

Discovery of 5-Amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide Inhibitors of IRAK4

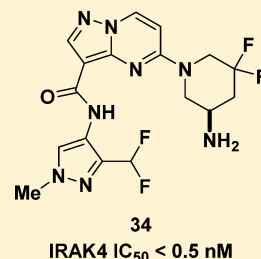
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## Supporting Information

**ABSTRACT:** Interleukin-1 receptor associated kinase 4 (IRAK4) is an essential signal transducer downstream of the IL-1R and TLR superfamily, and selective inhibition of the kinase activity of the protein represents an attractive target for the treatment of inflammatory diseases. A series of 5-amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamides was developed via sequential modifications to the 5-position of the pyrazolopyrimidine ring and the 3-position of the pyrazole ring. Replacement of substituents responsible for poor permeability and improvement of physical properties guided by cLogD led to the identification of IRAK4 inhibitors with excellent potency, kinase selectivity, and pharmacokinetic properties suitable for oral dosing.

**KEYWORDS:** IRAK4, 5-amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, SAR, serine-threonine kinase, kinase inhibitor, inflammatory disease



Interleukin-1 receptor associated kinase 4 (IRAK4) is an intracellular serine-threonine kinase that belongs to the IRAK family of kinases (IRAK1, IRAK2, IRAK-M, and IRAK4).<sup>1,2</sup> It has been demonstrated that IRAK4 is an essential signal transducer downstream of the interleukin-1 receptor (IL-1R) and toll-like receptor (TLR) superfamily that mediates the innate immune response by upregulating the expression of inflammatory genes in multiple target cells.<sup>3</sup> IRAK4<sup>-/-</sup> mice showed severe defects in cytokine responses and downstream signaling pathways induced by IL-1R and TLRs.<sup>4</sup> In addition, cells derived from IRAK4-deficient patients failed to induce downstream cytokines in response to known IL-1R and TLR ligands.<sup>5</sup> In view of the generic evidence of the critical role of IRAK4 in IL-1R and TLR signaling, IRAK4 could be an attractive target for the treatment of inflammatory diseases,<sup>6</sup> including rheumatoid arthritis (RA),<sup>7,8</sup> inflammatory bowel disease (IBD),<sup>9,10</sup> asthma,<sup>11</sup> and systemic lupus erythematosus (SLE).<sup>12</sup> In fact, the discovery of novel IRAK4 inhibitors has been actively pursued by many research groups, and various classes of IRAK4 inhibitors have been reported to date.<sup>13–19</sup>

In a high-throughput screening (HTS) campaign, *N*-(1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamides were identified as promising hits. Further exploration of the scaffold, including hybrids with known IRAK4 inhibitors,<sup>20</sup> led to the identification of *N*-(3-carbamoyl-1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**1**) as a lead. Compound **1** not only displayed attractive lead-like properties such as low molecular weight (285 g/mol), high ligand binding efficiency (LBE) (0.44), and moderate cell permeability ( $P_{app}$  =

$17 \times 10^{-6}$  cm/s) but also offered a good kinome profile (>100-fold selective against 89% of the kinases) (Table 1).

Herein we report a series of modifications to the 5-position of the pyrazolopyrimidine ring and the 3-position of the pyrazole ring of the *N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]-

Table 1. Key Properties of Compound 1

IRAK4 IC <sub>50</sub> (nM)	110
hPBMC IC <sub>50</sub> (nM)	2300
LBE	0.44
no. of kinases tested	101
% of kinases >100×	89 <sup>a</sup>
PSA (Å)	127
cLogD (pH 7.4)	-1.7 <sup>b</sup>
$P_{app}$ (10 <sup>-6</sup> cm/s)	17 <sup>c</sup>

<sup>a</sup>Fold selectivity against in-house IRAK4 IC<sub>50</sub>. <sup>b</sup>From ACD Labs v10. <sup>c</sup>From MDCK cells.

