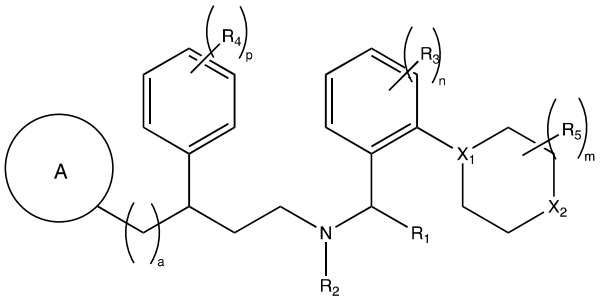
antibodies displaying high binding affinity for α4β7 have displayed therapeutic benefits for gastrointestinal auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis. Anti-integrin antibody therapy for IBD was first introduced with the approval of the non-specific α4 integrin inhibitor natalizumab for Crohn's disease, an indication approved following its initial approval for multiple sclerosis. Vedolizumab, a monoclonal antibody inhibitor of the integrin $\alpha_4\beta_7$, is approved for the induction and maintenance of remission in late-line ulcerative colitis and does not carry a black box warning. Vedolizumab is also approved as a late-line option for Crohn's disease. However, these therapies also have certain undesirable properties for the patient. A monoclonal antibody $\alpha_4\beta_7$ integrin inhibitor is administered by parenteral administration, has a long half-life with inability to rapidly modify exposures, and a reduced activity due to anti-drug antibody formation. In addition to issues with administration, monoclonal antibody therapies can be challenging to manufacture compared to small molecule therapies.

[0006] There remains a medical need for an effective and safe oral $\alpha_4\beta_7$ integrin inhibitor as an important addition to the therapeutic armamentarium for $\alpha_4\beta_7$ integrin-mediated conditions, such as inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD).

[0007] In particular, there remains an unmet need for a small molecule designed to selectively inhibit integrin $\alpha_4\beta_7$ including a need for such a small molecule for administration orally, avoiding the need for periodic therapeutic infusions and the complications associated with this form of drug administration.

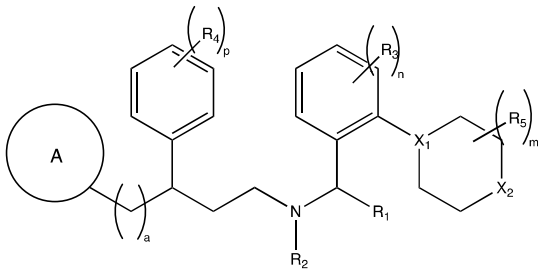
SUMMARY

[0008] The disclosure features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

[0008a] In one aspect, the disclosure features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein:



is a 3 to 12 member heterocyclyl ring structure optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen;

a is 0, 1, 2 or 3;

X_1 is N or CR_a;

R_a is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b´R_b´´$;

R_b is H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

$R_b´$ and $R_b´´$ are each independently H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

R_1 is H or -$COOR_{1b}$;

R_{1b} is H or C_{1-4} alkyl;

R_2 is H or C_{1-4} alkyl;

R_3 is H, C_{1-4} alkyl, or halogen;

n is 0, 1, 2, 3, or 4;

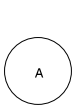
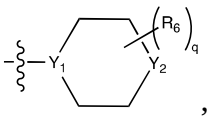
R_4 is H, C_{1-4} alkyl optionally substituted with one or more halogen, or halogen;

p is 0, 1, 2, 3, 4 or 5;

R_5 is H, C_{1-4}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, is optionally substituted with 1 to 4 R_7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

[0009] In one example, the disclosure features a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein  is , and

Y_1 is N or CR_c;

R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

Y_2 is NR_d or $CR_d´R_d´´$;

R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

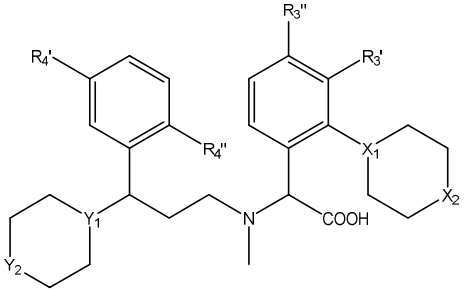
$R_d´$ and $R_d´´$ are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

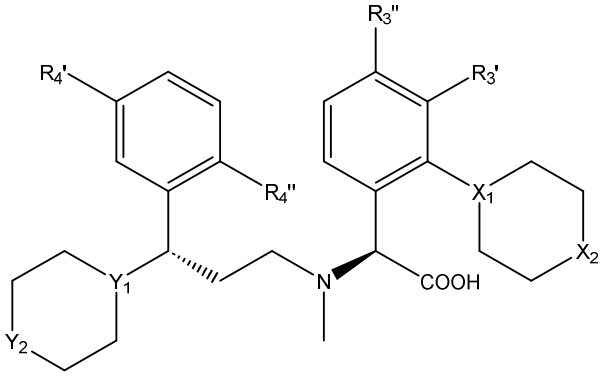
R_6 is H, C_{1-5}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy,is optionally substituted with 1 to 4 R_8; and

each R_8 is independently halogen.

[00010] In one example, the disclosure features a compound of Formula (I) having a chemical structure of Formula (II) or Formula (II-A), or a pharmaceutically acceptable salt thereof,



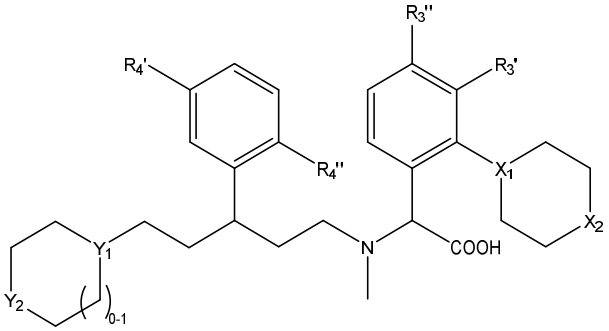
(II)



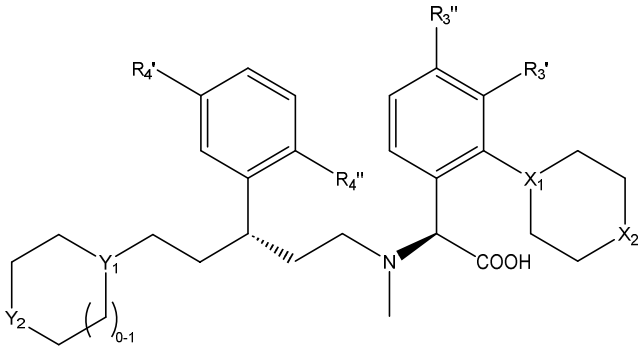
(II-A)

wherein X_1, X_2, Y_1 and Y_2 are each defined as described in Formula (I) and R_3', R_3'', R_4', and R_4'' are each independently H, halogen or $C_{1\text{-}4}$ alkyl optionally substituted with one or more halogen.

