

(12) BREVET D'INVENTION

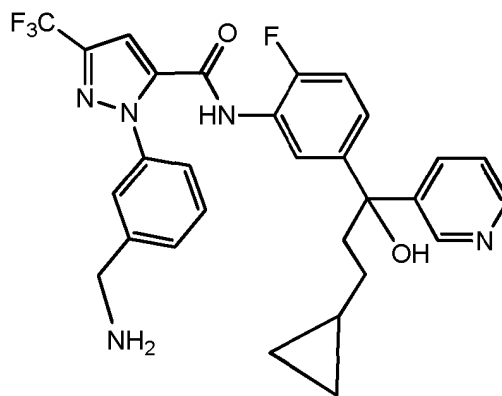
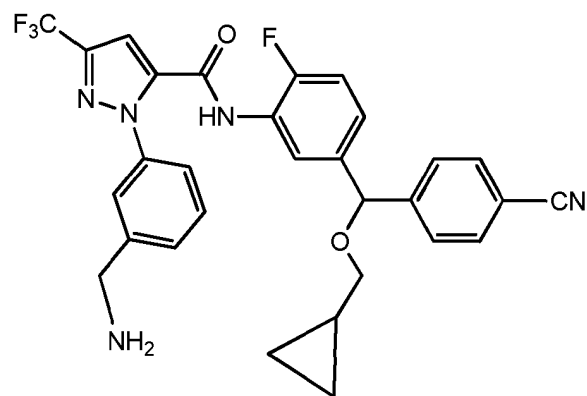
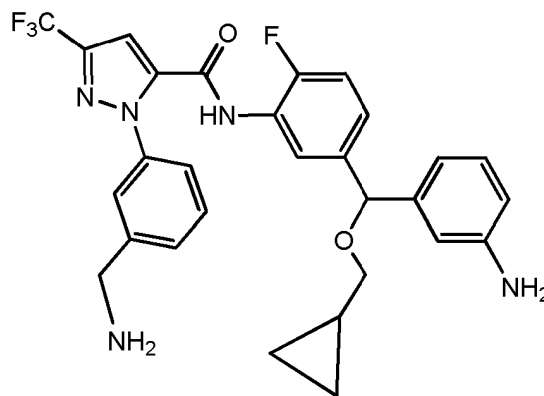
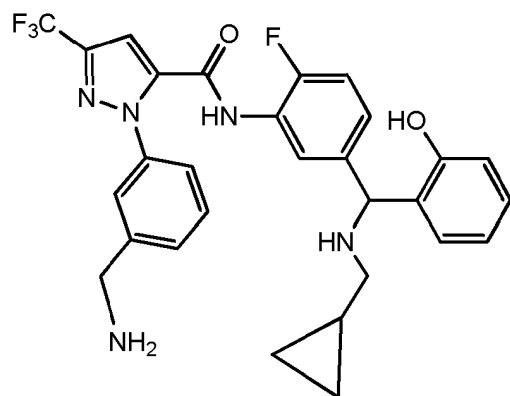
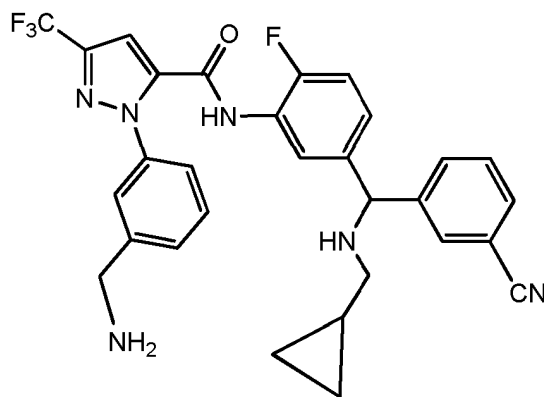
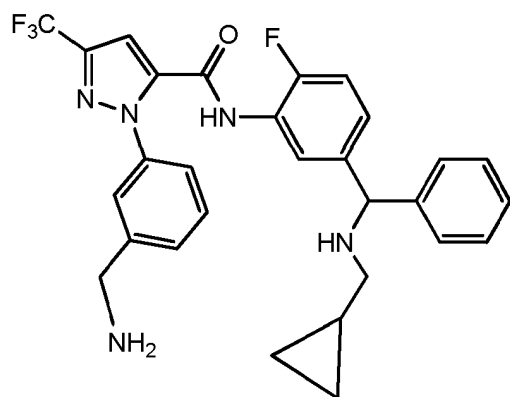
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- (71) Demandeur(s) : **Biocryst Pharmaceuticals, Inc., 4505 Emperor Blvd. Durham, North Carolina 27703 (US)**
- (72) Inventeur(s) : **WU, Minwan ; ZHANG, Weihe ; BABU, Yarlagadda S. ; KOTIAN, Pravin L. ; CHINTAREDDY, Venkat R. ; KUMAR, Satish V.**
- (74) Mandataire : **ABU-GHAZALEH INTELLECTUAL PROPERTY (TMP AGENTS)**
- (86) N° de dépôt auprès de l'organisme de validation: EP15759254.4

(54) Titre : **PYRAZOLES SUBSTITUÉS PAR UN TRIFLUOROMETHYLE EN TANT QU'INHIBITEURS DE LA KALLICRÉINE PLASMATIQUE HUMAINE**

(57) Abrégé : Cette invention concerne des composés de formule (I), et leurs sels de qualité pharmaceutique. Les composés sont des inhibiteurs de la kallistéine plasmatique. L'invention concerne également des compositions pharmaceutiques comprenant au moins un composé de l'invention, et des procédés impliquant l'utilisation des composés et des compositions de l'invention dans le traitement et la prévention de maladies et de pathologies caractérisées par une activité indésirable de la kallistéine plasmatique.

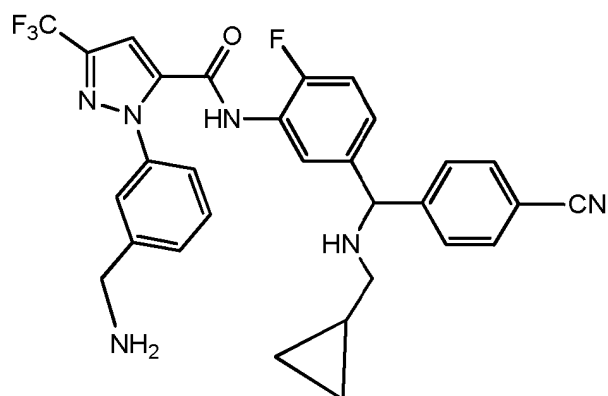
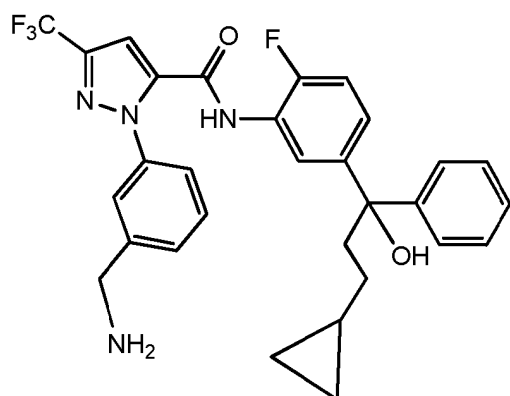
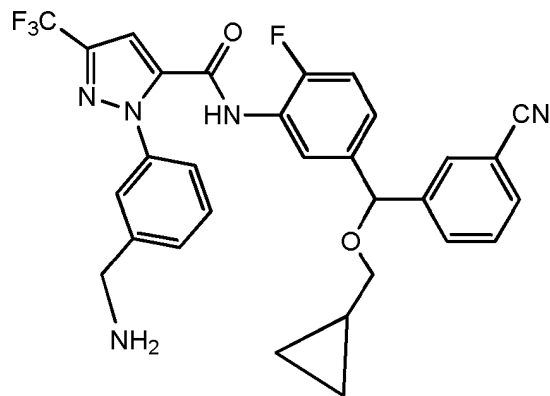
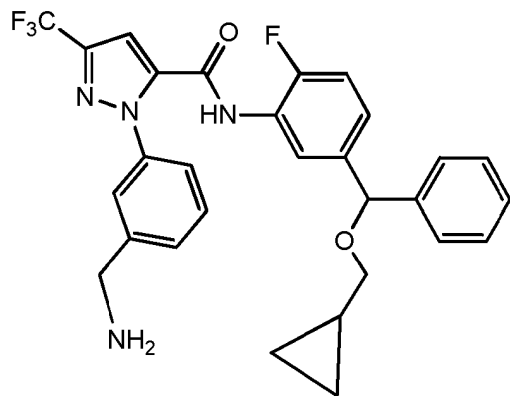
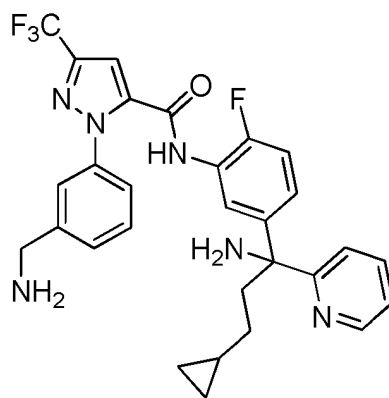
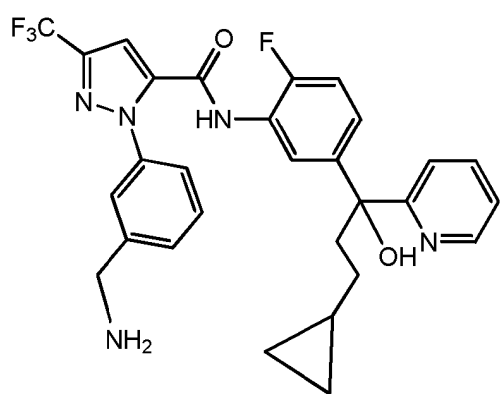
Revendications

