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Dihydropyrrolo[2,3-*d*]pyrimidines: Selective Toll-Like Receptor 9 Antagonists from Scaffold Morphing Efforts

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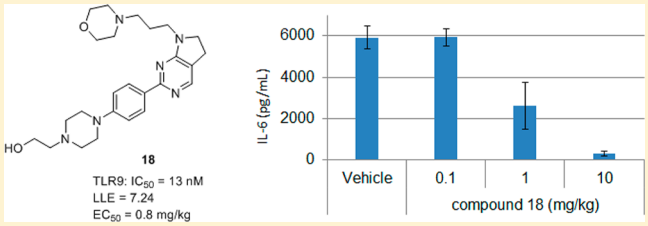
Supporting Information

ABSTRACT: Toll-like receptors (TLRs) play important roles in the innate immune system. In fact, recognition of endogenous immune complexes containing self-nucleic acids as pathogen- or damage-associated molecular patterns contributes to certain autoimmune diseases, and inhibition of these recognition signals is expected to have therapeutic value. We identified dihydropyrrolo[2,3-*d*]pyrimidines as novel selective TLR9 antagonists with high aqueous solubility. A structure−activity relationship study of a known TLR9 antagonist led to the promising compound **18**, which showed potent TLR9 antagonistic activity, sufficient aqueous solubility for parenteral formulation, and druggable properties. Compound **18** suppressed the production of the proinflammatory cytokine IL-6 in CpG-induced mouse model. It is therefore believed that compound **18** has great potential in the treatment of TLR9-mediated systemic uncontrollable inflammatory response like sepsis.



KEYWORDS: *Toll-like receptor 9, sepsis, autoimmune disease, dihydropyrrolo[2,3-d]pyrimidine, LLE*

Toll-like receptors (TLRs) are a family of type I transmembrane receptors and the central components of the innate immune system.[1,2] Thirteen TLRs have so far been reported as fundamental in recognition of pathogen-associated molecular patterns (PAMPs), which are expressed by microbial pathogens, or damage-associated molecular patterns (DAMPs), which are transmitted by necrotic or dying cells.[3,4] Among the reported TLRs, TLR1−10 have been identified in human. Human TLR3, TLR7, TLR8, and TLR9 are expressed on endosomal membranes in the cells and recognize pathogen-derived nucleic acid molecular patterns.[5] However, recognition of endogenous immune complexes containing self-nucleic acids as PAMPs or DAMPs contributes to certain autoimmune diseases, such as systemic lupus erythematosus (SLE),[6] psoriasis,[7] arthritis, and multiple sclerosis.[8] Therefore, inhibition of these recognition signals is expected to have therapeutic value.

TLR9 has been identified as a key receptor for innate immune response to unmethylated CpG-DNA.[9] Accordingly, a number of TLR9 antagonists have been suggested to be potentially useful in the treatment of diseases characterized by undesired innate immune response, such as systemic autoimmune diseases, sepsis,[10] Graft-versus-host disease,[11] and malaria infection.[12] Recently, Plitas and co-workers reported that TLR9 knockout mice with cecal ligation and puncture (CLP), as peritonitis model, showed increased bacterial clearance, decreased serum cytokine production, and increased granulocyte influx in the peritoneum as compared to wild-type animals. The researchers also showed that administration of an inhibitory CpG sequence to block TLR9 signals just before CLP treatment improves mortality in the wild-type animals. These findings have provided a rationale for the pursuit of small molecule TLR9 antagonists as potential candidates for treatment of systemic uncontrollable inflammatory responses, including sepsis. As part of our efforts to find new agents for the treatment of sepsis, we focused on TLR9 selective antagonists. To date, a number of TLR9 antagonists have been reported[12−15] with promising candidates reaching clinical development.[16] It was recently reported that the hydroxychloroquine **1**, a TLR9 antagonist classified as an antimalarial drug and also used for SLE and rheumatoid arthritis therapy, directly blocks interaction between TLR9 and CpG-DNA.[17] In addition, CPG-52364 (**2**), a small molecule TLR7/8/9 antagonist (the reported ratio of TLR7/TLR9 antagonism was 0.8),[18,22] has recently completed phase 1 clinical trial for SLE therapy (NCT00547014) (Figure 1).

