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Design and Synthesis of 2-Alkylpyrimidine-4,6-diol and 6-Alkylpyridine-2,4-diol as Potent GPR84 Agonists

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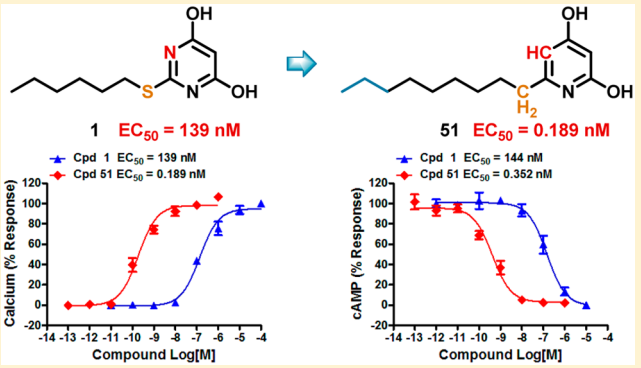
S *Supporting Information*

ABSTRACT: A series of alkylpyrimidine-4,6-diol derivatives were designed and synthesized as novel GRP84 agonists based on a high-throughput screening (HTS) hit **1**. 6-Nonylpyridine-2,4-diol was identified as the most potent agonist of GPR84 reported so far, with an EC_{50} of 0.189 nM. These novel GPR84 agonists will provide valuable tools for the study of the physiological functions of GPR84.



KEYWORDS: *GPR84, agonists, 2-alkylpyrimidine-4,6-diol, 6-alkylpyridine-2,4-diol, structural modification*

Free fatty acid receptors (FFARs) are G protein-coupled receptors (GPCRs) activated by free fatty acids (FFAs). FFARs are categorized according to the chain length of FFA ligands.[1−3] GPR84 belongs to the rhodopsin-like family of GPCRs and was originally identified by the expressed sequence tag (EST) data mining strategy.[4] GPR84 is expressed mainly in hematopoietic tissue, such as bone marrow and peripheral leukocytes.[5,6] Under physiological conditions, the expression of GPR84 is low, but it can be remarkably increased in monocytes/macrophages upon activation by lipopolysaccharide.[5] Medium-chain fatty acids (MCFA) can amplify lipopolysaccharide stimulated production of the proinflammatory cytokine interleukin-12 p40 (IL-12 p40) by activating GPR84.[5] Deficiency of GPR84 in T cells results in increased IL-4 production in response to CD3 cross-linking, indicating a novel role of GPR84 in regulating early IL-4 gene expression.[7] Several recent studies also showed that GPR84 plays a significant role in inflammation.[8−11] GPR84 has been reported to be involved in many diseases such as Alzheimer's disease,[12] neuropathic pain,[13] acute myeloid leukemia,[14] reflux esophagitis,[15] and inflammatory bowel disease.[16] In addition, GPR84 is necessary for proper development of the retina in *Xenopus laevis*.[17] Therefore, the development of small molecule ligands including agonists and antagonists of GPR84 will provide useful tools for investigating the physiological roles of GPR84.

GPR84 can be activated by MCFAs with carbon chain lengths of 9−14. Capric acid (C10:0), undecanoic acid (C11:0), and lauric acid (C12:0, Figure 1) are the most potent endogenous agonists of GPR84 reported so far.[5] Diindolylmethane (DIM) (Figure 1) has also been discovered to have an

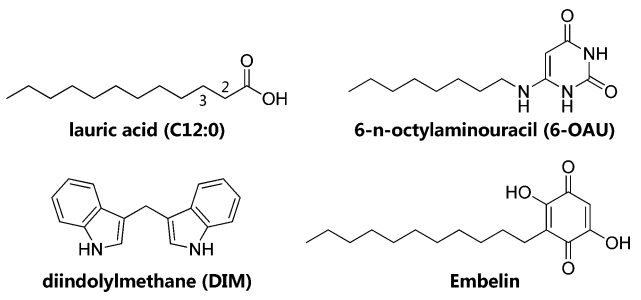


Figure 1. Structures of known GPR84 agonists and modulator.