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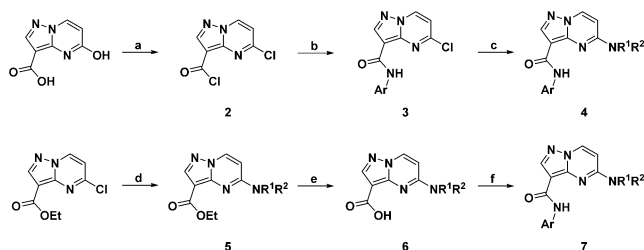
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pyrimidine-3-carboxamide core of **1**. The discovery of potent, selective, and bioavailable IRAK4 inhibitors through sequential improvements in cell permeability via cLogD-guided optimization of physical properties is described. In addition, initial results for a highly potent and kinome-selective IRAK4 inhibitor, **14**, in a rat pharmacodynamic (PD) model are reported.

Synthetic routes for the target molecules discussed in this communication are described in Scheme 1. Rapid derivatization

### Scheme 1. Synthesis of the 5-Aminopyrazolo[1,5-*a*]pyrimidine-3-carboxamides<sup>a</sup>



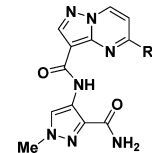
<sup>a</sup>(a) POCl<sub>3</sub>, Hünig's base, reflux; (b) ArNH<sub>2</sub>, Hünig's base, CH<sub>2</sub>Cl<sub>2</sub>; (c) R<sup>1</sup>R<sup>2</sup>NH, Hünig's base, EtOH, reflux; (d) R<sup>1</sup>R<sup>2</sup>NH, EtOH, reflux; (e) LiOH, THF/water; (f) ArNH<sub>2</sub>, HATU, Hünig's base, CH<sub>3</sub>CN.

at the 5-position of the pyrazolo[1,5-*a*]pyrimidine was realized via S<sub>N</sub>Ar reaction of the 5-chloropyrazolo[1,5-*a*]pyrimidine intermediates **3** with an array of amines. Compounds **3** were prepared from 5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid via chlorination with POCl<sub>3</sub> followed by amide formation with various arylamines. Alternatively, amines were introduced to ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate via S<sub>N</sub>Ar reaction. After saponification of esters **5**, acids **6** were coupled with various arylamines employing coupling reagents such as HATU for an efficient structure–activity relationship (SAR) study on the arylamides.

Crystal structures of the IRAK4 kinase domain in the literature<sup>21,22</sup> hinted that hydrogen-bond donors growing from the 5-position of the pyrazolopyrimidine ring might have positive interactions with the carboxylate of Asp329 and thereby improve the intrinsic potency. Our initial SAR efforts were directed toward introducing various substituents bearing hydrogen-bond donors at this position to improve the IRAK4 potency. When straight chains were examined, it was found that neither the 3-aminopropyl analogue **8** nor the 2-aminoethoxy analogue **9** was more potent than **1** (Table 2). On the other hand, the 2-aminoethylamino analogue **10** showed a greater than 50-fold potency improvement. The stark difference in potency among **8**, **9**, and **10** is presumably due to the different trajectories of the substituents in the binding pocket, with the amino linker of **10** positioning the terminal amine toward Asp329 while the methylene linker of **8** and the ether linker of **9** do not.

We next explored various cycloalkyl groups in place of the ethylene moiety of the 2-aminoethylamino analogue **10** (Table 2). Compared with **10**, the cyclopentane-1,2-diamine analogues showed a greater than 10-fold loss of potency even when the most potent enantiomer of **11** was assumed to exclusively contribute to the potency. It was found that *trans*-cyclohexane-1,2-diamine **12** and (1*S*,2*R*)-cyclohexane-1,2-diamine **13** were 10- and 4-fold less potent, respectively. On the other hand, a 7-fold potency improvement was achieved with **14** bearing the

Table 2. Initial SAR of Amines at the 5-Position of the Pyrazolopyrimidine Ring



	R	IRAK4 IC <sub>50</sub> (nM)	PSA (Å <sup>2</sup> )	cLogD <sup>d</sup>	P <sub>app</sub> (x 10 <sup>-6</sup> cm/s) <sup>e</sup>
<b>1</b>	H	110	127	-1.7	17
<b>8</b>		150	154	-4.3	< 2
<b>9</b>		9,200	162	-3.3	ND <sup>d</sup>
<b>10</b>		2	166	-4.8	ND <sup>d</sup>
<b>11</b>		95	155	-5.1	ND <sup>d</sup>
<b>12<sup>c</sup></b>		20	156	-4.3	ND <sup>d</sup>
<b>13</b>		8	153	-4.3	< 2
<b>14</b>		0.3	152	-4.3	2 <sup>c</sup>

