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4-(2-Pyridyl)piperazine-1-carboxamides: Potent Vanilloid Receptor 1 Antagonists

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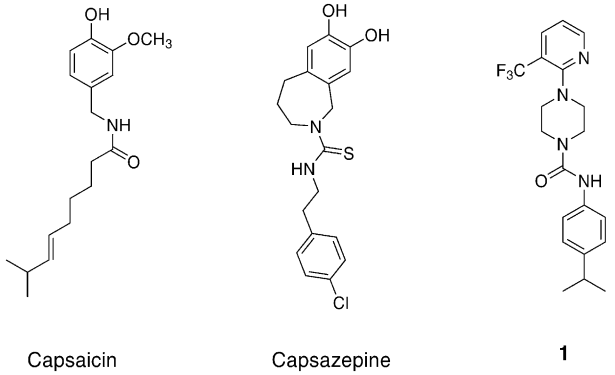
Abstract—A series of 4-(2-pyridyl)piperazine-1-carboxamide analogues based on the lead compound **1** was synthesized and evaluated for VR1 antagonist activity in capsaicin-induced (CAP) and pH (5.5)-induced (pH) FLIPR assays in a rat VR1-expressing HEK293 cell line. Potent VR1 antagonists were identified through SAR studies. From these studies, **18** was found to be very potent in the in vitro assay [$IC_{50} = 4.8$ nM (pH) and 35 nM (CAP)] and orally available in rat (F% = 15.1).

Vanilloid receptor 1, VR1, is a member of the transient receptor potential (TRP) ion channel family.[1] It functions as a ligand-gated nonselective cation channel activated by capsaicin (CAP), the pungent principle of hot peppers.[2] In humans, activation of VR1 by CAP results in a sensation of burning pain. VR1 is also activated by noxious heat (≥42 °C), low extracellular pH (≤6.3),[3,4] and endogenous mediators of inflammation such as the cannabanoid anandamide as well as arachidonic acid metabolites.[5] Knockout of the VR1 gene in mice results in reductions in both thermal nociception and thermal hyperalgesia.[6,7] These data suggest that VR1 may represent a useful target for the discovery of novel analgesics.

Several classes of compounds have been shown to have biological activity at VR1.[8,9] Structurally-related vanilloid analogues of CAP such as olvanil and resiniferatoxin (RTX) are VR1 agonists. In particular, RTX has a potency three or four orders of magnitude greater than that of CAP. The synthetic vanilloid analogue, capsazepine (CPZ), is a competitive VR1 antagonist that has been well characterized.[10] However, capsazepine has several drawbacks such as moderate potency, poor metabolic and pharmacokinetic properties, undergoing extensive first-pass metabolism when dosed orally to rodents. More recently, several new classes of VR1 antagonists have been reported in the literature with moderate potencies at human and rat VR1 against CAP-mediated activation.[11,12] The chemical structures of capsaicin and capsazepine are shown in Figure 1.

In this paper, we report for the first time a series of 4-(2-pyridyl)piperazine-1-carboxamides as potent VR1 antagonists. The synthesis of similar chemical structures was recently described in a US patent application and these compounds were claimed to be VR1 antagonists, although no supporting data was presented.[13] A similar class of compounds as VR1 antagonists was also disclosed at a recent conference.[14] Our work was initiated



Capsaicin Capsazepine 1

Figure 1. Structures of capsaicin, capsazepine, and compound **1**.

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when compound **1** (Fig. 1) was discovered as a potent VR1 antagonist through our internal high-throughput screening efforts. Similar to CPZ, this compound inhibited CAP-induced activation of rat VR1 with an IC_{50} value of 58 nM. Moreover, compound **1** was found to be a potent antagonist against acid-induced activation of rat VR1 (IC_{50} value: 39 nM), while CPZ was inactive. However, further pharmacokinetic (PK) studies indicated that **1** was not orally bioavailable in rat. Thus we initiated a medicinal chemistry effort aimed to explore the SAR of this lead molecule as a VR1 antagonist and improve the oral bioavailability.