1. Composé, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué par :



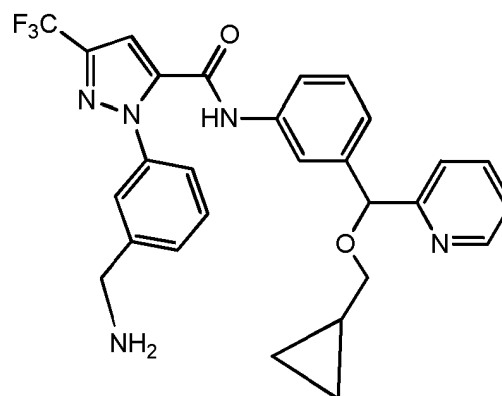
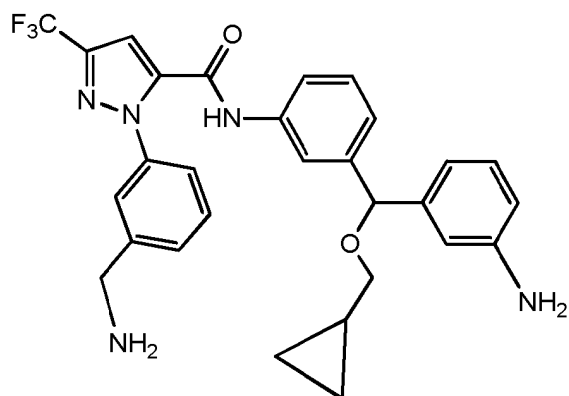
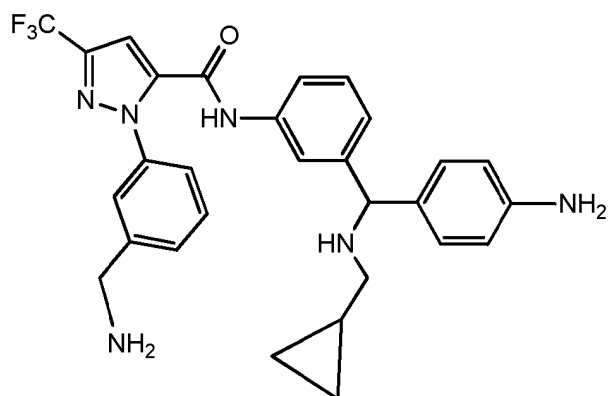
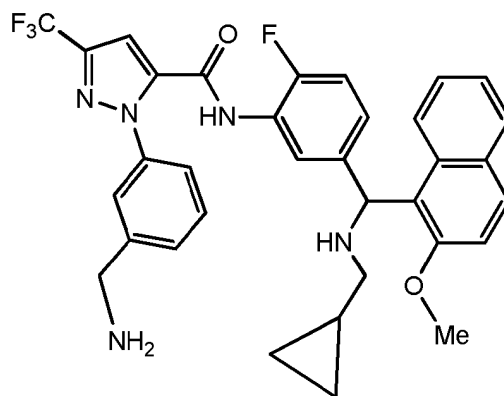
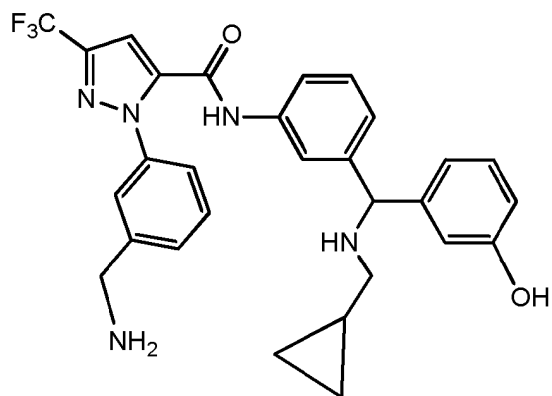
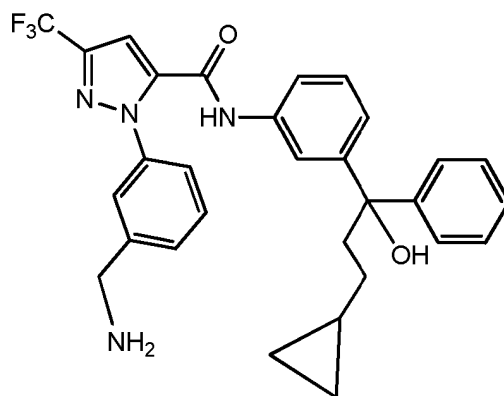
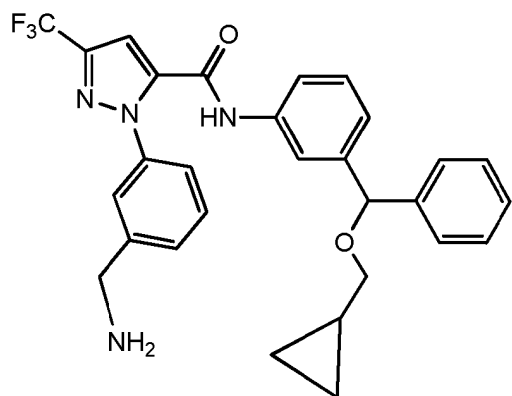
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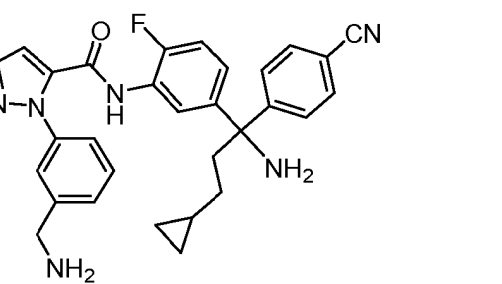
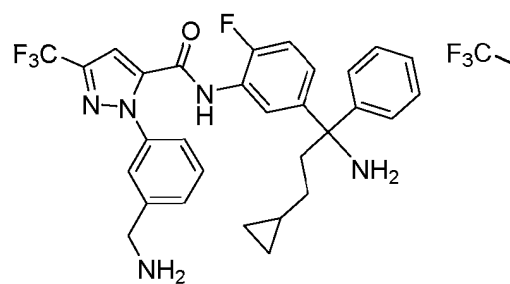
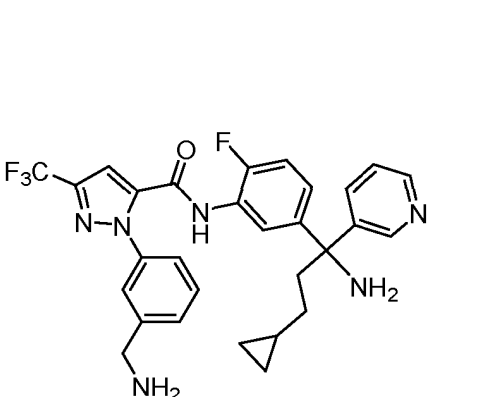
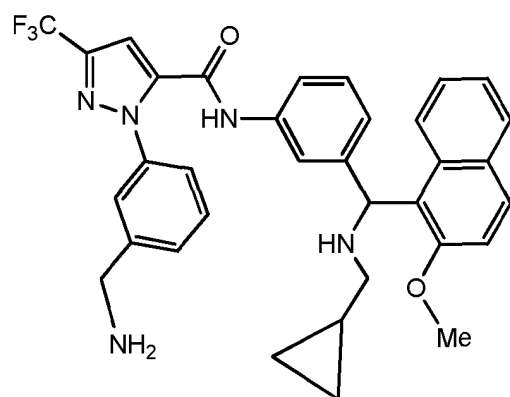
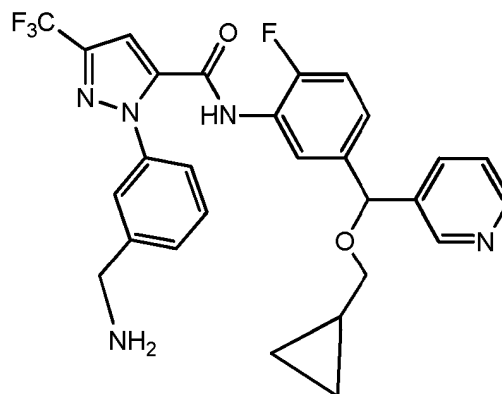
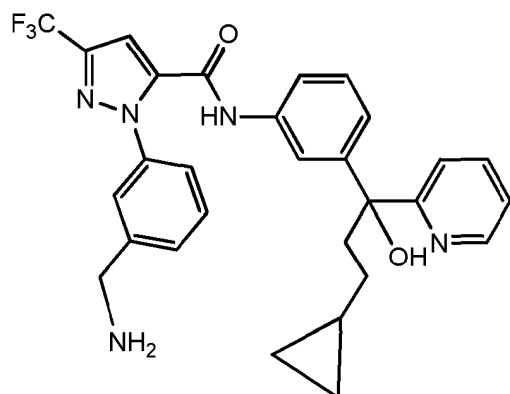
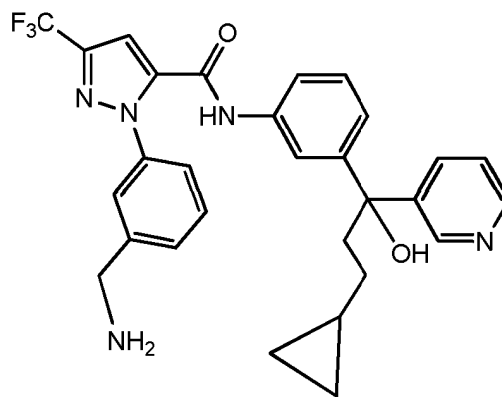
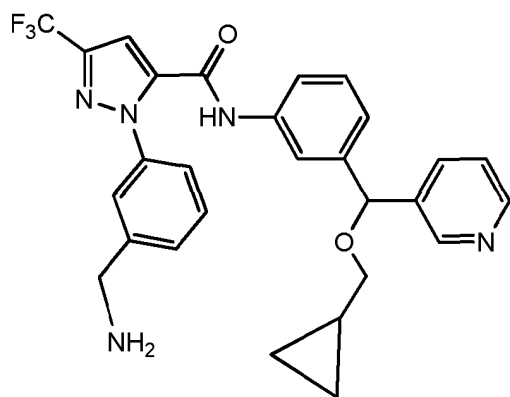
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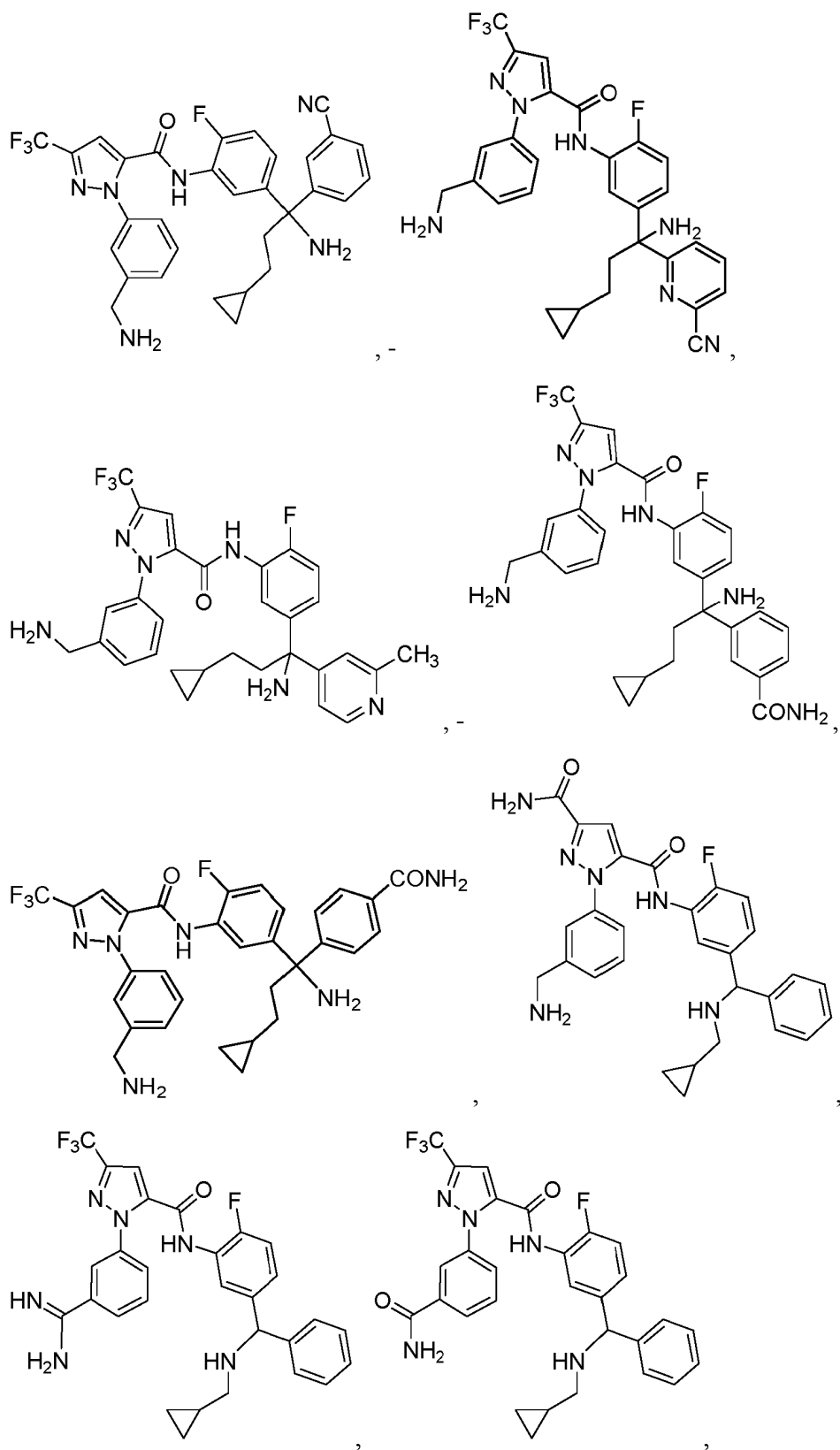
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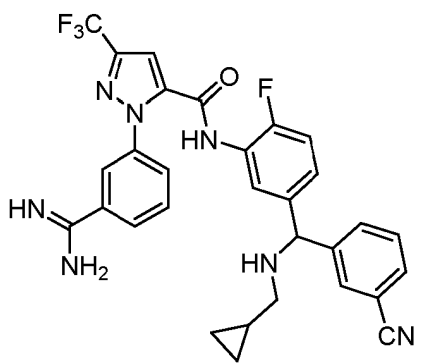
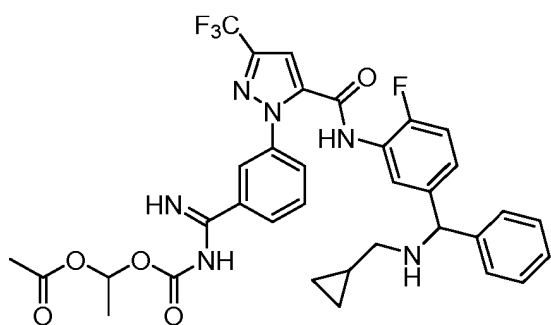
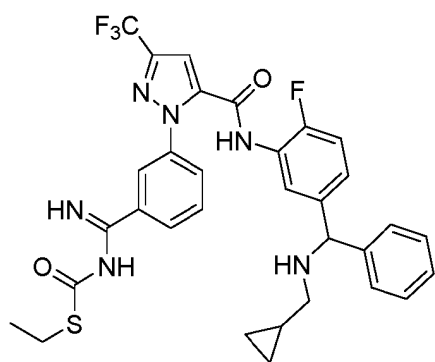
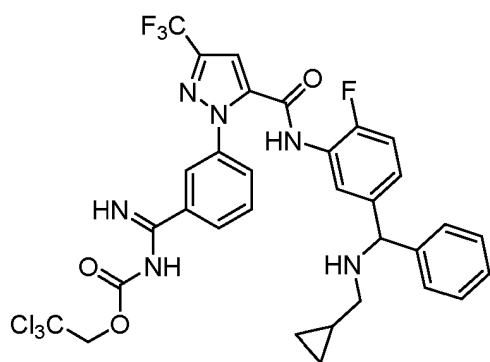
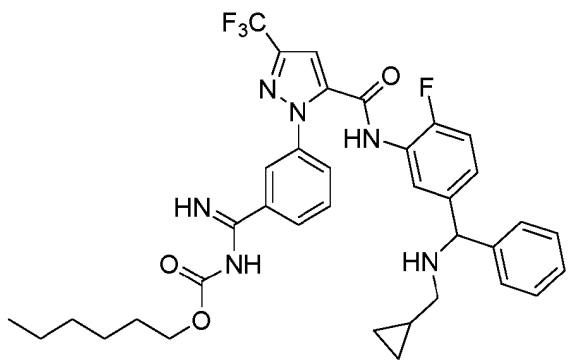
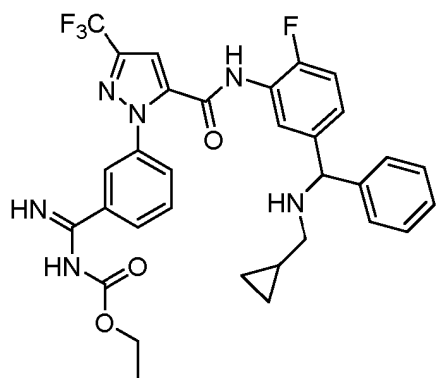
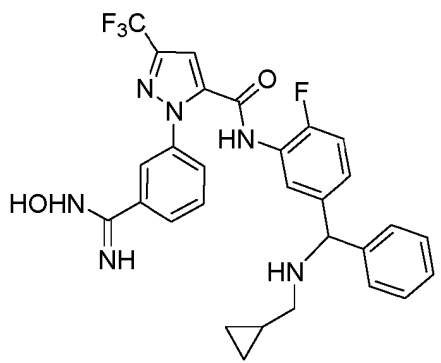
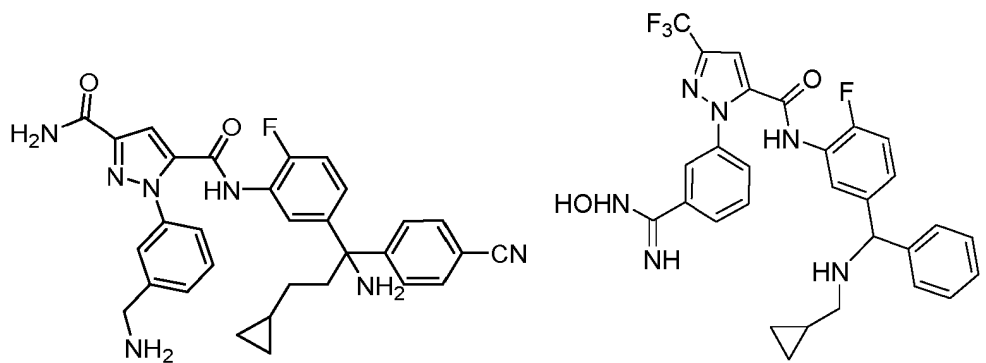
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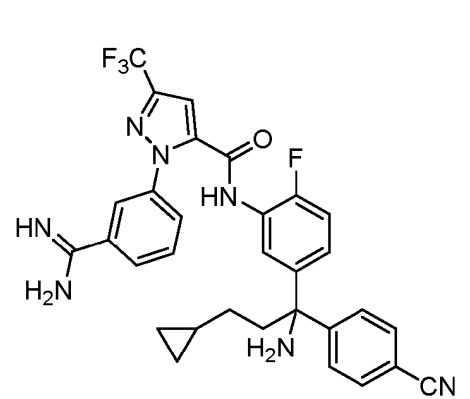
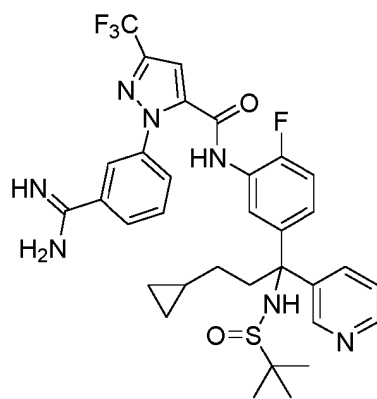
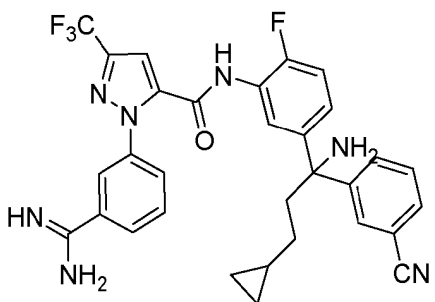
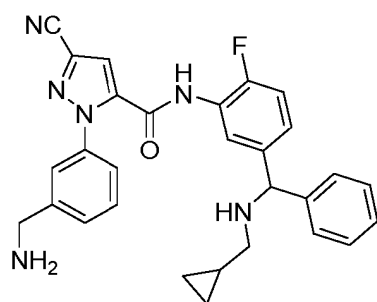
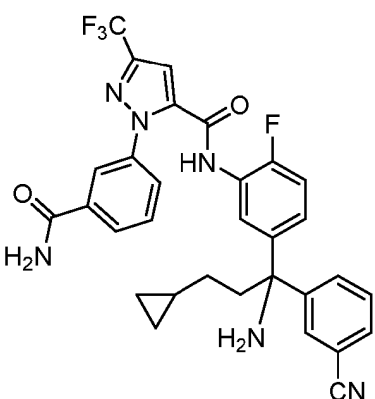
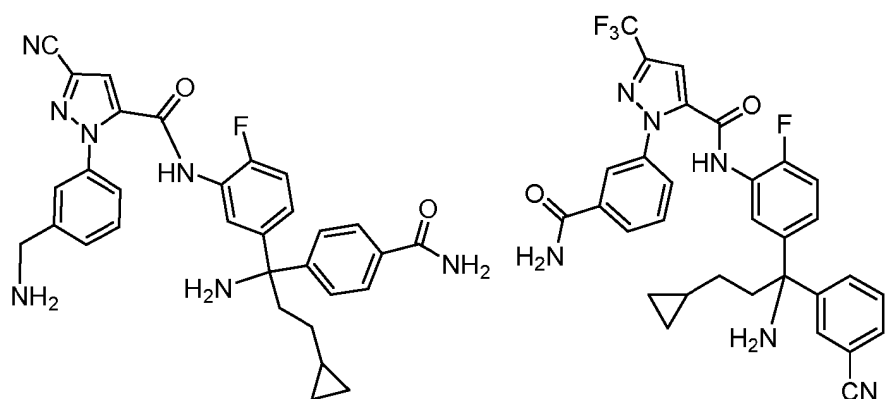
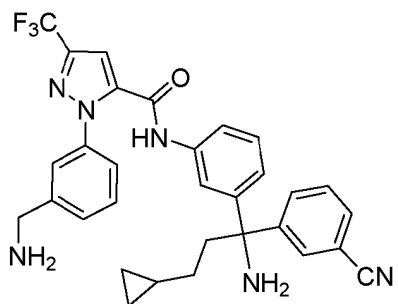
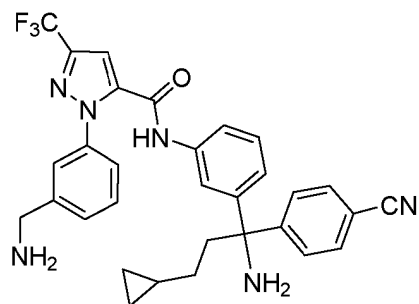