Although there has been tremendous progress in the development of selective TLR9 antagonists as a small molecule, most known TLR9 antagonists are reported to also inhibit TLR7. Activation or inhibition of TLR7 and TLR9 is very complex as these receptors have opposing inflammatory and regulatory roles.[19−21] Therefore, compounds that inhibit the signal cascades of both receptors may induce unwanted

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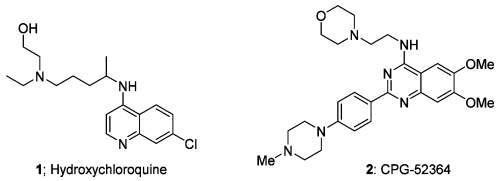
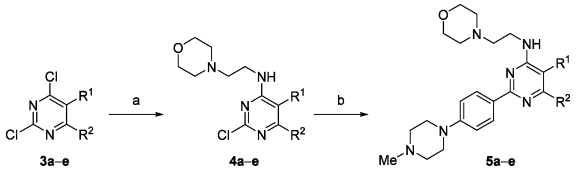


Figure 1. Structures of small molecule TLR9 antagonists.

Scheme 1. Synthesis of the Pyrimidine Derivatives[a]



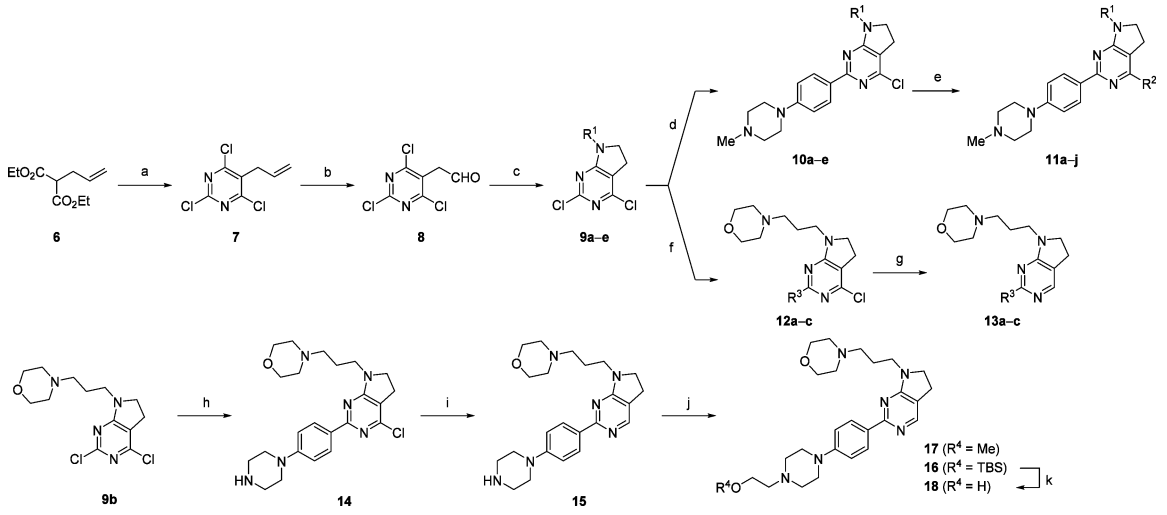
[a]Reagents and conditions: (a) 4-(2-aminoethyl)morpholine, *N*,*N*-diisopropylethylamine or K_2CO_3, *i*-PrOH or DMF, 60 °C; (b) $Pd(PPh_3)_4$, 4-(4-methylpiperazin-1-yl)phenylboronic acid pinacol ester, 3 M NaOH, 1,4-dioxane, 120–150 °C (microwave).