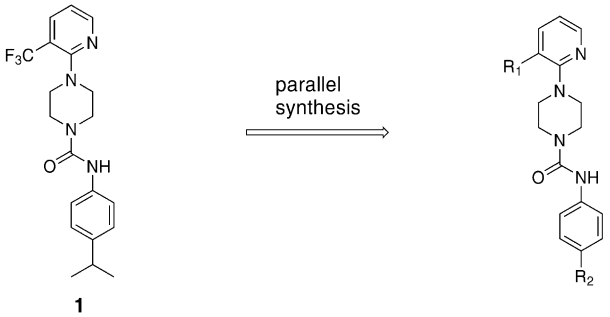
The synthesis of compound **1** is highly amenable to parallel synthesis as an efficient way to prepare analogues. Our initial strategy was to synthesize analogues with modifications to the CF_3 group on the pyridine ring and the isopropyl group on the *para* position of the phenyl ring (Scheme 1). Most of the compounds in Tables 1–3 were synthesized via method A (Scheme 2). It was started by reacting the piperazine with different 3-substituted 2-chloropyridines at 100 °C in DMSO to form the intermediate 4-(2-pyridyl)piperazines. The 4-(2-pyridyl)piperazines were then reacted with a variety of isocyanates or isothiocyanates to give the final products. In both steps, the reactions were run in parallel.

When the desired isocyanates were not readily available, method B (Scheme 3) was used to prepare compounds **20**, **23**, and **31**. It involved reacting an aniline or amine with 4-nitrophenylchloroformate in dichloromethane (DCM) with triethylamine (TEA) as base to form the reactive 4-nitrophenylcarbamate intermediate. Without isolation, 4-(3-chloropyridin-2-yl)piperazine was added to the reaction mixtures to yield the final products.

Compounds **15**, **16**, and **17** were prepared through the route described in Scheme 4. The synthesis started with compound **9**, which was prepared using method A. Treatment of compound **9** with DIBAL at 0 °C in toluene/THF afforded compound **17**. Reacting compound **17** with DAST in DCM gave the difluoromethylpyridine analogue **16**. Compound **17** was also subjected to a Wittig reaction to give the 3-vinylpyridine intermediate, which was reduced with H_2 on Pd/C to afford the 3-ethylpyridine analogue **15**.

All final compounds were purified to >97%. The purity of the compounds **2**–**31** was determined by RP-HPLC and correct molecular weight was confirmed by mass spectrometry (LC/MS with an electrospray sample inlet system).[15] Structures were further confirmed by ^1H NMR spectroscopy.[16]

The compounds were evaluated for VR1 antagonist activity based on their ability to block CAP-induced activation or low pH-induced activation of the rat VR1 channel in a HEK293 cell line. The tests were carried out measuring CAP- or pH-mediated calcium influx with a Fluorometric Imaging Plate Reader (FLIPR).



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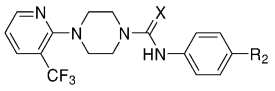
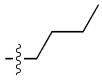
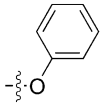
Scheme 1. Parallel synthesis of the analogues of compound **1**.

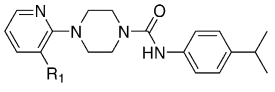
Table 1. 4-Substituents on phenyl ring and linker variation



No.	R_2	X	IC_{50} (nM) pH	IC_{50} (nM) CAP
1		O	39.2±8.0	57.5±13.1
2		O	121±41	111±42
3		O	1551±550	556±220
4		O	5181±2354	1365±635
5		O	57.7±15.1	11.3±4.1
6		O	916±373	258±57
7		S	575±191	872±215
8		S	441±55	246±112

IC_{50} values are the mean±SEM of at least three determinations.