<sup>a</sup>At pH 7.4 from ACD Labs v10. <sup>b</sup>From MDCK cells. <sup>c</sup>A racemic mixture. <sup>d</sup>ND = not determined. <sup>e</sup>From LLC-PK1 cells.

(1*R*,2*S*)-cyclohexane-1,2-diamine at the 5-position of the pyrazolopyrimidine ring (IC<sub>50</sub> = 0.3 nM).

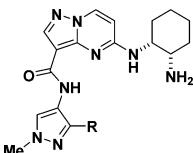
As envisioned, the IRAK4 potency was greatly improved by introducing optimal diamines at the 5-position of the pyrazolopyrimidine ring, as in **10** and **14**. However, the polarity of the molecules was much higher, as indicated by the polar surface area (PSA) and cLogD<sup>23,24</sup> values for **10** (PSA = 166 Å<sup>2</sup>, cLogD = -4.8) and **14** (PSA = 152 Å<sup>2</sup>, cLogD = -4.3) compared with those of **1** (PSA = 127 Å<sup>2</sup>, cLogD = -1.7) (Table 2), because of the added high intrinsic polarity of the diamines. As a result of the high polarity, these molecules displayed poor passive permeability (P<sub>app</sub> < 5 × 10<sup>-6</sup> cm/s).<sup>25</sup> More importantly, the oral bioavailability correlated well with the membrane permeability of the molecules in this series in pharmacokinetic (PK) studies in rats.<sup>26</sup> Accordingly, none of the molecules with high polarity in this series offered oral bioavailability even though they showed moderate plasma clearance (Cl<sub>p</sub>), which made them unsuitable for oral dosing (see the Supporting Information).

Diamines at the 5-position of the pyrazolopyrimidine ring not only account for high intrinsic potency but also are responsible for poor bioavailability in rats. It was quite challenging to lower polarity of the molecules to obtain high permeability and good oral bioavailability while maintaining high IRAK4 potency. Our strategy was to identify the substituents responsible for the poor membrane permeability and low bioavailability and to find replacements through SAR studies to optimize the polarity as well as the potency. To this end, we examined the company database of historic molecules and found that the carboxamide group was frequently seen in molecules with poor permeability. Next, with (1*R*,2*S*)-cyclohexane-1,2-diamine at the 5-position of the pyrazolopyrimidine

ring, we explored carboxamide replacements that historically offered improved membrane permeability.

Although replacements of the carboxamide group with hydrogen (**15**) or a methoxymethyl group (**16**) decreased the PSA by 42 and 36 Å<sup>2</sup>, respectively, both compounds displayed poor membrane permeability (Table 3). However, replace-

Table 3. Carboxamide Replacements



	R	IRAK4 IC <sub>50</sub> (nM)	PSA (Å <sup>2</sup> )	cLogD <sup>a</sup>	P <sub>app</sub> (x 10 <sup>-6</sup> cm/s) <sup>b</sup>
<b>14</b>		0.3	152	-4.3	2
<b>15</b>	H	14	110	-3.9	< 2
<b>16</b>		6	116	-4.2	2
<b>17</b>		0.8	134	-4.2	17
<b>18</b>		0.3	106	-2.8	16
<b>19</b>		0.2	107	-3.6	13
<b>20</b>		2	104	-2.7	18
<b>21</b>		6	151	-3.8	2
<b>22</b>		62	121	-2.4	1
<b>23</b>		160	136	-3.6	3

<sup>a</sup>At pH 7.4 from ACD Labs v10. <sup>b</sup>From MDCK cells.

ments with nitrile, trifluoromethyl, difluoromethyl, and pentafluoroethyl groups (**17–20**, respectively) offered moderate membrane permeability, with P<sub>app</sub> values in the range of (13–18) × 10<sup>-6</sup> cm/s, even though their PSA values are in the same range as those of **15** and **16**. Gratifyingly, the intrinsic IRAK4 potency was maintained, especially for **18** and **19** (IC<sub>50</sub> = 0.3 and 0.2 nM, respectively). Carboxamide replacements with some heterocyclic groups that historically offered permeability improvements failed to improve the membrane permeability in our case (**21–23**).