[00011] In one example, the disclosure features a compound of Formula (I) having a chemical structure of Formula (III), or Formula (III-A), or a pharmaceutically acceptable salt thereof,



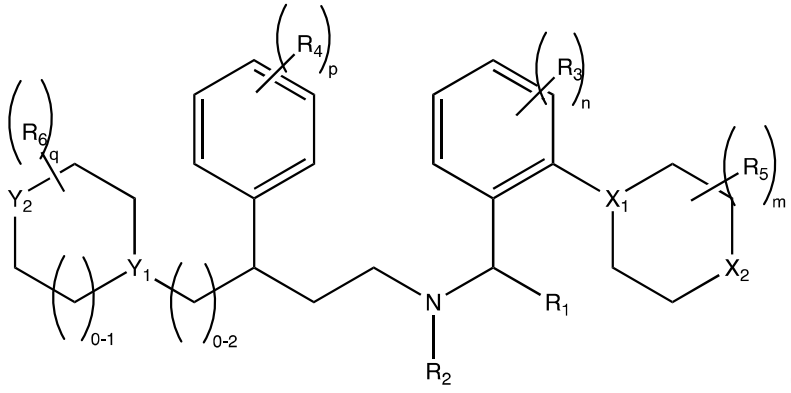
(III),



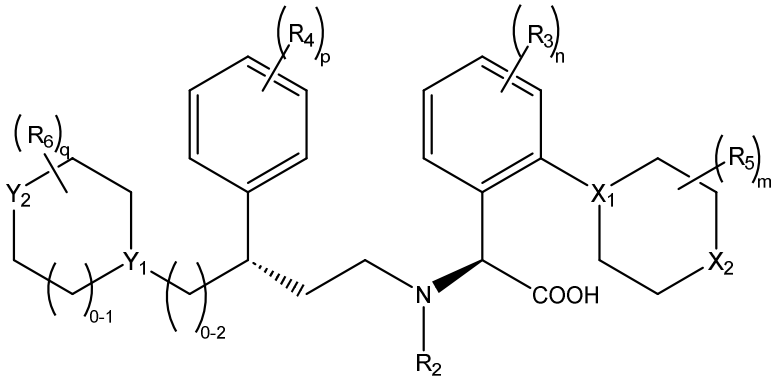
(III-A)

wherein X_1, X_2, Y_1 and Y_2 are each defined as described in Formula (I) and R_3', R_3'', R_4', and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00012] In one example, the disclosure features a compound of Formula (I) having a chemical structure of Formula (IV) or Formula (IV-A), or a pharmaceutically acceptable salt thereof,



(IV),



(IV-A).

wherein

Y_1 is N or CR_c;

R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

Y_2 is NR_d or $CR_d'R_d''$;

R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

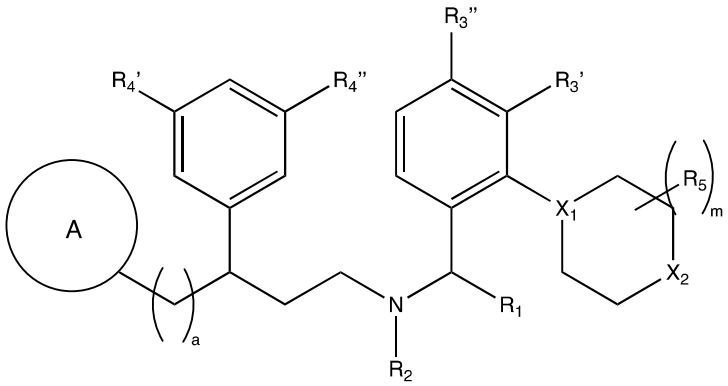
R_d' and R_d'' are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

R_6 is H, C_{1-5}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy,is optionally substituted with 1 to 4 R_8;

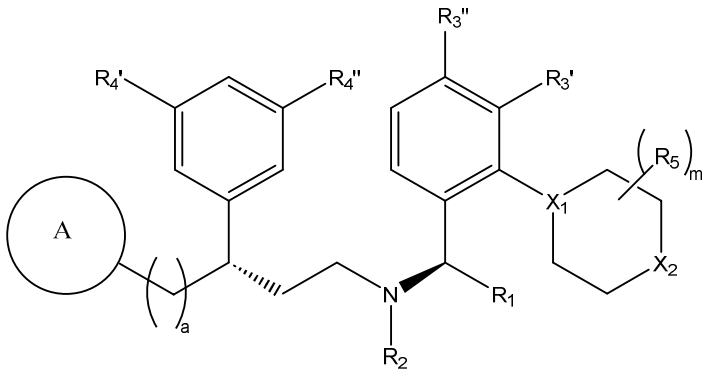
q is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_8 is independently halogen.