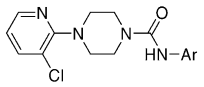
Table 2. 3-Substituents on pyridyl ring

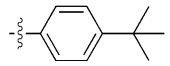
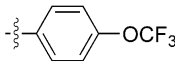
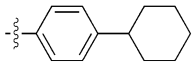
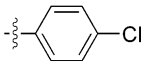
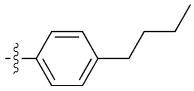
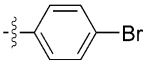
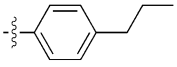
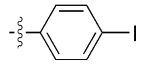
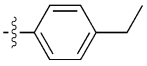
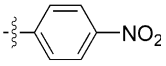
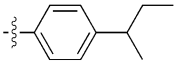
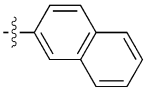
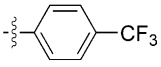
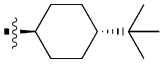


No.	R_1	IC_{50} (nM) pH	IC_{50} (nM) CAP
1	$-CF_3$	39.2±8.0	57.5±13.1
9	–CN	>25,000	287±90
10	$-NO_2$	245±21	190±50
11	–Cl	17.3±7.2	11.5±3.4
12	–Br	27.1±11.4	4.6±1.0
13	–I	77.4±19.9	56.7±15.3
14	$-CH_3$	173±82	25.3±7.0
15	$-CH_2CH_3$	828±414	230±96
16	$-CHF_2$	61.5±18.2	27.7±8.5
17	–CHO	1400±856	201±49

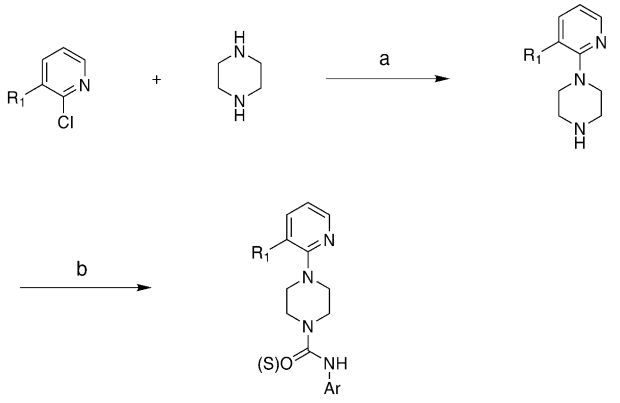
IC_{50} values are the mean±SEM of at least three determinations.

Table 3. Aryl modifications

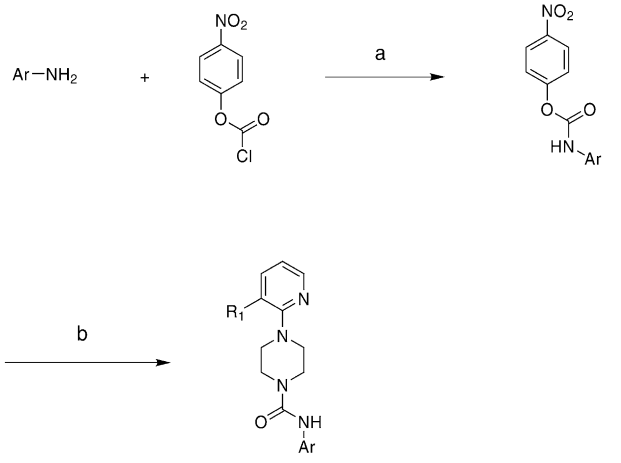


No.	Ar	IC_{50} (nM) pH	IC_{50} (nM) CAP	No.	Ar	IC_{50} (nM) pH	IC_{50} (nM) CAP
18		4.8±2.5	34.9±19.4	**25**		261±39	93.2±15.5
19		91.7±18.3	29.8±13.6	**26**		2669±1386	655±210
20		203±81	117±58	**27**		1010±585	491±121
21		73±50	41.6±26.8	**28**		310±141	285±75
22		56.6±31.7	107±11.3	**29**		>25,000	1106±521
23		23.3±12.3	17.4±7.6	**30**		278±123	479±230
24		81.4±48.0	63.5±9.3	**31**		17.2±2.9	3.9±1.6

IC_{50} values are the mean±SEM of at least three determinations.



Scheme 2. Reagents and conditions for method A: (a) DMSO, 100 °C, 6 h; (b) Ar-NCO or Ar-NCS, DCM, rt, 2 h.

