METHODS OF TREATING HIDRADENITIS SUPPURATIVA

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial No. 63/106,557 filed October 28, 2020 and U.S. Provisional Application Serial No. 63/106,858, the contents of each is herein incorporated by reference in their entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Hidradenitis suppurativa (HS), also called acne inversa, is a chronic inflammatory skin disease characterized by inflammatory nodule, abscess, sinus and fistula formation, and scarring of the skin, most commonly in apocrine gland rich areas such as the axilla, inframammary area, inguinal area, perineum, and perianal area. In its moderate and severe forms, HS is debilitating and causes significant discomfort, pain, anxiety and depression, as well as impairment of quality of life.

[0005] The exact cause of HS has not been identified, although genetic defects in the gene encoding for gamma-secretase have been described in subjects with HS. Potential target proteins include Notch, E-cadherin, and nicastrin. Notch plays an important role in hair follicle development, and a defect in Notch may lead to formation of epidermal cysts, dysregulation of normal T-cell mediated immune responses, and suppression of Toll-like receptor-4-induced pro-inflammatory macrophage mediated cytokine responses (Radtke et al, 2010; Wang et al, 2010). Smoking and obesity have been associated with HS (Prens and Deckers, 2015) as well as, excessive sweating, androgen dysfunction, or possible genetic causes. Some reports suggest that HS is, at least in part, a neutrophil mediated disease.

[0006] Current therapy for subjects with HS includes local and systemic antibiotics, pain medication, and anti-TNF-α agents such as adalimumab. Other drugs such as cyclosporin A, dapsone, and isotretinoin have been used with limited success (Napolitano et al, 2017). Despite the treatment options available, most patients only partially and/or temporarily respond.

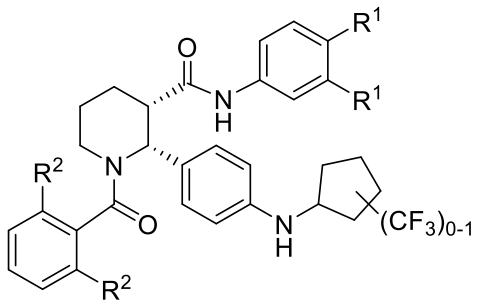
[0007] A recent treatment option advanced in US2018/0280530 and US2018/028425 is the use of a C5a targeting antibody to treat patients suffering from HS. C5a is known to be a potent chemotactic anaphylatoxin, and the binding of C5a to C5aR modulates leucocyte trafficking, migration, and activation. However, targeting C5a directly with an antibody disrupts not only the C5a/C5aR axis, but also disrupts C5a binding to the C5L2 receptor. The C5a/C5L2 pathway includes beneficial biological functions including limiting or suppressing the pro-inflammatory response caused by C5a (Gerard et al. J Biol Chem. 2005. 280(48):39677-80, Wang et al. J Immunol. 2013. 191(8):4001-9). In fact, disrupting the C5a-C5L2 pathway has been shown to exacerbate inflammation resulting in a more severe reaction to C5a. (Xiao et al. J Am Soc Nephrol. 2014. 25(2):225-31, Karsten et al., Front Immunol. 2018, 15;9:488). Thus, the direct targeting of C5a involves blocking signaling pathways associated with mitigating C5a response.

[0008] Moreover, antibody treatments carry other disadvantages such as the need for intravenous delivery, the potential for patients to develop human anti-chimeric antibodies (HACAs), the need for patients to travel to a medical center to receive treatment, and reduced patient compliance.