[00013] In one example, the disclosure features a compound of Formula (I) having a chemical structure of Formula (V) or Formula (V-A), or a pharmaceutically acceptable salt thereof,



(V),



(V-A).

wherein,

a is 1 or 2;

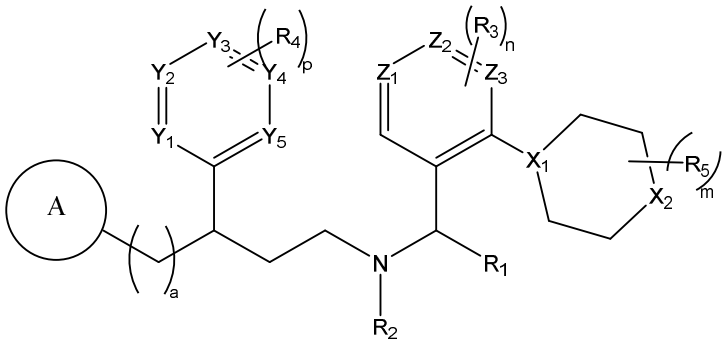
R_3', R_3'', R_4', and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

R_5 is H, C_{1-4}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy,is optionally substituted with 1 to 4 R_7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

[00014] In another aspect, the compound is a compound Formula (VI) or a pharmaceutically acceptable salt thereof,



(VI),

wherein

Y_1, Y_2, Y_3, Y_4, Y_5 and Z_1, Z_2 and Z_3 are each CH or N, provided that at least three of Y_1, Y_2, Y_3, Y_4, and Y_5 are CH and at least one of Z_1, Z_2 and Z_3 is CH;



is a 3 to 12 member heterocyclyl ring structure (including monocyclic heterocyclic, bicyclic bridged, and bicyclic spirocyclic ring structures) optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl (e.g., methyl) and C_{1-4}alkyloxy (e.g., methoxy) are optionally substituted with one or more halogen (e.g., one or more fluoro);

a is 0, 1, 2 or 3;

X_1 is N or CR_a;

R_a is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b´R_b´´$;

R_b is H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

$R_b´$ and $R_b´´$ are each independently H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-}

$_4$alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

R_1 is H or -$COOR_{1b}$;

R_{1b} is H or C_{1-4} alkyl;

R_2 is H or C_{1-4} alkyl;

R_3 is H, C_{1-4} alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R_4 is H, C_{1-4} alkyl optionally substituted with one or more halogen, or halogen;

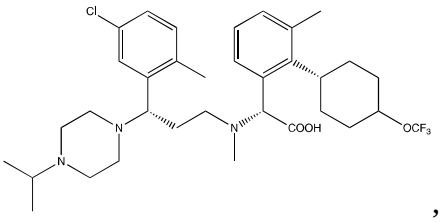
p is 0, 1, 2, 3, 4 or 5;

R_5 is H, C_{1-4}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, is optionally substituted with 1 to 4 R_7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

[00014a] In another aspect, the disclosure features a compound selected from



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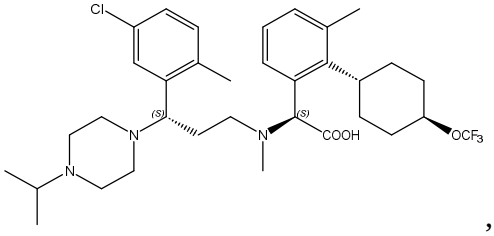

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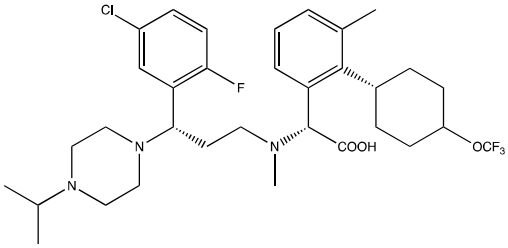

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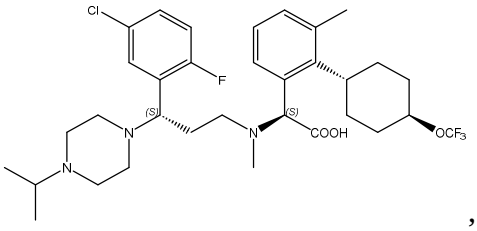

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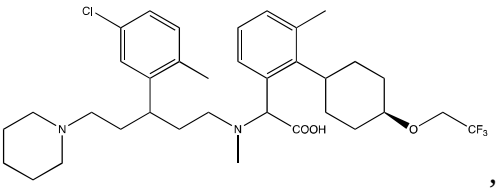

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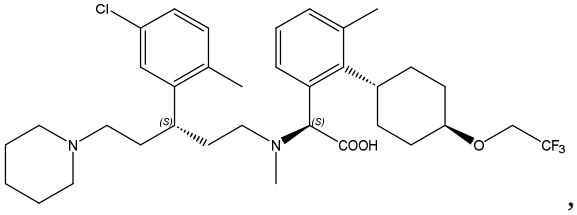

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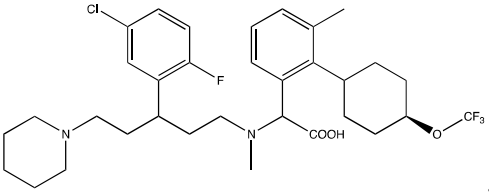

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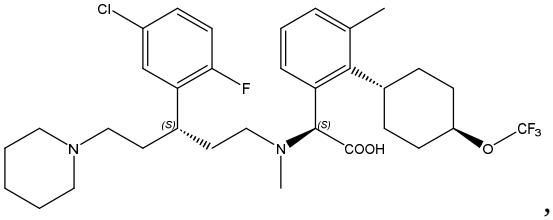

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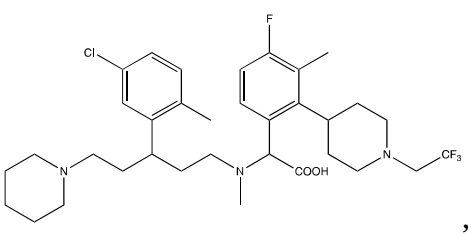
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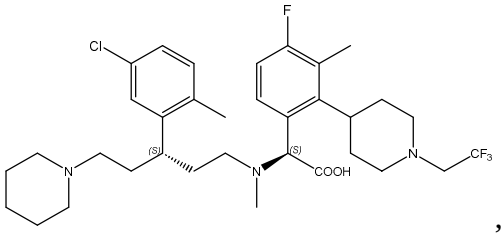
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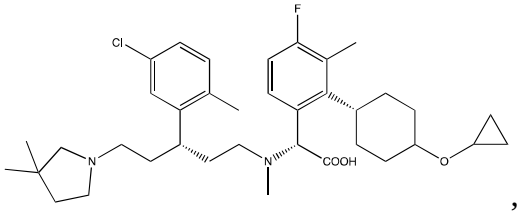
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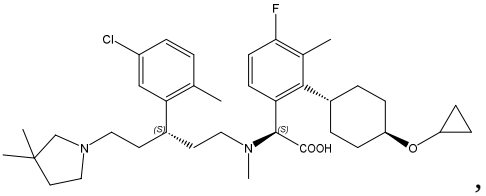
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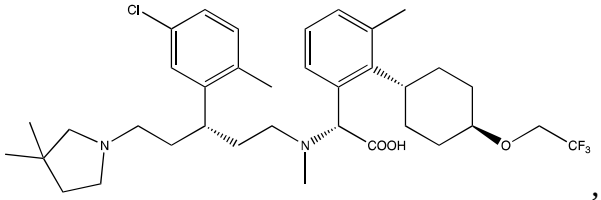
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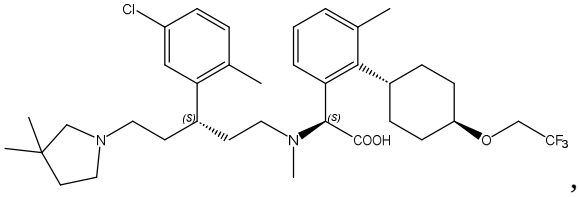
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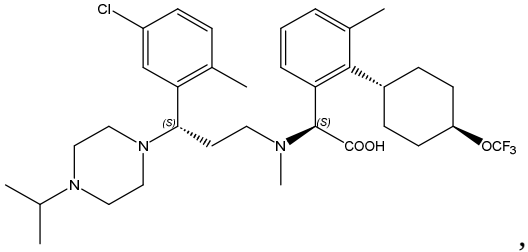
or a pharmaceutically acceptable salt thereof.