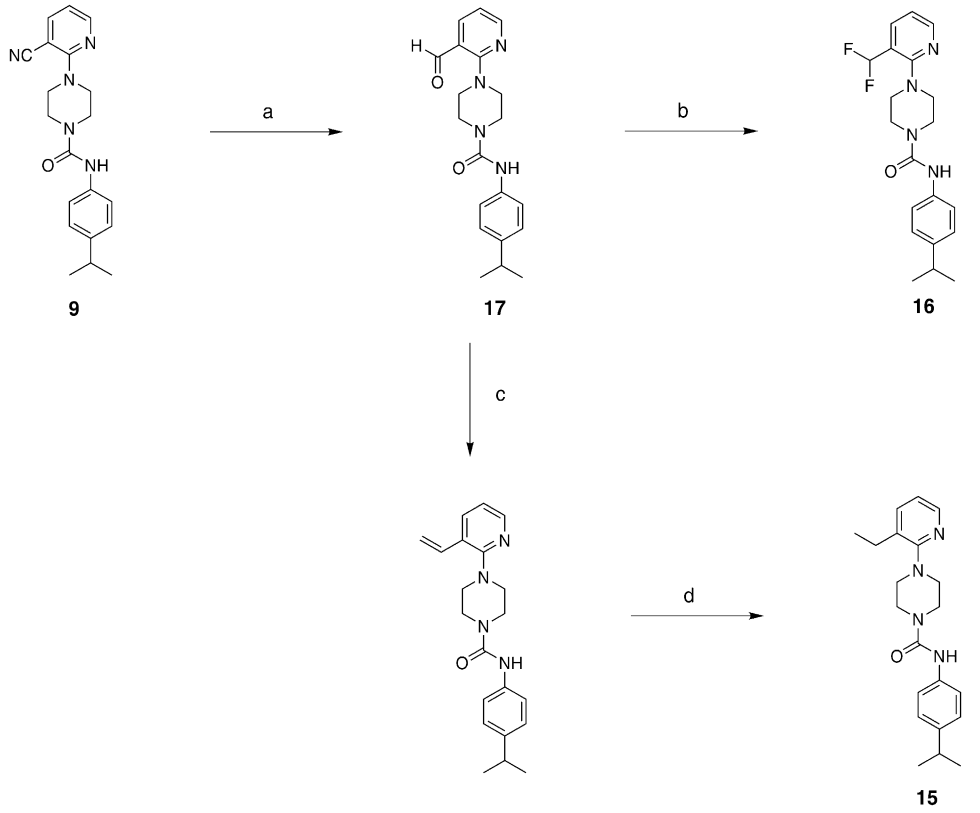


Scheme 3. Reagents and conditions for method B: (a) DCM, TEA, rt, 10 min; (b) 4-(2-pyridyl)piperazine, DCM, rt, 2 h.

Either 100 nM CAP or pH 5.5 were used as agonists for the respective assays.

Our initial SAR study was focused on modifying the 4-substituent on the phenyl ring of our lead compound **1**. The IC_{50} values in both pH and CAP assays for compounds **1**–**8** are shown in Table 1. The 4-*t*-butyl analogue **5** had similar activity [IC_{50} = 58 nM (pH) and 11 nM (CAP)] compared to compound **1**, whereas the 4-ethyl derivative **2** was slightly less potent and the 4-methyl and 4-*n*-butyl analogues **3** and **4** were very weak VR1 antagonists, suggesting that the *i*-propyl and *t*-butyl substituents were probably optimized substituents in term of size and shape among the alkyl groups. Substituting a phenoxy group at the 4-position of the phenyl ring also decreased the potency (analogue **6**). Replacing the urea linker in compound **1** with a thiourea group (compounds **7** and **8**) caused a reduction in activity in both pH and CAP assays.

In parallel to the modification of the 4-substituent on the phenyl ring, the SAR of the 3-position of the pyridine moiety of **1** was also explored. The IC_{50} values in both pH and CAP assays for compounds **9**–**17** are shown in Table 2. Adding more polar substituents, such as –CN, $-NO_2$, or –CHO, to replace 3-CF_3 group on the



Scheme 4. Reagents and conditions: (a) DIBAL, toluene/THF, 0 °C, 16 h; (b) DAST, DCM, rt, 24 h; (c) $CH_3P(Ph)_3Br$, *t*-BuOK, THF, rt, 16 h; (d) H_2, Pd/C, MeOH, rt, 1 h.