immunosuppression. Herein we describe the discovery of a promising TLR9 antagonist obtained by optimization of the known TLR9 antagonist **2**. While **2** exhibits strong TLR9 antagonistic activity,[22] it is lipophilic and has a large molecular weight to be used as lead compound. Also **2** has insufficient solubility (0.12 mg/mL, pH 7.4) for parenteral formulation. To identify a potential lead compound, we focused on compound lipophilic efficiency (LLE = pIC_{50} − *c*logP) as an index because compounds with low *c*logP generally exhibit high solubility and good physiochemical properties.[23−25]

The pyrimidine derivatives **5a−e** were synthesized as shown in Scheme 1. Displacement of the 4-chloro group in **3a−e** with 4-(2-aminoethyl)morpholine afforded **4a−e**. Suzuki−Miyaura cross coupling reaction with the corresponding pinacol boronates under microwave heat yielded the desired compounds **5a−e**. Dihydropyrrolo[2,3-*d*]pyrimidine derivatives were prepared as shown in Scheme 2. The diethyl allylmalonate **6** was treated with urea followed by chlorination of 5-allylbarbituric acid using $POCl_3$ to give trichloro compound **7** in high yield. Oxidative cleavage of the olefin using sodium periodate in the presence of potassium osmate gave the key intermediate **8**. Tandem reaction via reductive amination with various alkyl amines followed by cyclization produced the desired dihydropyrrolopyrimidines **9a−e**. Suzuki−Miyaura cross coupling reaction with the corresponding pinacol boronates provided compounds **10a−e**, **12a−c**, and **14**. The desired compounds **11a−j** and **13a−c** were obtained by conversion of the 4-chloro group into a methyl, methoxy, dimethylamino, or hydrogen group. The substituted piperazine derivatives **17** and **18** were synthesized from the dihydropyrrolopyrimidine **9b**.

As a first step toward exploration of a lead compound, we attempted to identify the minimal core structure of the quinazoline framework for inhibition of TLR9 signal. TLR9 antagonistic activity was evaluated in NF-κB reporter assay as shown in Table 1. This reporter assay was carried out with HEK293-human TLR9 cells transfected with pNF-κB-Luc reporter vectors. To obtain other bicyclic pyrimidines, we replaced the dimethoxyphenyl moiety of **2** with a tetrahydropyran or cyclohexane ring. The obtained fused-ring compounds were less lipophilic compared to the quinazoline core structure (**2**, *c*logP 2.96, versus **5a**, 0.43, and **5b**, 2.15).

Scheme 2. Synthesis of Dihydropyrrolo[2,3-*d*]pyrimidine Derivatives[a]



[a]Reagents and Conditions: (a)(1) urea, NaOEt, EtOH, reflux; (2) $POCl_3$, *N*,*N*-dimethylaniline, 120 °C; (b) K_2OsO_4, $NaIO_4$, acetone, H_2O, rt; (c) R^3NH_2, $NaBH_3CN$, AcOH, MeOH, rt; (d) $Pd(PPh_3)_4$, 4-(4-methylpiperazin-1-yl)phenylboronic acid pinacol ester, Na_2CO_3, H_2O, 1,4-dioxane, 110−120 °C (microwave); (e) for **11a−d**, 2 M MeZnCl or MeZnBr/THF, $Pd(t\text{-}Bu_3P)_2$, THF; for **11e**, NaOMe, MeOH, 120 °C (microwave); for **11f**, 2 M Me_2NH/THF, *N*-methylpyrrolidone, 180 °C (microwave); for **11g**, **11i**, **11j**, 10% Pd/C, H_2, trifluoroacetic acid, MeOH, rt; for **11h**, 10% Pd/C, HCO_2NH_4, trifluoroacetic acid, MeOH, 50 °C; (f) $Pd(PPh_3)_4$, substituted phenylboronic acid pinacol ester, 3 M Na_2CO_3, 1,4-dioxane, 110−120 °C (microwave); (g) for **13a**, lithium aluminum hydride, THF, reflux; for **13b**, (1) 10% Pd/C, HCO_2NH_4, MeOH, 50 °C; (2) lithium aluminum hydride, THF, reflux; for **13c**, (1) 4 M HCl/1,4-dioxane, MeOH, rt; (2) 10% Pd/C, HCO_2NH_4, MeOH, 50 °C; (3) 30% formaldehyde solution, $NaBH_3CN$, AcOH, MeOH, rt; (h)(1) $Pd(PPh_3)_4$, *t*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate, 3 M Na_2CO_3, 1,4-dioxane, 120 °C (microwave); (2) 4 M HCl/1,4-dioxane, MeOH; (i) 10% Pd/C, HCO_2NH_4, MeOH, 50 °C; (j) R^4OCH_2CHO, $NaBH_3CN$, AcOH, MeOH, rt; (k) 1 M TBAF/THF, THF, rt.