[00015] In some examples, the compound is a compound selected from the group consisting of: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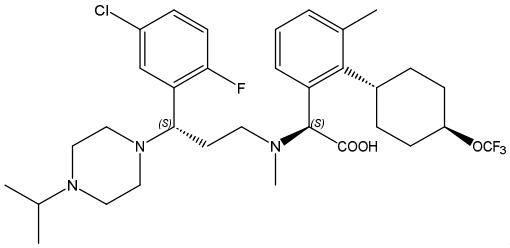
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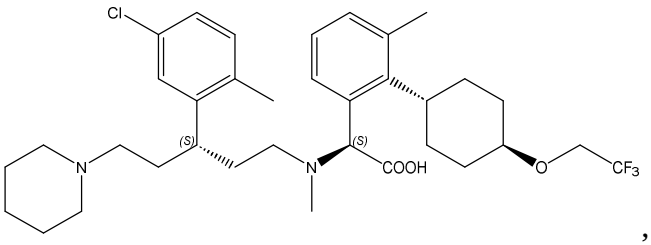
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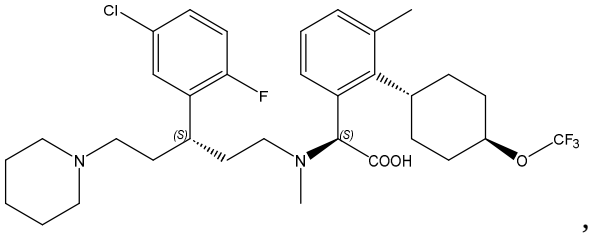
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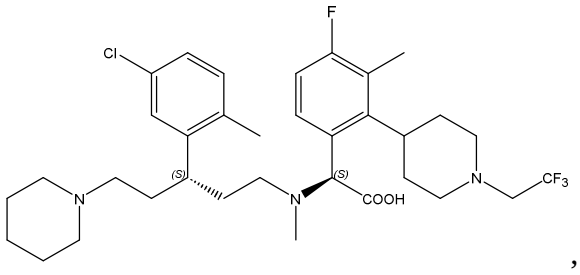
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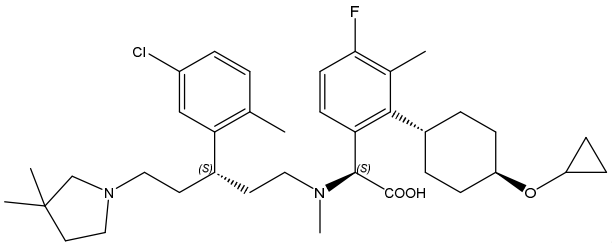

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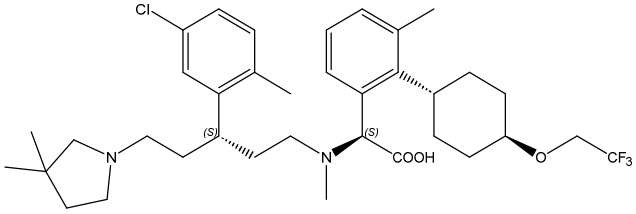


, or a pharmaceutically acceptable salt thereof.

[00015a] In another aspect, the disclosure features a compound selected from the group consisting of the compounds in Figure 1, or a pharmaceutically acceptable salt thereof, in Table 2, or a pharmaceutically acceptable salt thereof, in Table 3, or a pharmaceutically acceptable salt thereof, and in Table 4, or a pharmaceutically acceptable salt thereof.

[00015b] In another aspect, the disclosure features a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00015c] In another aspect, the disclosure features a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein for use in therapy.

[00015d] In another aspect, the disclosure features use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn’s disease.

BRIEF DESCRIPTION OF THE FIGURES

[00016] Figure 1 is a table of compounds disclosed herein.

DETAILED DESCRIPTION

[00017] Compounds of Formula (I), which includes compounds of Formulae (Ia), (Ib), and (Ic), and their respective pharmaceutically acceptable salt forms, are small-molecule

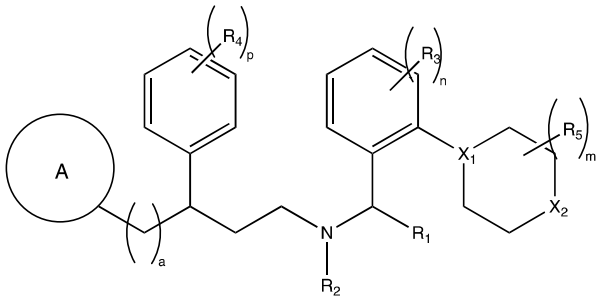
integrin therapeutics targeting α4β7 that can be administered to treat patients with diseases and conditions that are responsive to α4β7 integrin inhibition.