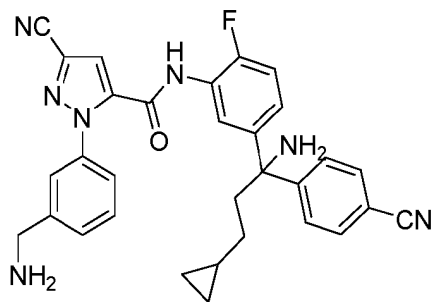
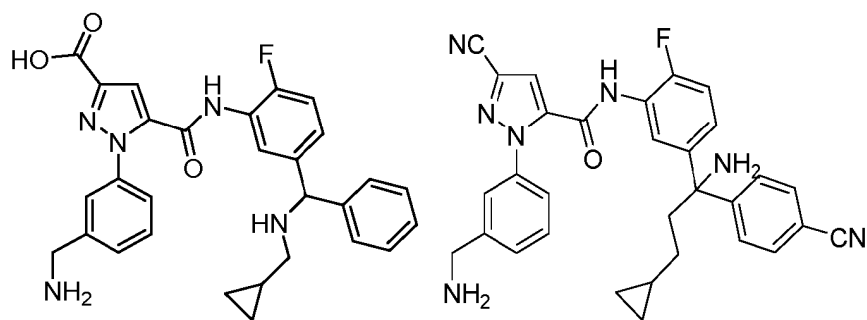
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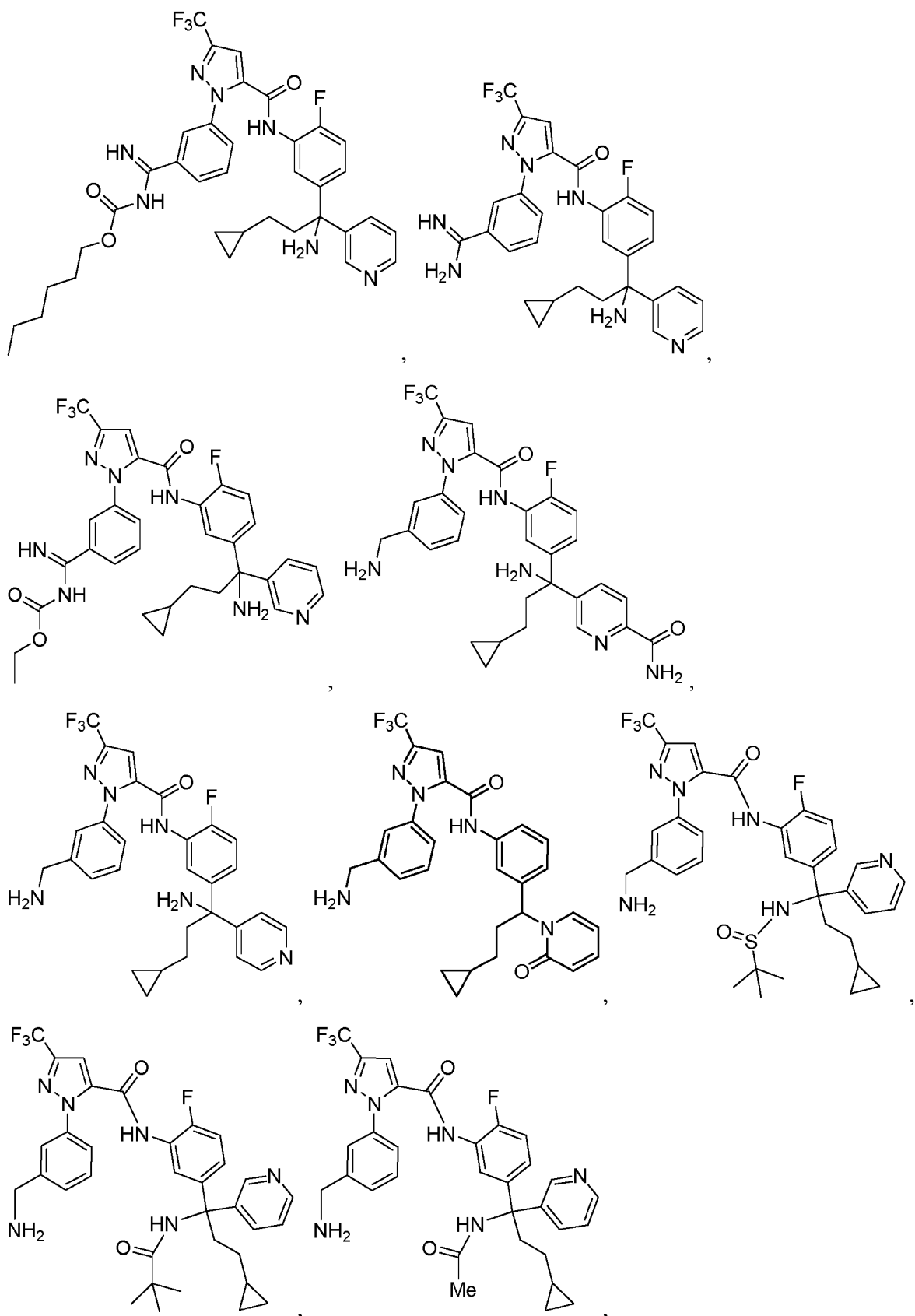
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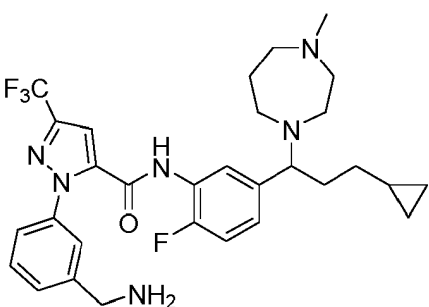
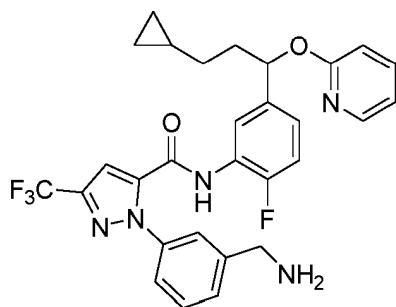
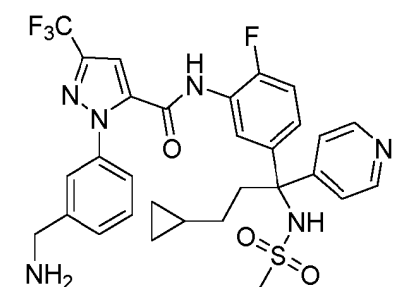
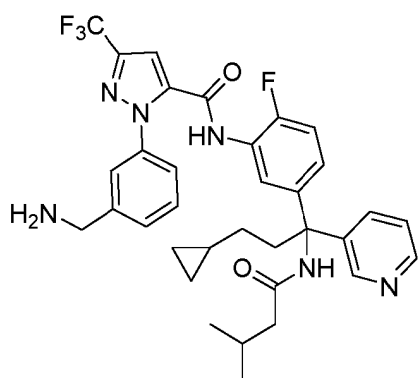
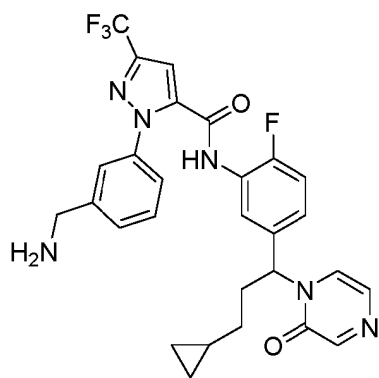
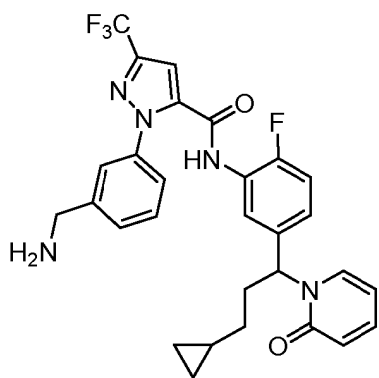
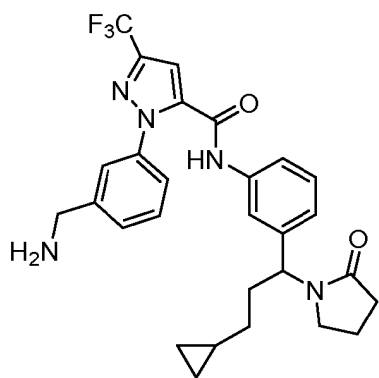
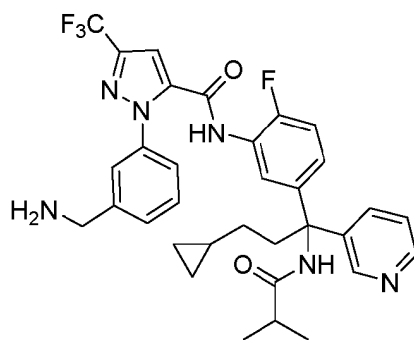
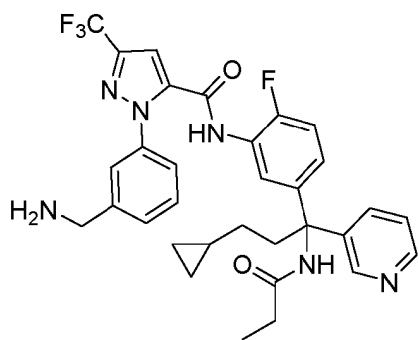
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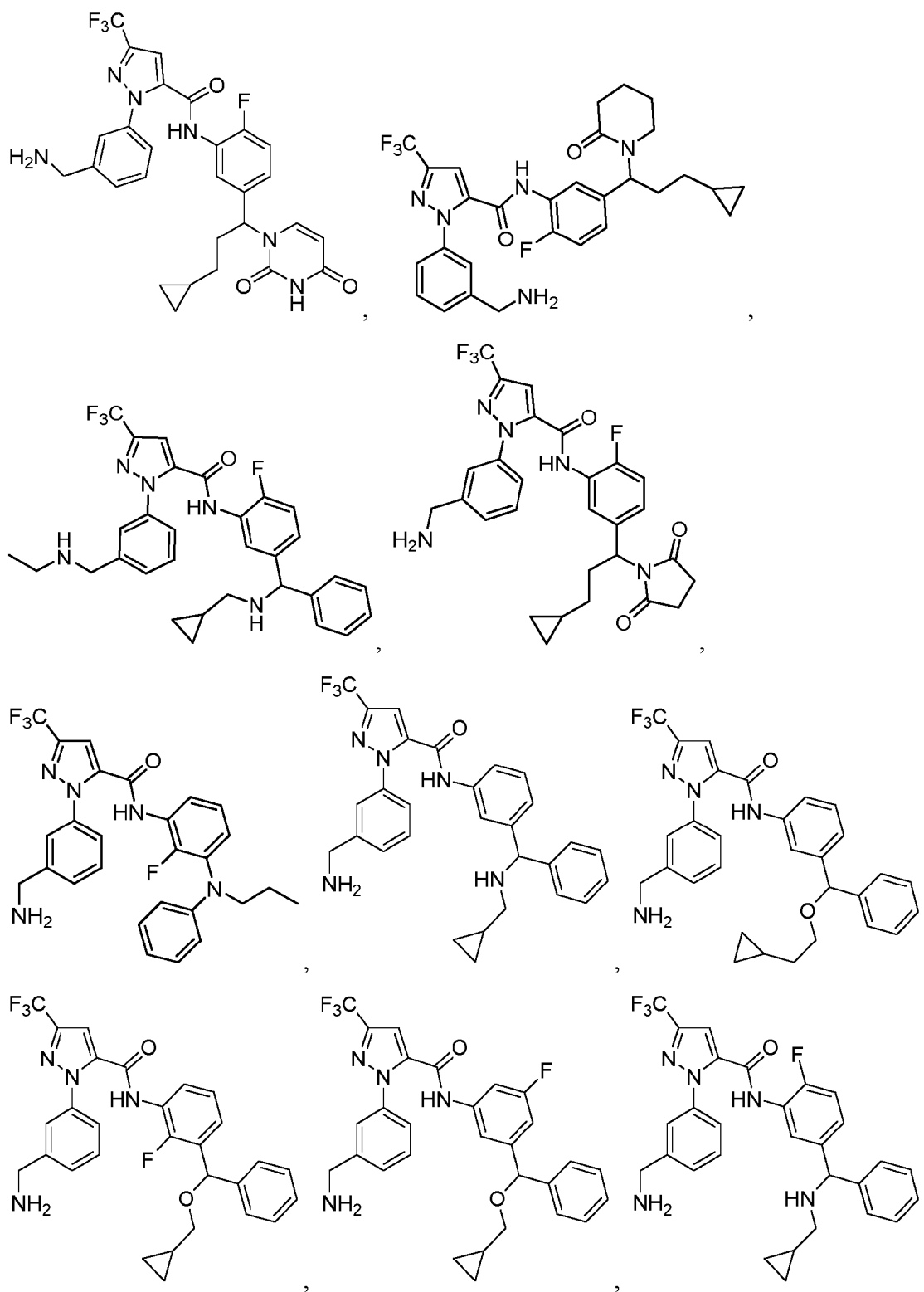
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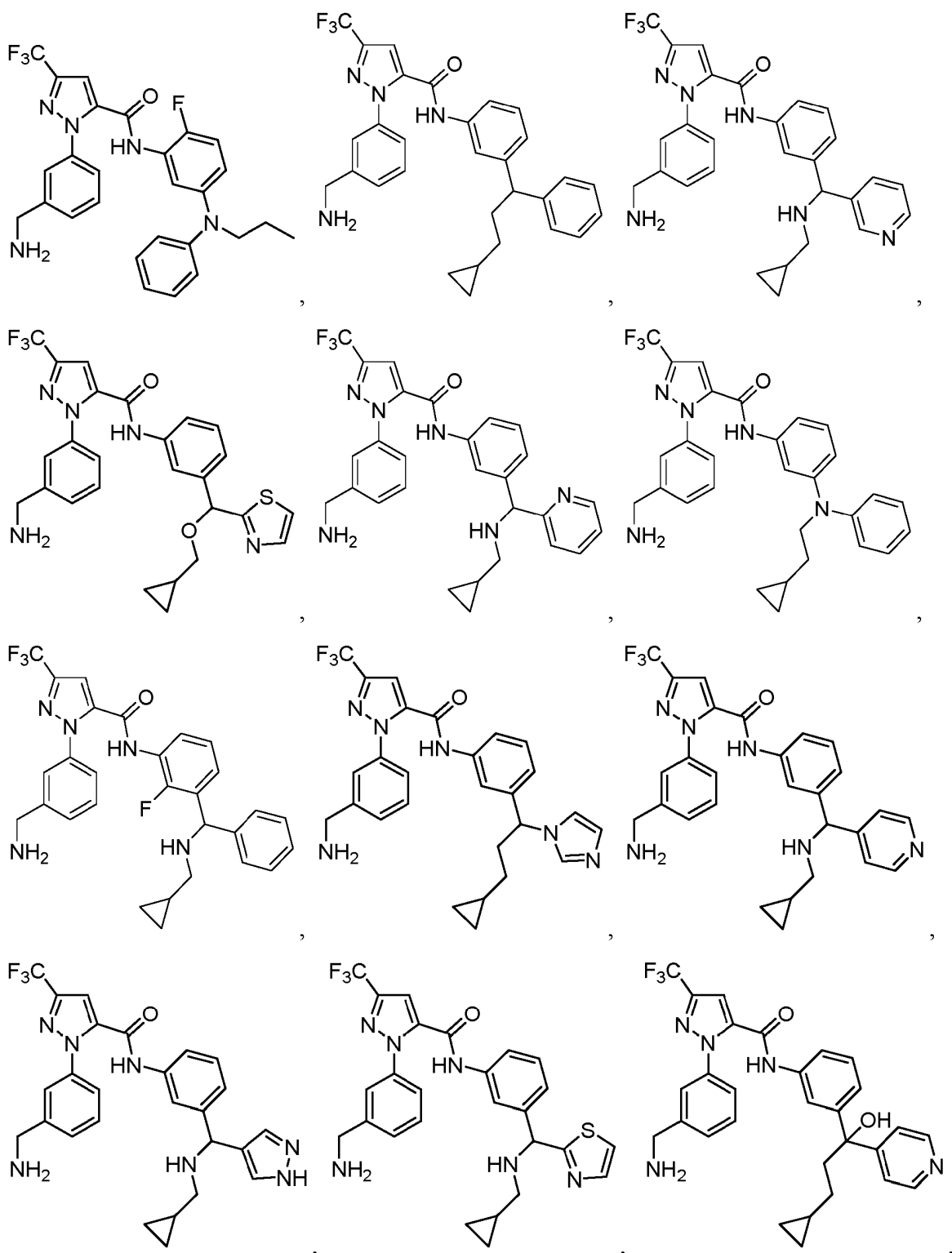
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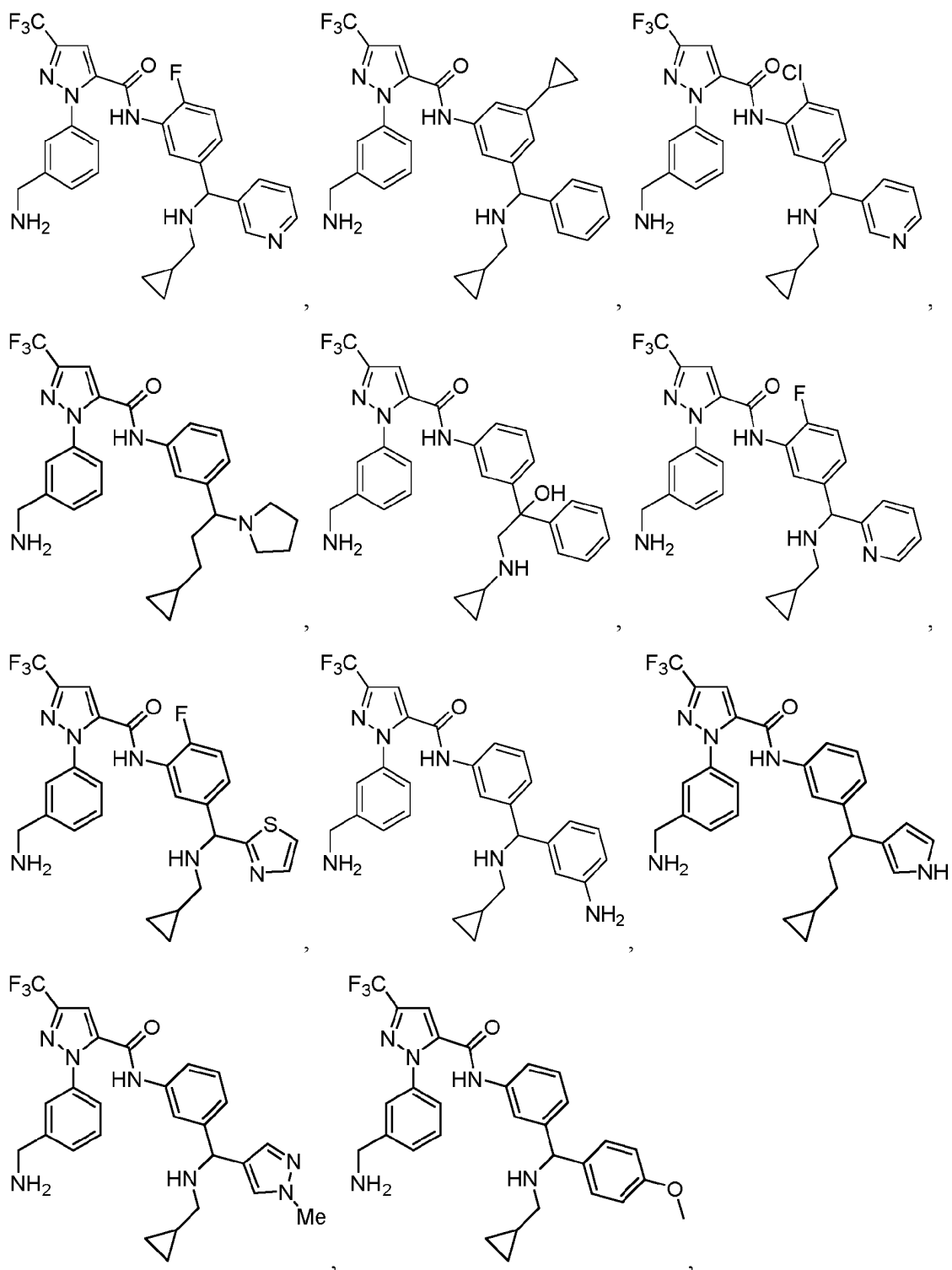
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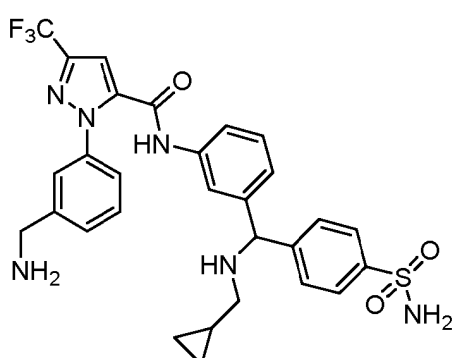
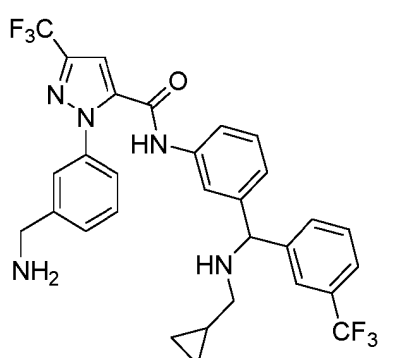
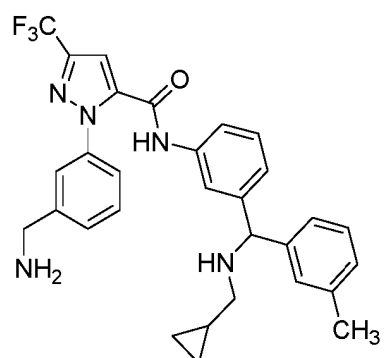
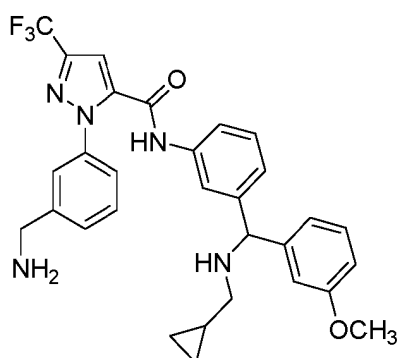
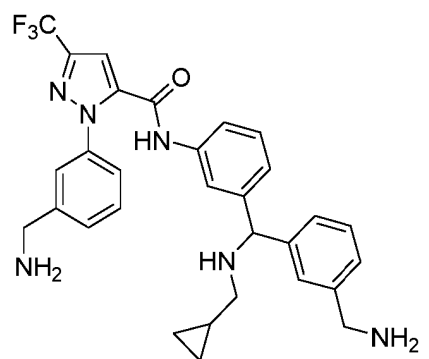
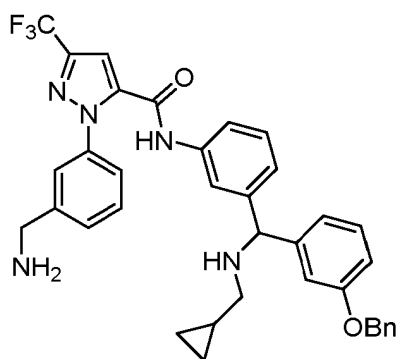
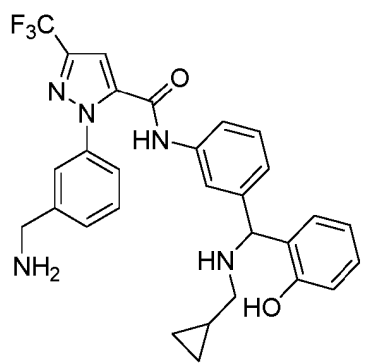
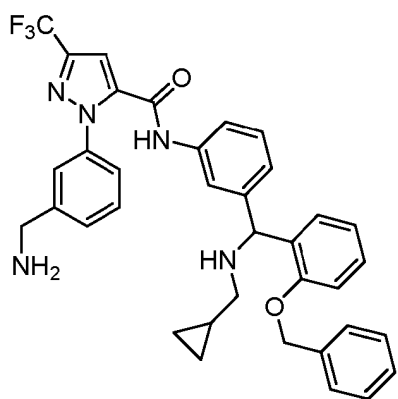
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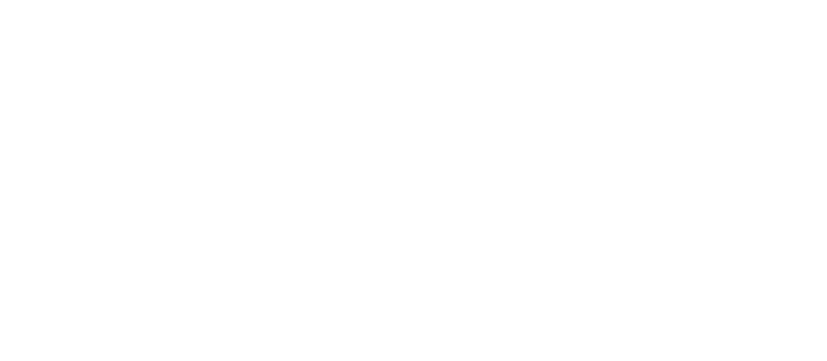
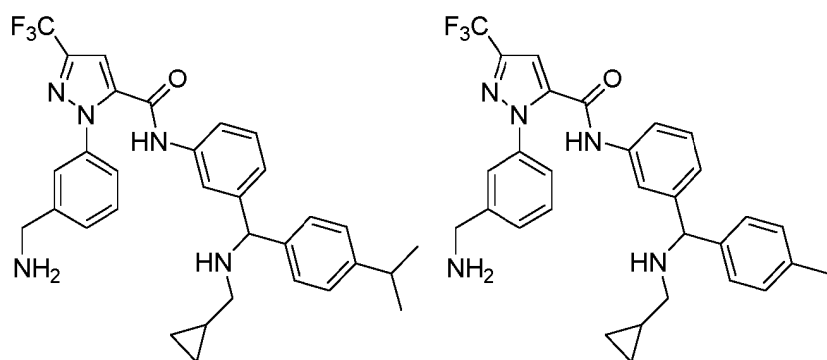
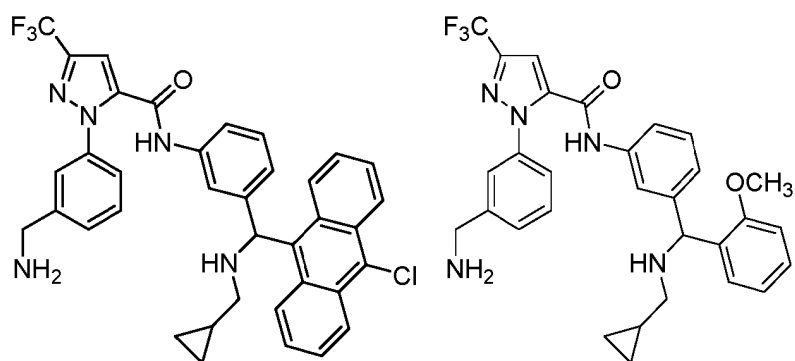
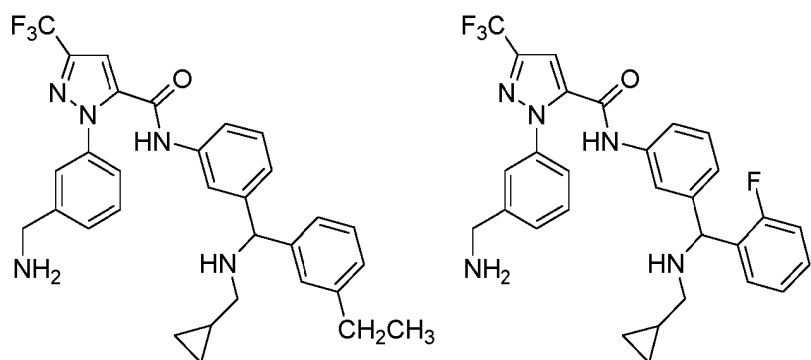
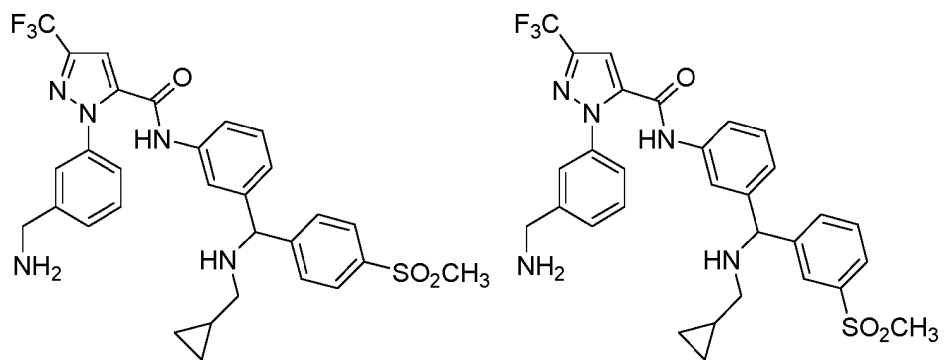
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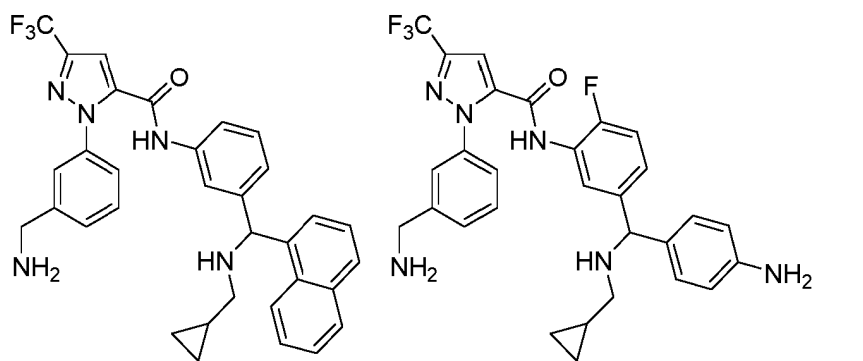