Table 4. PK parameters of compound **18** following single 3 mg/kg iv and 40 mg/kg oral dose

Vz	5.8 L/kg
CL	4.6 L/h/kg
$t_{1/2}$	0.9 h
F%	15.1

pyridine fragment significantly reduced the activity, especially in the pH assay (compounds **9**, **10** and **17**). 4-Halo-substituted analogues **11**, **12**, and **13** were very potent VR1 antagonists. In particular, 4-Cl derivative **11** and 4-Br analogue **12** were found to be more potent than compound **1** [$IC_{50} = 17$ nM (pH) and 12 nM (CAP) for compound **11**; 27 nM (pH) and 4.6 nM (CAP) for compound **12**]. 3-Methyl analogue **14** and 3-CHF_2 derivative **16** showed good potency. However, adding a more bulky ethyl group to the 3-position of pyridine moiety dramatically reduced activity. 3-Ethyl analogue **15** was 5–10-fold less potent than 3-methyl derivative **14**. The preliminary SAR study on the 3-position of the pyridine fragment suggested that relatively non-polar and smaller substituents, such as Cl, were preferred in this position.

Having optimized the 3-position of the pyridine fragment, attention was turned to further explore the SAR of the phenyl moiety in compound **1**. All the compounds prepared in this series had a 3-Cl substituent on the pyridine ring. The IC_{50} values in both pH and CAP assays for these compounds are shown in Table 3. Compounds **18**–**23** varied alkyl substituents, from an ethyl group to a cyclohexyl group, on the 4-position of the phenyl ring. While all six compounds were potent analogues, compound **18** with a *t*-butyl substituent was the most potent in the VR1 pH assay ($IC_{50} = 4.8$ nM). 4-CF_3 Phenyl derivative **24** was quite potent in both VR1 FLIPR assays [$IC_{50} = 81$ nM (pH) and 64 nM (CAP)], whereas compound **25** with a more polar 4-OCF_3 substituent on the phenyl ring reduced the potency, particularly in the pH assay. Adding a more polar 4-nitro group to the phenyl ring totally abolished activity in the pH assay (compound **29**), suggesting that hydrophobic substituents at the 4-position of the phenyl ring are important for activity. Different halo groups were also tried at the 4-position of the phenyl ring (compounds **26**, **27**, and **28**). The 4-I phenyl analogue **28** was the most potent [$IC_{50} = 310$ nM (pH) and 285 nM (CAP)]. The activity was observed to decrease with decreasing size, 4-I versus 4-Cl substituent. Two other compounds (**30** and **31**) were synthesized using a 2-naphthyl group and a *trans*-4-*t*-butyl-cyclohexyl group to replace the phenyl moiety. The *trans*-4-*t*-butyl-cyclohexyl analogue **31** was found to be a very potent compound [$IC_{50} = 17$ nM (pH) and 3.9 nM (CAP)], whereas the 2-naphthyl compound **30** showed reduced potency.

Compound **18** was one of the most potent analogues [$IC_{50} = 4.8$ nM (pH) and 35 nM (CAP)] found from our SAR studies. This compound is approximately 10-fold more potent in the pH assay and slightly more potent in the CAP assay compared to compound **1**. Thus **18** was

selected for in vivo pharmacokinetic (PK) study in rat. The in vivo profile of **18** is summarized in Table 4. The PK study was designed to estimate systemic drug exposure following a single 3 mg/kg iv and 40 mg/kg po administration to rats. Following IV administration of 3 mg/kg, compound **18** showed a moderate terminal half life ($t_{1/2}=0.9$ h), due to its relatively rapid clearance (CL = 4.6 L/h/kg). Following oral administration of 40 mg/kg, compound **18** was rapidly absorbed ($T_{max}=0.5$ h, $C_{max}=1116$ ng/mL). More importantly, the oral dosing confirmed that **18** was orally bioavailable ($F\%=15.1$), which was clearly lacking in the initial lead **1**.