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agonistic activity on GPR84,[5] possibly via a positive allosteric mechanism.[18] Moreover, Suzuki et al. reported that 2- or 3-position hydroxylated MCFAs are slightly more potent than nonhydroxylated MCFAs. They also discovered that 6-*n*-octylaminouracil (6-OAU, Figure 1) is a surrogate agonist of GPR84 with an EC_{50} value of 512 nM.[10] In addition, embelin (Figure 1) reported by Yaronet al. is also a GPR84 agonist with moderate potency.[19]

The lack of highly potent and selective ligands for GPR84 has hindered the study of its physiological functions and the development of potential clinical applications. Therefore, we carried out a high-throughput screening of 160,000 small-molecule compounds using a calcium mobilization assay in HEK293 cells expressing GPR84.[20] The screening resulted in the identification of 2-(hexylthio)pyrimidine-4,6-diol (**1**) as a GPR84 agonist with an EC_{50} of 139 nM (Figure 2), which is 5-fold more potent than the reported agonist 6-OAU (EC_{50} = 653 ± 58 nM in our system).

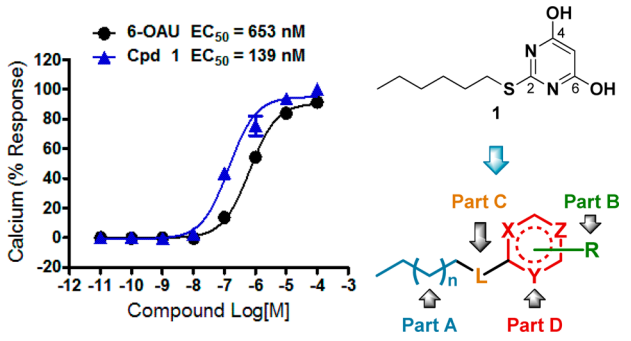


Figure 2. Structure and activity of HTS hit **1** and the strategy for the SAR study.

HTS hit **1** shares some structural similarities with 6-OAU. Both compounds have a pyrimidine ring and an alkyl side chain. The only differences between the structures are the orientation of the pyrimidine ring and the minor variation in the side chain, which result in a significant activity difference, indicating that the activity of this scaffold is susceptible to structural modification. Considering the potential for activity improvement, a structure optimization was carried out in four areas (Figure 2) to elucidate the structure−activity relationship (SAR) of this scaffold: (A) length of the alkyl chain, (B) substitutions on the pyrimidine ring, (C) type of the linker group, and (D) replacement of the pyrimidine ring.

As GPR84 is sensitive to FFAs with carbon chain lengths of 9−14, we first designed compounds **5**−**23** by retaining the pyrimidine-4,6-diol core structure while changing the carbon chain with diversified substitutions. These compounds were prepared by the alkylation of commercially available 2-mercaptopyrimidine-4,6-diol with various alkyl tosylates or alkyl bromides under basic conditions (Scheme 1).

As demonstrated in Table 1, the carbon chain length has a significant influence on the activity of these compounds. The

Scheme 1. Synthesis of Compounds 1 and 5−23

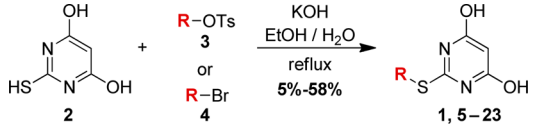
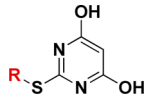


Table 1. In Vitro GPR84 Agonistic Activities of 5−23



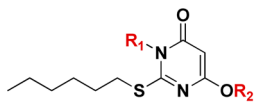
compd	R	EC_{50} (μM)[a]	% max[a,b]
1	$CH_3(CH_2)_5$−	0.139 ± 0.009	100 ± 1
5	$CH_3(CH_2)_4$−	2.48 ± 0.19	83.4 ± 2.5
6	$(CH_3)_2CH(CH_2)_3$−	0.641 ± 0.058	112 ± 4
7	$CH_3(CH_2)_6$−	0.231 ± 0.058	115 ± 4
8	$CH_3(CH_2)_7$−	0.264 ± 0.019	27.2 ± 8.1
9	$CH_3(CH_2)_{11}$−	1.16 ± 0.35	34.3 ± 4.1
10	$CH_3(CH_2)_{13}$−	25.7 ± 3.5	18.4 ± 3.7
11	$CH_3(CH_2)_{15}$−	11.3 ± 1.5	52.4 ± 8.8
12	$HC{\equiv}C(CH_2)_2$−	8.85 ± 0.96	80.0 ± 2.7
13	$HC{\equiv}C(CH_2)_3$−	21.6 ± 8.9	26.3 ± 4.7
14	$C_2H_5C{\equiv}C(CH_2)_2$−	0.653 ± 0.019	92.0 ± 1.1
15	(*Z*)-$C_2H_5CH{=}CH(CH_2)_2$−	0.938 ± 0.105	69.3 ± 1.7
16	$^{cy}BuCH_2$−	43.4 ± 16.4	79.8 ± 2.3
17	$NC(CH_2)_4$−	>100	55.2 ± 3.6
18	$HO(CH_2)_8$−	>100	2.48 ± 0.36
19	$C_6H_5(CH_2)_2$−	3.86 ± 0.46	52.9 ± 4.7
20	$C_6H_5(CH_2)_3$−	0.573 ± 0.074	40.4 ± 2.3
21	$C_6H_5(CH_2)_4$−	0.435 ± 0.209	67.2 ± 1.6
22	$C_6H_5(CH_2)_5$−	1.08 ± 0.15	28.6 ± 1.1
23	*p*-C_2H_5−$C_6H_4CH_2$−	0.271 ± 0.011	70.7 ± 3.8