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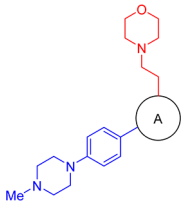
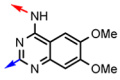
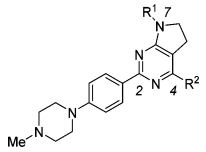
Table 1. IC_{50} Values, LLE, and *c*logP of the Prepared Pyrimidine Analogues

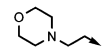
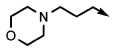
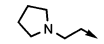
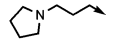
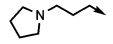
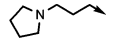
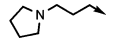
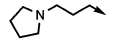
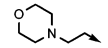
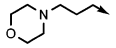
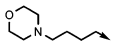


Comp	A	hTLR9: IC_{50} (nM)[a]	LLE	*c*logP[c]
2		4.6	5.38	2.96
5a		190[b]	6.30	0.43
5b		27[b]	5.42	2.15
5c		190	5.16	1.56
5d		120	5.49	1.43
5e		35	5.86	1.60
11a		20	6.26	1.43

[a]Average (N = 2). [b]Mean (N = 3). [c]Calculated by ACD/Log*P*.

Table 2. Optimization of the Substituents in the R^1 -and R^2-Positions of the Dihydropyrrolo[2,3-*d*]pyrimidine



Comp	R^1	R^2	hTLR9: IC_{50} (nM)[a]	LLE	*c*logP[d]
11a		Me	20	6.26	1.43
11b		Me	16[c]	6.16	1.64
11c		Me	11	5.47	2.48
11d		Me	3.5	5.77	2.69
10d		Cl	84[b]	4.14	2.93
11e		OMe	120[b]	3.77	3.13
11f		NMe_2	73[b]	3.65	3.48
11g		H	3.9	6.01	2.40
11h		H	73	6.00	1.14
11i		H	8.6[c]	6.72	1.35
11j		H	11[c]	6.18	1.77

[a]Average (N = 2). [b]N = 1. [c]N = 3. [d]Calculated by ACD/Log*P*.

Although compound **5a** showed better LLE value than **2**, we had to optimize its selectivity against TLR7 (**5a**, TLR7: IC_{50} = 50 nM). Fortunately, compound **5b** showed acceptable TLR9 antagonistic activity with good selectivity against TLR7 (**5b**, TLR9/TLR7 = 71-fold). These findings suggested that lipophilic substituents at the 5- and/or 6-position of the pyrimidine are optimal for generation of lead compounds with high TLR9 selectivity. To reduce molecular weight, the ring of tetrahydroquinazoline **5b** was simplified by removal of the cyclohexane ring to give the dimethyl pyrimidine **5e**. Compound **5e** showed improvement in LLE value with weaker selectivity for TLR7 than **5b** (TLR7: IC_{50} = 928 nM). On the basis of these findings, it was concluded that the pyrimidine derivatives could provide the minimum core structure for TLR9 antagonism. Next, we turned our attention to compounds **5c** and **5d**, which were obtained by removal of the methyl group at the 5- and/or 6-position of the pyrimidine ring. Both compounds exhibited reduced TLR9 antagonistic activity, likely due to a decrease in hydrophobic interaction and lower basicity of the pyrimidine nitrogen than **5e** (Table S2, Supporting Information). Therefore, we focused on substituted or fused pyrimidine derivatives. In general, conformationally locked compounds with appropriate interaction are expected to improve the activity.[26] In order to reduce the number of rotatable bonds in the 4-amino group, we cyclized the 5-methyl group of compound **5e** with the nitrogen at the 4-position to form the dihydropyrrolopyrimidine **11a**. As expected, **11a** showed potent TLR9 antagonistic activity with a lower *c*logP relative to compound **5e**. We speculate that a fixed 4-substituted side chain led to strong interaction with the receptor. Furthermore, the metabolic stability of compound **11a** was improved compared to that of **5e** (human MS: **11a** <0.010 vs **5e** 0.069 mL/min/mg protein), probably due to interrupted oxidation of the 6-methyl group (metabolic site) by cyclization steric hindrance. As for receptor selectivity, compound **11a** showed good selectivity against TLR7 (TLR9/TLR7 = 93-fold). Overall, the dihydropyrrolo[2,3-*d*]pyrimidine was found to be superior to other core structures in terms of TLR9 selectivity, low lipophilicity, and ligand efficiency.