In summary, we have prepared a series of VR1 antagonists based on the lead compound **1**. The SAR studies promptly led to a potent and orally available VR1 antagonist **18**, which might aid in the elucidation of the role of the VR1 receptor in the pain pathway and determine the therapeutic potential of VR1 antagonists as analgesics.[17] Further in vivo studies of **18** in different rat pain models will be the subject of future publications.

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15. LC–MS was performed on an Agilent Series 1100 MSD instrument with an electrospray sample inlet system. HPLC profile generated on an Eclipse XDB-C18 rapid resolution 4.6×50 mm column with a gradient of 85:15 to 10:90 of 0.1% TFA/acetonitrile with 0.1% TFA and UV detection at 260 nm.
16. NMR data for compounds **2**–**31**: **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, 1H), 7.90 (dd, 1H), 7.27 (d, 2H), 7.12 (d, 2H), 7.06 (dd, 1H), 6.34 (br s, 1H), 3.66–3.62 (m, 4H), 3.36–3.32 (m, 4H), 2.61 (q, 2H), 1.22 (t, 3H). **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, 1H), 7.90 (dd, 1H), 7.26 (dd, 2H), 7.10 (d, 2H), 7.06–7.04 (m, 1H), 6.32 (s, 1H), 3.63 (t, 4H), 3.35 (t, 4H), 2.30 (s, 3H). 4: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, 1H), 7.92 (dd, 1H), 7.28 (d, 2H), 7.13 (d, 2H), 7.07 (dd, 1H), 6.32 (br s, 1H), 3.68–3.64 (m, 4H), 3.39–3.34 (m, 4H), 2.58 (t, 2H), 1.61–1.53 (m, 2H), 1.41–1.32 (m, 2H), 0.93 (t, 3H). **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (t, 1H), 7.89–7.88 (m, 1H), 7.45–7.42 (m, 4H), 7.13–7.11 (m, 1H), 6.42 (s, 1H), 3.71–3.70 (m, 4H), 3.31–3.30 (m, 4H), 1.31 (s, 9H). **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, 1H), 7.90 (dd, 1H), 7.35–7.29 (m, 4H), 7.09–7.04 (m, 2H), 7.00–6.96 (m, 4H), 6.35 (br s, 1H), 3.68–3.64 (m, 4H), 3.37–3.33 (m, 4H). **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H), 7.90 (dd, 1H), 7.19 (br s, 1H), 7.18 (d, 2H), 7.10 (d, 2H), 7.04 (dd, 1H), 3.99–3.95 (m, 4H), 3.41–3.36 (m, 4H), 2.94–2.84 (m, 1H), 1.24 (d, 6H). **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, 1H), 7.89 (dd, 1H), 7.36 (d, 2H), 7.25 (br s, 1H), 7.10 (d, 2H), 7.05 (dd, 1H), 3.99–3.96 (m, 4H), 3.40–3.37 (m, 4H), 1.31 (s, 9H). **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (t,1H), 7.85 (t, 1H), 7.35–7.32 (m, 2H), 7.25–7.22 (m, 2H), 6.86–6.83 (m, 1H), 6.35 (s, 1H), 3.86–3.84 (m, 4H), 3.73–3.70 (m, 4H), 2.98–2.90 (m, 1H), 1.31 (s, 6H). **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.15 (d, 1H), 7.23–7.20 (m, 3H), 6.76–6.74 (m, 1H), 6.25 (s, 1H), 3.64–3.61 (m, 4H), 3.53–3.50 (m, 4H), 2.97–2.91 (m, 1H), 1.31 (s, 6H). **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br d, 1H), 7.62 (d, 1H), 7.29 (d, 2H), 7.15 (d, 2H), 6.87 (dd, 1), 6.58 (br s, 1H), 3.67–3.64 (m, 4H), 3.41–3.39 (m, 4H), 2.91–2.84 (m, 1H), 1.23 (d, 6H). **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, 1H), 7.84 (dd, 1H), 7.35–7.29 (m, 4H), 6.85 (dd, 1H), 6.35 (br s, 1H), 3.70–3.67 (m, 4H), 3.42–3.40 (m, 4H), 1.32 (s, 9H). **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, 1H,), 8.15 (dd, 1H), 7.34 (d, 2H), 7.21 (d, 2H), 6.76 (dd, 1H), 6.41 (s, 1H), 3.75–3.72 (m, 4H), 3.39–3.36 (m, 4H), 2.94–2.91 (m, 1H), 1.28 (d, 6H). **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 1H), 7.45 (dd, 1H), 7.29 (d, 2H), 7.18 (d, 2H), 6.93 (dd, 1H), 6.38 (br s, 1H), 3.68–3.64 (m, 4H), 3.25–3.21 (m, 4H), 2.94–2.85 (m, 1H), 2.33 (s, 3H), 1.26 (d, 6H). **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, 1H), 7.52 (dd, 1H), 7.27 (d, 2H), 7.16 (d, 2H), 6.97 (dd, 1H), 6.33 (br s, 1H), 3.65–3.63 (m, 4H), 3.19–3.16 (m, 4H), 2.90–2.84 (m, 1H), 2.67 (q, 2H), 1.28 (t, 3H), 1.23 (d, 6H). **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H), 7.95 (d, 1H), 7.27 (d, 2H), 7.17–7.11 (m, 3H), 6.87 (t, 1H), 6.37 (br s, 1H), 3.66–3.63 (m, 4H), 3.27–3.24 (m, 4H), 2.89–2.84 (m, 1H), 1.22 (d, 6H). **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H); 8.43 (dd, 1H), 8.05 (dd, 1H), 7.30 (d, 2H), 7.18 (d, 2H), 7.00 (dd, 1H), 6.35 (br s, 1H), 3.72 (dd, 4H), 3.57 (dd, 4H), 2.93–2.86 (m, 1H), 1.25 (d, 6H). **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, 1H),