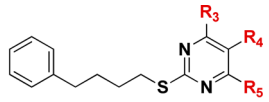
[a]Data are means ± SEM (n = 3). [b]Max response vs Ctrl (**1**).

activity of these compounds improved while increasing the chain length and reached a maximum with the hexyl chain (hit **1**). Further lengthening of the carbon chain reduced the activity. Other groups such as alkynyl (**12**−**14**), alkenyl (**15**), cyclobutyl (**16**), and aryl (**19**−**23**) reduced the activity to different degrees, while the introduction of cyano (**17**) and hydroxyl (**18**) groups resulted in a loss of agonist activity (Table 1). Comparing **5** and **6**, it is reasonable to conclude that the agonistic activity could be improved by adding a side chain to the terminal end of the carbon chain.

We then synthesized compounds **24**−**32** (Table 2; for the synthesis see Supporting Information) with different substituents on the pyrimidine ring to evaluate their contribution to agonistic activity. It was interesting to find none of these

Table 2. In Vitro GPR84 Agonistic Activities of 24−30





compd	R_1	R_2	R_3	R_4	R_5	EC_{50} (μM)[a]
24	H	C_6H_{13}−				>100
25	H	$HO(CH_2)_7$−				>100
26	CH_3	H				>100
27	$C_6H_5CH_2$−	H				>100
28			NH_2	H	OH	>100
29			NH_2	H	NH_2	>100
30			CH_3	H	OH	>100
31			CF_3	H	OH	>100
32			OH	CH_3	OH	>100

[a]Data are means ± SEM (n = 3).

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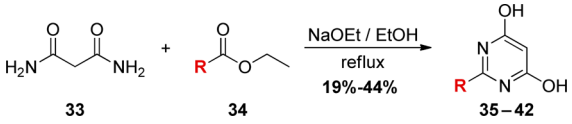
compounds showed any activity, indicating that the hydroxyl groups on the pyrimidine ring are indispensable. Replacement of hydroxyl groups on the pyrimidine ring with hexyloxy (**24**), hydroxyalkyloxy (**25**), one or two amino groups (**28**, **29**), methyl (**30**), or trifluoromethyl (**31**) resulted in a loss of agonistic activity. In addition, capping the nitrogen on the pyrimidine ring with a methyl (**26**) or benzyl group (**27**) also eliminated activity. The 5-methyl pyrimidine derivative (**32**) lost agonist activity, indicating that substitutions on the pyrimidine ring were also not tolerated. These results indicate that the hydroxyl groups on the pyrimidine ring are essential and cannot be replaced.

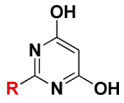
We then fixed the 4,6-dihydroxypyrimidine moiety and replaced sulfur with carbon to yield compounds **35**–**42**. These compounds were prepared by the condensation of malondiamide **33** with various esters **34** under reflux conditions employing sodium ethoxide as the base (Scheme 2).

Scheme 2. Synthesis of Compounds 35–42



Compounds **35**, **36**, and **37** (Table 3) with a five or six carbon side chain in this series displayed low to moderate potency in activating GPR84. Considering the larger size of sulfur compared to carbon, we decided to increase the length of the alkyl chain, which led to **38**. Pleasantly surprised, we found that **38** is 10-fold more potent than hit **1** (Table 1).