[00018] In particular, methods described herein can be effective in the treatment of inflammatory bowel disease such as ulcerative colitis or Crohn's disease. For example, administration of a compound of Formula (I) according to methods described herein provides unexpected therapeutic benefit within twelve weeks of therapy to subjects with moderately to severely active ulcerative colitis, including patients who have received prior advanced therapy (AT) for ulcerative colitis and/or those with a baseline endoscopy of 3. Further, methods described herein show that administration of a compound according to Formula (I) can be well-tolerated and with a favorable safety profile.

[00019] Accordingly, methods as described herein can expand the therapies available for subjects with inflammatory bowel disease such as ulcerative colitis or Crohn's disease.

CLAIMS

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein:



is a 3 to 12 member heterocyclyl ring structure optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen;

a is 0, 1, 2 or 3;

X_1 is N or CR_a;

R_a is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b´R_b´´$;

R_b is H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

$R_b´$ and $R_b´´$ are each independently H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

R_1 is H or -$COOR_{1b}$;

R_{1b} is H or C_{1-4} alkyl;

R_2 is H or C_{1-4} alkyl;

R_3 is H, C_{1-4} alkyl, or halogen;

n is 0, 1, 2, 3, or 4;

R_4 is H, C_{1-4} alkyl optionally substituted with one or more halogen, or halogen;

p is 0, 1, 2, 3, 4 or 5;

R_5 is H, C_{1-4}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, is optionally substituted with 1 to 4 R_7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

2. The compound of claim 1, wherein R_1 is COOH, R_2 is methyl, R_b´´ is H, X_1 is CR_a, R_a is H.

3. The compound of claim 1 or 2, wherein X_2 is NR_b.

4. The compound of claim 3, wherein R_b is C_{1-4}alkyl optionally substituted with one or more halogen.

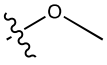
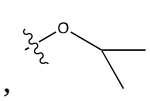
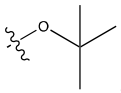
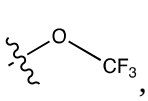
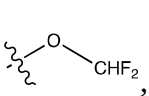
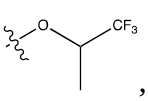
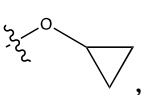
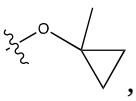
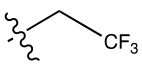
5. The compound of claim 4, wherein R_b is C_{1-4}alkyl optionally substituted with one or more fluoro.

6. The compound of claim 5, wherein R_b is $-CH_2CF_3$.

7. The compound of claim 1 or 2, wherein X_2 is $CR_b´R_b´´$, $R_b´´$ is H, $R_b´$ is -O-C_{1-4} alkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen.

8. The compound of claim 7, wherein $R_b´$ is -O-C_{1-4} alkyl or -O-C_{3-6} cycloalkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more fluoro.

9. The compound of claim 8, wherein $R_b´$ is $-O-CF_3$, $-O-CH_3$, -O-C_3 cycloalkyl optionally substituted with C_{1-4} alkyl, -O-C_3 cycloalkyl optionally substituted with methyl, or -O-C_{1-4} alkyl optionally substituted with one or more fluoro.

10. The compound of claim 1 or 2, wherein X_1 is CH and X_2 is $CHR_b´$ and $R_b´$ is , , , , , , , , or .

11. The compound of any one of claims 1-10, wherein m is 0.

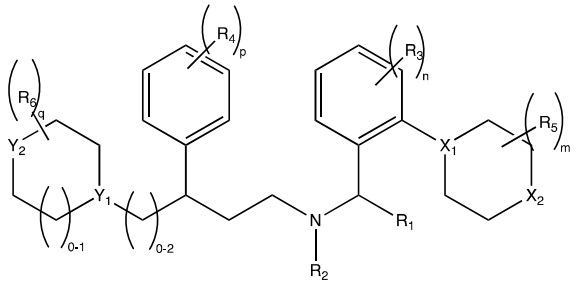
12. The compound of any one of claims 1-11, wherein R_3 and R_4 are each independently halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

13. The compound of any one of claims 1-12, wherein R_3 and R_4 are each independently fluoro, chloro or methyl optionally substituted with one or more fluoro.

14. The compound of any one of claims 1-13, wherein n and p are each independently 1 or 2.

15. The compound of any one of claims 1-14, wherein m is 1 or 2.

16. The compound of any one of claims 1-15, wherein the compound is a compound of Formula (IV), or a pharmaceutically acceptable salt thereof,



(IV)

wherein

Y_1 is N or CR_c;

R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

Y_2 is NR_d or $CR_d´R_d´´$;

R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

$R_d´$ and $R_d´´$ are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

R_6 is H, C_{1-5}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, is optionally substituted with 1 to 4 R_8;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_8 is independently halogen.

17. The compound of claim 16, wherein Y_1 is N and Y_2 is NR_d, R_d is C_{1-4} alkyl, C_{3-6} cycloalkyl or 3-6 member heterocycloalkyl.

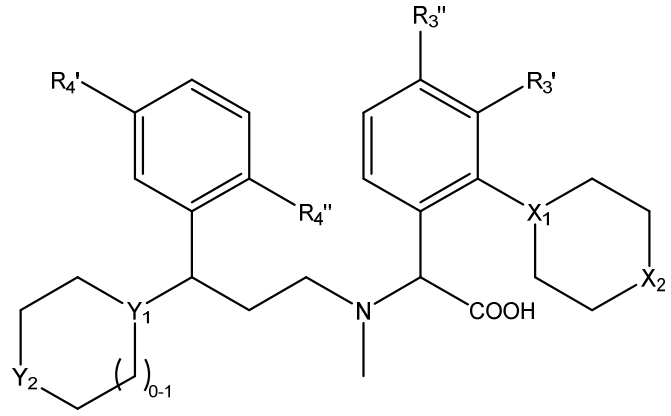
18. The compound of claim 17, wherein R_d is methyl, isopropyl, cyclopropyl, or tetrahydrofuran.

19. The compound of claim 16, wherein Y_2 is $CR_d´R_d´´$.

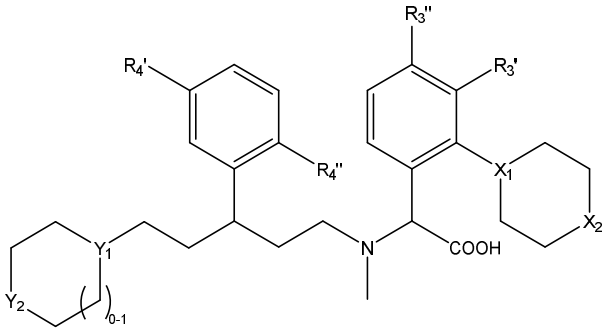
20. The compound of claim 19, wherein $R_d´´$ is H, or methyl.