As we had a good lead compound (**11a**) in our hand, we looked at the SAR of the side chains. The compounds listed in Table 2 were designed and synthesized to extensively explore suitable substituents at the 7-position (R^1) and 4-position (R^2) of the dihydropyrrolo[2,3-*d*]pyrimidine core structure. Among **11a**−**d**, the order of activity was consistent with the basicity of the terminal amino group. This finding indicated that basicity of the amino group could be an important factor for high TLR9 antagonistic activity (Table S3, Supporting Information). Despite its strong antagonism of TLR9 (IC_{50} = 3.5 nM), the

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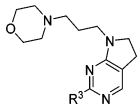
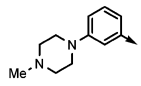
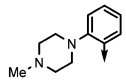
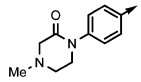
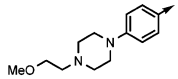
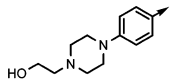
Table 3. Optimization of the Substituents in the R^3-Position of the Dihydropyrrolo[2,3-*d*]pyrimidine



Comp	R^3	hTLR9: IC_{50} (nM)[a]	LLE	*clogP*[c]
13a		**56**[b]	**5.55**	**1.71**
13b		**56**[b]	**5.99**	**1.27**
13c		**>1000**	**-**	**1.19**
17		**28**	**6.41**	**1.15**
18		**13**	**7.24**	**0.65**

[a]Average (N = 2). [b]N = 1. [c]Calculated by ACD/LogP.

Table 4. *In Vitro* Profile of Compound 18

evaluation	IC_{50} (nM)[a]
human TLR9	13
human TLR7	970[b]
human TLR8	>10000[b]
CpG-induced IL-6 inhibition in mouse spleen	74
CpG-induced IL-6 inhibition in human PBMC	244[b]

[a]Average (N = 2). [b]N = 1.

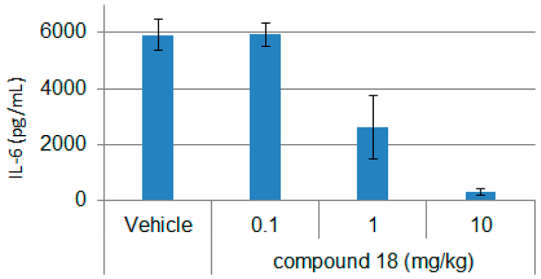


Figure 2. Compound **18** dose-dependent inhibition of CpG-induced IL-6 production in mice (N = 4).