Table 3. In Vitro GPR84 Agonistic Activities of 35–42



compd	R	EC_{50} (nM)[a]	% max[a,b]
35	$CH_3(CH_2)_4$–	3669 ± 411	84.9 ± 1.1
36	$(CH_3)_2CH(CH_2)_3$	2105 ± 124	85.6 ± 0.8
37	$CH_3(CH_2)_5$–	454 ± 27	99.7 ± 2.4
38	$CH_3(CH_2)_6$–	12.7 ± 1.3	103 ± 1
39	$CH_3(CH_2)_7$–	11.4 ± 1.5	110 ± 5
40	$CH_3(CH_2)_8$–	48.7 ± 0.3	84.1 ± 3.4
41	$CH_3(CH_2)_6(CH_3)CH$–	299 ± 10	103 ± 1
42	p-C_2H_5–$C_6H_4(CH_2)_2$–	88.1 ± 13.3	97.4 ± 1.8

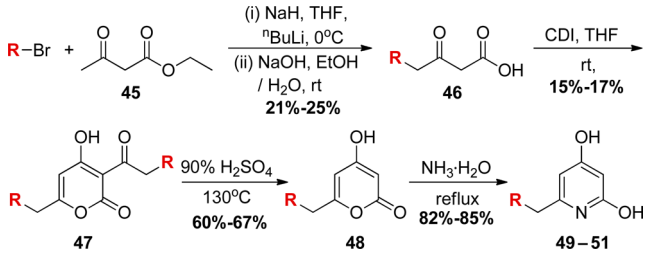
[a]Data are means ± SEM (n = 3). [b]Max response vs Ctrl (**1**).

Furthermore, **42** is 3-fold more potent than **23** (Table 1), indicating that carbon is the preferred linker atom. Similarly, we studied the chain length and the influence of terminal side chain and found that the trends are consistent with Table 1. Compound **39** with an eight carbon side chain was the most potent agonist in these series of compounds (Table 3), with an EC_{50} of 11.4 nM, which is approximately a 13-fold improvement over hit **1**.

To further understand the SAR of the novel 4,6-dihydroxylprimidine analogues on GPR84 agonism, we reorganized the key moiety of compound **39** and the known agonist 6-OAU, which generated compounds **43** with an octylamino group in the 2-position of pyrimidine-4,6-diol and **44** with an octyl group in the 6-position of pyrimidine-2,4-diol (Table 4; for the synthesis see Supporting Information). Compound **43** showed a similar level of potency as compound **39**, while compound **44** showed a significant reduction in potency.

We then turned to varying the pyrimidine ring while fixing the carbon chain, and compounds **49**–**51** were synthesized as shown in Scheme 3.[21] Ethyl acetoacetate was treated with NaH and *n*-BuLi then reacted with bromides to get the β-oxo carboxylic esters, which was followed by hydrolysis to β-oxo carboxylic acid **46**. Cyclization of **46** using carbonyldiimidazole in THF afforded the acylpyrone skeleton **47**, then deacylation of **47** by heating at 130 °C in 90% H_2SO_4 gave compound **48**, which was refluxed in ammonia to give **49**–**51**.

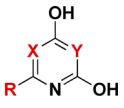
Scheme 3. Synthesis of Compounds 49–51



As shown in Table 4, compound **50**, in which carbon replaced one nitrogen in the pyrimidine ring, showed significantly increased potency compared to compound **39**, with an EC_{50} of 1.34 nM. Compound **49** with a shorter carbon chain showed similar potency compared to compound **50**.

However, compound **51**, containing a longer chain with one more carbon, showed a dramatic increase in the agonist potency, with an EC_{50} of 0.189 nM, which is approximately 730-fold more potent than hit **1** and 3400-fold more potent

Table 4. In Vitro GPR84 Agonistic Activities of 43, 44, and 49–51



compd	R	X	Y	EC_{50} (nM)[a]	% max[a,b]
43	$CH_3(CH_2)_7NH$–	N	CH	6.14 ± 1.21	91.8 ± 0.3
44	$CH_3(CH_2)_7$–	CH	N	811 ± 127	91.2 ± 1.8
49	$CH_3(CH_2)_6$–	CH	CH	1.26 ± 0.05	87.8 ± 2.9
50	$CH_3(CH_2)_7$–	CH	CH	1.34 ± 0.08	82.6 ± 4.9
51	$CH_3(CH_2)_8$–	CH	CH	0.189 ± 0.039	107 ± 1

[a]Data are means ± SEM (n = 3). [b]Max response vs Ctrl (**1**).