An X-ray cocrystal structure of **18** bound to the kinase domain of IRAK4 revealed the expected mode of binding (Figure 1). The (2*S*)-amino group is in the axial position of the cyclohexane, and it interacts with the side-chain amide oxygen of Asn316 and, with the (1*R*)-amino group, donates a hydrogen-bonding interaction to the side-chain carboxylate of Asp329. The pyrazolopyrimidine core interacts at an angle with the phenol side-chain of the gatekeeper residue, Tyr262. There is a single polar hinge interaction provided by the amide oxygen with the backbone NH of Met265. The CF<sub>3</sub> group stacks intramolecularly with the cyclohexyl ring on the other side of the compound.

Encouraged by the permeability improvements with some carboxamide replacements such as CF<sub>3</sub> and CHF<sub>2</sub> groups, we next looked for calculated values for the molecules that offer a good correlation with measured membrane permeability so that

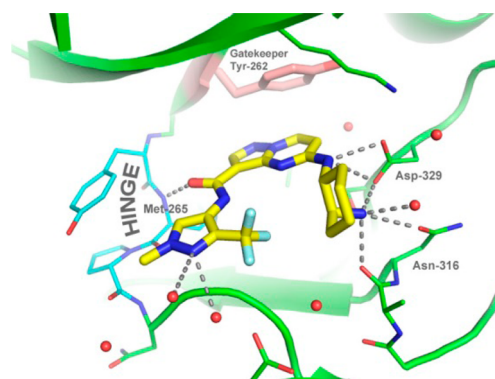


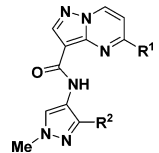
Figure 1. X-ray crystal structure of **18** bound to IRAK4.

we could prioritize target molecules on the basis of the calculated values and efficiently drive our SAR efforts. To this end, we plotted all of the P<sub>app</sub> values of compounds in this series versus calculated values such as PSA, cLogD, and LogP (see the Supporting Information). It was found that P<sub>app</sub> correlated reasonably well with cLogD<sup>23</sup> with a minimal number of outliers. Accordingly, we focused our SAR efforts on improving the cLogD value while maintaining high IRAK4 potency.

As previously discussed, diamines at the 5-position of the pyrazolopyrimidine ring account for the high polarity and poor membrane permeability of the molecules. Having identified promising carboxamide replacements, we next explored an array of diamines at the 5-position of the pyrazolopyrimidine ring with either CF<sub>3</sub> or CHF<sub>2</sub> at the 3-position of the pyrazole ring to further improve the membrane permeability (Table 4). As expected, removal of the primary amine offered much higher cLogD and P<sub>app</sub> values (**24**, cLogD = 1.2, P<sub>app</sub> = 23 × 10<sup>-6</sup> cm/s). However, **24** suffered from greater than 1000-fold loss of potency compared with **18**, confirming that a hydrogen-bond donor is required for high IRAK4 potency. The (1*R*,2*S*)-2-hydroxycyclohexylamine analogues **25** and **26** also displayed much higher cLogD and P<sub>app</sub> values, but they were intrinsically less potent than **18** and **19** by 70-fold and 25-fold, respectively. A piperazine group was also pursued, since piperazine is less basic than cyclohexane-1,2-diamine (ACD Labs pK<sub>a</sub> = 9.8 and 8.5 for **18** and **27**, respectively), thereby increasing the cLogD value. As expected, piperazines **27** and **28** displayed higher cLogD values by 1.5 units and high membrane permeabilities (P<sub>app</sub> = 29 × 10<sup>-6</sup> and 24 × 10<sup>-6</sup> cm/s for **27** and **28**, respectively). Potency loss was also observed for **27** and **28** compared with **18** and **19**, albeit to a lesser extent. It was generally observed that the CHF<sub>2</sub> analogues offered higher intrinsic IRAK4 potency and comparable membrane permeability compared with the corresponding CF<sub>3</sub> analogues, as seen with (1*R*,2*S*)-cyclohexane-1,2-diamine, (1*R*,2*S*)-2-hydroxycyclohexylamine, and piperazine groups on the pyrazolopyrimidine ring (**18**, **19**, **25**, **26**, **27**, and **28** in Table 4).