21. The compound of claim 19, wherein $R_d´$ is fluoro, methoxy, or methyl.

22. The compound of claim 16, wherein the compound is a compound of Formula (II), Formula (III), or a pharmaceutically acceptable salt thereof,



(II)



(III)

wherein

$R_3´$, $R_3´´$, $R_4´$, and $R_4´´$ are each independently H, halogen or $C_{1\text{-}4}$ alkyl optionally substituted with one or more halogen.

23. The compound of claim 22, wherein X_1 is N, and X_2 is NR_b.

24. The compound of claim 23, wherein R_b is $C_{1\text{-}4}$alkyl optionally substituted with one or more halogen.

25. The compound of claim 24, wherein R_b is $C_{1\text{-}4}$alkyl optionally substituted with one or more fluoro.

26. The compound of claim 22, wherein R_b is $-CH_2CF_3$, X_2 is $CR_b´R_b´´$, and $R_b´´$ is H.

27. The compound of claim 26, wherein R_b' is -O-C_{1-4} alkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen, wherein the halogen is fluoro.

28. The compound of claim 27, wherein R_b' is -O-CF_3, -O-CH_3, -O-C_3 cycloalkyl optionally substituted with C_{1-4} alkyl, O-C_3 cycloalkyl optionally substituted with methyl, or -O-C_{1-4} alkyl optionally substituted with one or more fluoro.

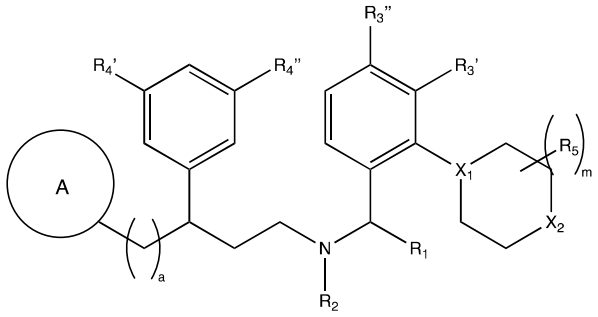
29. The compound of any one of claims 22-28, wherein Y_1 is N, and Y_2 is NR_d.

30. The compound of claim 29, wherein R_d is C_{1-4} alkyl, C_{3-6} cycloalkyl or 3-6 member heterocycloalkyl.

31. The compound of claim 30, wherein R_d is methyl, isopropyl, cyclopropyl, or tetrahydrofuran.

32. The compound of claim 28, wherein Y_2 is $CR_d'R_d''$, and wherein R_d'' is H, or methyl and R_d' is fluoro, methoxy, or methyl.

33. The compound of claim 1, wherein the compound is a compound of Formula (V)



(V),

wherein,

a is 1 or 2;

R_3', R_3'', R_4', and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

R_5 is H, C_{1-4}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy,is optionally substituted with 1 to 4 R_7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

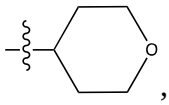
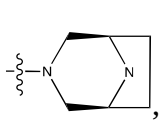
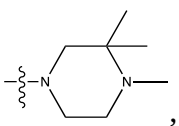
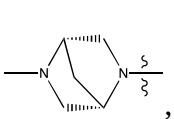
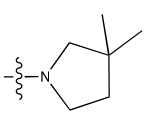
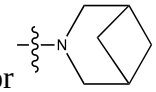
each R_7 is independently halogen.

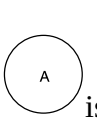
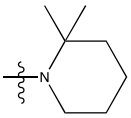
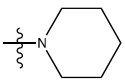
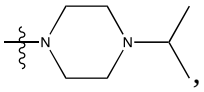
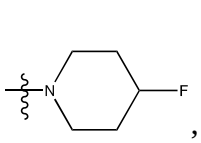
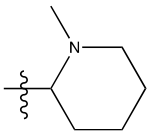
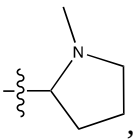
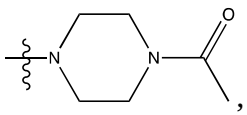
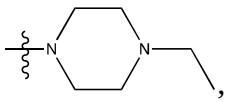
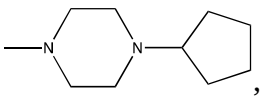
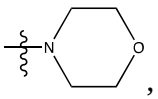
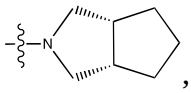
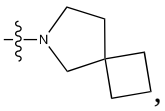
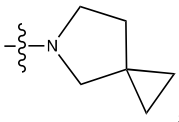
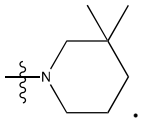
34. The compound of claim 33, wherein  is a 5- to 10-membered heterocyclyl ring structure, whose ring structures include one to four heteroatoms, optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen.

35. The compound of claim 34, wherein  is a 5- to 10-membered heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen.

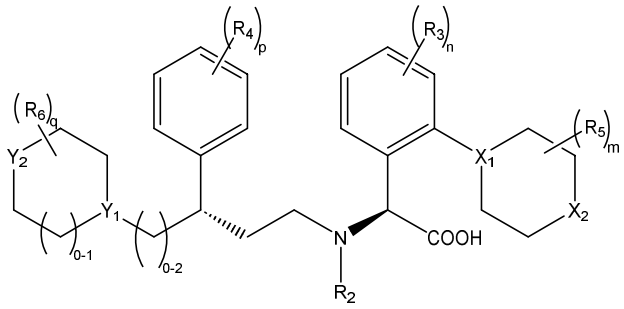
36. The compound of claim 35, wherein  is a 5- to 6-membered monocyclic heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen, or  is a 7- to 8-membered bicyclic bridged heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen, or  is a 7- to 8-membered spirocyclic heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl and C_{1-4}alkyloxy are optionally substituted with one or more halogen.

