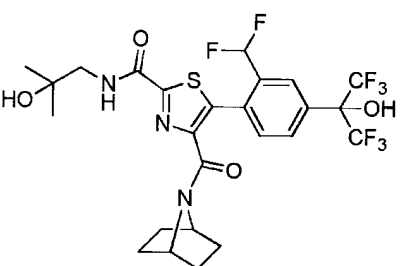
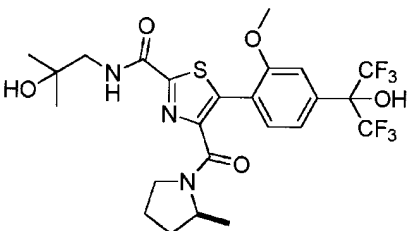
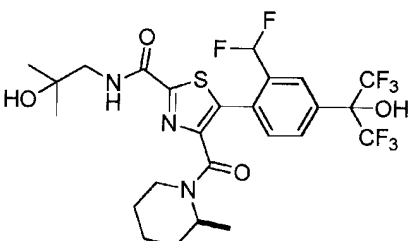
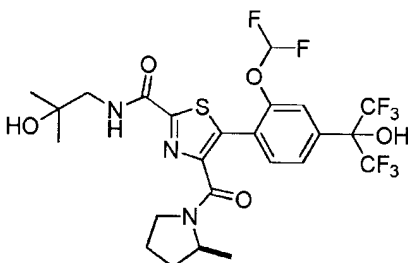
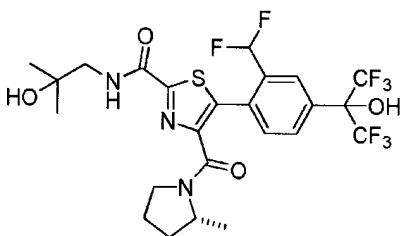
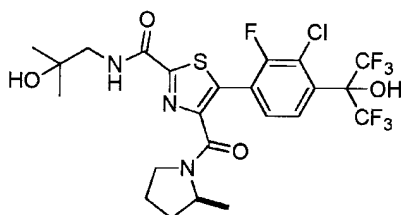
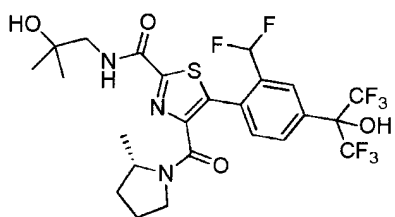
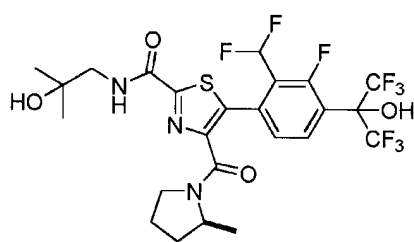
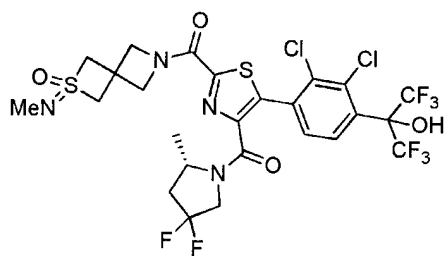
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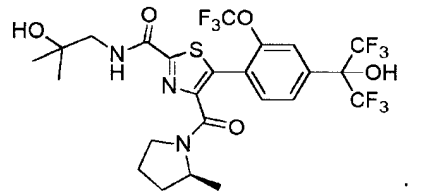
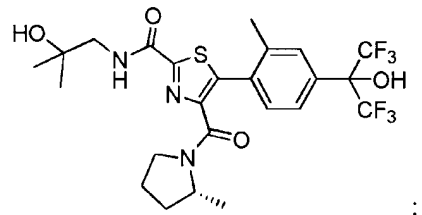
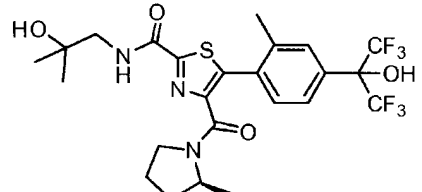
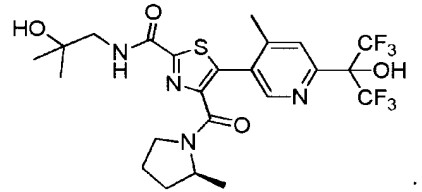
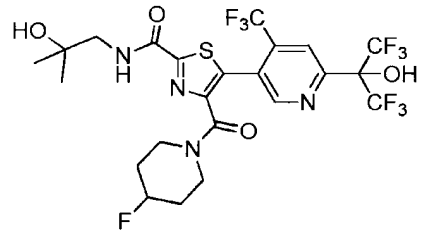
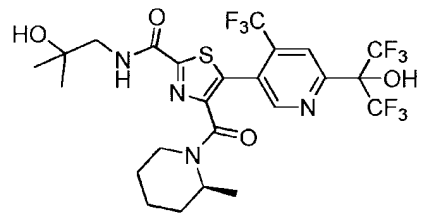
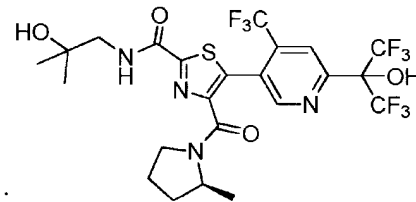
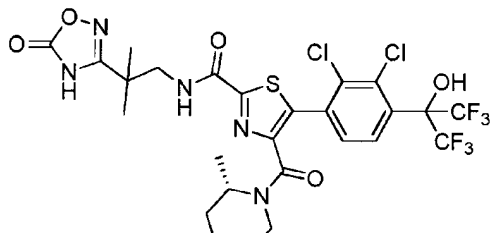
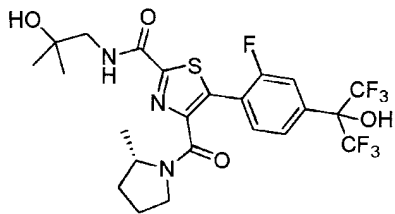
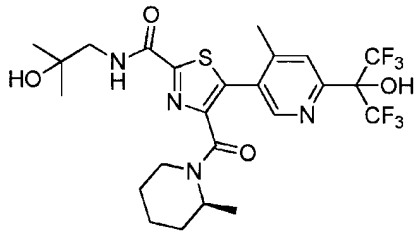
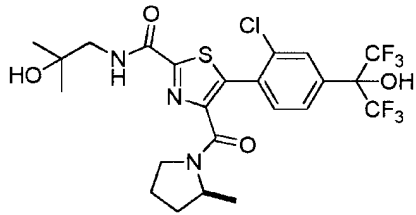
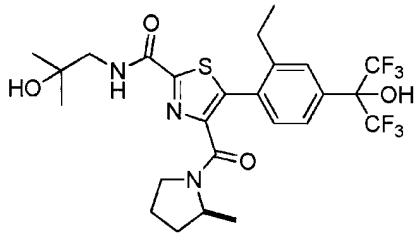