As fluorine atoms β, γ, or δ to a basic nitrogen would reduce the basicity of the nitrogen, increase the cLogD value, and potentially improve the metabolic stability of the molecule, fluorine atoms at various positions of the promising amines on the pyrazolopyrimidine ring were explored (Table 4). Compared with **18** and **19**, the 3,3-, 4,4-, and 5,5-difluoro analogues (**29–32**) showed improved high membrane permeability (P<sub>app</sub> ≥ 20 × 10<sup>-6</sup> cm/s). It was observed that the IRAK4 potency deteriorated as the carbon atoms bearing

Table 4. SAR of Diamines at the 5-Position of the Pyrazolopyrimidine Ring



	R <sup>1</sup>	R <sup>2</sup>	IRAK4 IC <sub>50</sub> (nM)	cLogD <sup>a</sup>	P <sub>app</sub> (x 10 <sup>-6</sup> cm/s) <sup>b</sup>
18			0.3	-2.8	16
19			0.2	-3.6	13
24			480	1.2	23
25			21	-0.6	26
26			4	-1.3	32
27			10	-1.3	29
28			1	-2.1	24
29			23	-1.0	29
30			13	-1.8	29
31 <sup>c</sup>			3	-2.0	26
32 <sup>c</sup>			3	-2.8	20
33 <sup>c</sup>			1	-2.0	25
34 <sup>c</sup>			< 0.5	-2.8	30 <sup>d</sup>
35			0.5	-2.6	31
36 <sup>c</sup>			6	-2.0	28

<sup>a</sup>At pH 7.4 from ACD Labs v10. <sup>b</sup>From MDCK cells. <sup>c</sup>Absolute stereochemistry unknown. <sup>d</sup>From LLC-PK1 cells.

fluorine atoms were closer to the basic amine. The (3*R*)-3-aminopiperidine analogues with fluorine atoms at the 5*S*-, (5*R*)-, and (4*S*)-positions (**33**–**36**) displayed not only high membrane permeability ( $P_{app} \geq 25 \times 10^{-6}$  cm/s) but also high

IRAK4 intrinsic potency, especially in the case of **33**, **34**, and **35** ( $IC_{50} \leq 1$  nM).

Throughout the SAR studies, IRAK4 inhibitors with high intrinsic potency were evaluated in both human peripheral blood mononuclear cell (hPBMC) assay and rat whole-blood (rWB) assay to assess their cell activities. The kinome selectivity profile was also closely monitored against a broad panel of kinases (101 or 264 kinases) for key IRAK4 inhibitors in order to assess potential in vivo adverse events caused by inhibition of off-target kinases. Key inhibitors with high passive permeability in Table 4 were dosed to rats in standard iv/po dosing protocols to evaluate their PK properties.

Compounds **14** and **18**, which displayed low to moderate passive permeability ( $P_{app} = 2 \times 10^{-6}$  and  $16 \times 10^{-6}$  cm/s, respectively), were poorly bioavailable in rats ( $F = 0$  and 5%, respectively; Table 5). On the other hand, the highly permeable compounds **25**, **26**, **29**, **30**, and **34** ( $P_{app} = (26\text{--}32) \times 10^{-6}$  cm/s) offered significantly improved bioavailability in the range of 24–49% in rats. The (1*R*,2*S*)-2-hydroxycyclohexylamine analogues **25** and **26**, however, showed a moderate erosion in kinase selectivity compared with **14** and **18**, and **25** suffered from a loss of rat whole-blood potency. Balanced properties in cell potency, kinase selectivity, and PK properties were observed with the (1*R*,2*R*)-2-amino-3,3-difluorocyclohexylamine analogues **29** and **30** and the (3*R*)-3-amino-5,5-difluoropiperidine analogue **34**. They offered good rat whole-blood potency, excellent kinase selectivity, and moderate  $Cl_p$  and good bioavailability in rats suitable for oral in vivo studies.