37. The compound of any one of claims 34-36, wherein the heterocyclyl ring structure is saturated.

38. The compound of claim 33, wherein  is tetrahydrofuran, , , , , , or .

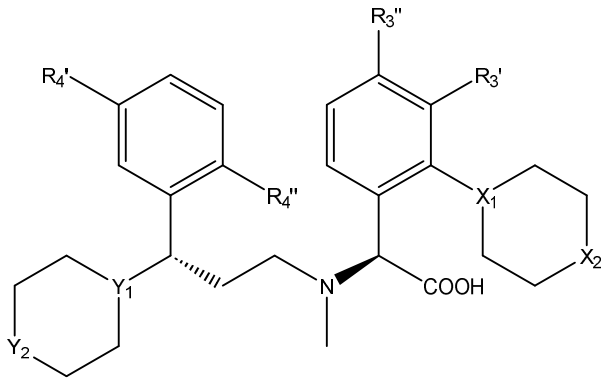
39. The compound of claim 33, wherein  is , , , , , , , , , , , , , or .

40. The compound of any one of claims 16-21, wherein the compound is a compound of Formula (IV-A), or a pharmaceutically acceptable salt thereof,

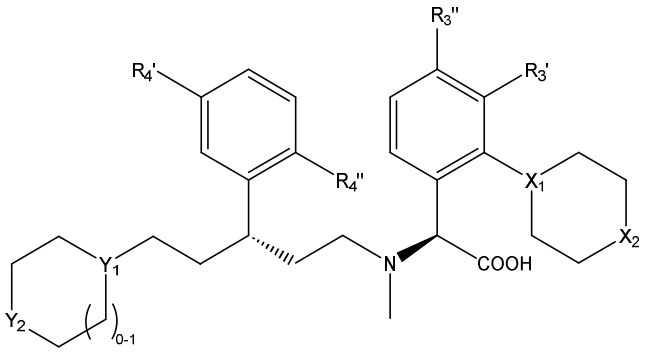


(IV-A).

41. The compound of any one of claims 22-32, wherein the compound is a compound of Formula (II-A), Formula (III-A), or a pharmaceutically acceptable salt thereof,



(II-A)

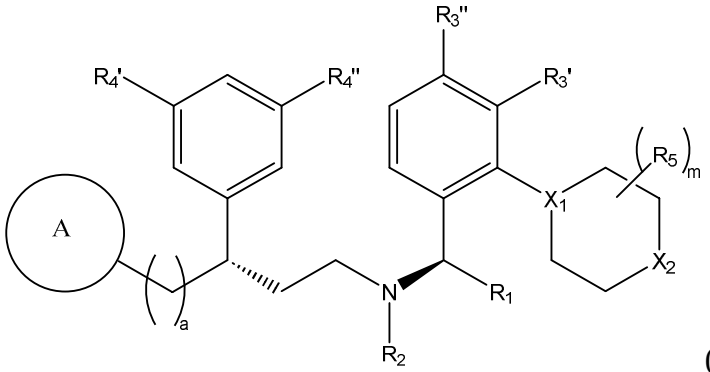


(III-A)

wherein

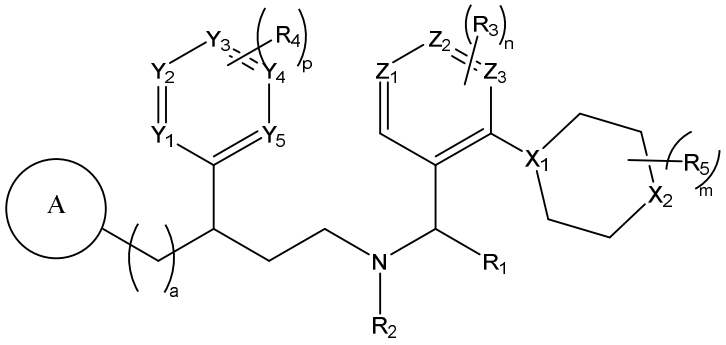
R_3', R_3'', R_4', and R_4'' are each independently H, halogen or $C_{1\text{-}4}$ alkyl optionally substituted with one or more halogen, and wherein Y_1 is N and Y_2 is CH_2 or $C(CH_3)_2$.

42. The compound of any one of claims 33-39, wherein the compound is a compound of Formula (V-A), or a pharmaceutically acceptable salt thereof



(V-A).

43. A compound Formula (VI) or a pharmaceutically acceptable salt thereof,



(VI),

wherein

Y_1, Y_2, Y_3, Y_4, Y_5 and Z_1, Z_2 and Z_3 are each CH or N, provided that at least three of Y_1, Y_2, Y_3, Y_4, and Y_5 are CH and at least one of Z_1, Z_2 and Z_3 is CH;



is a 3 to 12 member heterocyclyl ring structure (including monocyclic heterocyclic, bicyclic bridged, and bicyclic spirocyclic ring structures) optionally substituted with halogen, C_{1-5} alkyl or C_{1-4}alkyloxy, wherein the C_{1-4} alkyl (e.g., methyl) and C_{1-4}alkyloxy (e.g., methoxy) are optionally substituted with one or more halogen (e.g., one or more fluoro);

a is 0, 1, 2 or 3;

X_1 is N or CR_a;

R_a is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b´R_b´´$;

R_b is H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

$R_b´$ and $R_b´´$ are each independently H, halogen, C_{1-4} alkyl, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, C_{3-6}cycloalkyloxy, or C_{1-4}alkyl-C_{3-6}cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

R_1 is H or -$COOR_{1b}$;

R_{1b} is H or C_{1-4} alkyl;

R_2 is H or C_{1-4} alkyl;

R_3 is H, C_{1-4} alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R_4 is H, C_{1-4} alkyl optionally substituted with one or more halogen, or halogen;

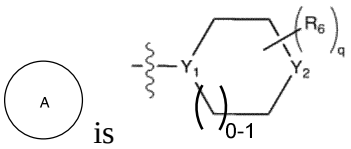
p is 0, 1, 2, 3, 4 or 5;

R_5 is H, C_{1-4}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, is optionally substituted with 1 to 4 R_7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

44. The compound of claim 40, wherein



is , and

Y_1 is N or CR_c;

R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

Y_2 is NR_d or $CR_d´R_d´´$;

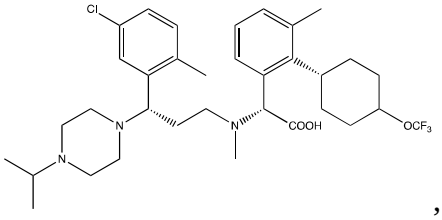
R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

$R_d´$ and $R_d´´$ are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4}alkyloxy;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

R_6 is H, C_{1-5}alkyl, halogen, C_{1-4}alkyloxy, OH, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy, and each C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyl-OH, C_{1-4}alkyl-C_{1-4}alkyloxy, C_{1-4}alkyloxy-C_{1-4}alkyloxy,is optionally substituted with 1 to 4 R_8; and

each R_8 is independently halogen.