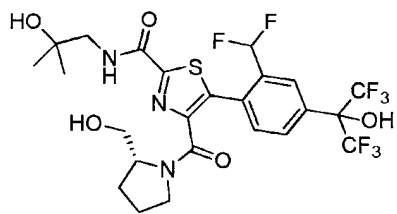
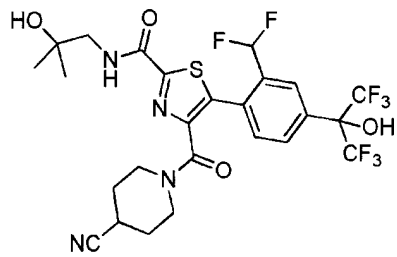
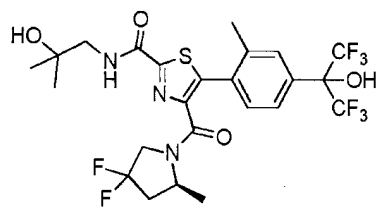
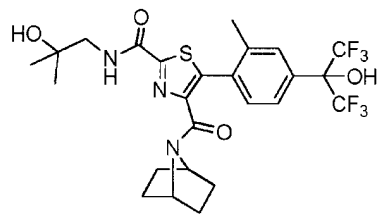
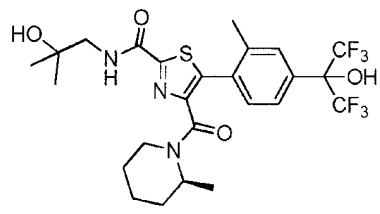
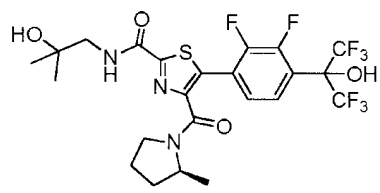




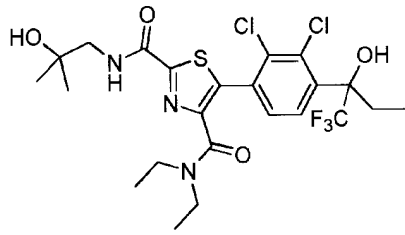




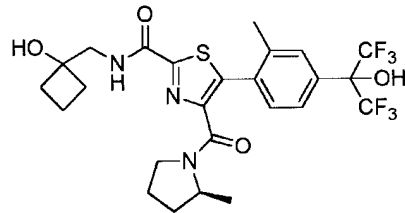




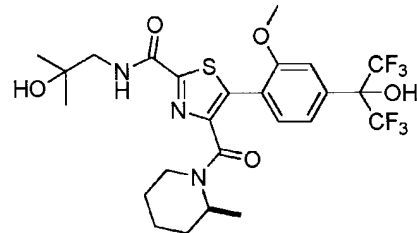
- 13 -



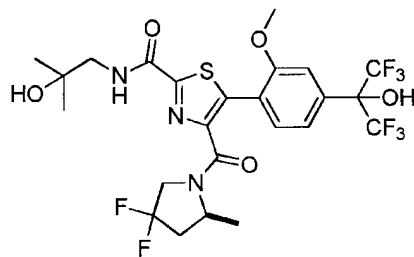
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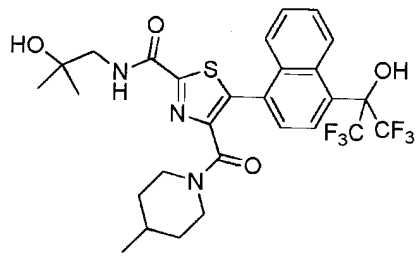
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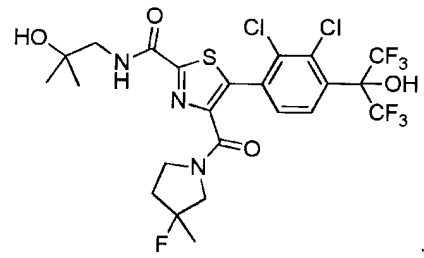
et les sels pharmaceutiquement acceptables de ceux-ci.

- 5 5. Composé selon la revendication 3, choisi dans le groupe constitué par les suivants :

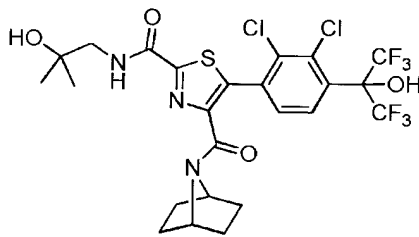
- 14 -



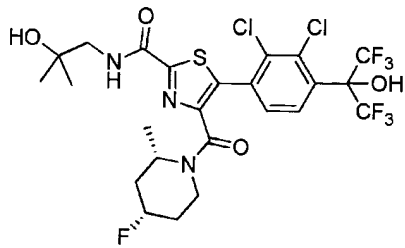
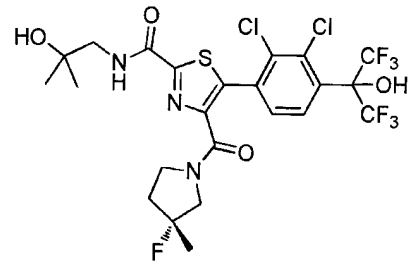
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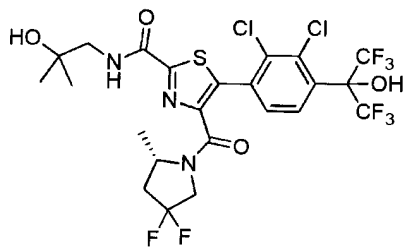
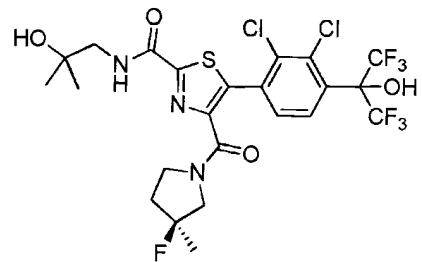
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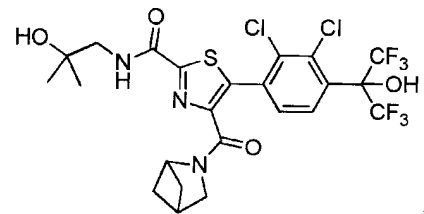
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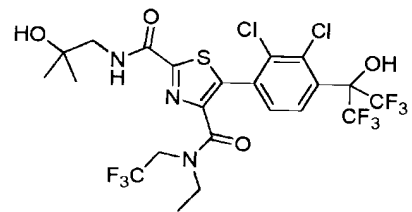
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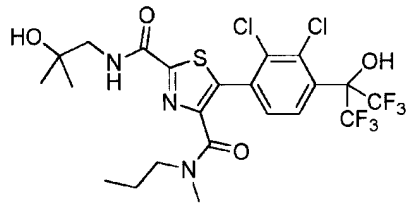


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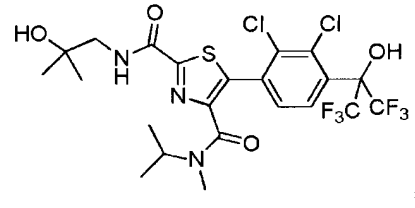


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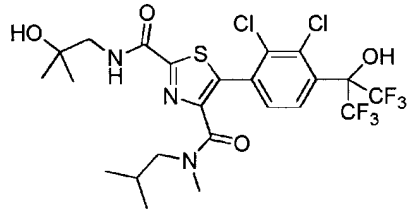
- 15 -