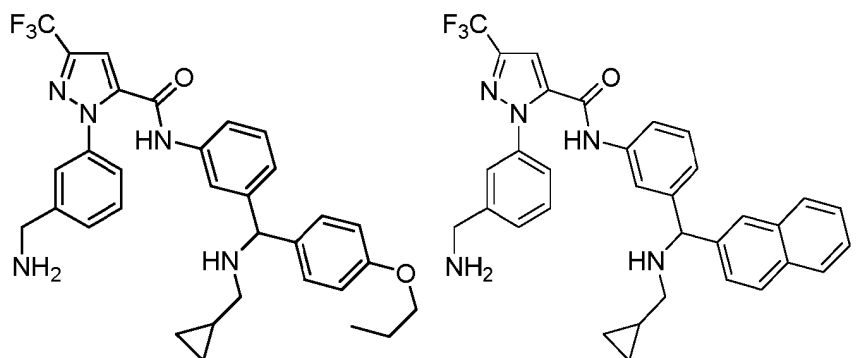
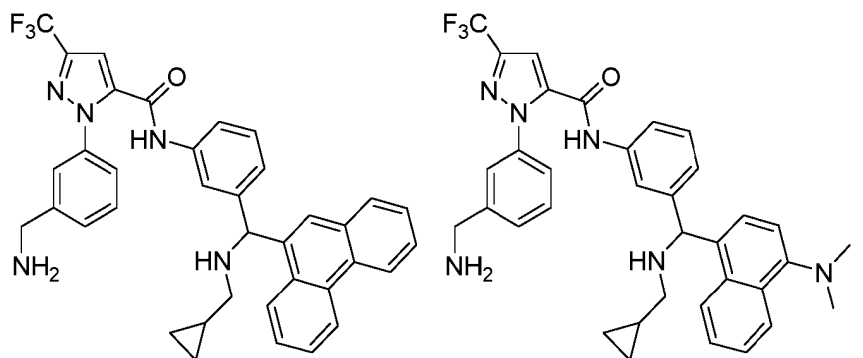
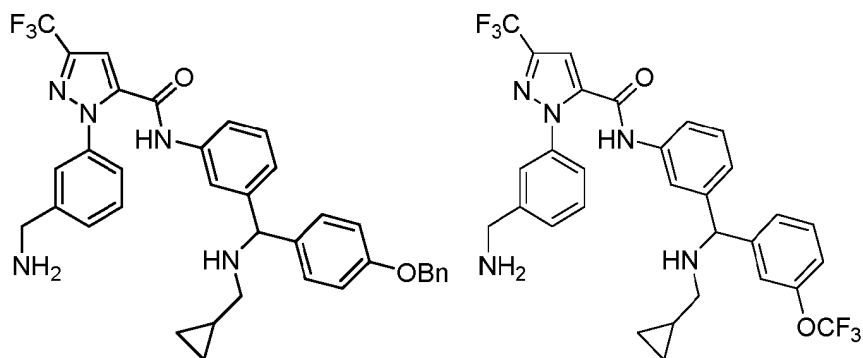
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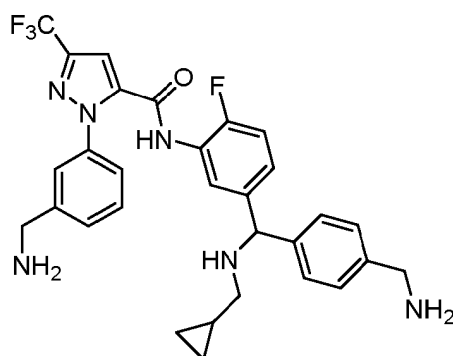
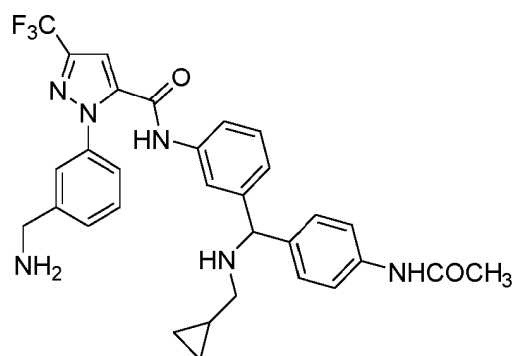
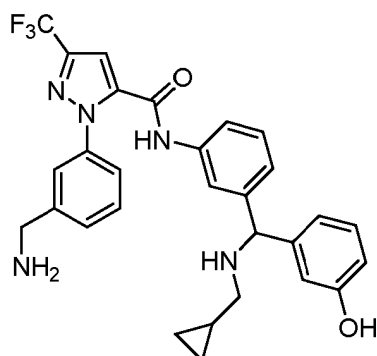
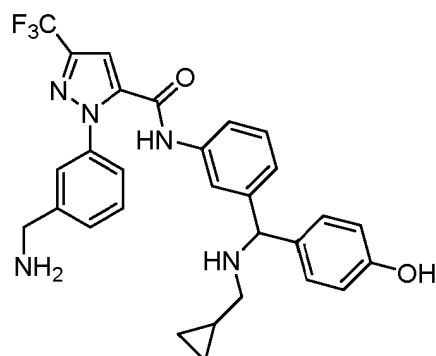
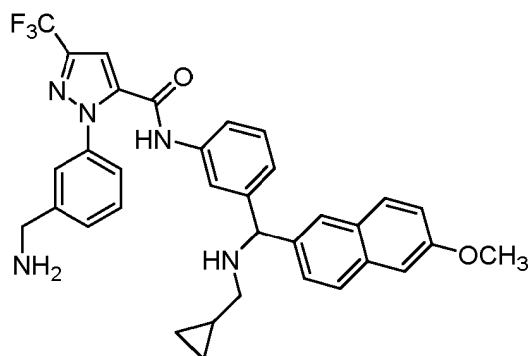
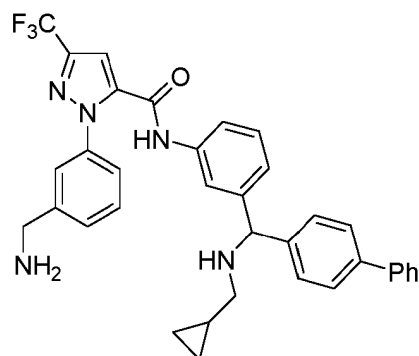
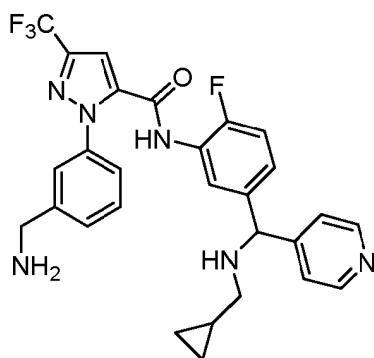
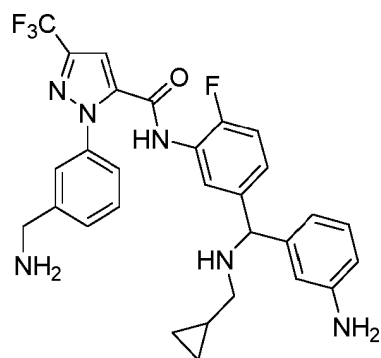
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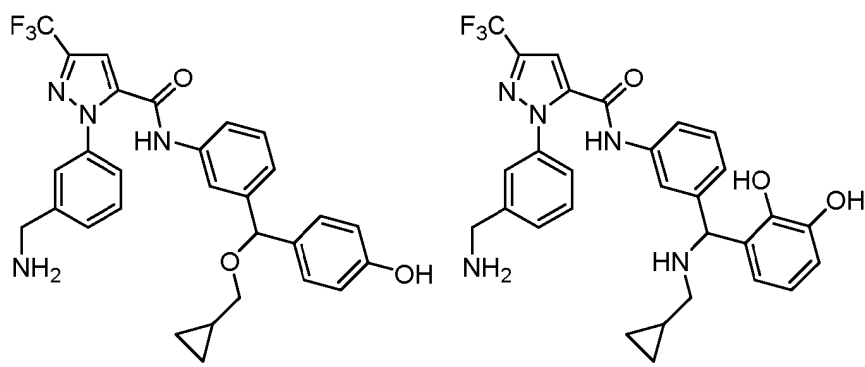
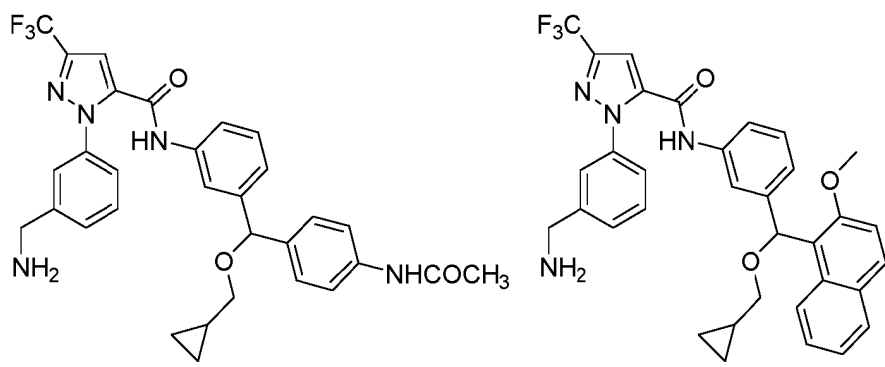
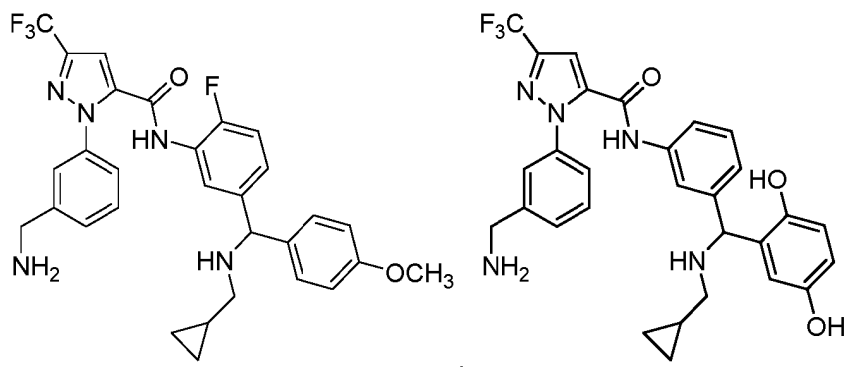
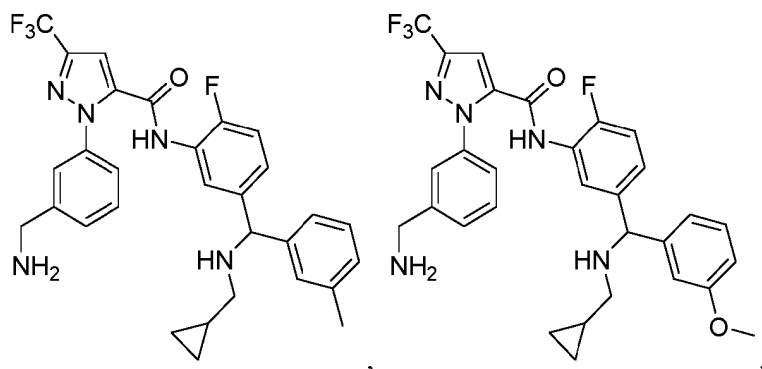
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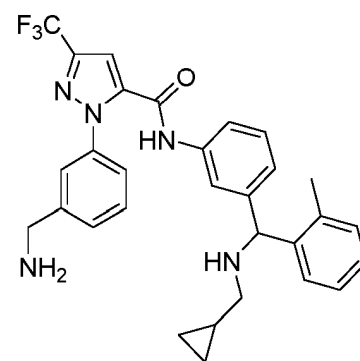
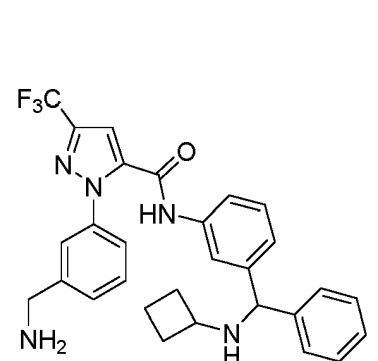
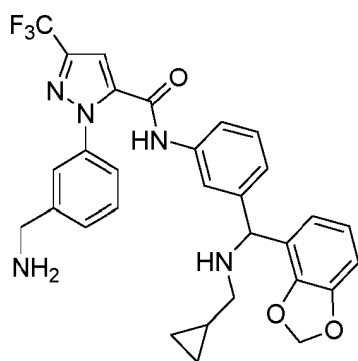
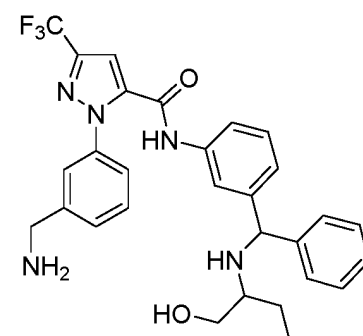
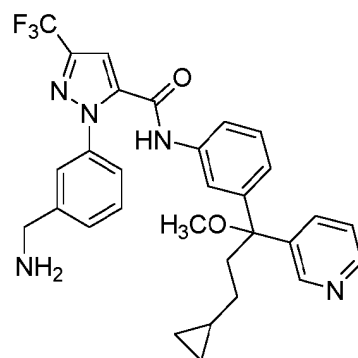
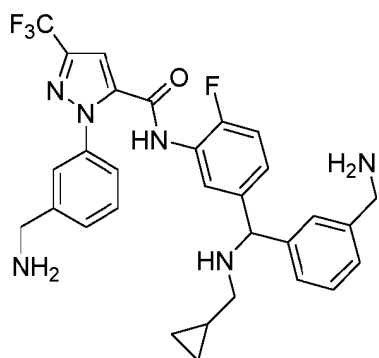
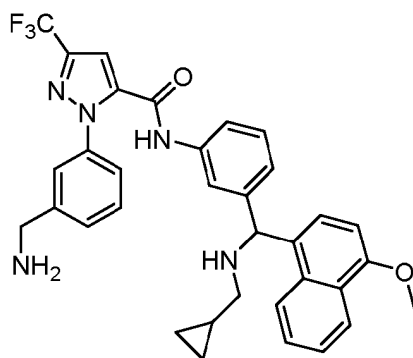
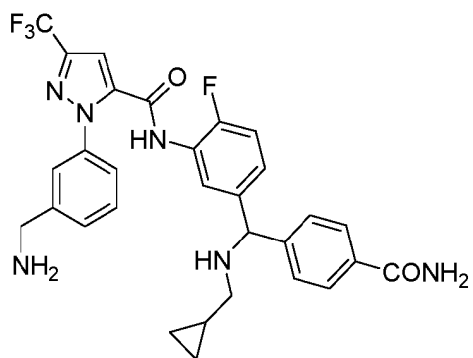
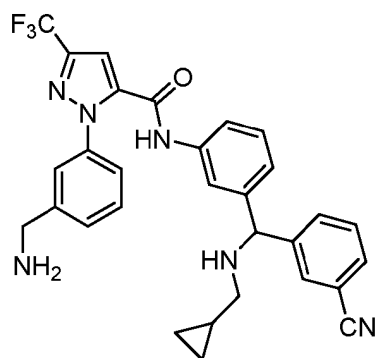
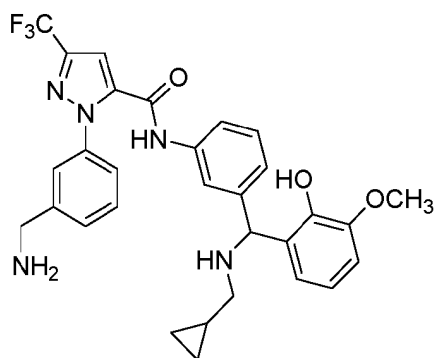
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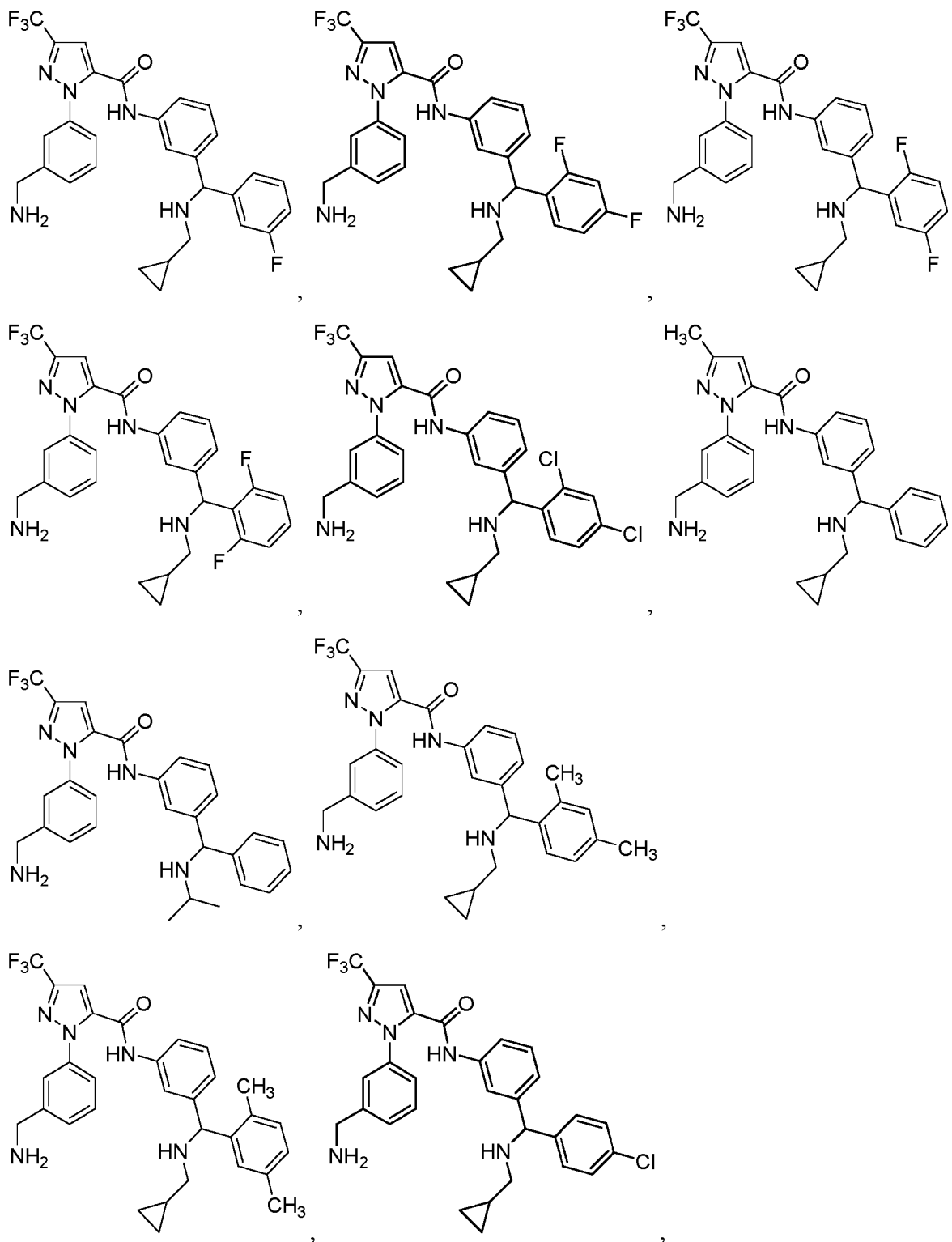
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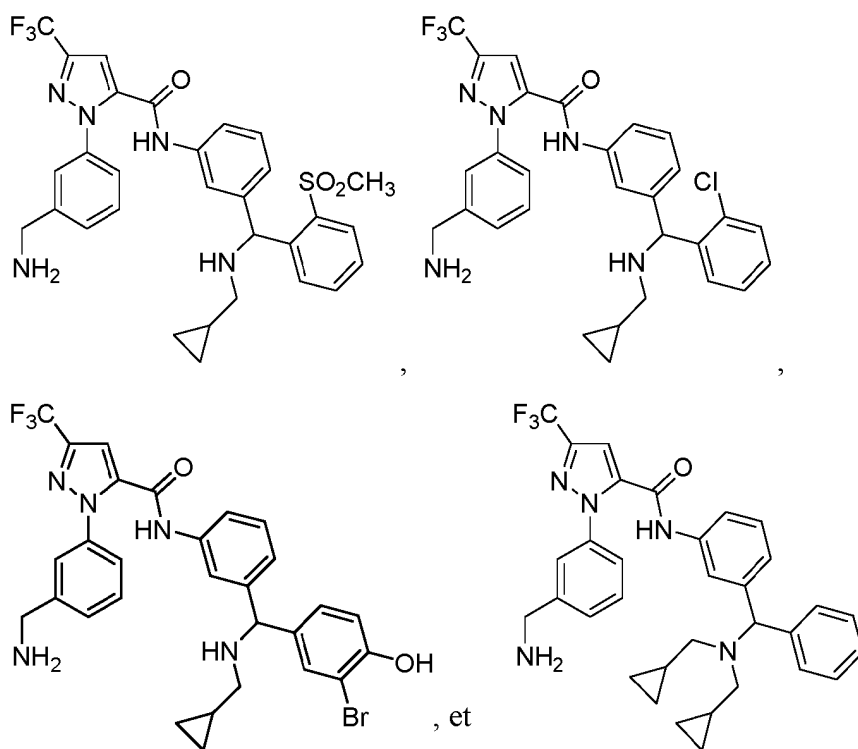
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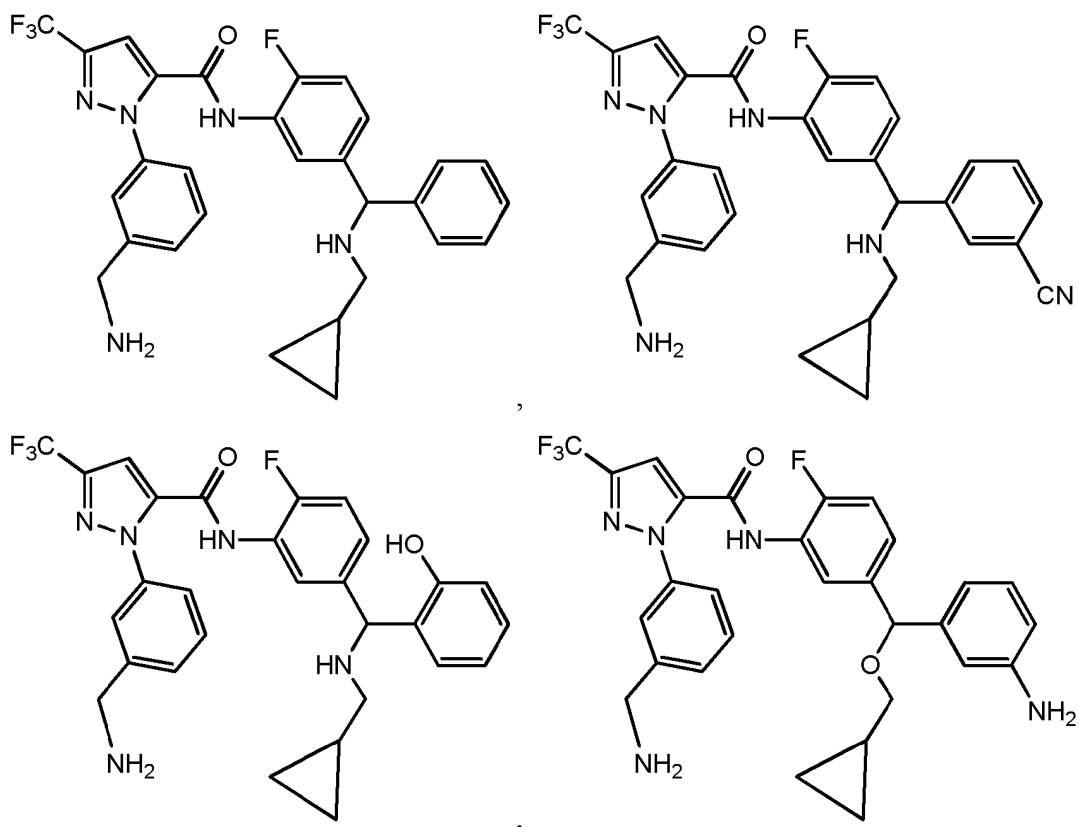
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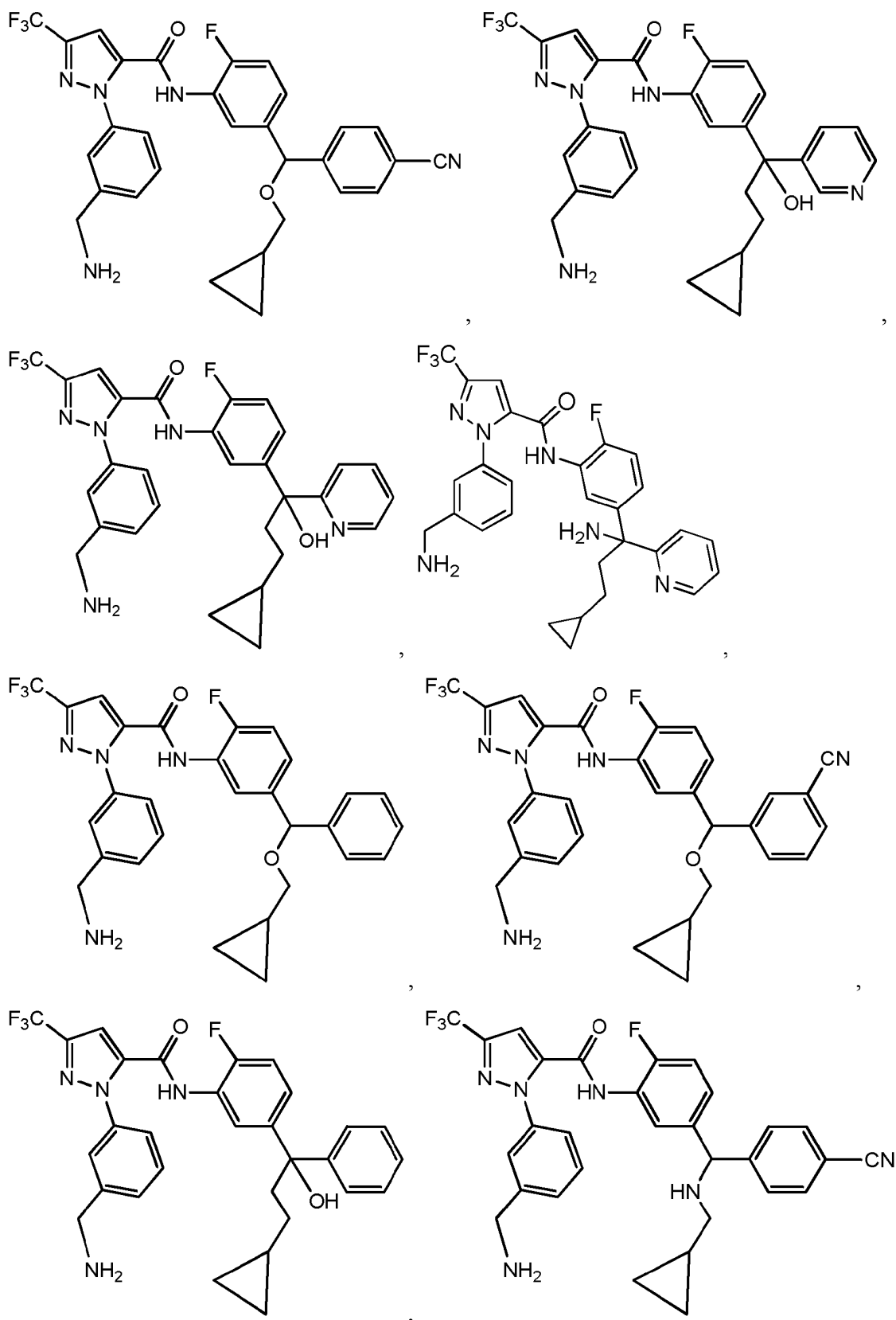


2. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué par :



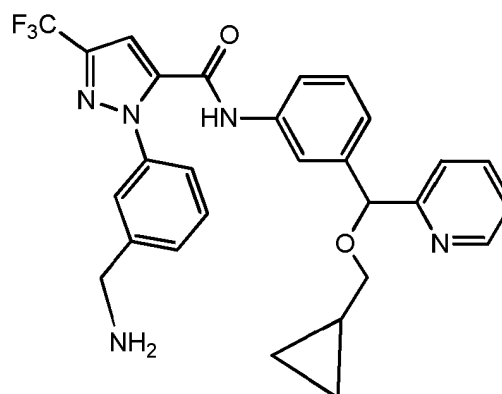
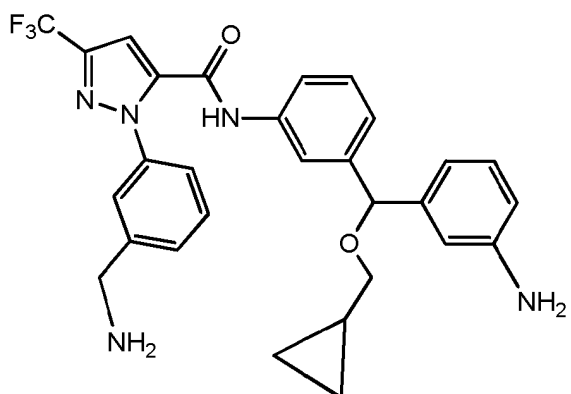
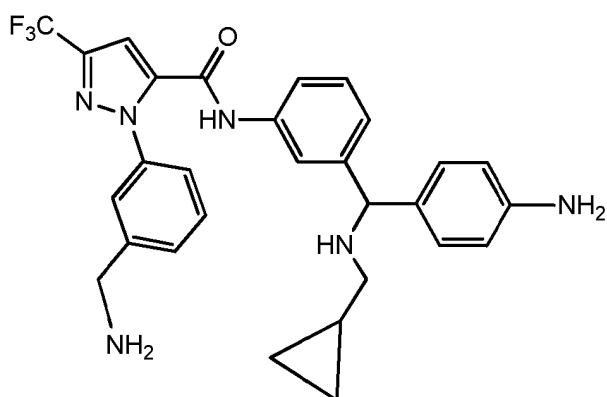
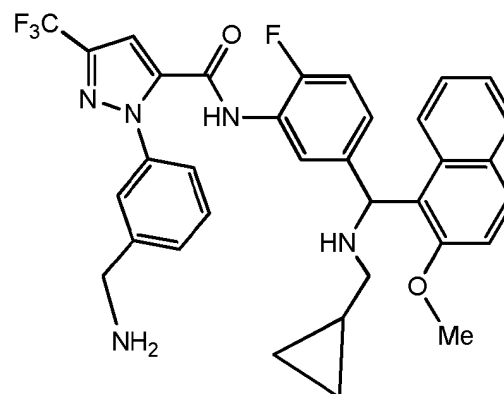
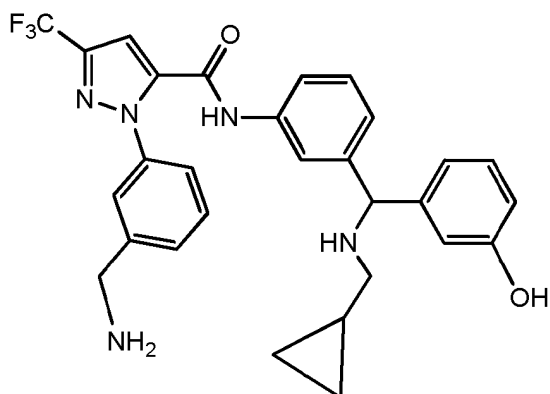
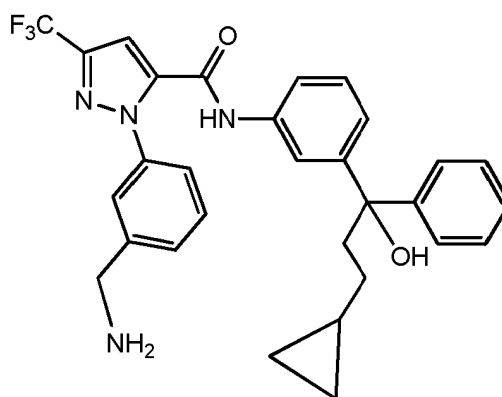
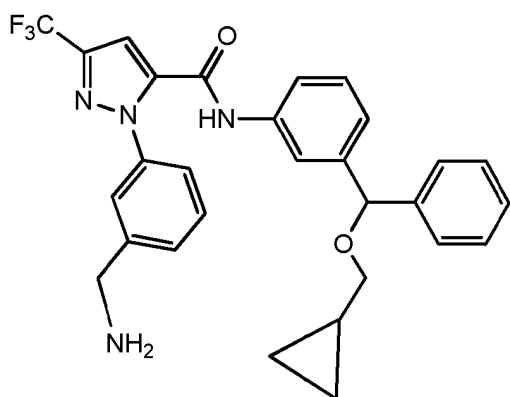
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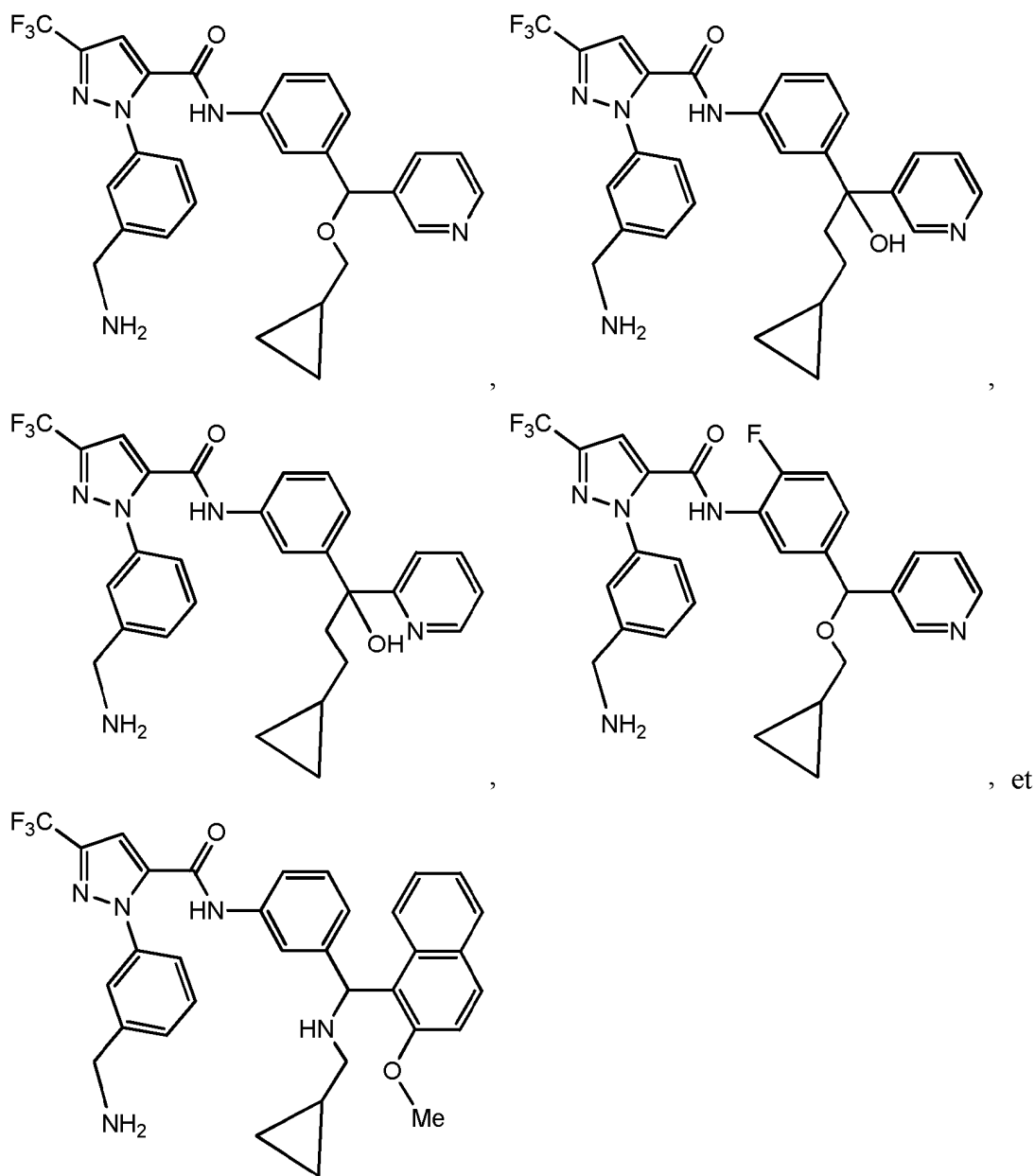
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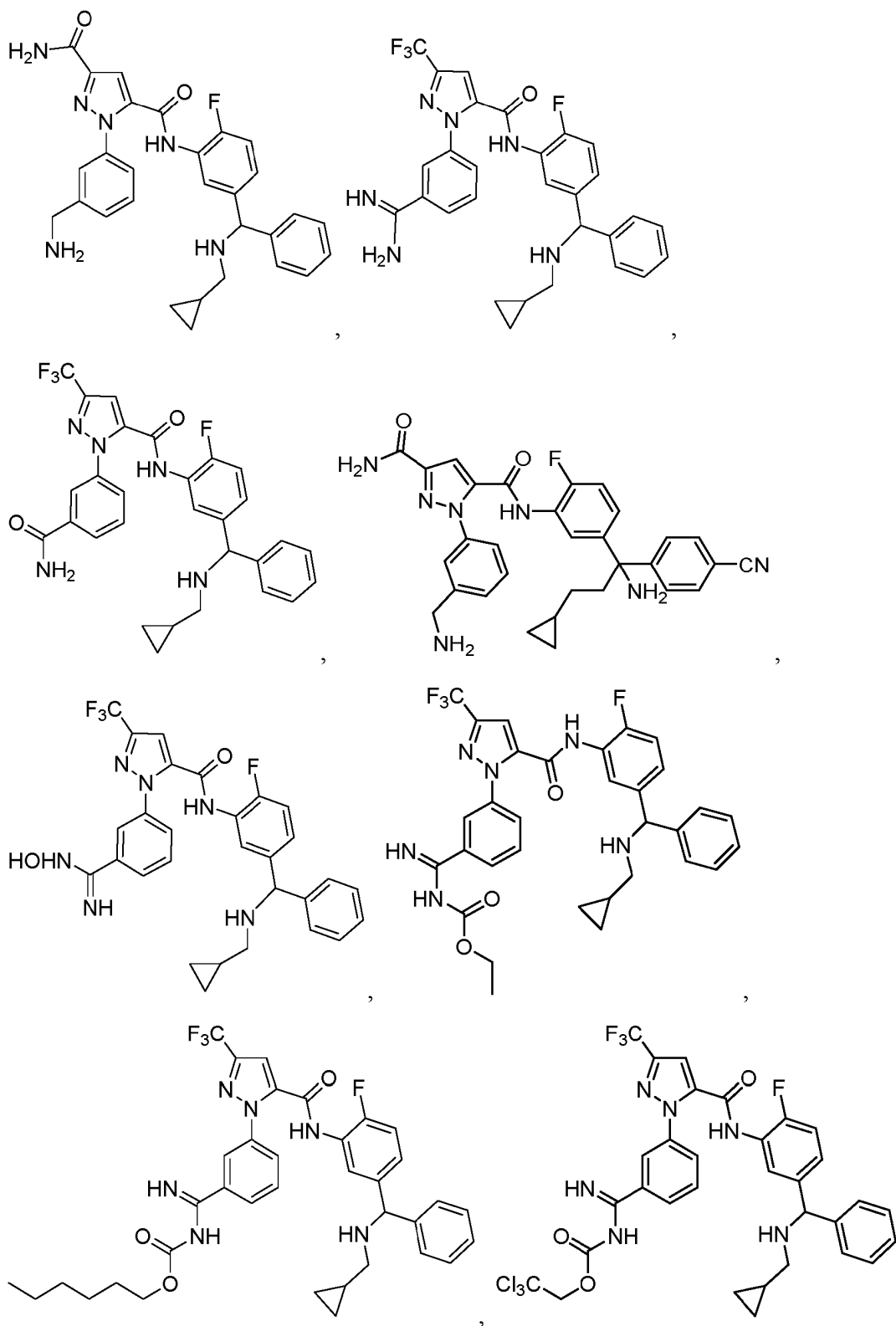




3. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué par :

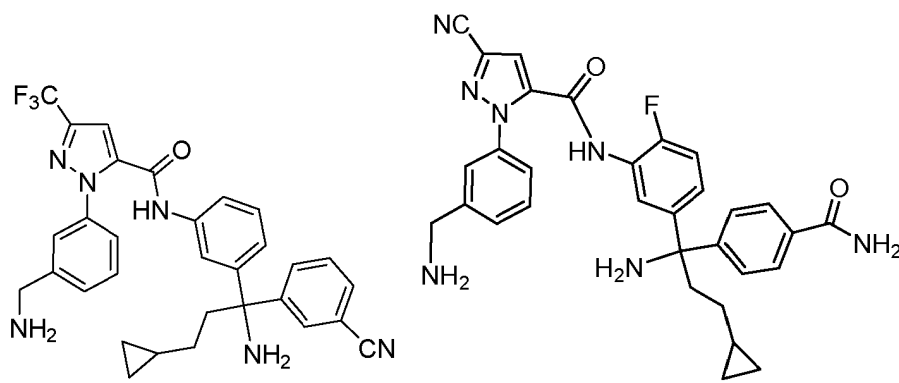
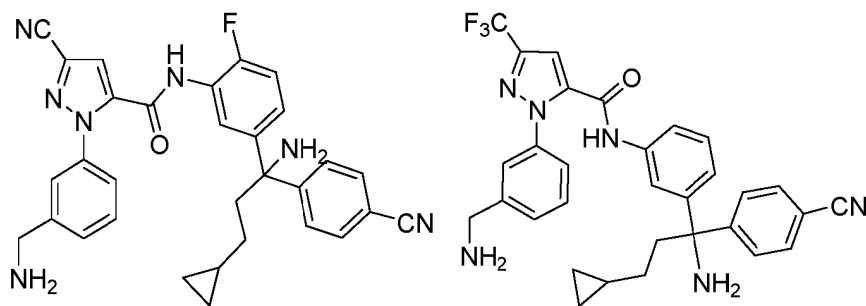
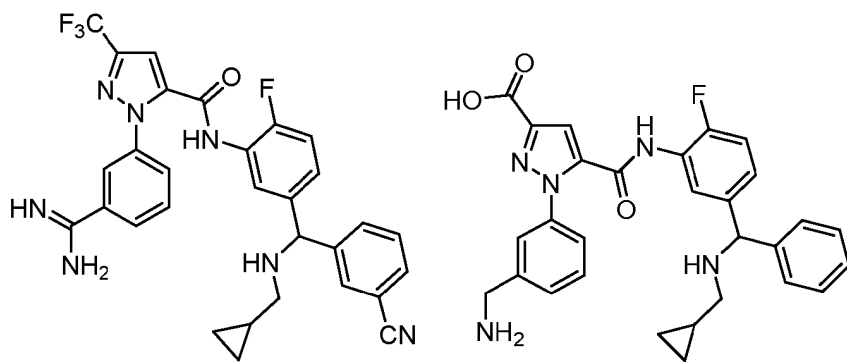
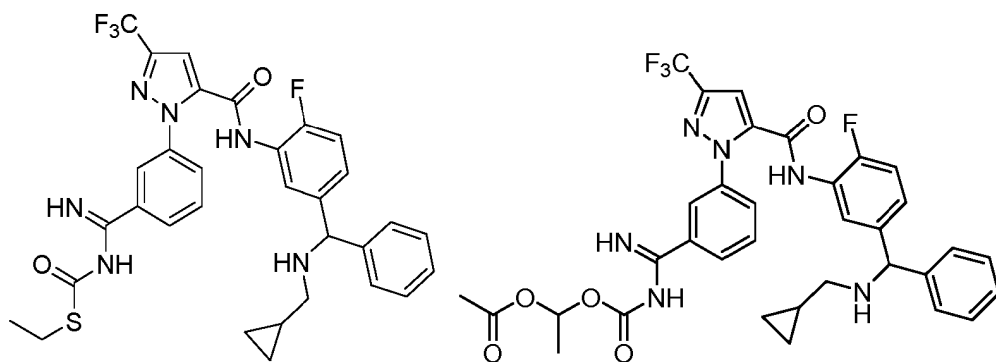
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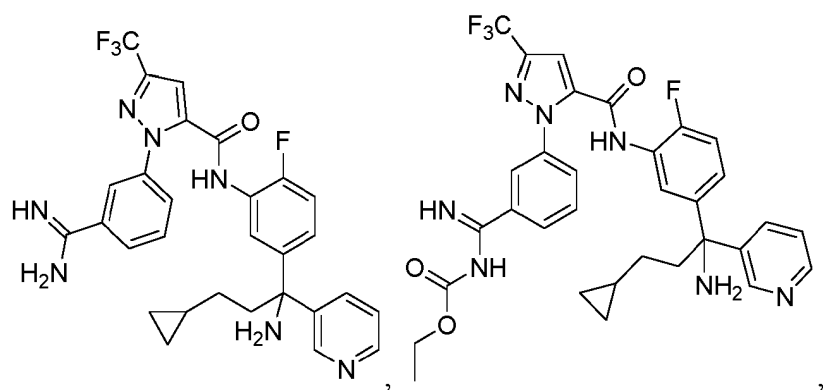
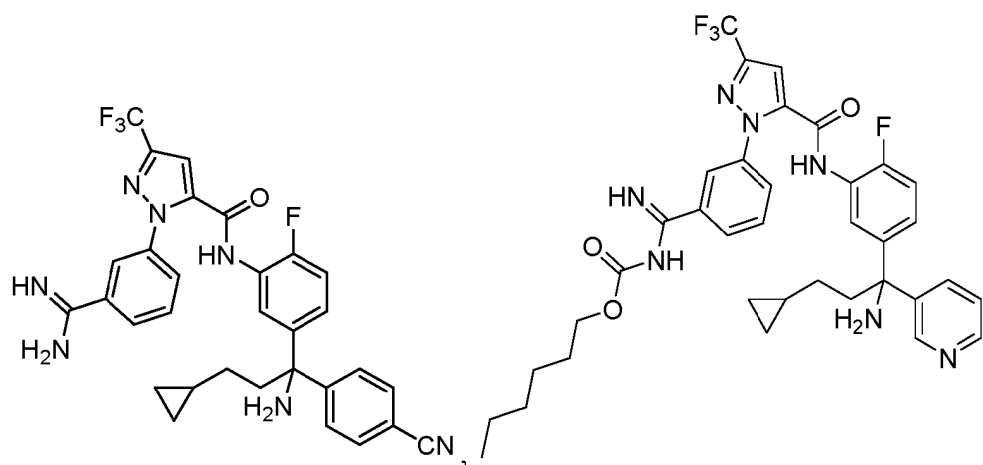
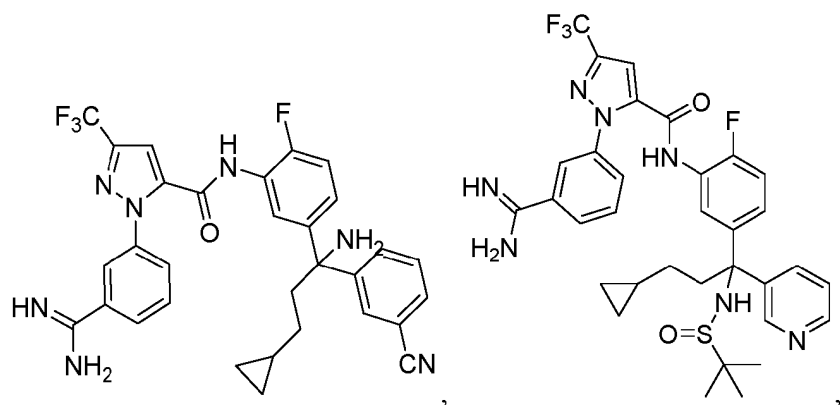
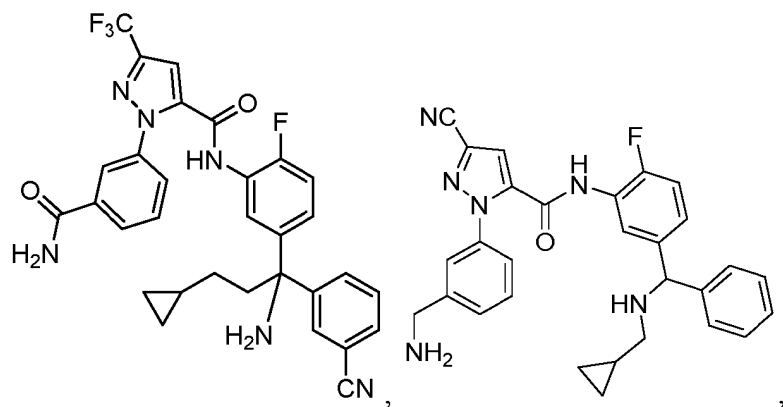
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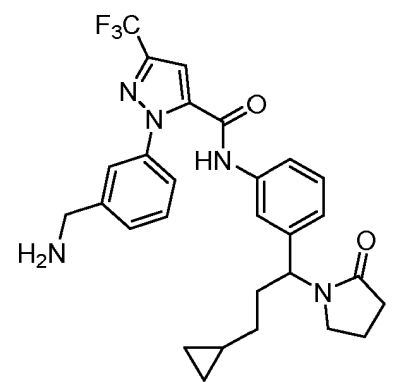
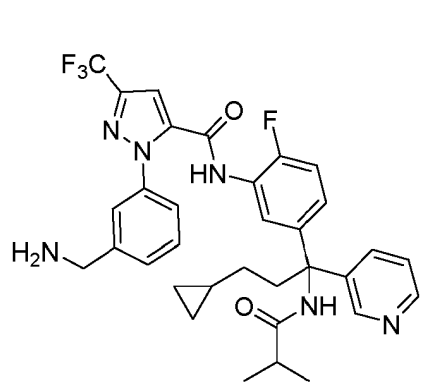
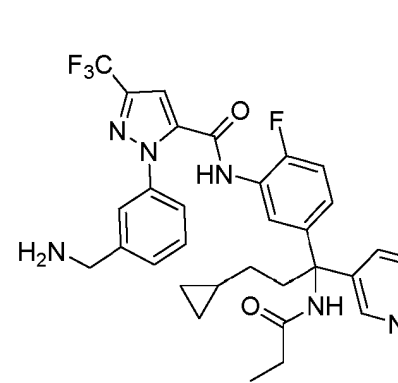
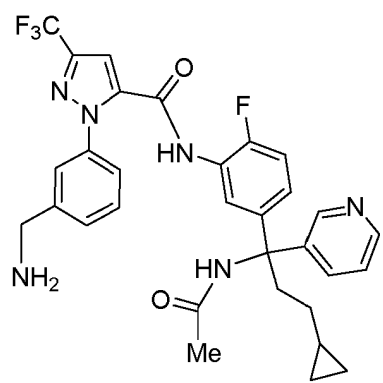
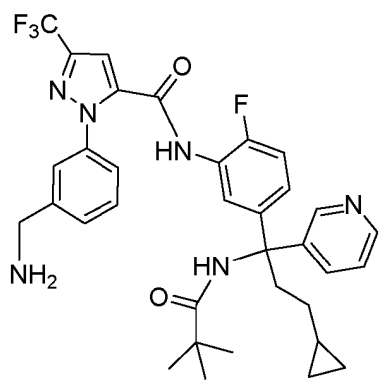
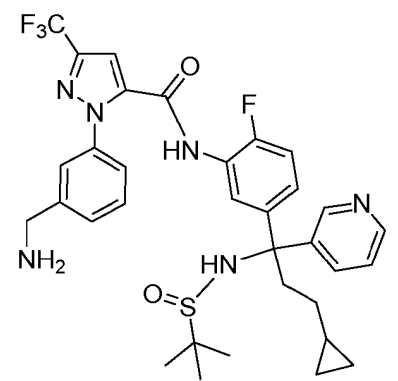
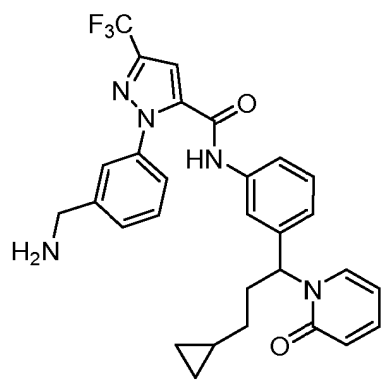
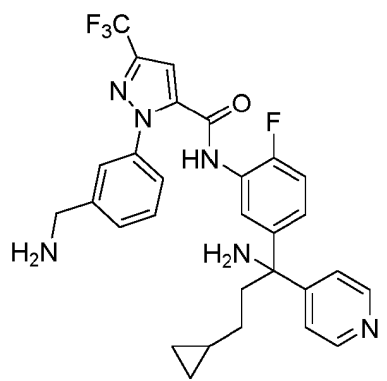
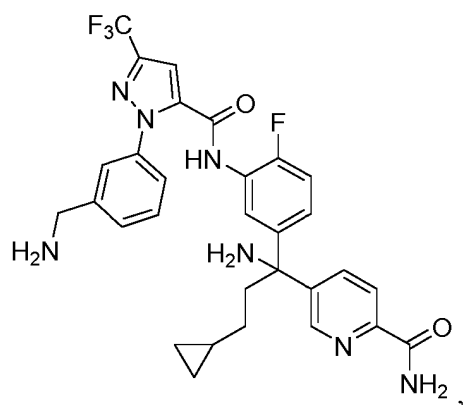
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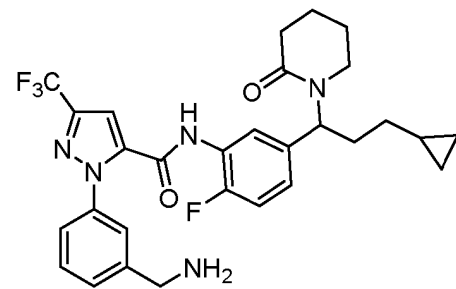
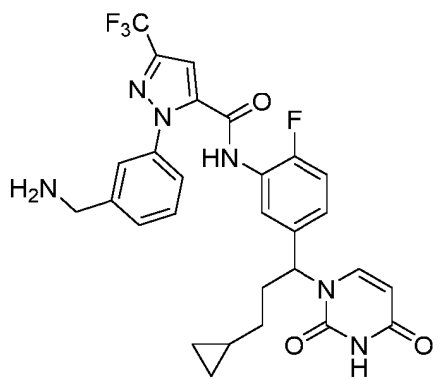
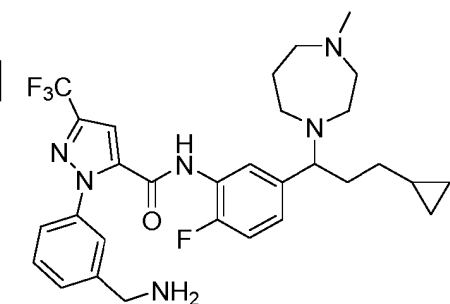
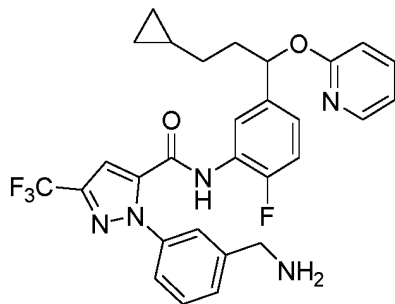
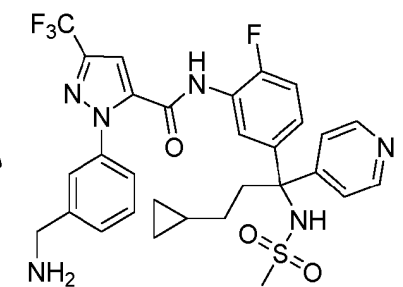
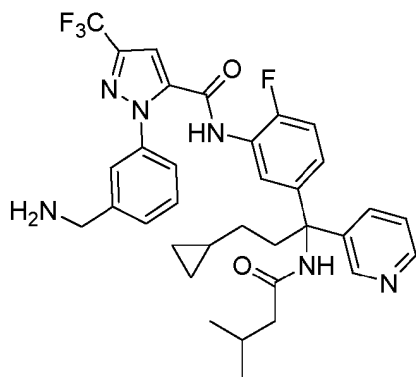
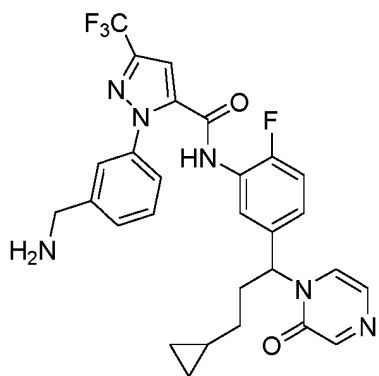
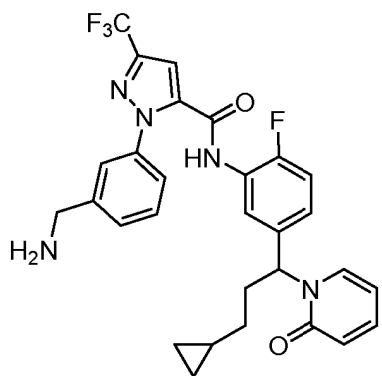
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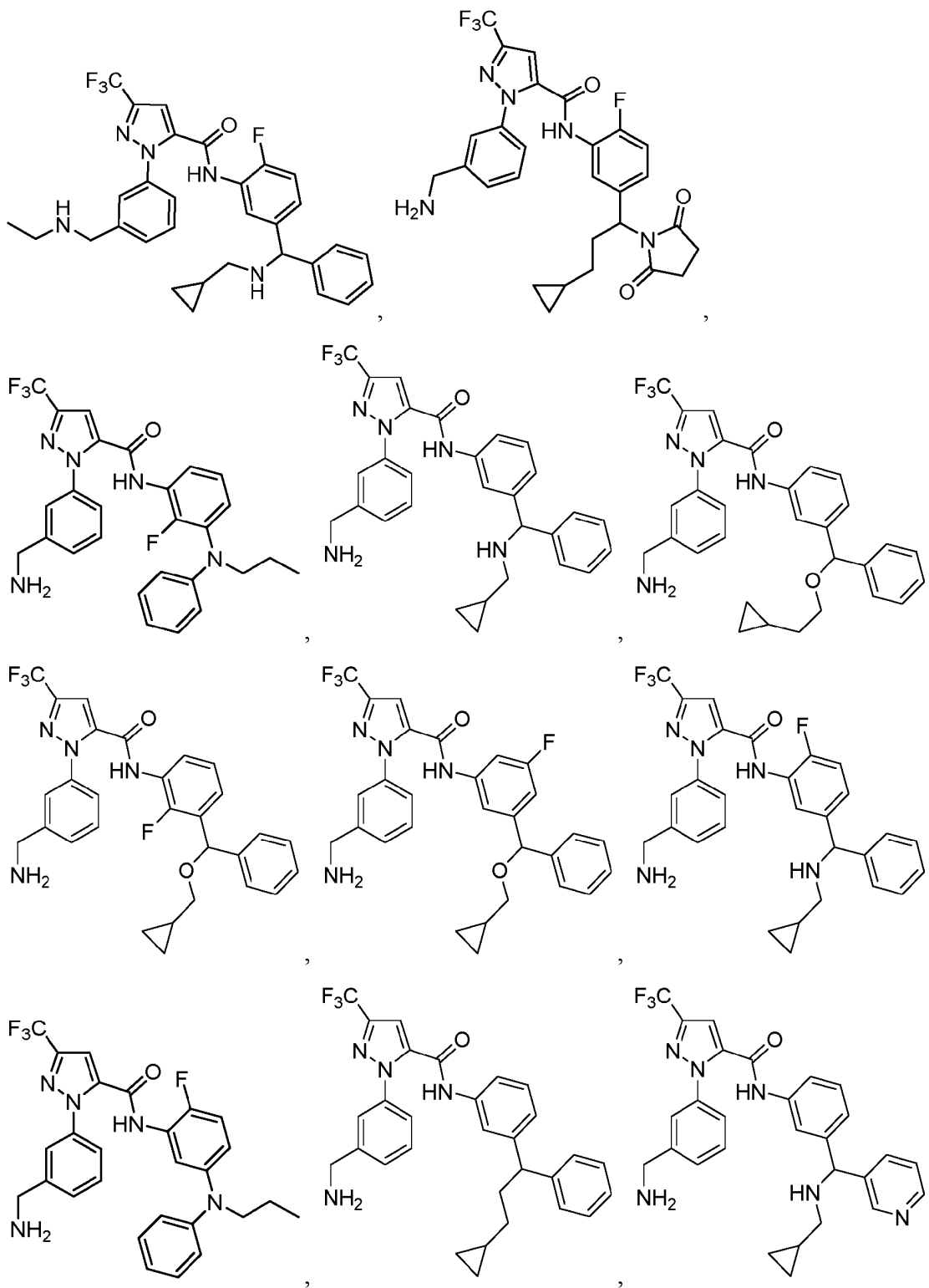
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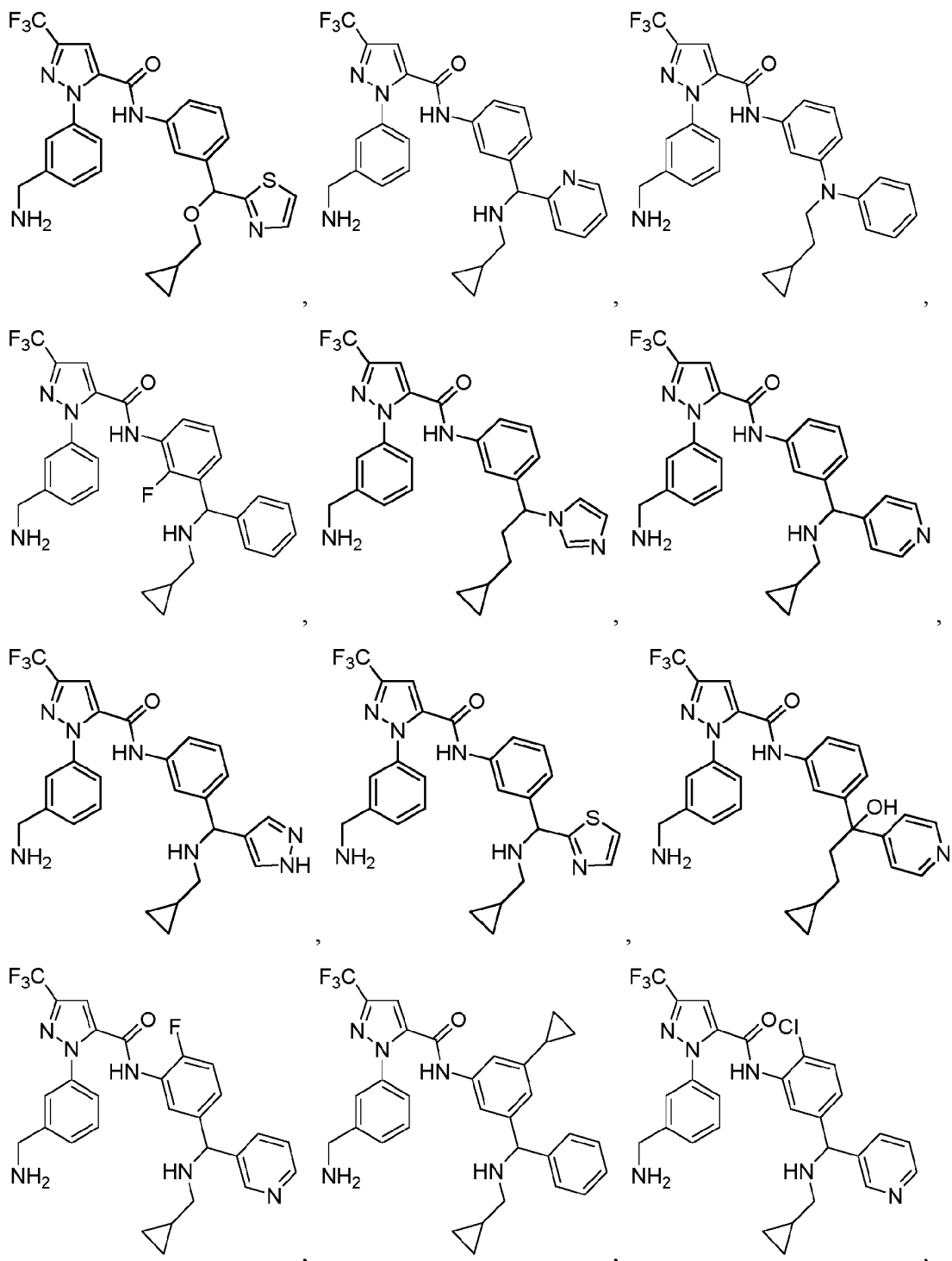
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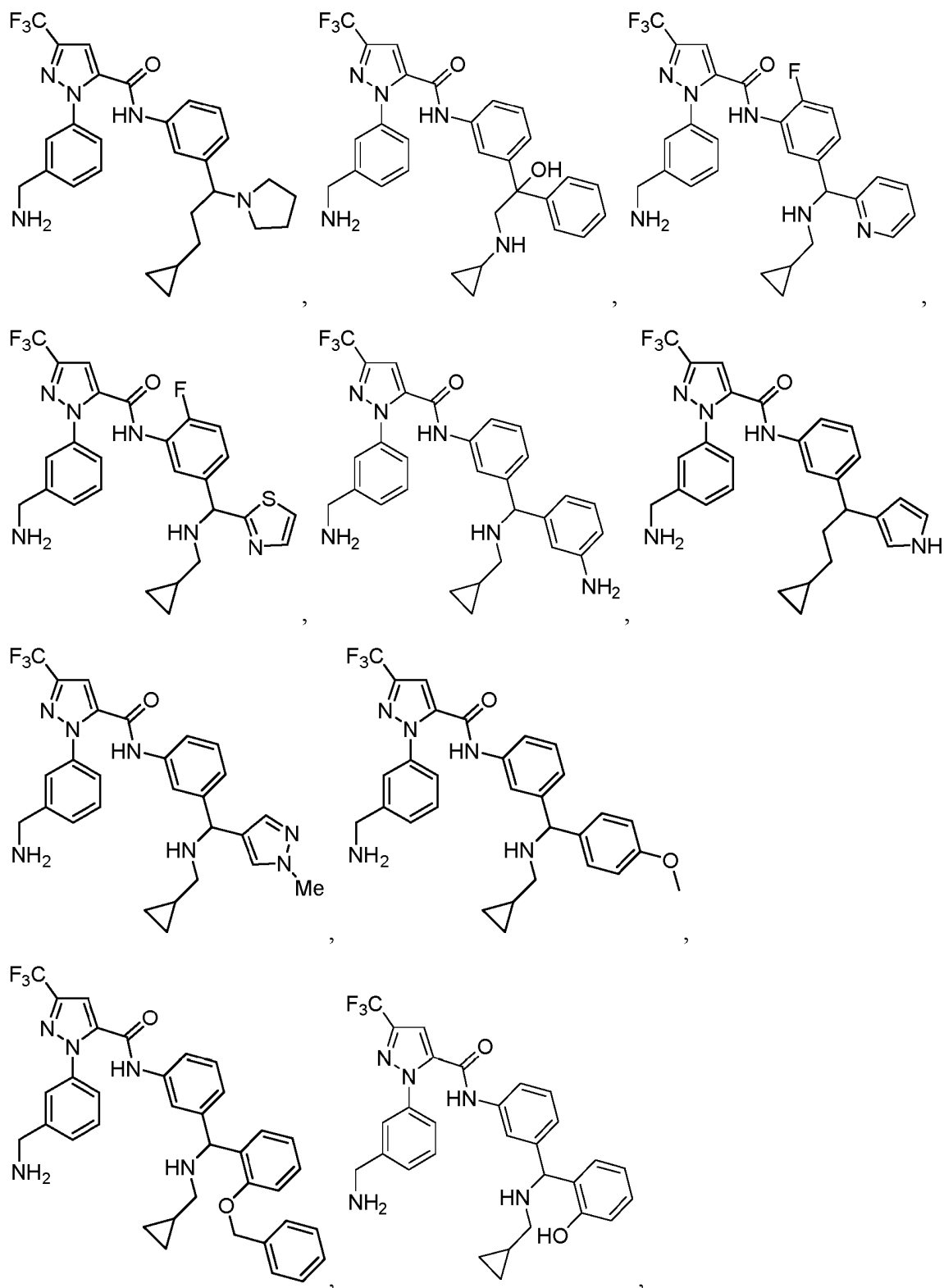
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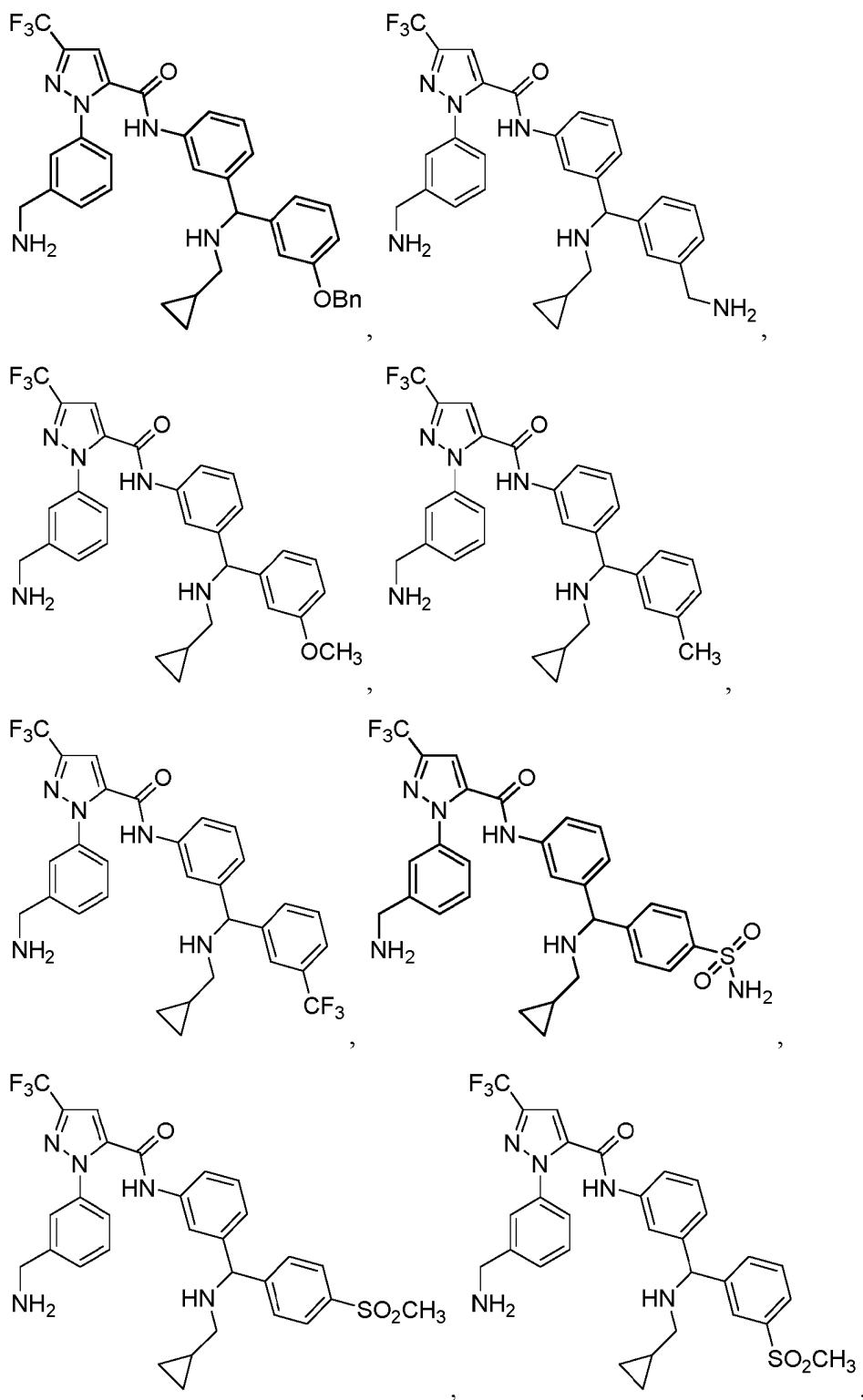
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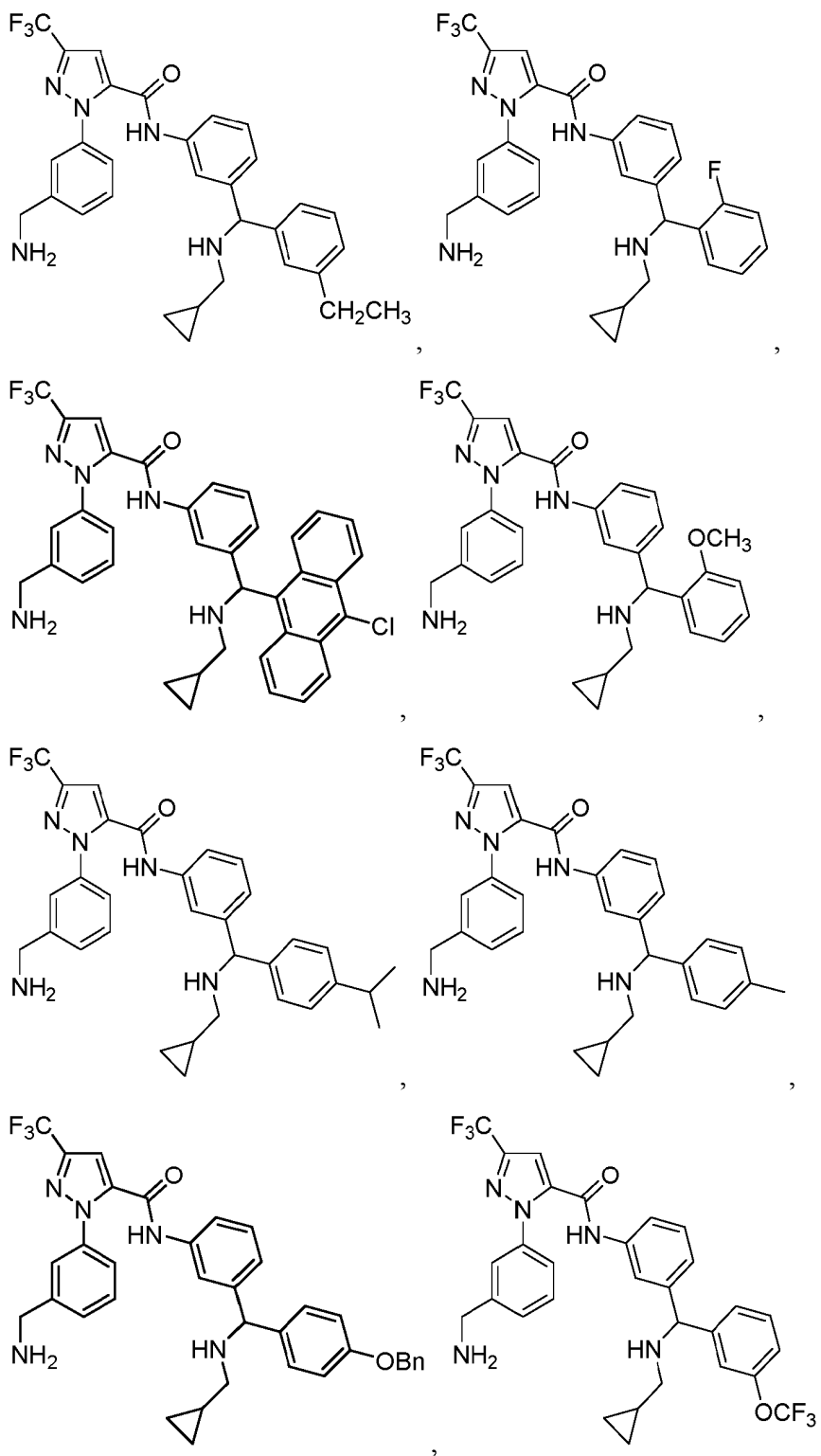
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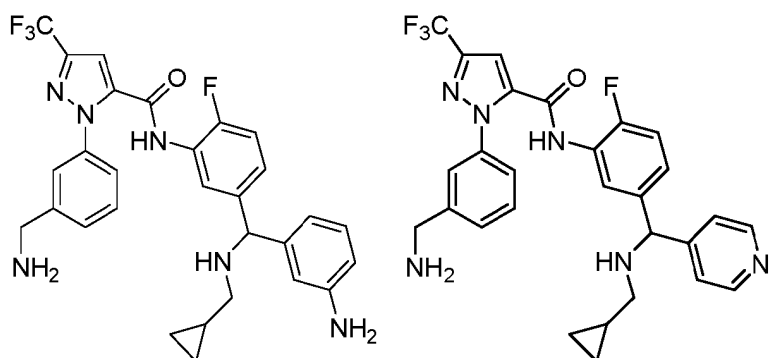
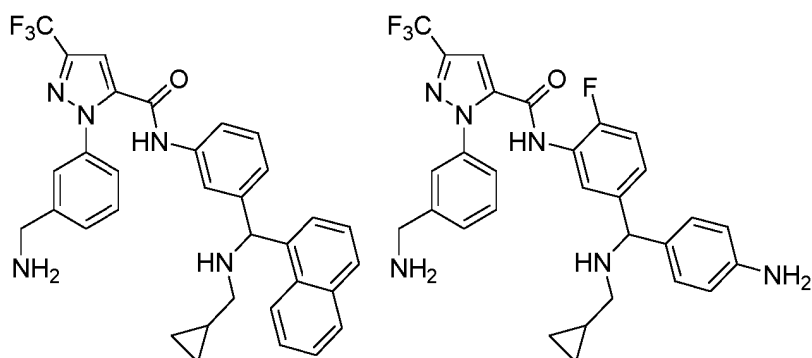
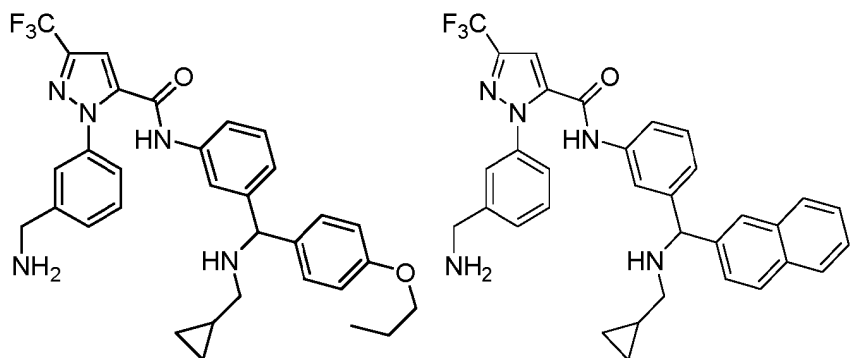
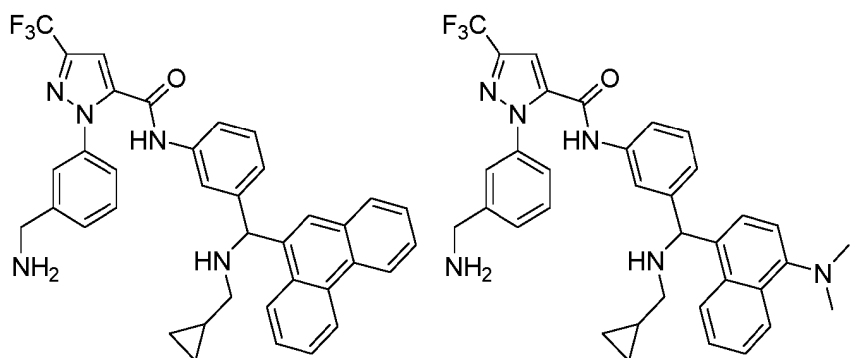
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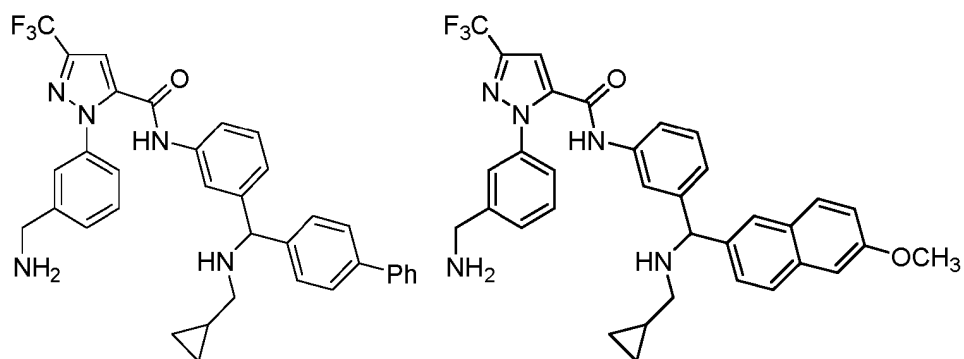
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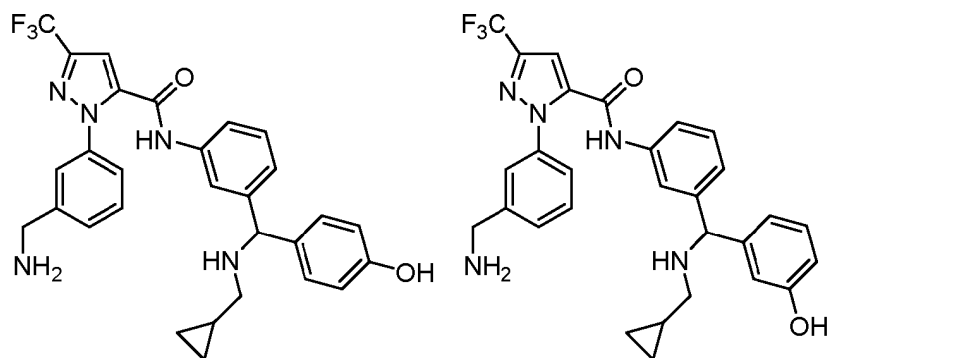


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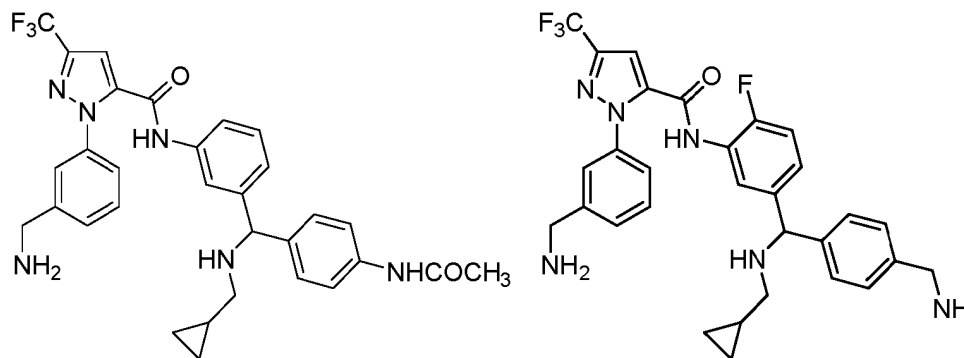
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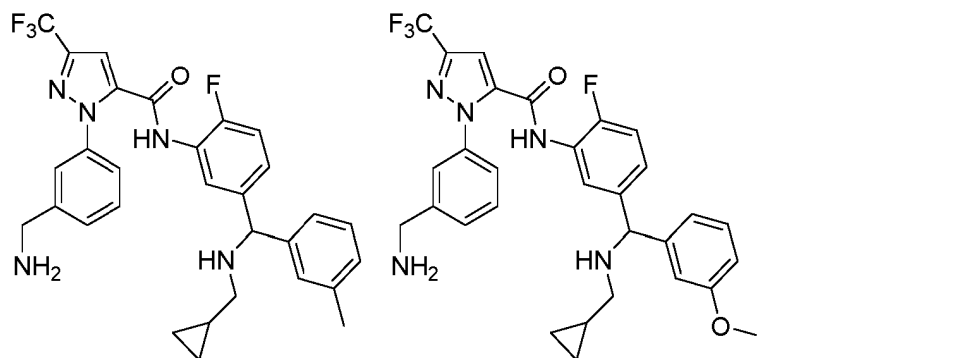
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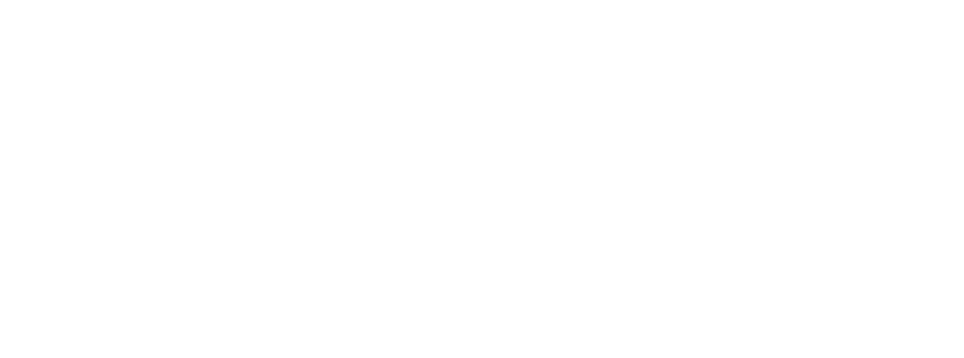
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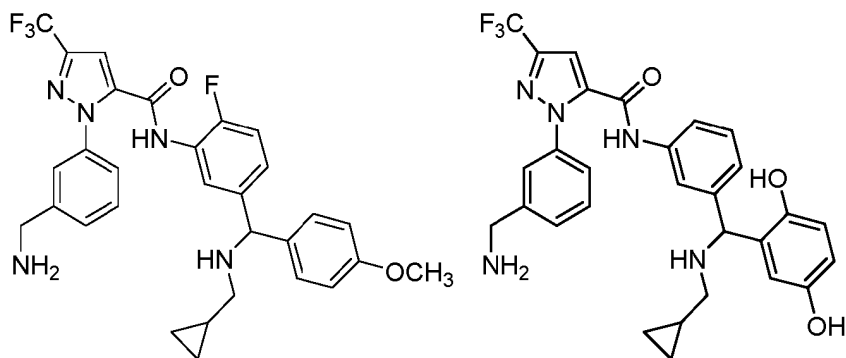