pyrrolidine derivative **11d** displayed slightly lower LLE and metabolic stability than the corresponding morpholine derivative **11b**, presumably due to its higher lipophilicity (human MS: **11d** 0.035 versus **11b** < 0.01 mL/min/mg protein). Next, we evaluated the effects of a substitution at the 4-position of **11d**. The chloro (**10d**), methoxy (**11e**), and dimethylamino (**11f**) compounds showed significantly reduced TLR9 antagonistic activity. Although the unsubstituted compound **11g** exhibited strong activity, its metabolic stability was not sufficient (human MS: 0.071 mL/min/mg protein). These results suggested that morpholine derivatives were more favorable as drug candidates than pyrrolidine derivatives. As 4-hydrogen substitution gave good result for LLE, we replaced the 4-methyl group with a hydrogen in the morpholine compounds **11a** and **11b**, which had high LLE value and low *clogP*. Remarkably, compound **11i** showed strong TLR9 antagonistic activity with the best LLE value among the compounds in Table 2. In addition, the solubility of **11i** (1.1 mg/mL at pH 7.4) was much improved compared to that of compound **2** (0.12 mg/mL at pH 7.4), and its TLR9 selectivity remained over 50-fold that for TLR7 (**11i**, IC_{50} = 480 nM). Therefore, we selected **11i** as lead compound for further investigation.

The strong TLR9 antagonistic activity and good aqueous solubility of compound **11i** encouraged us to further investigate substitutions on the phenyl ring at the 2-position of the pyrimidine. It is reported that the aqueous solubility of a compound can be improved by disruption of its molecular symmetry.[27] Accordingly, we decided to change the position of the piperazine group to the meta- or ortho-position. Unfortunately, the resulting compounds **13a** and **13b** showed 6- to 7-fold decline in the antagonistic activity. Compound **13c**, a keto piperidine derivative, had no TLR9 antagonistic activity. These results suggested that the basic nitrogen (an aniline group) at the para-position of the benzene ring is crucial for interaction with TLR9. Finally, to further improve the solubility of **11i** for intravenous administration, the methyl group on the piperazine was replaced by a methoxyethyl or hydroxyethyl group that can act as a hydrophilic group. Among the prepared compounds, the 2-hydroxyethyl derivative **18** showed strong TLR9 antagonistic activity with high LLE value. It is noteworthy to mention here that compound **18** exhibited enough aqueous solubility for parenteral formulation (>10 mg/mL, pH 7.4) with the lowest lipophilicity (*clogP* = 0.65) (Table 3). Next, we determined compound **18** selectivity for TLR9. Compound **18** IC_{50} values for inhibition of the off-target receptors TLR7 and TLR8 were 970 and >10000 nM, respectively. Compound **18** IC_{50} (TLR7)/IC_{50} (TLR9) ratio was 75-fold. In *in vitro* experiments, compound **18** inhibited CpG-induced IL-6 production in mouse spleen and human peripheral blood mononuclear cells (PBMC) with IC_{50} values of 74 and 244 nM, respectively (Table 4). On the basis of these results, we decided to evaluate the efficacy of compound **18** *in vivo* by measuring CpG-induced IL-6 production in the peritoneal lavage fluid (PLF) and plasma of mice. To our delight, compound **18** inhibited CpG-induced IL-6 production in a dose-dependent manner (ED_{50}(plasma) = 0.8 mg/kg; Figures 2, S1 and S2, Supporting Information).

In summary, we describe here the discovery of dihydropyrrolo[2,3-*d*]pyrimidine derivatives as novel TLR9 antagonists. The representative compound **18** possessed high TLR9 selectivity with excellent aqueous solubility and showed remarkable efficacy in CpG-induced mouse model. Although further efforts are required to assess the *in vivo* safety profile of this compound, it is believed that compound **18** has great potential in the treatment of TLR9-mediated systemic uncontrollable inflammatory response like sepsis. Besides, compound **18** would be a useful reagent for studying the physiological roles of TLR9.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, analytical data, and procedures for all biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through all authors contributions. All authors have given approval to the final version of the manuscript.

Notes

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ABBREVIATIONS

TLR9, toll-like receptor 9; PAMP, pathogen-associated molecular patterns; DAMP, damage-associated molecular patterns; SLE, systemic lupus erythematosus; CLP, cecal ligation and puncture; LLE, lipophilic ligand efficiency; TBS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; TBAF, tetrabutylammonium fluoride; ACD, advanced chemistry development; PBMC, peripheral blood mononuclear cells

REFERENCES

(1) Kawai, T.; Akira, S. TLR signaling. *Semin. Immunol.* **2007**, *19*, 24−32.