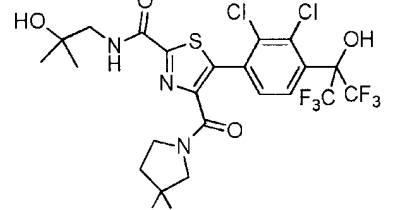
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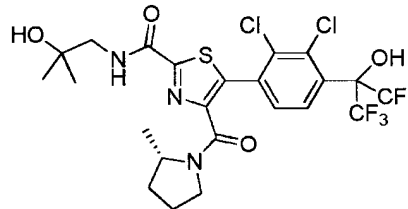
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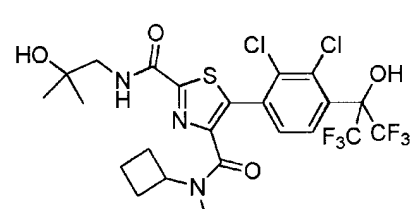
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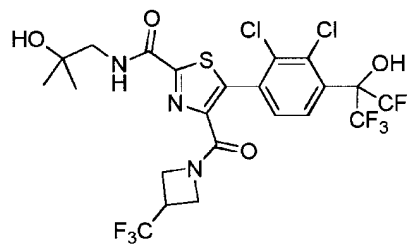
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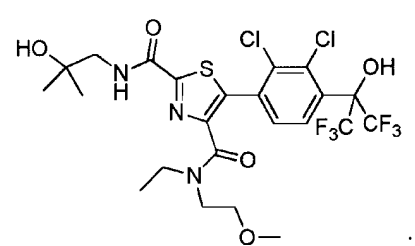
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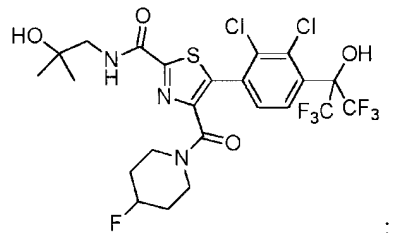
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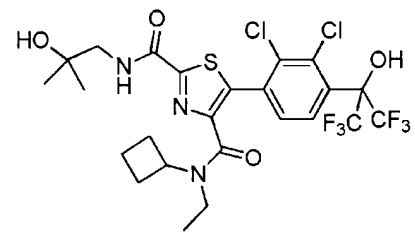
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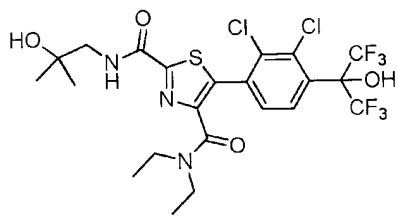
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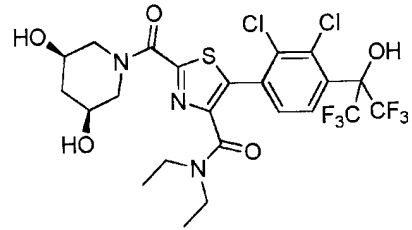
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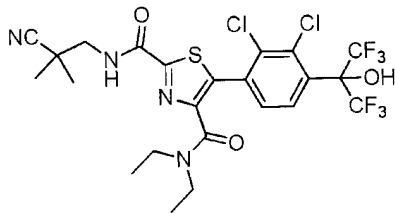
- 16 -



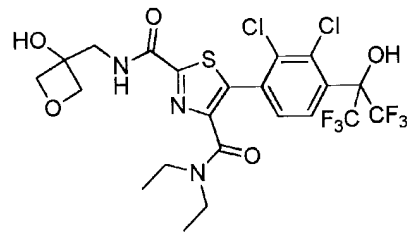
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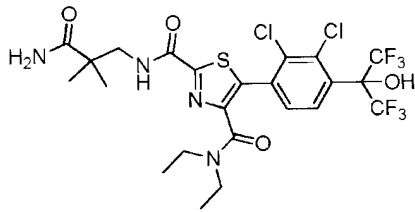
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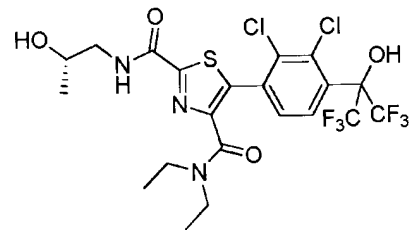
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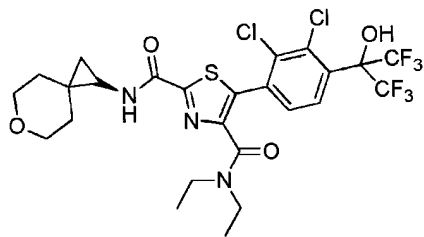
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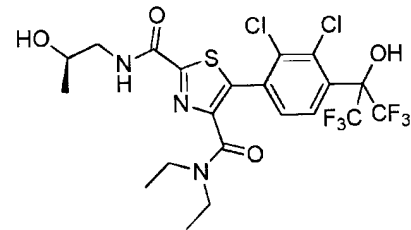
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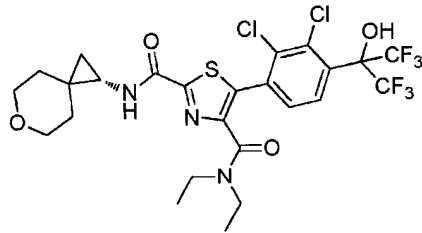
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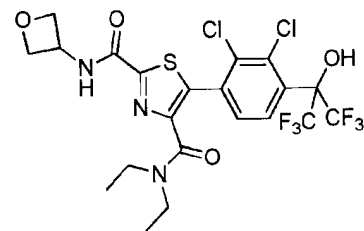
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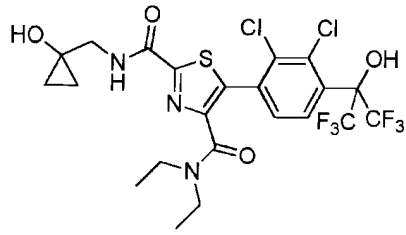


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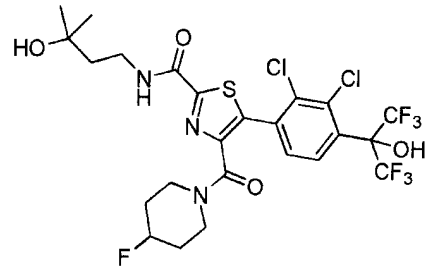