45. A compound selected from 

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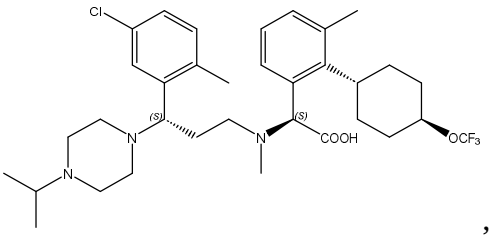

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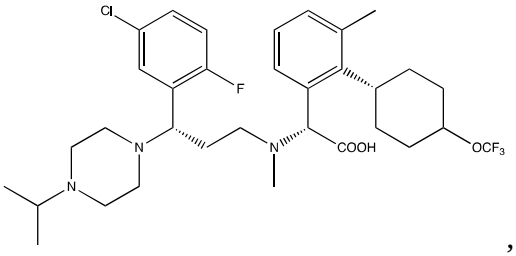

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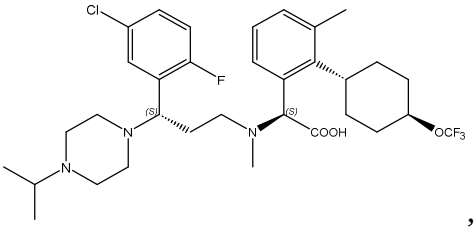
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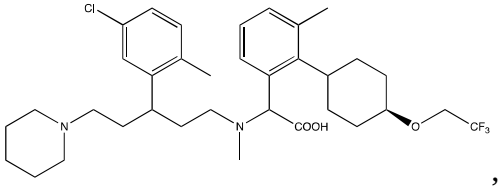
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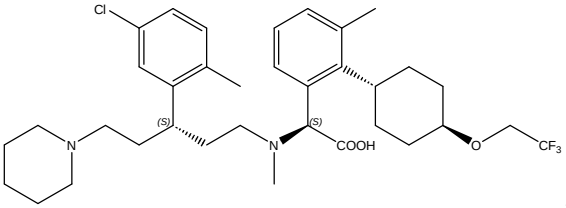
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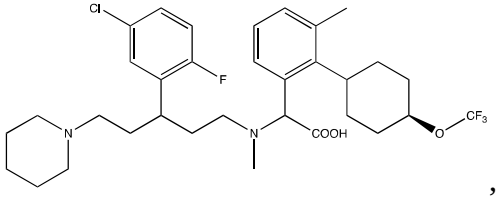
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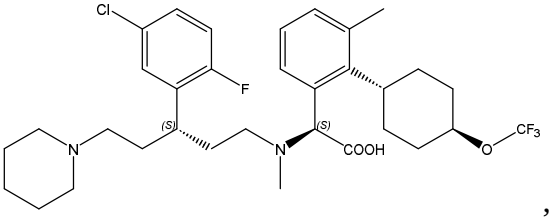
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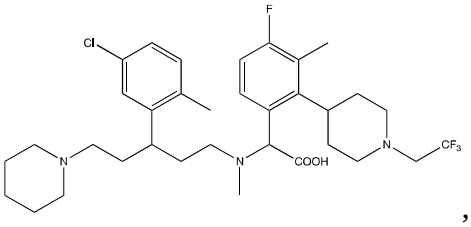
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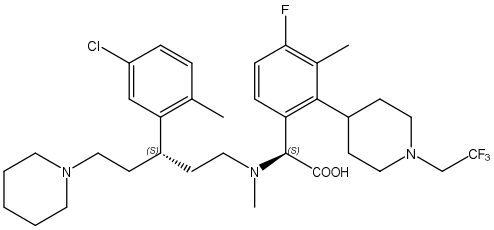
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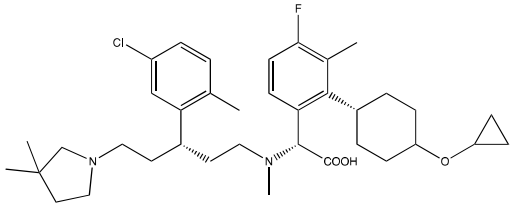
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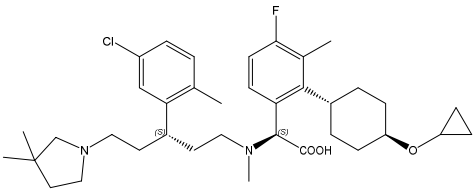
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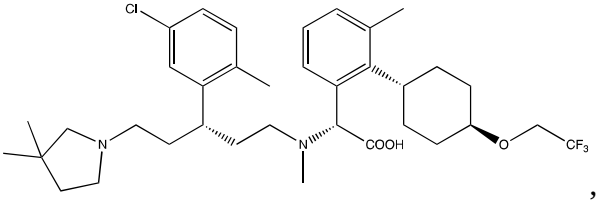
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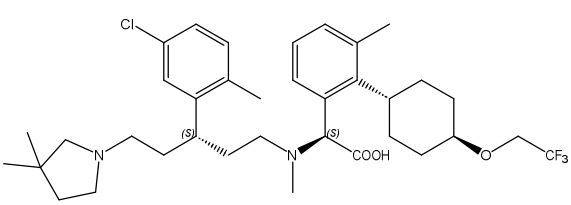
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, or a pharmaceutically acceptable salt thereof.

46. A compound selected from the group consisting of the compounds in Figure 1, or a pharmaceutically acceptable salt thereof, in Table 2, or a pharmaceutically acceptable salt thereof, in Table 3, or a pharmaceutically acceptable salt thereof, and in Table 4, or a pharmaceutically acceptable salt thereof.

47. A pharmaceutical composition comprising the compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

48. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47 for use in therapy.

49. Use of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47 in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.