[0009] As such, there remains a need in the art to identify and develop orally available compounds useful in the treatment of Hidradenitis Suppurativa (HS) and related cutaneous neutrophilic inflammatory diseases that do not block the C5a/C5L2 axis, thereby preserving the beneficial functions of the C5L2 pathway.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0009a] In another aspect, there is provided the use of a therapeutically effective amount of a compound of Formula I ,



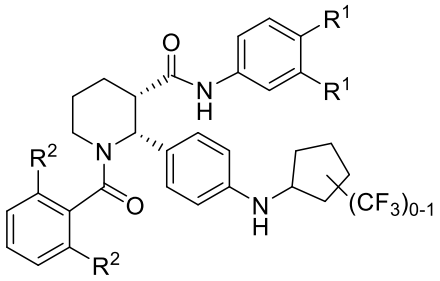
(I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cutaneous neutrophilic inflammatory disease in a subject in need thereof, wherein said therapeutically effective amount is about 10 mg or 30 mg of the compound twice daily, wherein

each R^1 is independently selected from the group consisting of CH_3, CF_3, CH_2CH_3, Cl, 1-pyrrolidine, -O-$CH(CH_3)_2$, and CH_2OH; and

each R^2 is independently selected from the group consisting of CH_3 and F.

[0010] In one ~~aspect~~example, the present disclosure provides methods treating a cutaneous neutrophilic inflammatory disease in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound of Formula I



(I);

or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are as defined herein.

[0011] In some ~~embodiments~~examples, the cutaneous neutrophilic inflammatory disease is Hidradenitis Suppurativa (HS).

[0012] In some ~~embodiments~~examples, the therapeutically effective amount of Formula I is a total daily dosage of about 5 to 200 mg. In some embodiments, the therapeutically effective amount of Formula I is a total daily dosage of 60 mg or 20 mg.

[0013] Other objects, features, and advantages of the present ~~invention~~ disclosure will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Error! Reference source not found. shows a schematic of the Phase II study design.

DETAILED DESCRIPTION OF THE INVENTION

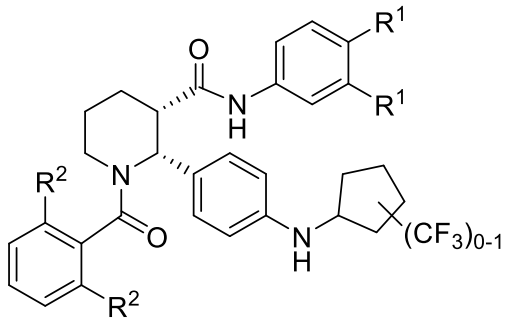
I. General

[0015] The current disclosure provides compounds and dosing regimens for the treatment of Hidradenitis Suppurativa and specific patient populations thereof. The compounds in the methods described herein specifically target C5aR and do not disrupt the C5a-C5L2 interaction. Advantageously, the C5aR inhibitors disclosed in this applicaiton effectively modulate neutrophil migration and activation by blocking the C5a-C5aR interaction while not blocking the C5a-C5L2 axis. Without being bound to any particular theory, it is believed that compounds binding to C5aR avoid the detrimental effects of interrupting the C5a-C5L2 signaling axis. This provides subjects receiving treatment for Hidradenitis Suppurativa and subpopulations thereof to benefit from the pro-inflammatory supressing activity of the C5a-C5L2 axis.

II. Definitions

WHAT IS CLAIMED IS:

1. Use of ~~A method of treating a cutaneous neutrophilic inflammatory disease in a subject in need thereof, said method comprising administering to said subject~~ a therapeutically effective amount of a compound of Formula I ,