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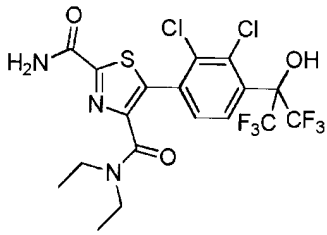
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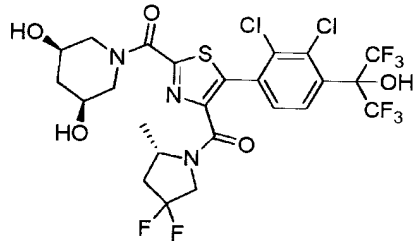
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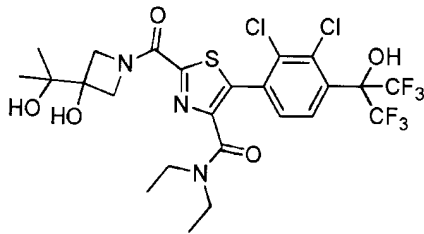
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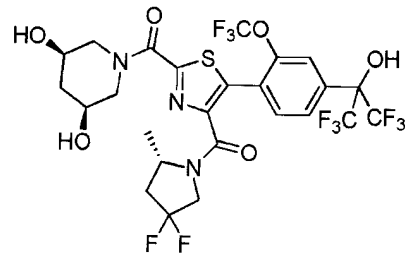
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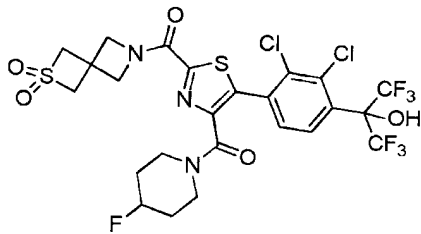
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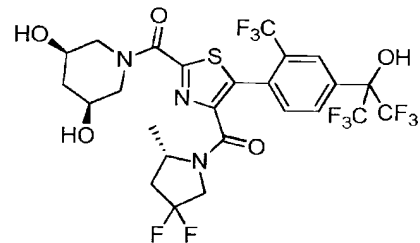
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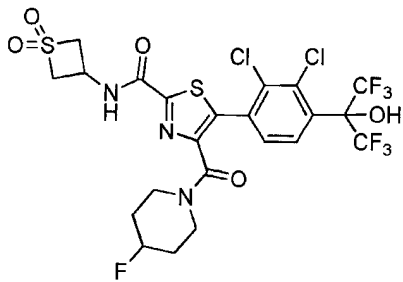
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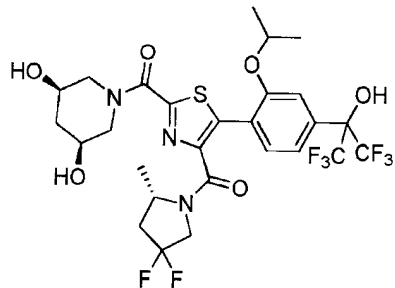
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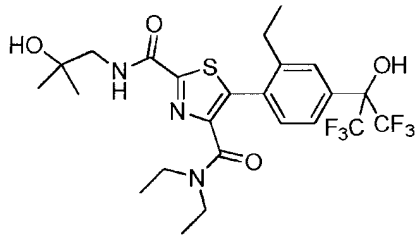
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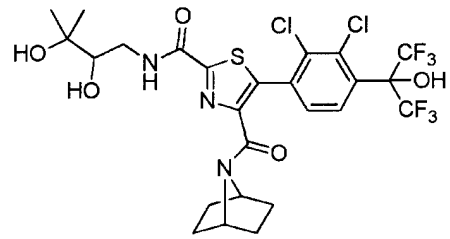
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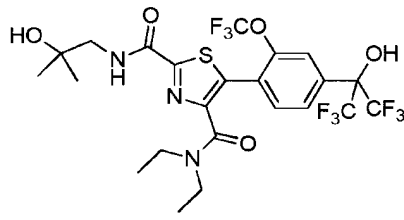
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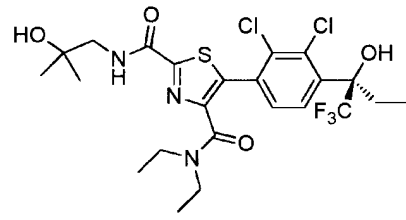
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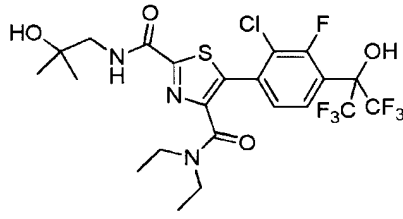
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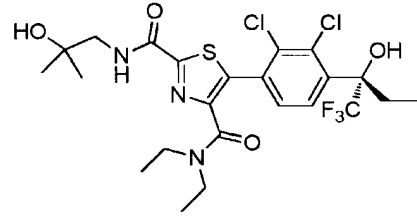
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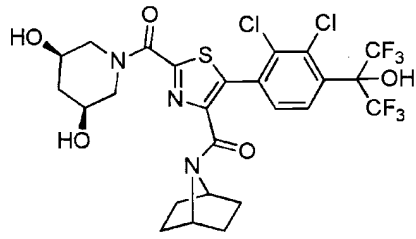
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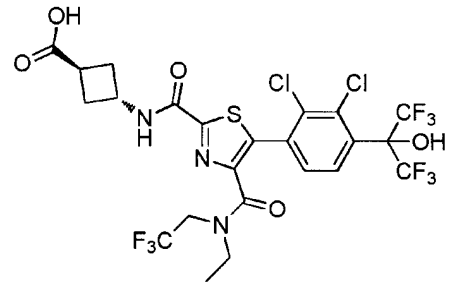
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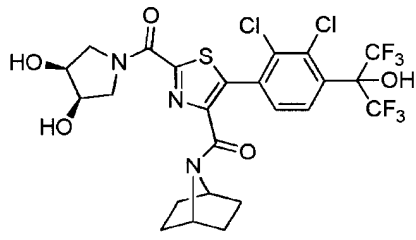