On the basis of its excellent rat whole-blood potency ( $IC_{50} = 300$  nM) and kinase selectivity profile (>100-fold selective against 99% of the 264 kinases tested) (Table 5), compound **14** was chosen for in vivo proof-of-mechanism studies before orally active compounds were available. In this in vivo model, female Lewis rats were dosed with either vehicle or compound **14** subcutaneously at 3, 10, 30, and 50 mg/kg 1 h prior to stimulation with R848 (5 mg/kg, ip), a TLR7 agonist. At 1.5 h post R848 stimulation, blood samples were obtained from the animals and cytokine levels were measured (Figure 2). The IL-6 level increased markedly in vehicle-treated animals in response to stimulation with R848. Rats dosed with **14**, however, showed inhibition of IL-6 secretion in a dose-dependent manner compared with vehicle-treated animals. It is noteworthy that the percent inhibition of IL-6 and terminal exposure of **14** in this in vivo study correlated well with the rat whole-blood potency of **14** (Figure 2).

In summary, the development of a series of 5-amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamides as IRAK4 inhibitors was achieved via sequential modifications to the 5-position of the pyrazolopyrimidine ring and the 3-position of the pyrazole ring. While the intrinsic potency was markedly improved when diamines were introduced at the 5-position of the pyrazolopyrimidine ring, the passive permeability and bioavailability of this series were initially poor. Replacement of the substituents responsible for the poor permeability and improvement of the physical properties guided by cLogD led to the identification of IRAK4 inhibitors with excellent potency, kinase selectivity, and PK properties suitable for oral dosing. Robust PK/PD response in the R848-induced rat model was observed with compound **14** in a dose-dependent manner.

Table 5. Cell Potencies, Kinase Selectivities, and Pharmacokinetic Profiles of Selected IRAK4 Inhibitors

compd	hPBMC IC <sub>50</sub> (nM)	rWB IC <sub>50</sub> (nM)	no. of kinases tested	% of kinases >100× <sup>a</sup>	rat Cl <sub>p</sub> (mL min <sup>-1</sup> kg <sup>-1</sup> ) <sup>b</sup>	rat %F <sup>c</sup>
14	31	300	264	99	56	0
18	9	89	101	96	98	5
25	130	5500	101	91	41	26
26	53	500	101	87	45	49
29	310	590	101	100	48	24
30	320	890	101	94	29	46
34	12	81	101	>95	46	42

<sup>a</sup>Fold selectivity against in-house IRAK4 IC<sub>50</sub>. <sup>b</sup>Dosed iv at 0.5 mg/kg as a solution in DMSO/PEG400/H<sub>2</sub>O (20:40:20 v/v/v). <sup>c</sup>Dosed po at 1 mg/kg as a solution in DMSO/PEG400/H<sub>2</sub>O (20:40:20 v/v/v).

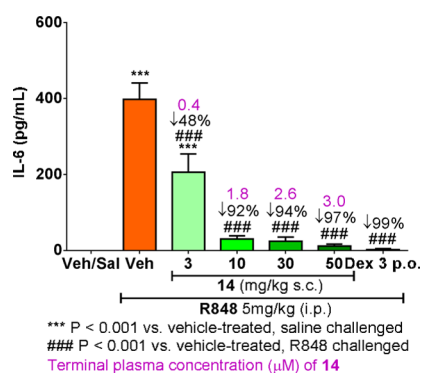


Figure 2. Effect of compound 14 on the IL-6 level in an R848-induced rat PD model.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic procedures and analytical data of selected compounds, conditions for all of the biological assays, PK profiles of 13 and 14, X-ray statistics for 18, and  $P_{app}$  plots. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00107.

### Accession Codes

The PDB code for 18 is 4Y73.

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### Notes

The authors declare no competing financial interest.

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