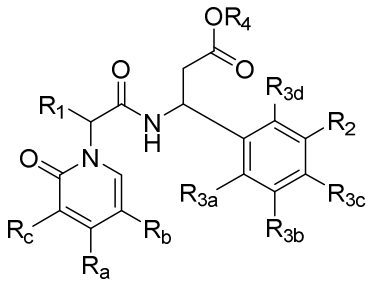
is implicated in emergence of progressive multifocal leukoencephalopathy (PML), a life-threatening and progressive brain infection, in immunosuppressed patients.

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).

SUMMARY

The disclosure relates to compounds of Formula (I):



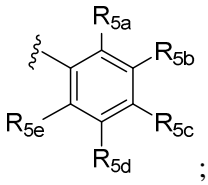
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CN, - OCF_3, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_1\text{-}C_5)$-alkoxy, $-CH_2CF_3$, and substituted or unsubstituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl, substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_3\text{-}C_6)$-cycloalkyl, or substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_3\text{-}C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -$(C_1$-

C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3 -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

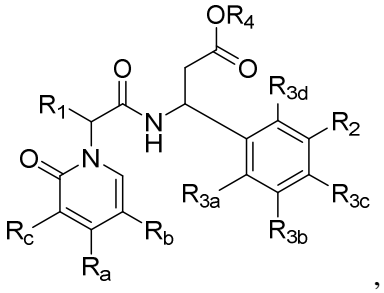
R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a compound of Formula (I):



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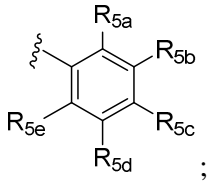
(I)

or a pharmaceutically acceptable salt thereof, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that at least one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form an unsubstituted 4-6 membered ring or a substituted 4-6 membered ring, substituted with at least one halide, unsubstituted (C_1-C_4)-alkyl, or OMe;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl, substituted or unsubstituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

R_{3d} is H;

R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

wherein, unless otherwise specified, substituted means substituted with one or more substituents selected from alkyl, cycloalkyl, heterocyclylalkyl, halogen, OH, OMe, $C(H)F_2$, $C(F)H_2$, CF_3, $C(H)_2CF_3$, SF_5 $CHFCH_2$amine, CH_2amine, and CN.

In some examples of the disclosure, a compound of Formula (I) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-

C_5)alkylene-N-(R_x)(R_y); R_1 is (C_1-C_6) alkyl (e.g., isobutyl); R_{3a} and R_{3b} are independently selected from the group consisting of H, (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, provided that R_{3a} and R_{3b} are not both H; and R_4 is H.

In some examples, a compound of Formula (I) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are each independently unsubstituted (C_1-C_6)-alkyl (e.g., methyl) or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring; R_1 is unsubstituted (C_1-C_6) alkyl (e.g., isobutyl); R_{3a} and R_{3b} are independently selected from the group consisting of H, unsubstituted (C_1-C_4)-alkyl (e.g.,

methyl, ethyl, etc.), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, provided that R_{3a} and R_{3b} are not both H; R_{3c} is selected from the group consisting of: H, F, Cl, hydroxyl, substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl), substituted or unsubstituted (C_3-C_6)-cycloalkyl (e.g., cyclopropyl), (C_1-C_4)-alkoxy (e.g., methoxy); R_{3d} is selected from the group consisting of H, halide (e.g., F, or Cl), substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl), and hydroxyl; and R_4 is H. In some examples, a compound of Formula (I), Formula (Ia) and/or Formula (Ib) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y each independently unsubstituted methyl or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring; R_1 is isobutyl; R_{3a} and R_{3b} are independently selected from the group consisting of unsubstituted (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, R_{3c} and R_{3d} are both H; and R_4 is H. For instance, a compound of Formula (I), Formula (Ia) and/or Formula (Ib) can be a compound wherein R_1 is isobutyl; R_{3a} and R_{3b} are independently selected from the group consisting of unsubstituted (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, R_{3c} and R_{3d} are both H; R_4 is H; and R_{5a}, and R_{5e} are each substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl). A compound of Formula (I) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y each independently unsubstituted methyl or R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with halide (e.g., F); R_1 is isobutyl; R_{3a} and R_{3b} are independently selected from the group consisting of unsubstituted (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, R_{3c} and R_{3d} are both H; R_4 is H; R_{5a}, and R_{5e} are each substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl), and R_{5b}, R_{5c}, and R_{5d} are each independently selected from the group consisting of H, CN, halide (e.g., F, Cl), CF_3, $C(H)F_2$, $C(F)H_2$, (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy. In certain examples, the disclsoure relates to a method of treating auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis; comprising the step of: administering to a subject in need thereof a therapeutically effective amount of any one of the compounds described herein.