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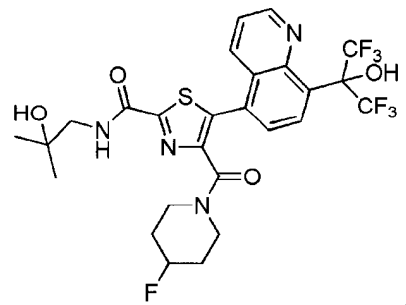
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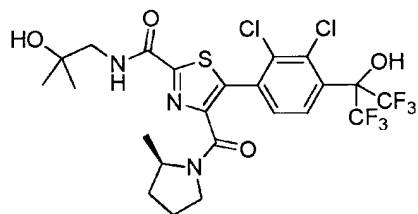
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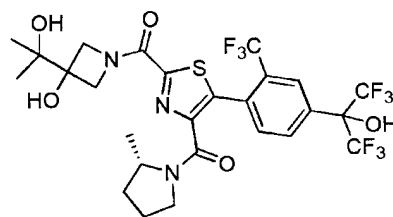
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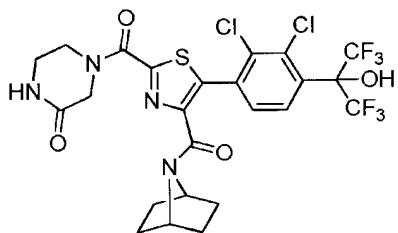
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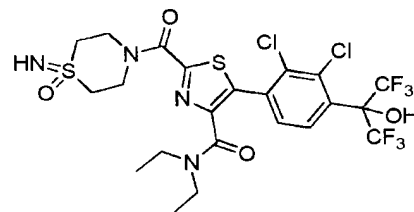
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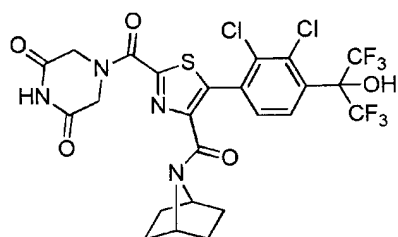
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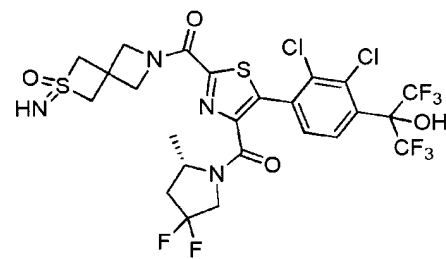
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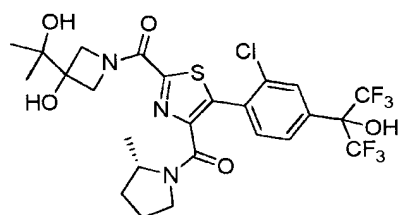
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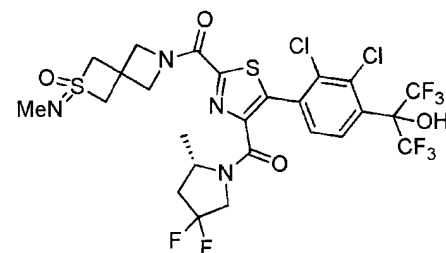
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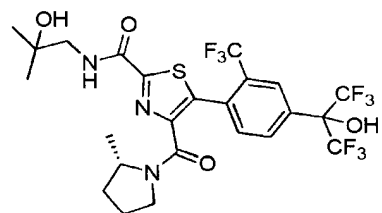
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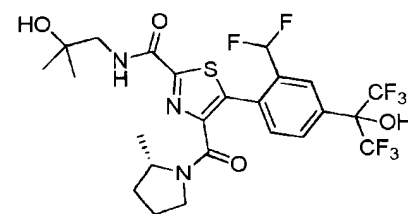
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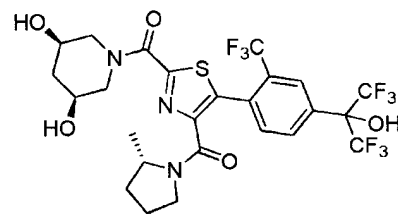
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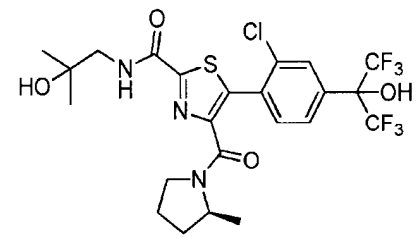
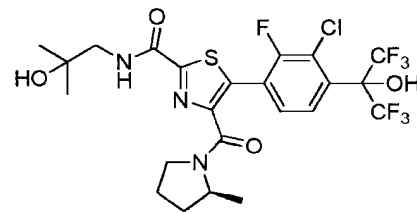
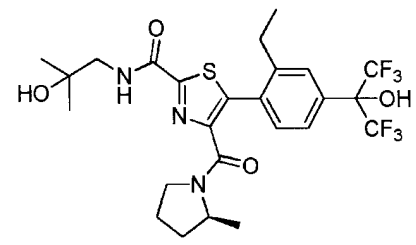
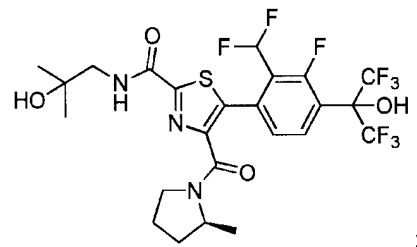
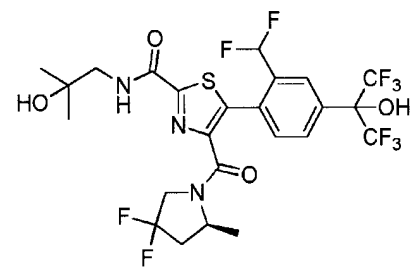
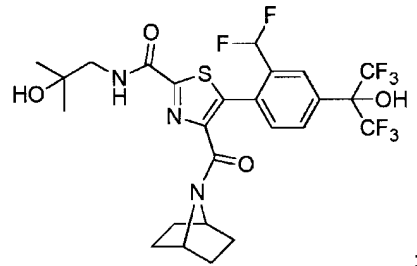
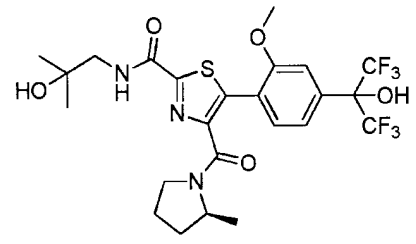
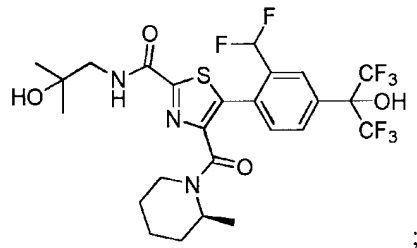
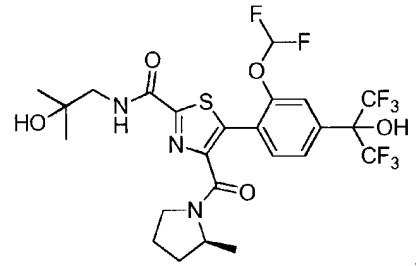
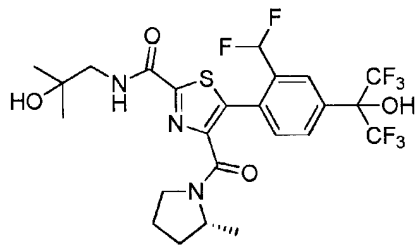
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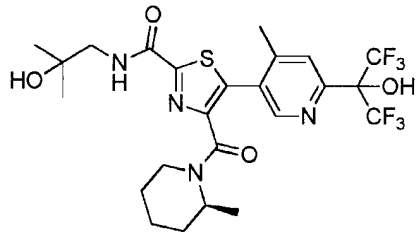