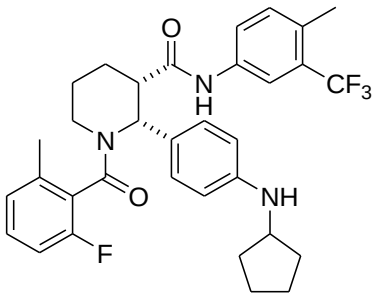
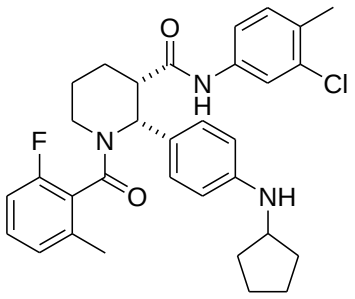
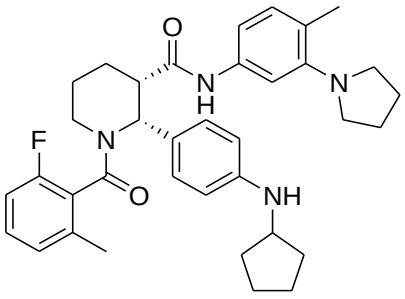
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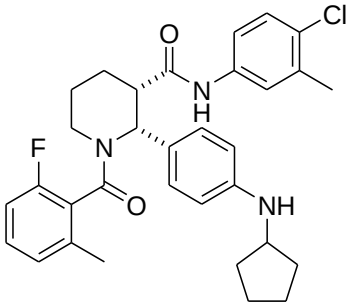
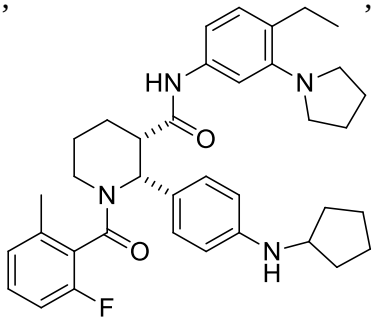
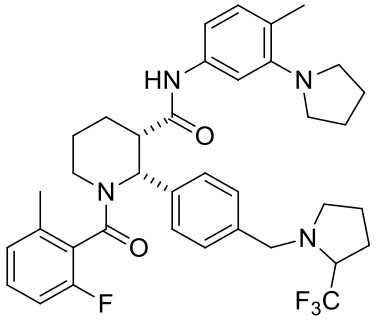
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cutaneous neutrophilic inflammatory disease in a subject in need thereof, wherein said therapeutically effective amount is about 10 mg or 30 mg of the compound twice daily, wherein

each R^1 is independently selected from the group consisting of CH_3, CF_3, CH_2CH_3, Cl, 1-pyrrolidine, -O-$CH(CH_3)_2$, and CH_2OH; and

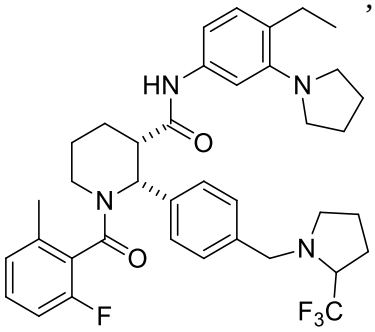
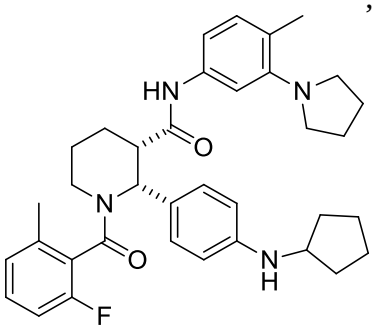
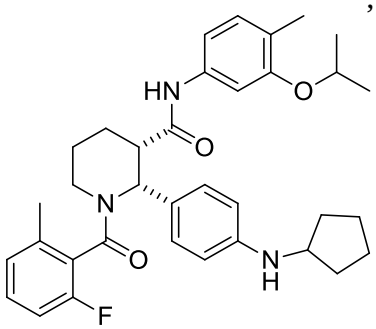
each R^2 is independently selected from the group consisting of CH_3 and F.