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than 6-OAU. The significant left-shift of the dose−response curve of **51** compared to those of hit **1** and 6-OAU is shown in Figure 3A.

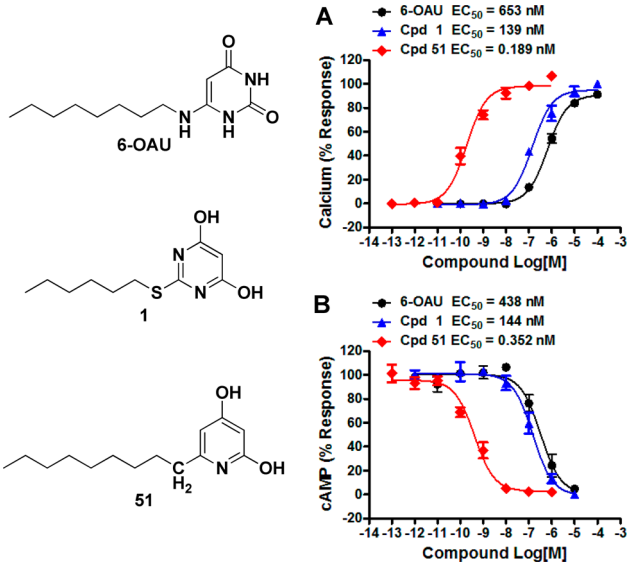

Figure 3. Compound **51** shows excellent agonistic activity in both calcium mobilization assay (A) and cAMP assay (B).

Since GPR84 couples endogenously with Gαi/o proteins, which decrease intracellular cAMP level upon activation,[5] we tested **1** and **51** in a cAMP assay. As shown in Figure 3B, both compounds induced a dose-dependent reduction of forskolin-stimulated cAMP accumulation in HEK293 cells expressing GPR84 with EC_{50} values very similar to those obtained in the calcium mobilization assay.

FFARs may share the same endogenous ligands. GPR40 and GPR120 are both activated by medium- to long-chain FFAs, while GPR41 and GPR43 are activated by short-chain FFAs. We tested the most potent compound **51** on several FFARs and were pleased to find that **51** did not activate other FFARs at concentrations up to 100 μM. In contrast, these FFARs could be activated by reported ligands (Table 5).

Table 5. Selectivity of 51 on Free Fatty Acid Receptors

		calcium assay [EC_{50} (μM)][a]	
receptor	agonists	agonists	compd **51**
GPR84	6-OAU	0.653 ± 0.058	0.000189 ± 0.000039
GPR40	DHA[b]	11.7 ± 2.3	NR[c]
GPR41	sodium butyrate	10.1 ± 0.5	NR
GPR119	PSN632408	5.13 ± 0.62	NR
GPR120	TUG891	0.471 ± 0.024	NR

[a]Data are means ± SEM (n = 3). [b]DHA, docosahexaenoic acid. [c]NR, no response at concentrations up to 100 μM.

In preliminary pharmacokinetic studies, compound **51** showed acceptable pharmacokinetic profiles for in vivo efficacy study characterized by C_{max} (229 ± 24.3 ng/mL) and $AUC_{0\text{-}t}$ (399 ± 91.4 h·ng/mL) and a moderate absolute bioavailability (F% = 24.3%) in ICR mice (10 mg/kg, P.O., Table S1, Supporting Information).

In summary, starting from the HTS hit 2-(hexylthio)-pyrimidine-4,6-diol, we performed a systematic SAR study and found that the length of side chain, the type of linker group, and the orientation of the pyrimidine ring influence the agonist activity of GPR84. Finally, we identified 6-nonylpyridine-2,4-diol as a potent and selective GPR84 agonist, with an EC_{50} of 0.189 nM. To the best of our knowledge, this compound is the most potent GPR84 agonist reported so far. Such GPR84 agonists with a novel chemical structure would be valuable tools for the study of the physiological functions of GPR84.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00025.

Experimental procedures and characterization of new chemical entities (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

SAR, structure−activity relationship; Cpd, compound; GPCR, G protein-coupled receptor

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