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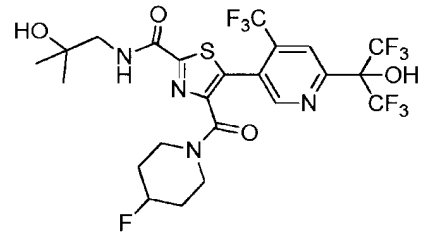


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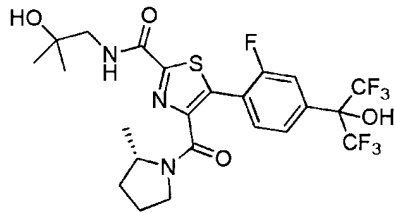




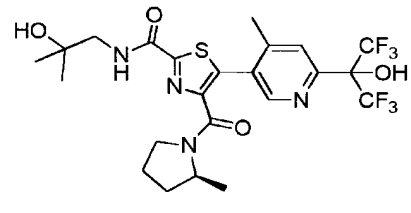
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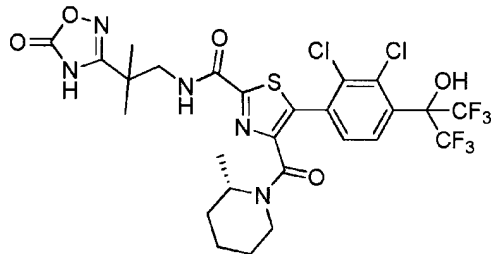
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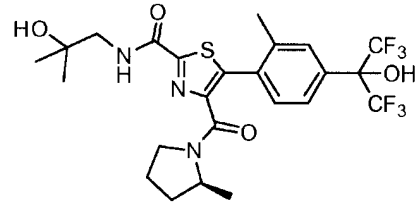
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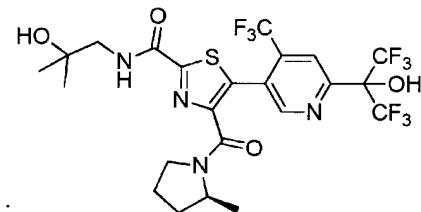
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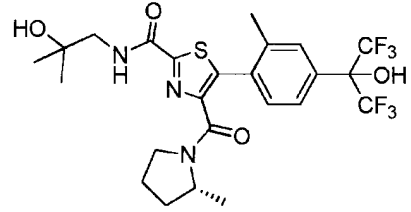
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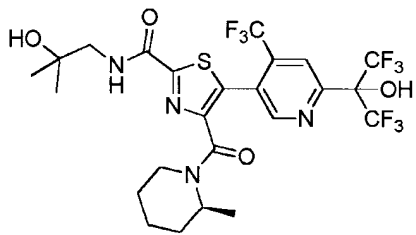
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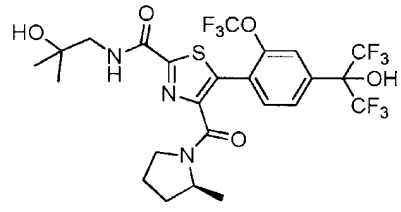
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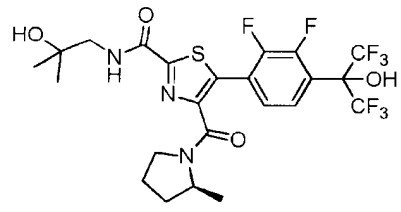
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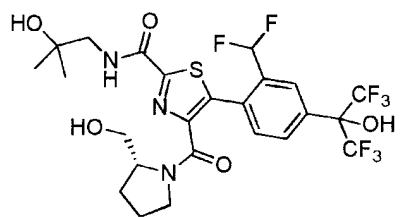
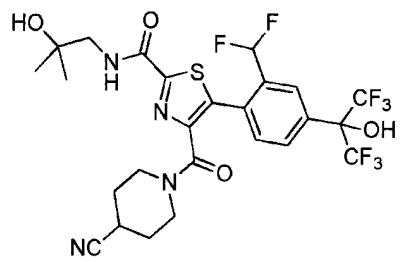
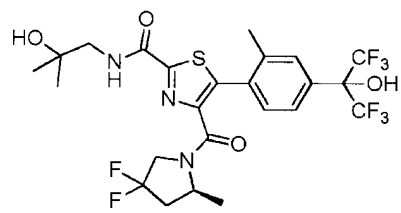
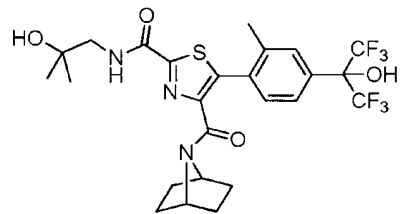
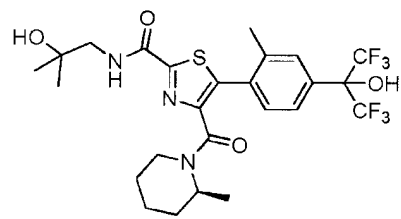
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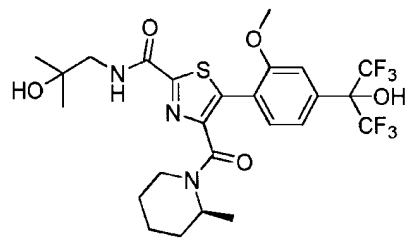
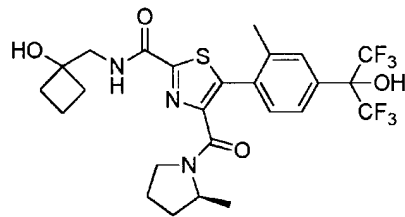
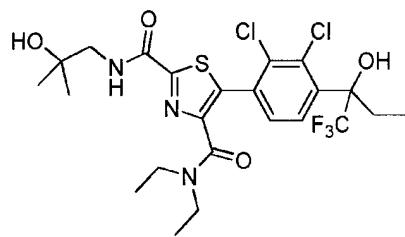
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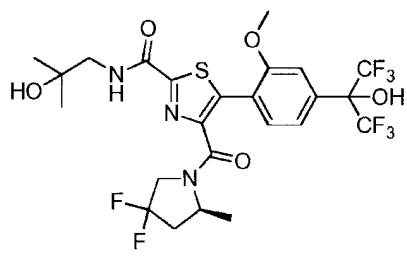
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- 23 -