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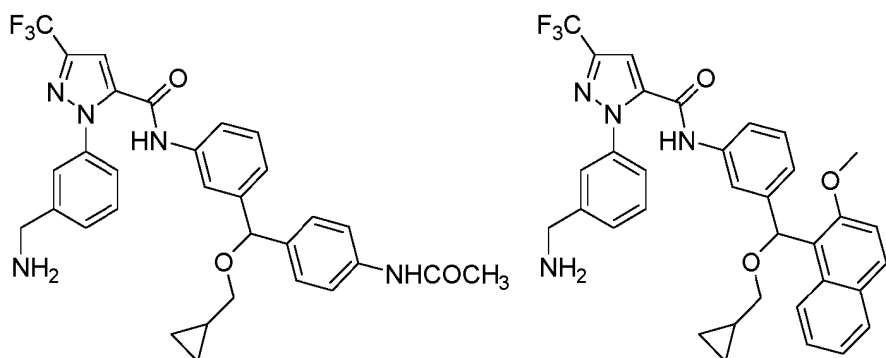


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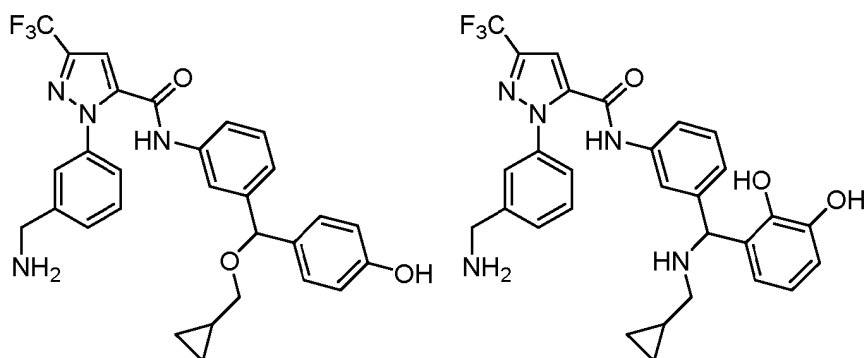
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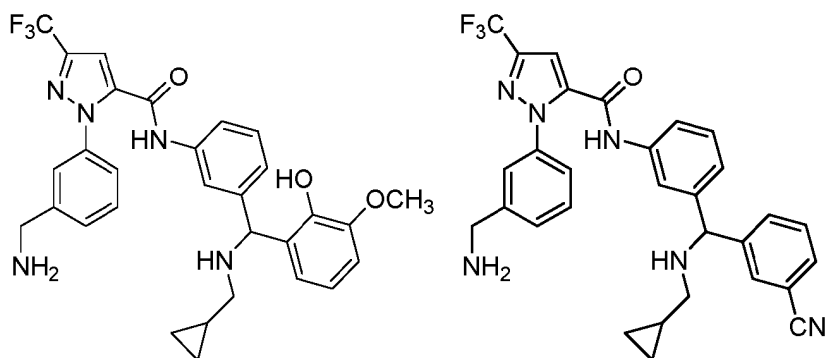
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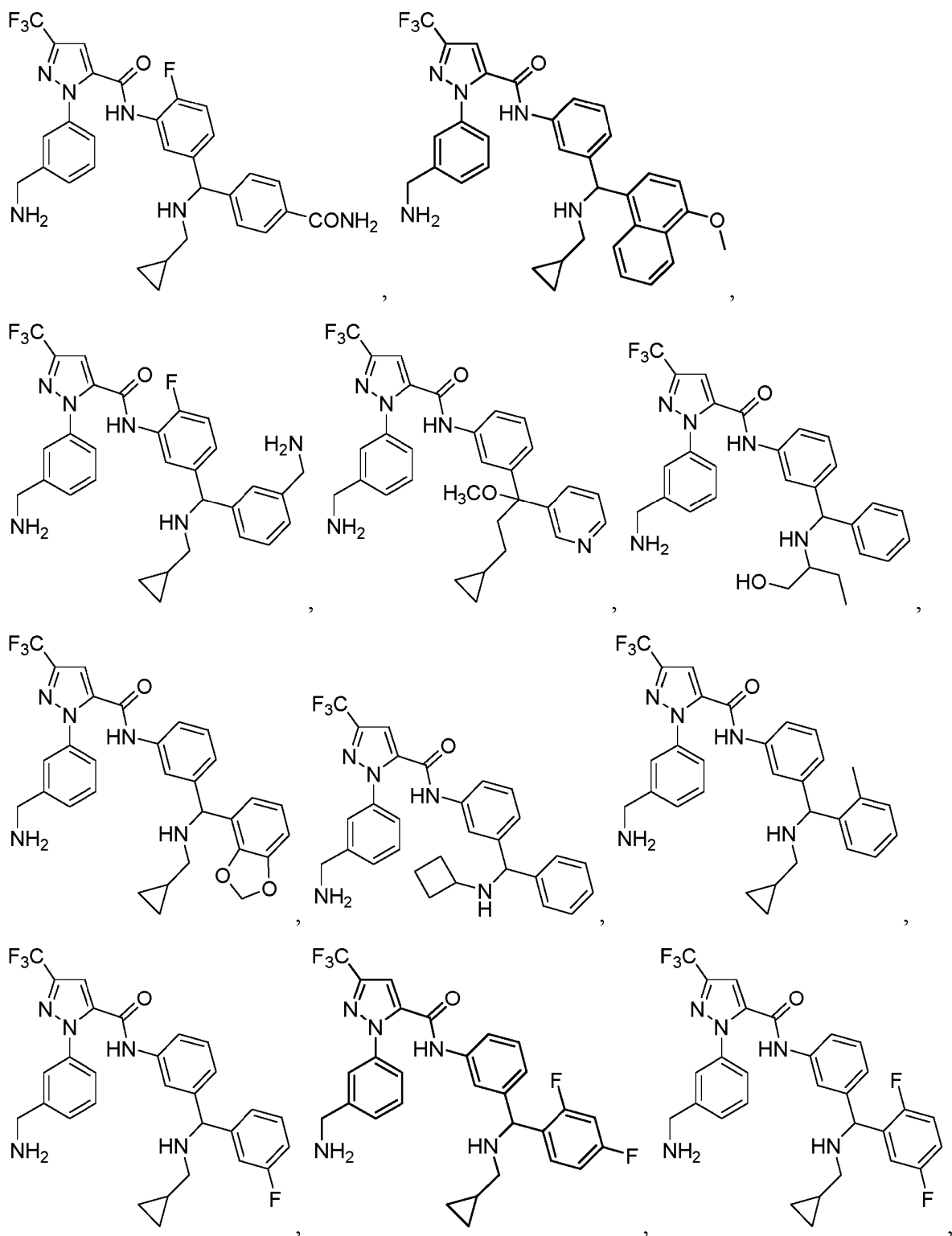


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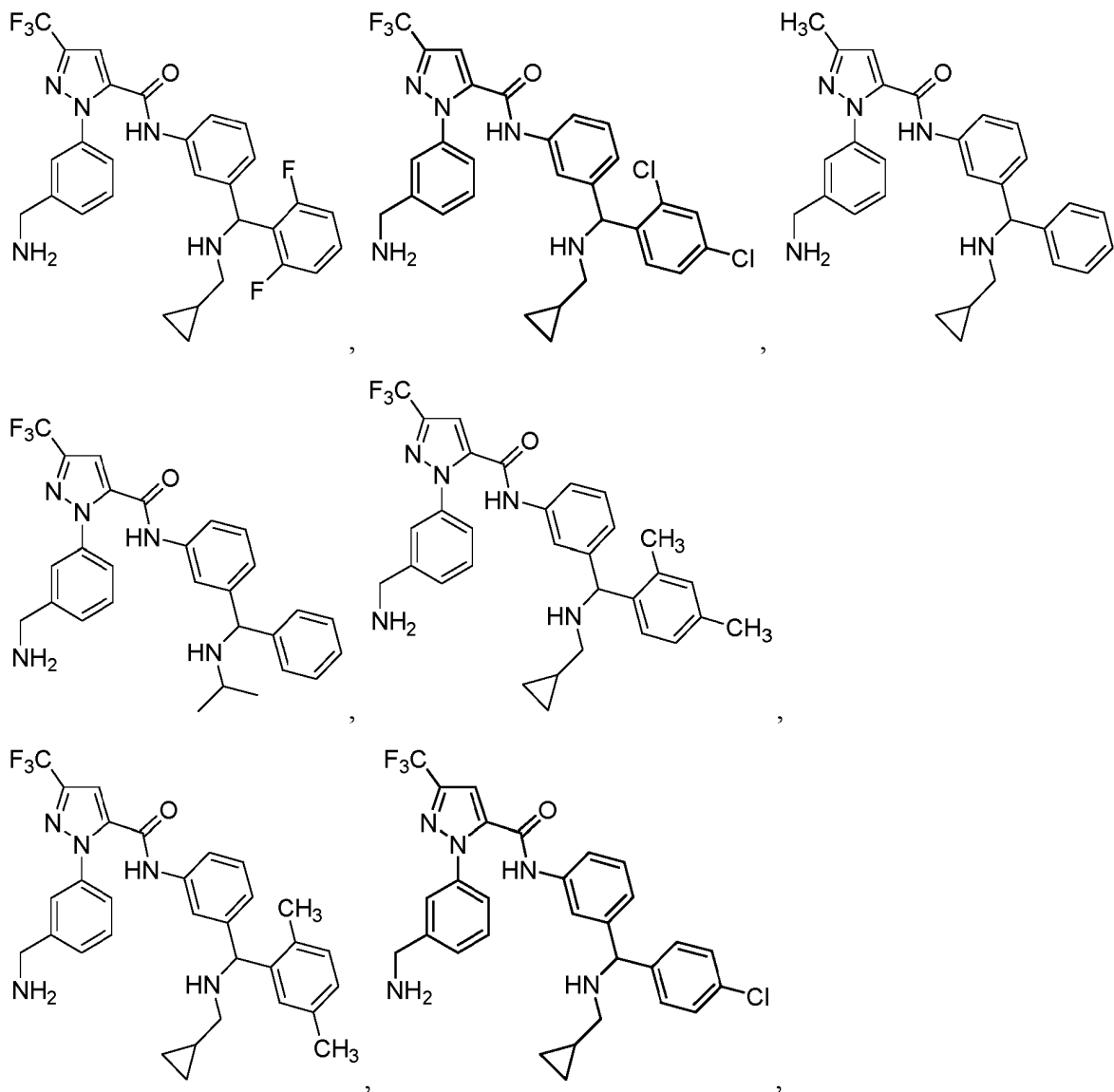
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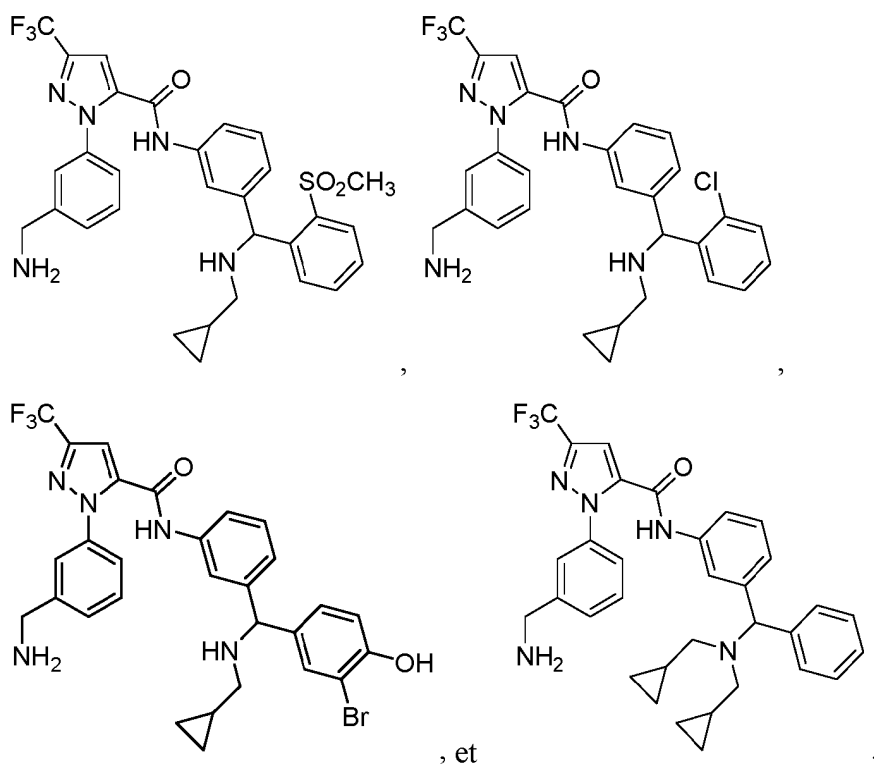
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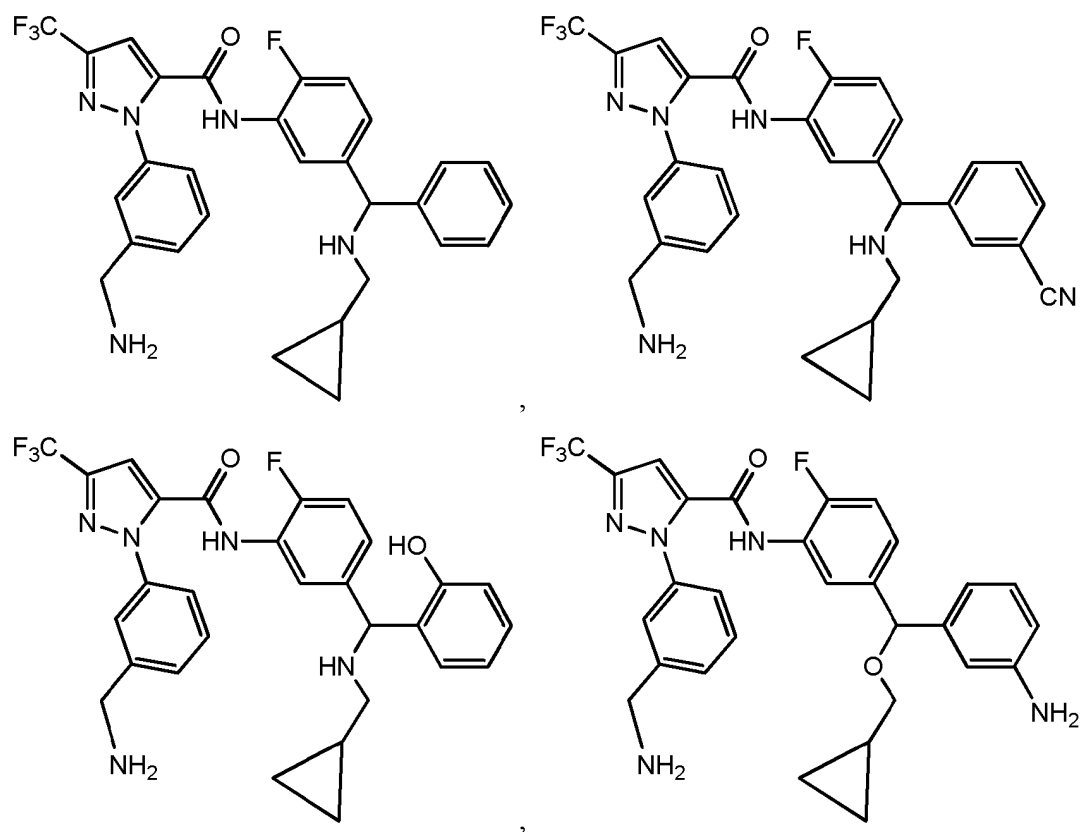
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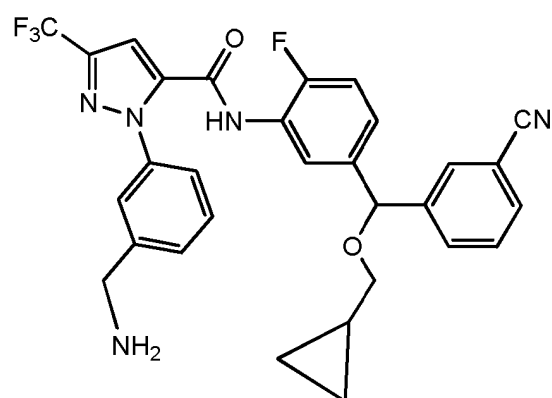
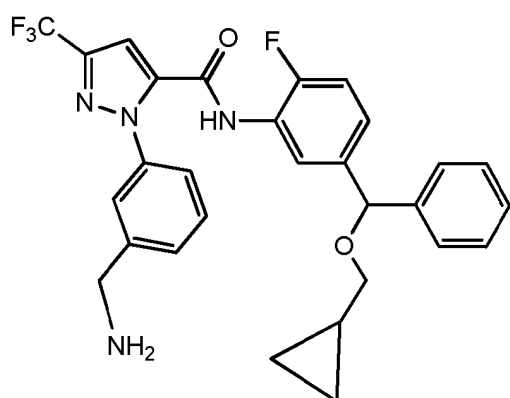
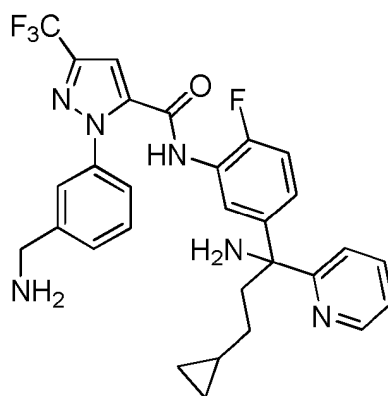
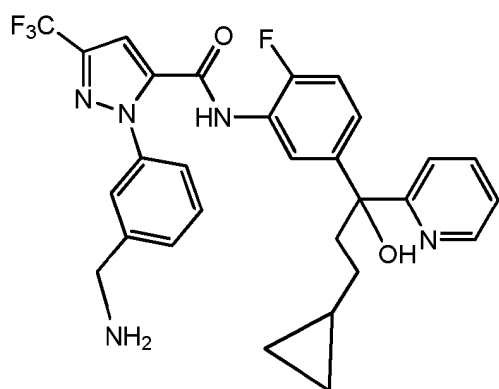
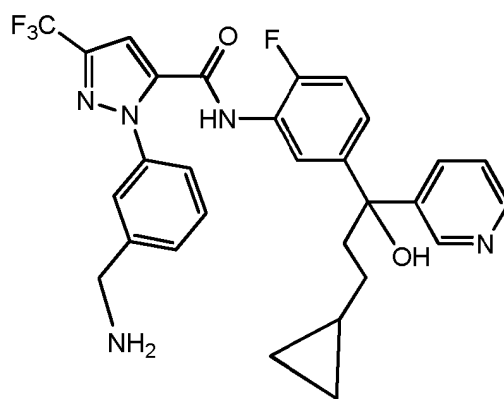
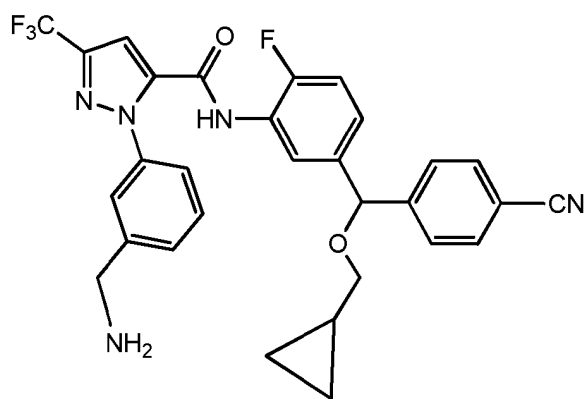


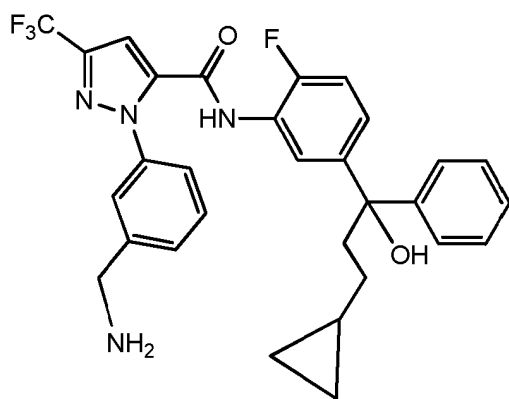
4. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué par :



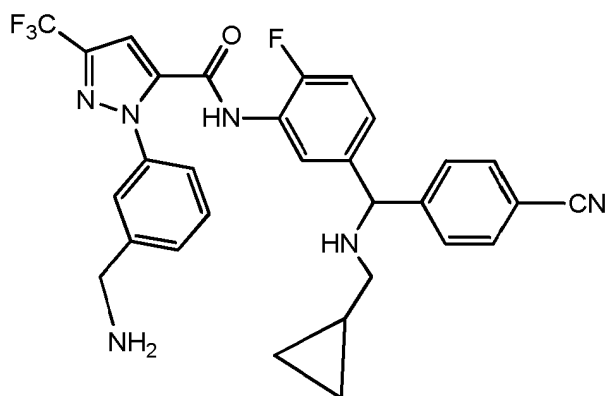
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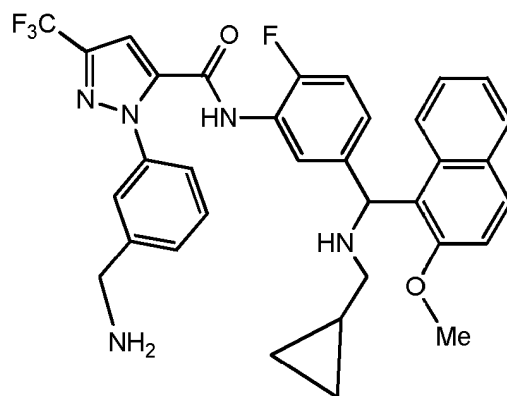
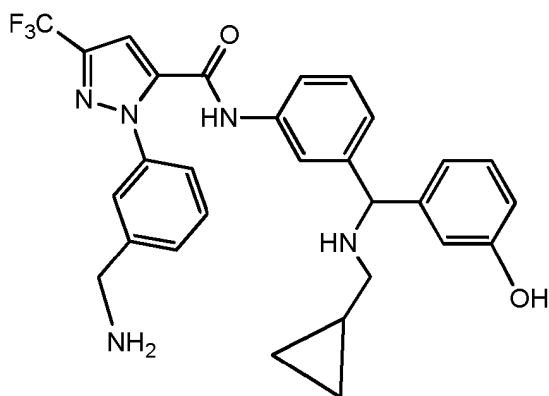
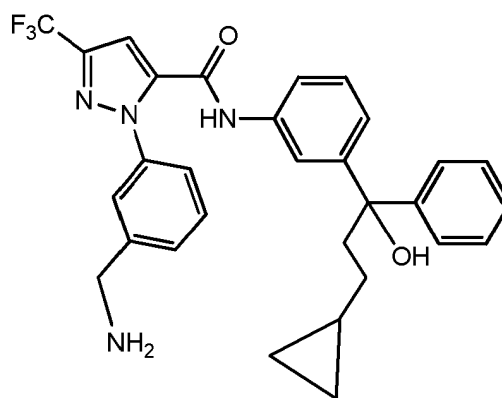
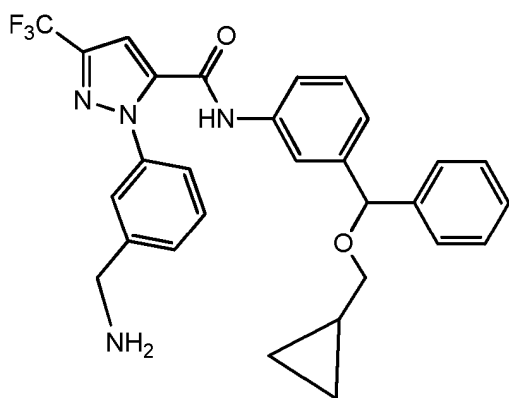