(2) Kumagai, Y.; Takeuchi, O.; Akira, S. Pathogen recognition by innate receptors. *J. Infect. Chemother.* **2008**, *14*, 86−92.

(3) Takeda, K.; Akira, S. Toll-like receptors in innate immunity. *Int. Immunol.* **2005**, *17*, 1−14.

(4) Tabeta, K.; Georgel, P.; Janssen, E.; Du, X.; Hoebe, K.; Crozat, K.; Mudd, S.; Shamel, L.; Sovath, S.; Goode, J.; Alexopoulou, L.; Flavell, R. A.; Beutler, B. Toll-like receptores 9 and 3 as essential components of innate immune defense against mouse cytomegalovirus infection. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 3516−3521.

(5) Akira, S.; Uematsu, S.; Takeuchi, O. Pathogon recognition and innate immunity. *Cell* **2006**, *124*, 783−801.

(6) Lindau, D.; Ronnefarth, V.; Annika Erbacher, A.; Rammensee, H.-G.; Decker, P. Nucleosome-induced neutrophil activation occurs independently of TLR9 and endosomal acidification: Implications for systemic lupus erythematosus. *Eur. J. Immunol.* **2011**, *41*, 669−681.

(7) Jiang, W.; Zhu, F.-G.; Bhagat, L.; Yu, D.; Tang, J. X.; Kandimalla, E. R.; Monica, N. L.; Agrawal, S. A Toll-like receptor 7, 8, and 9 antagonist inhibits Th1 and Th17 responses and inflammasome activation in a model of IL-23-induced psoriasis. *J. Invest. Dermatol.* **2013**, *133*, 1777−1784.

(8) Miranda-Hernandez, S.; Baxter, A. G. Roll of toll-like receptors in multiple sclerosis. *Am. J. Clin. Exp. Immunol.* **2013**, *2*, 75−93.

(9) Hemmi, H.; Takeuchi, O.; Kawai, T.; Kaisho, T.; Sato, S.; Sanjo, H.; Matsumoto, M.; Hoshino, I.; Wagner, H.; Takeda, K.; Akira, S. A toll-like receptor recognizes bacterial DNA. *Nature* **2000**, *408*, 740−745.

(10) Plitas, G.; Burt, B. M.; Nguyen, H. M.; Bamboat, Z. M.; DeMatteo, R. P. Toll-like receptor 9 inhibition reduces mortality in polymicrobial sepsis. *J. Exp. Med.* **2008**, *205*, 1277−1283.

(11) Calcaterra, C.; Sfondrini, L.; Rossini, A.; Sommariva, M.; Rumio, C.; Menard, S.; Balsari, A. Critical role of TLR9 in acute graft-versus-host disease. *J. Immun.* **2008**, *181*, 6132−6139.

(12) Franklin, B. S.; Ishizaka, S. T.; Lamphier, M.; Gusovsky, F.; Hansen, H.; Rose, J.; Zheng, W.; Ataíde, M. A.; de Oliveira, R. B.; Douglas, T.; Golenbock, D. T.; Gazzinelli, R. T. Therapeutical targeting of nucleic acid-sensing Toll-like receptors prevents experimental cerebral malaria. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 3689−3694.

(13) Wang, D.; Bhagat, L.; Yu, D.; Zhu, F.-G.; Tang, J. X.; Kandimalla, E. R.; Agrawal, S. Oligodeoxyribonucleotide-based antagonists for toll-like receptors 7 and 9. *J. Med. Chem.* **2009**, *52*, 551−558.

(14) Hoque, R.; Farooq, A.; Kalik, A.; Trawick, B. N.; Berberich, D. W.; McClurg, J. P.; Galen, K. P.; Mehal, W. A novel small-molecule enantiomeric analogue of traditional (−)-morphinans has specific TLR9 antagonist properties and reduces sterile inflammation-induced organ damage. *J. Immun.* **2013**, *190*, 4297−4304.

(15) Takemura, S.; Nishiyama, T.; Tabunoki, Y.; Yamabi, M.; Kouketsu, A.; Tokuda, O.; Miyake, Y. Thiophene Derivative Having TLR-Inhibiting Activity. WO 2013161871, 2013.