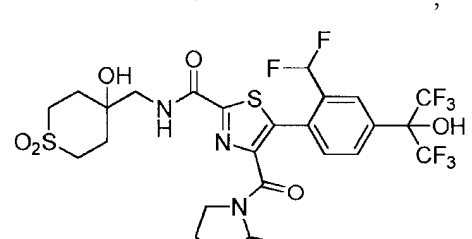
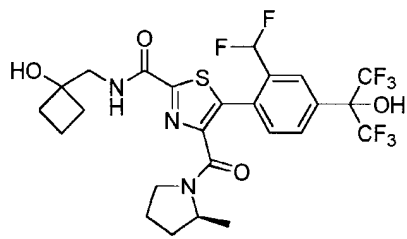
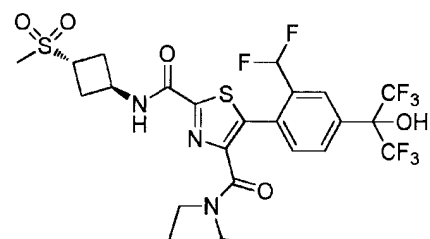
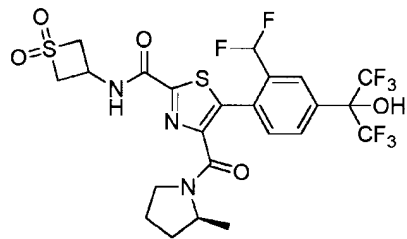
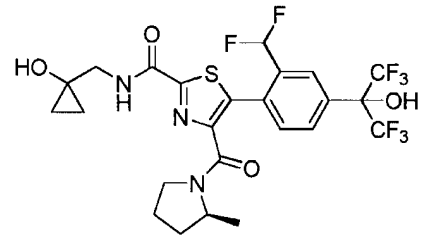
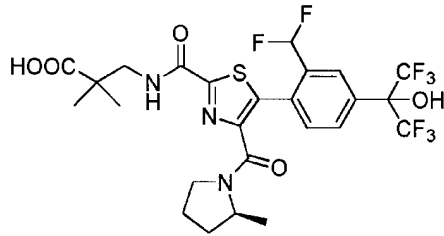
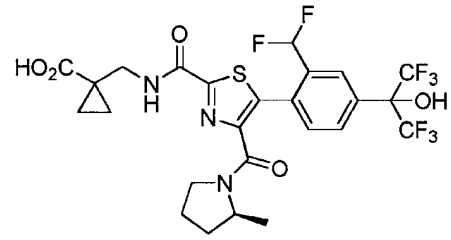
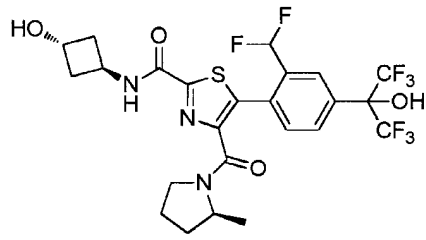
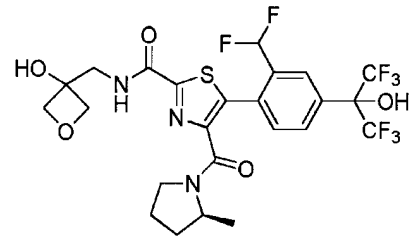
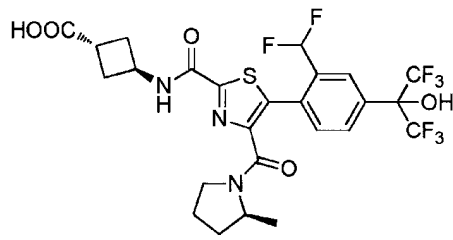
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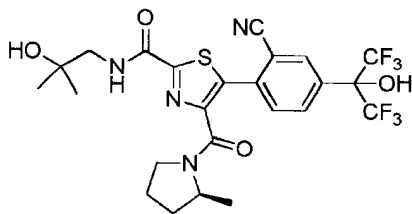
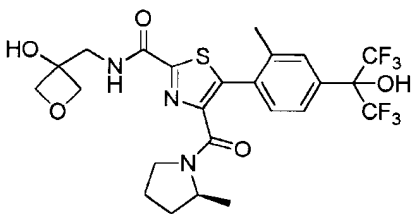
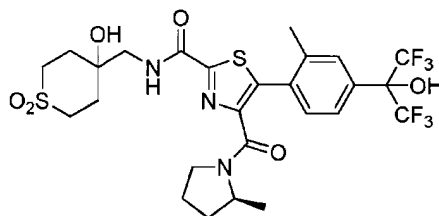
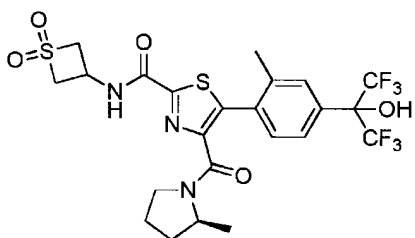
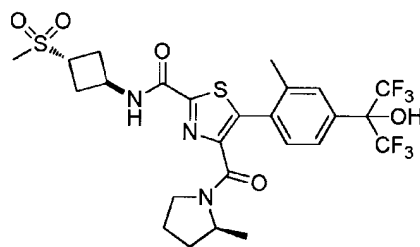
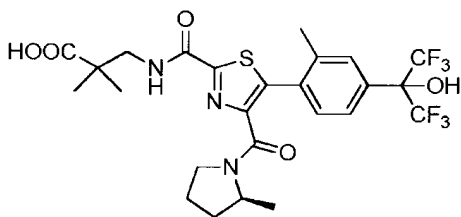
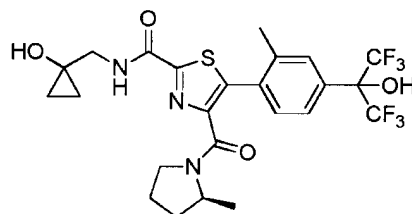
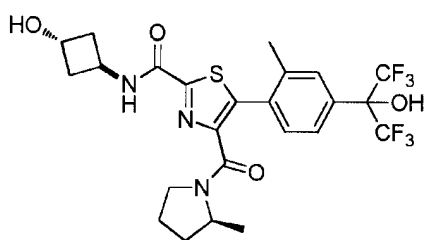
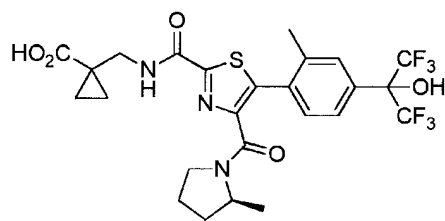
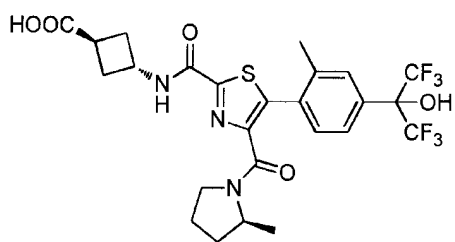


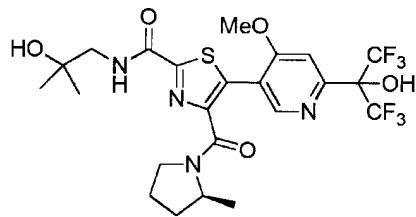
et les sels pharmaceutiquement acceptables de ceux-ci.

- 5 6. Composé selon la revendication 1, choisi dans le groupe constitué par les suivants :





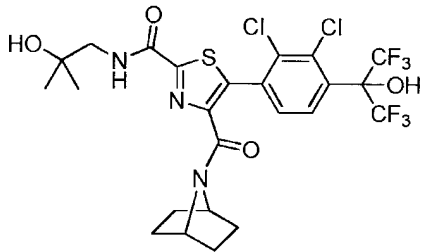




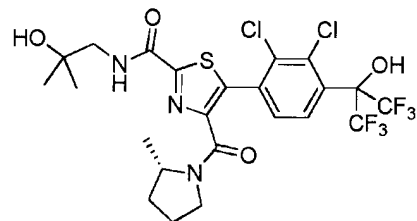
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et les sels pharmaceutiquement acceptables de ceux-ci.

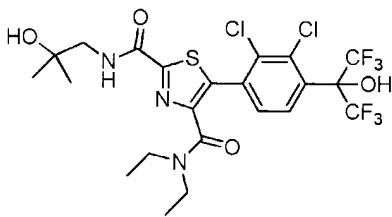
7. Composé selon la revendication 5, choisi dans le groupe constitué par les suivants :