2. The ~~method~~ use of claim **1**, wherein the compound is selected from the group consisting of

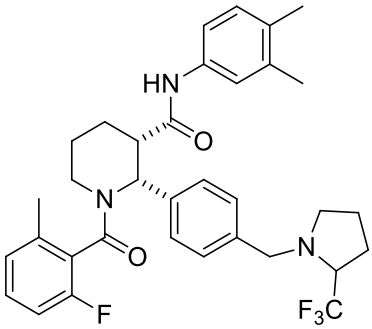
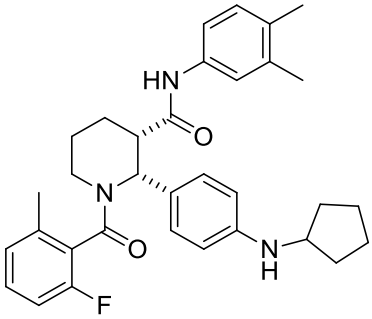
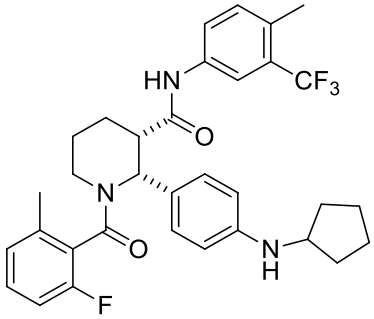
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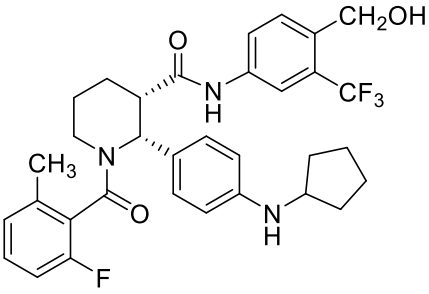
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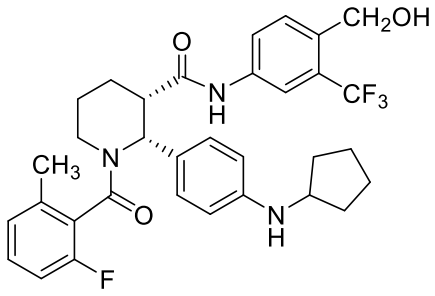
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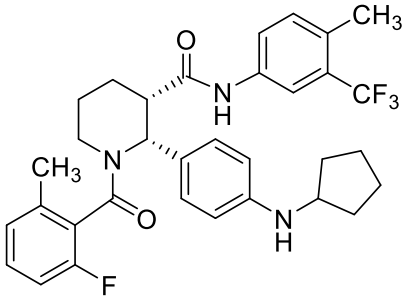
or a pharmaceutically acceptable salt thereof.

3. The ~~method~~ use of claim **1**, wherein the compound is



or a pharmaceutically acceptable salt thereof.

4. The ~~method~~use of claim **1**, wherein the compound is Avacopan, having the formula



or a pharmaceutically acceptable salt thereof.

5. The ~~method~~ use of any one of claims **1** to **4**, wherein the cutaneous neutrophilic inflammatory disease is selected from the group consisting of Hidradenitis Suppurativa (HS), Sweet syndrome (SS), Pyoderma gangrenosum (PG), PAPA (pyogenic arthritis, PG and acne), PASH (PG, acne and hidradenitis suppurativa), subcomeal pustular, dermatosis (SPD), PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa), elevatum diutinum (EED), neutrophilic panniculitis, epidermolysis bullosa acquisita, syndrome; rheumatoid neutrophilic dermatosis, familial Mediterranean fever, ; erythema, Schnitzler syndrome, bowel-associated dermatosis-arthritis syndrome (BADAS), SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) cryopyrin-associated disorders, and gout.

6. The ~~method~~ use of any one of claims **1** to **4**, wherein the cutaneous neutrophilic inflammatory disease is Hidradenitis Suppurativa (HS).

7. The ~~method~~use of any one of claims **1** to **6**, wherein the subject is to receive~~s~~ 30 mg of the compound twice daily.

8. The use~~method~~ of any one of claims **1** to **6**, wherein the subject has been diagnosed with HS, and having a Hurley score of II or III.

9. The use~~method~~ of any one of claims **1** to **6**, wherein the subject has been diagnosed with HS, and having a Hurley score of Stage III.

10. The use~~method~~ of claim **6**, wherein said subject has been diagnosed with HS, having a Hurley score of Stage III, and receives 30 mg of the compound twice daily.

11. The use~~method~~ of any one of claims **1** to **6**, wherein the subject is to receive~~s~~ 10 mg of the compound twice daily.

12. The use~~method~~ of any one of claims **1** to **11** wherein the subject is to receive~~s~~ treatment for 12 weeks.

13. The use~~method~~ of any one of claims **1** to **11** wherein the subject is to receive~~s~~ treatment for 26 weeks.

14. The use~~method~~ of any one of claims **1** to **11** wherein the subject is to receive~~s~~ treatment for 52 weeks.

15. The use~~method~~ of any one of claims **1** to **11** wherein the subject is to receive~~s~~ chronic treatment.