(16) Bhagat, L.; Jiang, W.; Yu, D.; Arbeit, R.; Sullivan, T. Phase 1 clinical trial of IMO-8400, an antagonist of toll-like receptor 7, 8 and 9: Pharmacodynamic activity. *Annual Meeting of the Federation of Clinical Immunology Societies*, June 27−30, Boston, 2013; Abst S.85.

(17) Rutz, M.; Metzger, J.; Gellert, T.; Luppa, P.; Lipford, G. B.; Wagner, H.; Bauer, S. Toll-like receptor 9 binds single-stranded CpG-DNA in a sequence- and pH-dependent manner. *Eur. J. Immunol.* **2004**, *34*, 2541−2550.

(18) Parkinson, T. The future of toll-like receptor therapeutics. *Curr. Opin. Mol. Ther.* **2008**, *10*, 21−31.

(19) Christensen, S. R.; Shupe, J.; Nickerson, K.; Kashgarian, M.; Flavell, R. A.; Shlomchik, M. J. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity* **2006**, *25*, 417−428.

(20) Santiago-Raber, M. L.; Dunand-Sauthier, I.; Wu, T.; Li, Q. Z.; Uematsu, S.; Akira, S.; Reith, W.; Mohan, C.; Kotzin, B. L.; Izui, S. Critical role of TLR7 in the acceleration of systemic lupus erythematosus in TLR9-deficient mice. *J. Autoimmun.* **2010**, *34*, 339−348.

(21) Fukui, R.; Saitoh, S.-I.; Kanno, A.; Onji, M.; Shibata, T.; Ito, A.; Onji, M.; Matsumoto, M.; Akira, S.; Yoshida, N.; Miyake, K. Unc93B1 restricts systemic lethal inflammation by orchestrating toll-like receptor 7 and 9 trafficking. *Immunity* **2011**, *35*, 69−81.

(22) Liprd, G. B.; Zepp, C. M. Quinazoline Derivative Useful as Toll-Like Receptor Antagonist. WO 2008152471, 2008.

(23) Leeson, P. D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discovery* **2007**, *6*, 881−890.

(24) Ryckmans, T.; Edwards, M. P.; Horne, V. A.; Correia, A. M.; Owena, D. R.; Thompson, L. R.; Tran, I.; Tutt, M. F.; Young, T. Rapid assessment of a novel series of selective CB2 agonists using parallel synthesis protocols: A lipophilic efficiency (LipE) analysis. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4406−4409.

(25) Cheng, H.; Li, C.; Bailey, S.; Baxi, S. M.; Goulet, L.; Guo, L.; Hoffman, J.; Jiang, Y.; Jhonson, T. O.; Knighton, D. R.; Li, J.; Liu, K. K.-C.; Liu, Z.; Marx, M. A.; Walls, M.; Wells, P. A.; Yin, M.-J.; Zhu, J.; Zientek, M. Discovery of the Highly potent PI3K/mTOR dual inhibitor PF-04979064 through structure-based drug design. *ACS Med. Chem. Lett.* **2013**, *4*, 91−97.

(26) Johnson, T. W.; Tanis, S. P.; Butler, S. L.; Dalvie, D.; DeLisle, D. M.; Dress, K. R.; Flahive, E. J.; Hu, Q.; Kuehler, J. E.; Kuki, A.; Liu, W.; McClellan, G. A.; Peng, Q.; Plewe, M. B.; Richardson, P. F.; Smith, G. L.; Solowiej, J.; Tran, K. T.; Wang, H.; Yu, X.; Zhang, J.; Zhu, H. Design and synthesis of novel *N*-hydroxy-dihydronaphthyridinones as potent and orally bioavailable HIV-1 integrase inhibitors. *J. Med. Chem.* **2011**, *54*, 3393−3417.

(27) Ishikawa, M.; Hashimoto, Y. Improvement in aqueous solubility in small molecule drug discovery programs by disruption of molecular planarity and symmetry. *J. Med. Chem.* **2011**, *54*, 1539−1554.