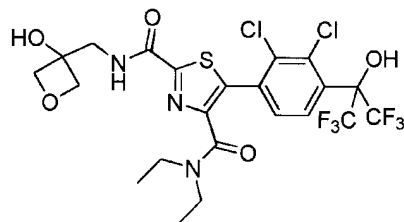
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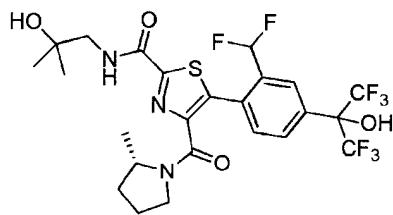
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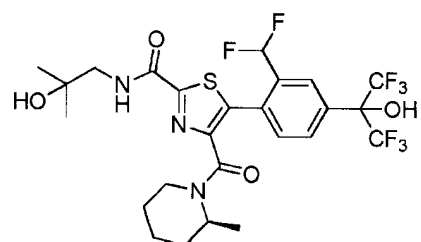
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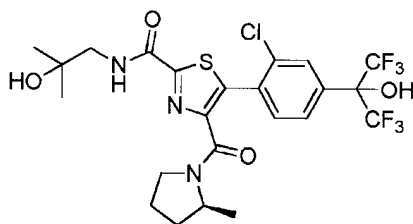
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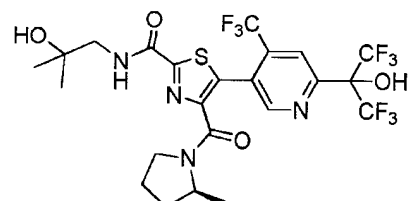
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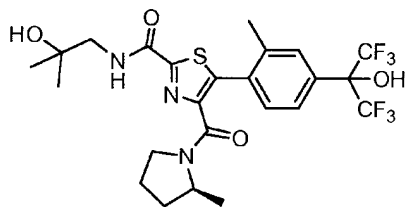
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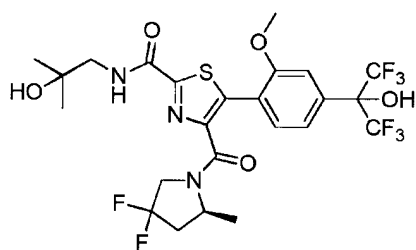


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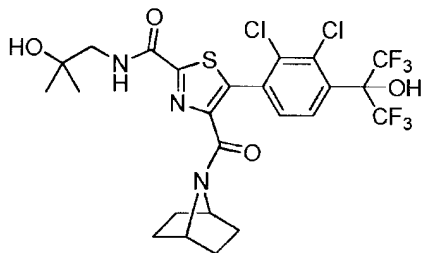


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et les sels pharmaceutiquement acceptables de ceux-ci.

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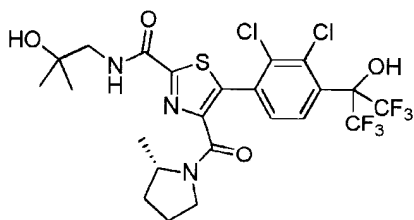
8. Composé selon la revendication 7, qui est :



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et les sels pharmaceutiquement acceptables de celui-ci.

10 9. Composé selon la revendication 7, qui est :

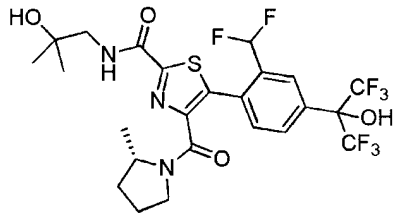


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et les sels pharmaceutiquement acceptables de celui-ci.

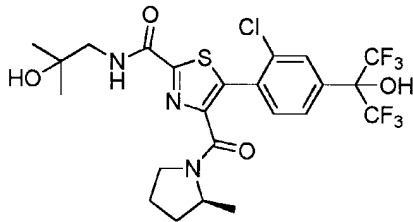
10. Composé selon la revendication 7, qui est :

- 28 -



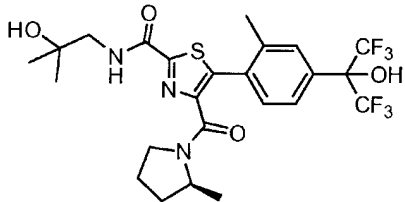
; et les sels pharmaceutiquement acceptables de celui-ci.

- 5 11. Composé selon la revendication 7, qui est :



et les sels pharmaceutiquement acceptables de celui-ci.

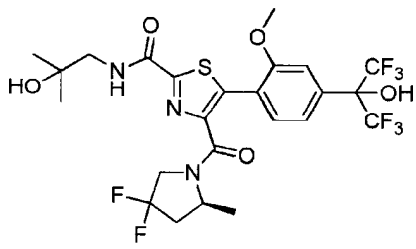
12. Composé selon la revendication 7, qui est :



10

et les sels pharmaceutiquement acceptables de celui-ci.

13. Composé selon la revendication 7, qui est :



15 et les sels pharmaceutiquement acceptables de celui-ci.

14. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 13 ainsi qu'un véhicule pharmaceutiquement acceptable.

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- 29 -

15. Composition pharmaceutique fabriquée en mélangeant un composé selon l'une quelconque des revendications 1 à 13 et un véhicule pharmaceutiquement acceptable.
- 5
16. Procédé de fabrication d'une composition pharmaceutique comprenant le mélangeage d'un composé selon l'une quelconque des revendications 1 à 13 et d'un véhicule pharmaceutiquement acceptable.
- 10
17. Composé selon l'une quelconque des revendications 1 à 13 pour utilisation dans une méthode de traitement d'un sujet souffrant d'un syndrome inflammatoire, d'un trouble ou d'une maladie faisant  
15 intervenir RORyt, ou ayant été diagnostiqué comme souffrant de tels syndrome inflammatoire, trouble ou maladie.
18. Composé selon la revendication 17, où la  
20 maladie est choisie dans le groupe constitué par les suivants : maladies inflammatoires chroniques de l'intestin, polyarthrite rhumatoïde, psoriasis, bronchopneumopathie chronique obstructive, arthrite psoriasique, spondylite ankylosante, asthme à  
25 neutrophiles, asthme résistant aux stéroïdes, sclérose en plaques et lupus érythémateux disséminé.
19. Composé pour utilisation selon la revendication 18, où la maladie est le psoriasis.
- 30
20. Composé pour utilisation selon la revendication 18, où la maladie est la polyarthrite rhumatoïde.
21. Composé pour utilisation selon la revendication  
35 18, où la maladie inflammatoire chronique de l'intestin est la rectocolite hémorragique.

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22. Composé pour utilisation selon la revendication  
18, où la maladie inflammatoire chronique de l'intestin  
est la maladie de Crohn.
- 5 23. Composé pour utilisation selon la revendication  
18, où la maladie est la sclérose en plaques.
24. Composé pour utilisation selon la revendication  
18, où la maladie est l'asthme à neutrophiles.
- 10 25. Composé pour utilisation selon la revendication  
18, où la maladie est l'asthme résistant aux stéroïdes.
26. Composé pour utilisation selon la revendication  
15 18, où la maladie est l'arthrite psoriasique.
27. Composé pour utilisation selon la revendication  
18, où la maladie est la spondylite ankylosante.
- 20 28. Composé pour utilisation selon la revendication  
18, où la maladie est le lupus érythémateux disséminé.
29. Composé pour utilisation selon la revendication  
18, où la maladie est la bronchopneumopathie chronique  
25 obstructive.
30. Composé selon l'une quelconque des  
revendications 1 à 13 ou composition ou médicament de  
celui-ci en combinaison avec un ou plusieurs agents  
30 anti-inflammatoires ou agents immunosuppresseurs pour  
utilisation dans une méthode de traitement d'un sujet  
souffrant d'un syndrome, d'un trouble ou d'une maladie  
choisis dans le groupe constitué par les suivants, ou  
diagnostiqué comme souffrant de tels syndrome, trouble  
35 ou maladie : polyarthrite rhumatoïde et psoriasis.