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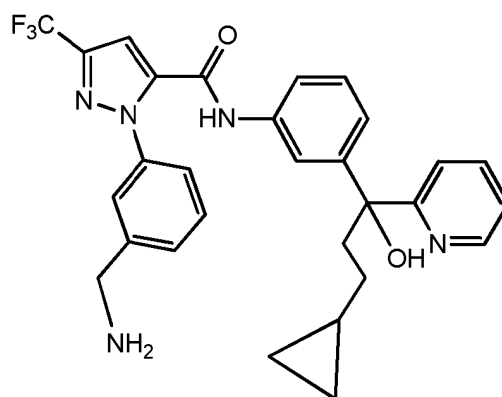
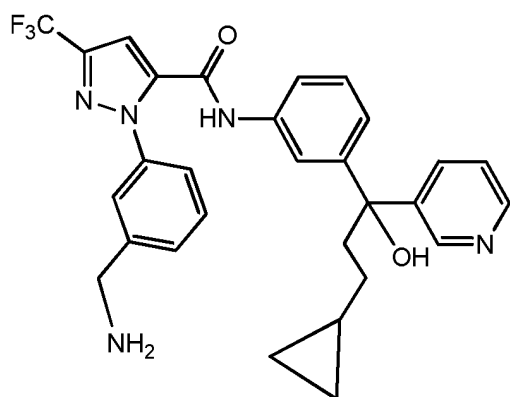
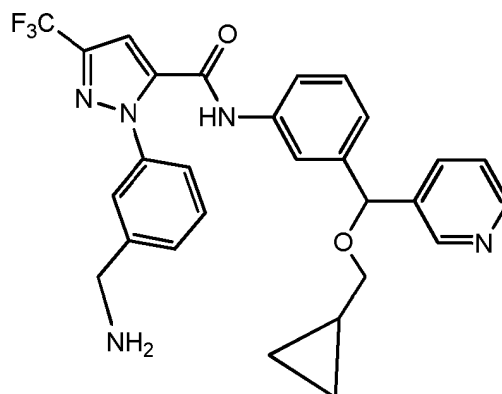
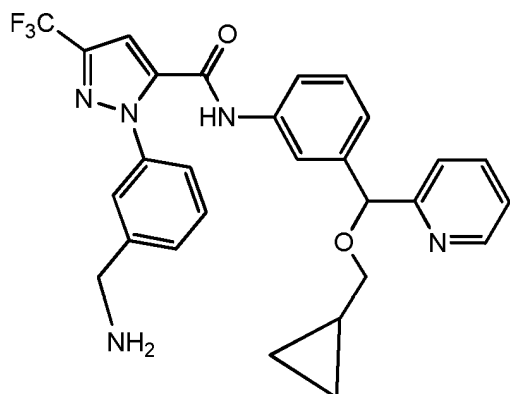
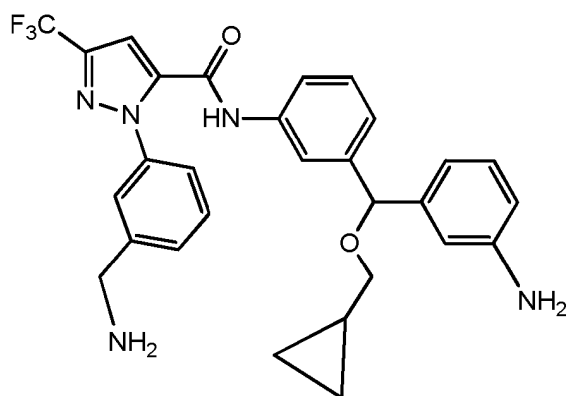
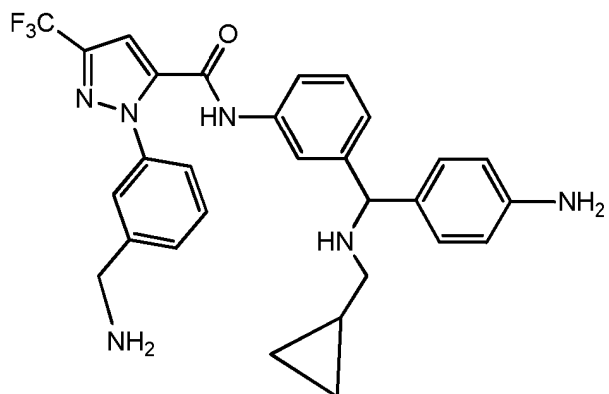


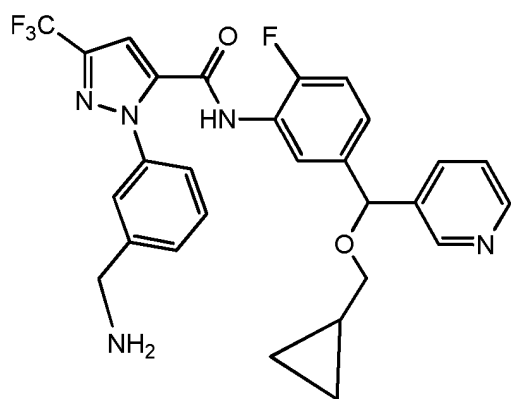
5. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué par :



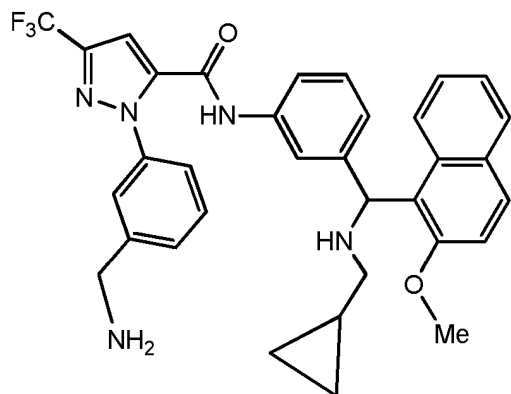
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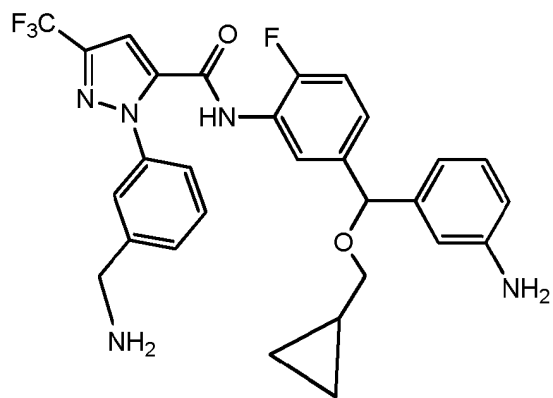
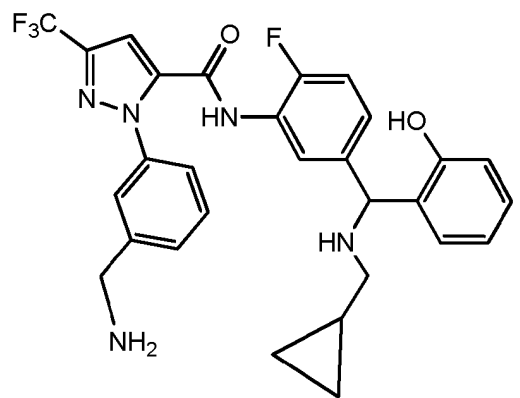
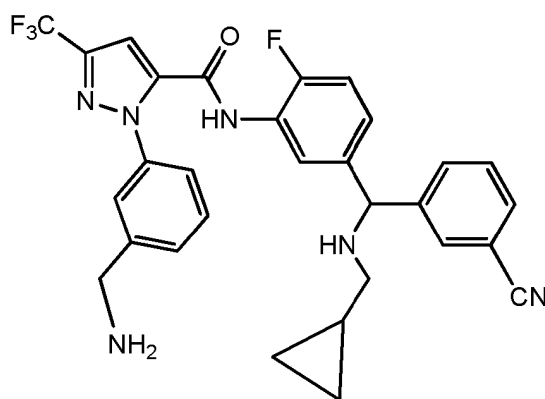
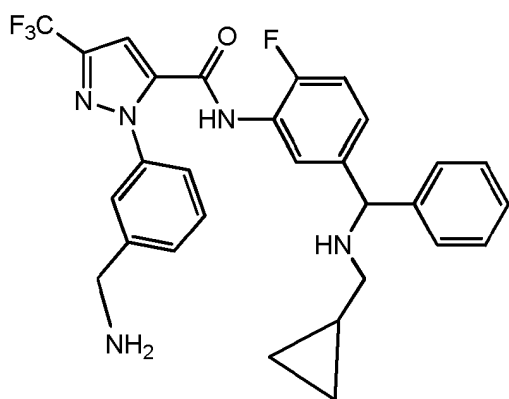




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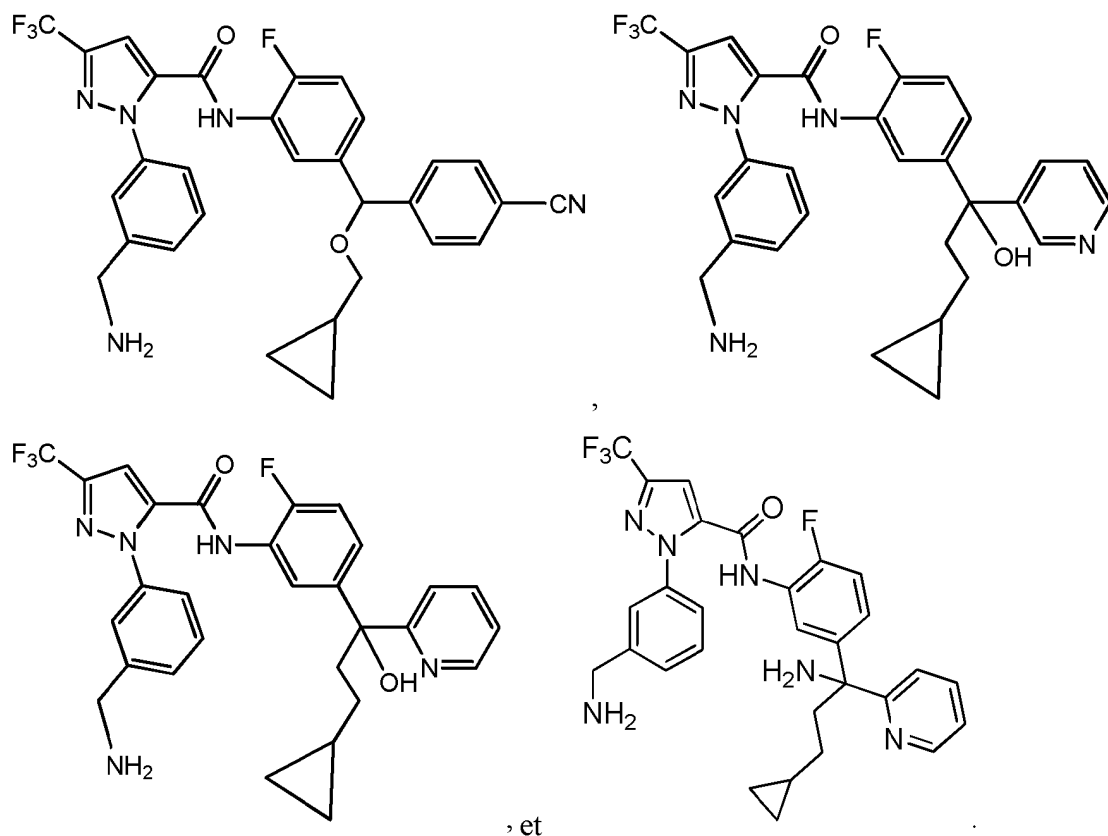


6. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le composé est choisi dans le groupe constitué par



, et

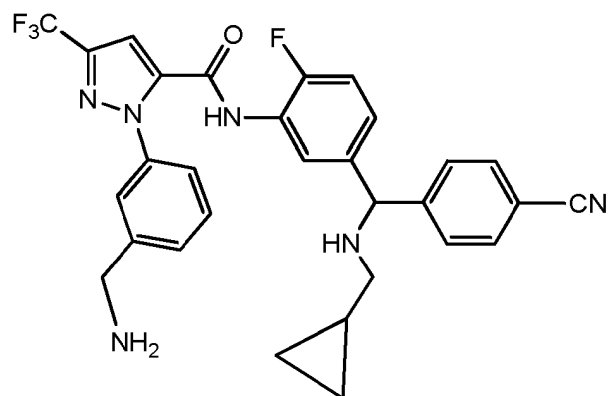
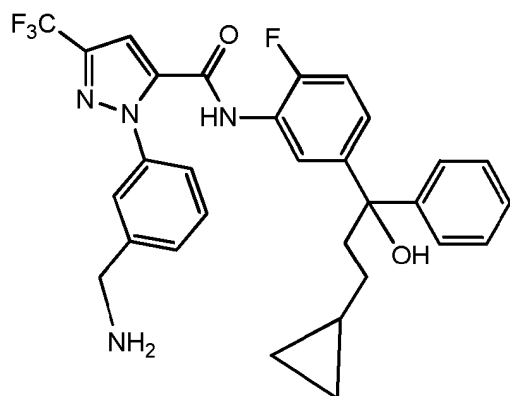
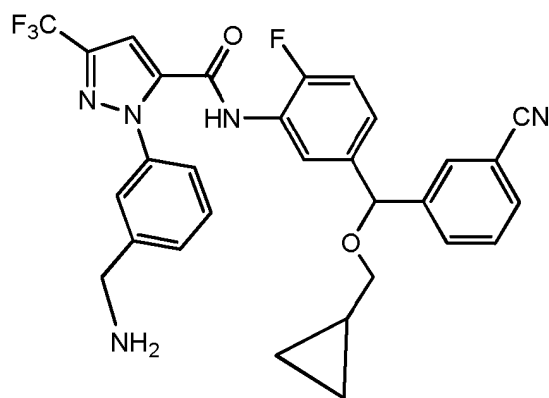
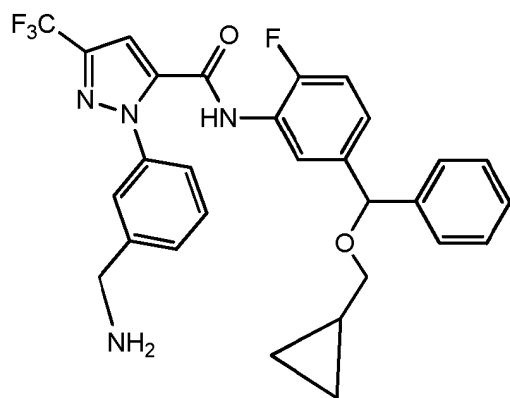
7. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le composé est choisi dans le groupe constitué par



8. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le composé est choisi dans le groupe constitué par

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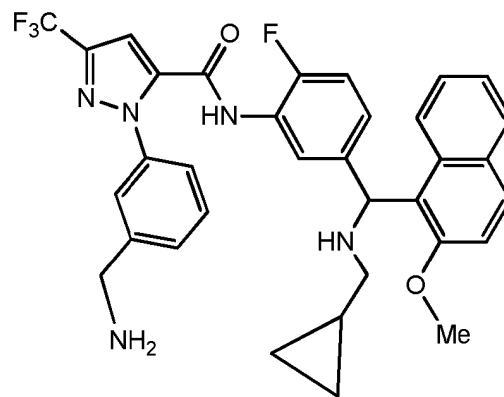
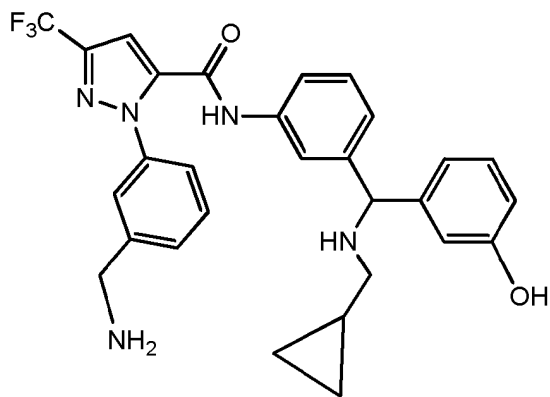
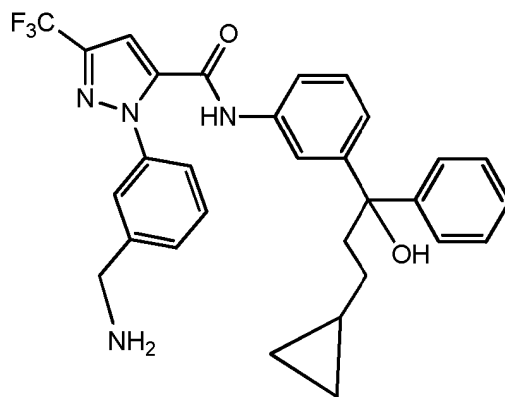
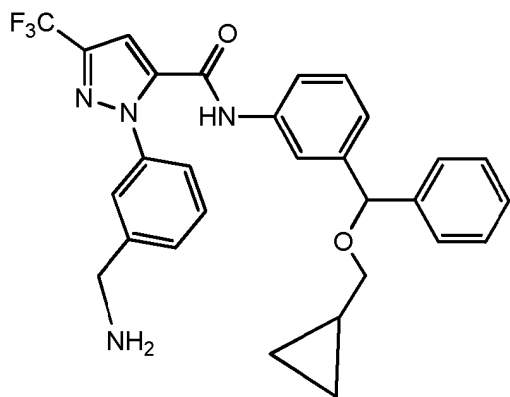


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9. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le composé est choisi dans le groupe constitué par

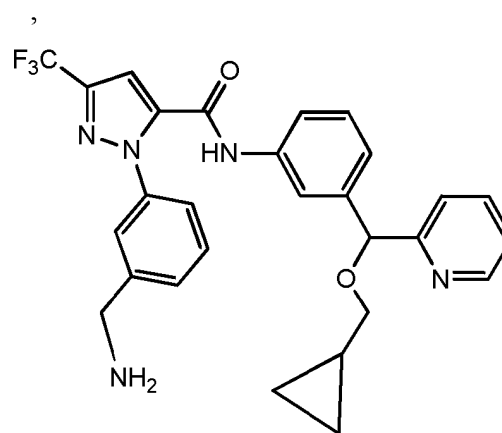
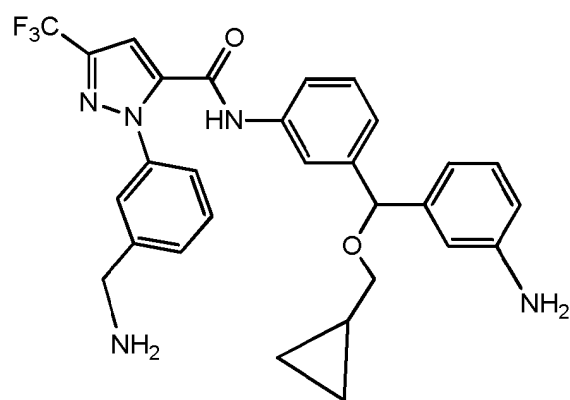
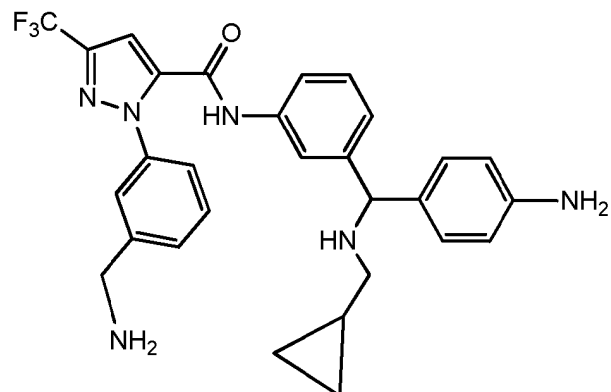
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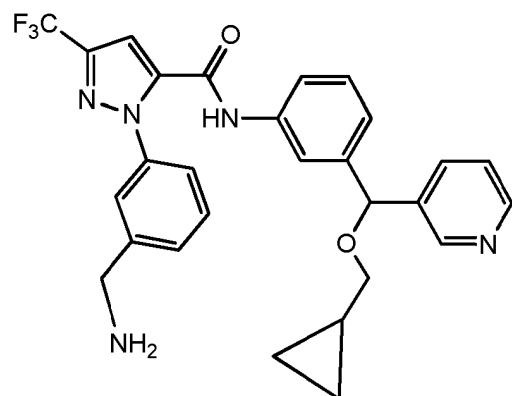


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10. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le composé est choisi dans le groupe constitué par



et



11. Composé selon la revendication 2, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le composé est choisi dans le groupe constitué par

un sel de bis(chlorhydrate).

17. Composition pharmaceutique, comprenant un composé selon l'une quelconque des revendications 1 à 16, ou un sel pharmaceutiquement acceptable de celui-ci, et un support pharmaceutiquement acceptable, la composition pharmaceutique étant éventuellement formulée pour une administration parentérale ou une administration orale, la composition pharmaceutique étant éventuellement formulée pour le traitement prophylactique ou thérapeutique d'une maladie ou d'un trouble dans lesquels il est souhaitable de réduire l'activité de la kallikréine plasmatique ;

dans laquelle la maladie ou le trouble est choisi dans le groupe constitué par l'accident vasculaire cérébral, l'inflammation, les lésions de reperfusion, l'infarctus aigu du myocarde, la thrombose veineuse profonde, la condition de traitement post-fibrinolytique, l'angine, l'œdème, l'angio-œdème, l'angio-œdème héréditaire, la sepsis, l'arthrite, l'hémorragie, la perte de sang lors d'un pontage cardio-pulmonaire, la maladie inflammatoire de l'intestin, le diabète sucré, la rétinopathie, la rétinopathie diabétique, l'œdème maculaire diabétique, la dégénérescence maculaire diabétique, l'œdème maculaire lié à l'âge, la dégénérescence maculaire liée à l'âge, la rétinopathie proliférative, la neuropathie, l'hypertension, l'œdème cérébral, une augmentation de l'excrétion d'albumine, la macroalbuminurie, et la néphropathie.

18. Composé selon l'une quelconque des revendications 1 à 16, ou un sel pharmaceutiquement acceptable de celui-ci, destiné à être utilisé dans le traitement ou la prévention d'une maladie ou d'un trouble dans lesquels il est souhaitable de réduire l'activité de la kallikréine plasmatique ;

dans lequel la maladie ou le trouble est choisi dans le groupe constitué par l'accident vasculaire cérébral, l'inflammation, les lésions de reperfusion, l'infarctus aigu du myocarde, la thrombose veineuse profonde, la condition de traitement post-fibrinolytique, l'angine, l'œdème, l'angio-œdème, l'angio-œdème héréditaire, la sepsis, l'arthrite, l'hémorragie, la perte de sang lors d'un pontage cardio-pulmonaire, la maladie inflammatoire de l'intestin, le diabète sucré, la rétinopathie, la rétinopathie diabétique, l'œdème maculaire diabétique, la dégénérescence maculaire diabétique, l'œdème maculaire lié à l'âge, la dégénérescence maculaire liée à l'âge, la rétinopathie proliférative, la neuropathie, l'hypertension, l'œdème cérébral, une augmentation de l'excrétion d'albumine, la macroalbuminurie, et la néphropathie.

19. Composé destiné à être utilisé selon la revendication 18, dans lequel la maladie ou le trouble est l'angio-œdème.

20. Composé destiné à être utilisé selon la revendication 18, dans lequel la maladie ou le

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trouble est l'angio-œdème héréditaire.

21. Composé selon l'une quelconque des revendications 1 à 16, ou un sel pharmaceutiquement acceptable de celui-ci, destiné à être utilisé en tant que médicament.