In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient.

In another aspect, there is provided use of the compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

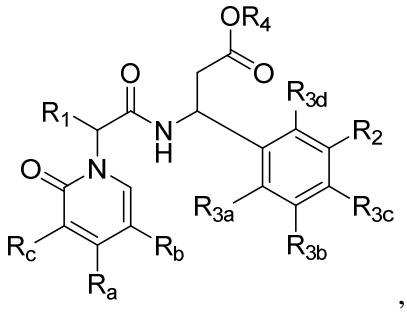
In another aspect, there is provided use of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

In another aspect, there is provided the compound as described herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In some examples, a compound of Formula (I) can be a compound of Formula (Ia):

Claims:

1. A compound of Formula (I):



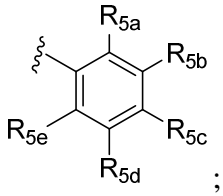
(I)

or a pharmaceutically acceptable salt thereof, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and substituted or unsubstituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form an unsubstituted 4-6 membered ring or a substituted 4-6 membered ring, substituted with at least one halide, unsubstituted $(C_1\text{-}C_4)$-alkyl, or OMe;

R_1 is substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl, substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_3\text{-}C_6)$-cycloalkyl, or substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy;

R_2 is ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_3\text{-}C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-(C_1\text{-}C_4)$-alkoxy, $-OCF_3$, and substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

R_{3d} is H;

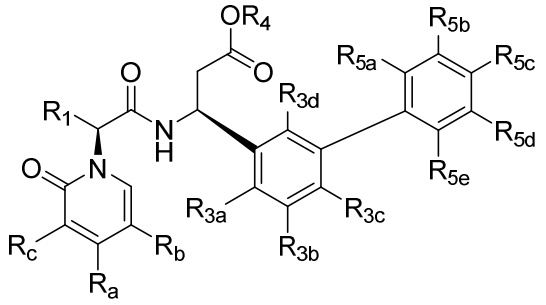
R_4 is H, or substituted or unsubstituted $(C_1\text{-}C_4)$-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

wherein, unless otherwise specified, substituted means substituted with one or more substituents selected from alkyl, cycloalkyl, heterocyclylalkyl, halogen, OH, OMe, $C(H)F_2$, $C(F)H_2$, CF_3, $C(H)_2CF_3$, SF_5 $CHFCH_2$amine, CH_2amine, and CN.

2. The compound of claim 1, wherein the compound is a compound of Formula (Ia):



(Ia)

wherein

at least one of R_a, R_b, and R_c is –(C_1-C_3)alkylene-N(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and methyl; or

R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring; and

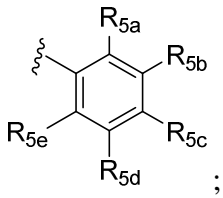
R_{3a}, and R_{3b} are each independently selected from the group consisting of methyl and F.

3. The compound of claim 1, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that at least one of R_a, R_b, and R_c is -(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of halide, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_4)-alkoxy, CF_3, $C(H)F_2$, and $C(F)H_2$;

R_{3c}, and R_{3d} are H;

R_4 is H;

R_{5a} is methyl;

R_{5b} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

R_{5c} is methyl;

R_{5d} is H; and

R_{5e} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy.

4. A pharmaceutical composition comprising a compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient.

5. Use of the compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

6. Use of the pharmaceutical composition of claim 4, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for use as a medicament.