7.67 (dd, 1H), 7.39–7.32 (m, 4H), 6.95 (dd, 1H), 6.41 (br s, 1H), 3.73–3.70 (m, 4H), 3.49–3.46 (m, 4H), 1.36 (s, 9H). **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, 1H), 7.68 (dd, 1H), 7.34 (br d, 2H), 7.21 (br d, 2H), 6.94 (dd, 1H), 6.37 (br s, 1H), 3.73–3.70 (m, 4H), 3.49–3.47 (m, 4H), 2.58–2.45 (m, 1H), 1.96–1.83 (m, 4H), 1.83–1.75 (m, 1H), 1.48–1.41 (m, 4H). **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, 1H), 7.61 (dd, 1H), 7.25 (d, 2H), 7.10 (d, 2H), 6.89 (dd, 1H), 6.34 (s, 1H), 3.67–3.64 (m, 2H), 3.42–3.40 (m, 4H), 2.58 (t, 2H), 1.64–1.51 (m, 2H), 1.40–1.27 (m, 2H), 0.91 (t, 3H). **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.62–7.60 (m, 1H), 7.22 (t, 2H), 7.10 (t, 2H), 6.73–6.70 (m, 1H), 6.41 (s, 1H), 3.73–3.71 (m, 4H), 3.43–3.40 (m, 4H), 2.52–2.48 (m, 2H), 1.54–1.49 (m, 2H), 1.12–0.99 (m, 3H). **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–8.23 (m, 1H), 7.70–7.66 (m, 1H), 7.50–7.45 (m, 2H), 7.41–7.36 (m, 2H), 6.98–6.92 (m, 1H), 6.50 (br s, 1H), 3.75–3.69 (m, 4H), 3.50–3.43 (m, 4H), 1.62 (br s, 5H). **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, 1H), 7.61 (dd, 1H), 7.28 (d, 2H), 7.10 (d, 2H), 6.88 (dd, 1H), 6.41 (br s, 1H), 3.65 (dd, 4H), 3.41 (dd, 4H), 2.57–2.52 (m, 1H), 1.59–1.52 (m, 2H), 1.20 (d, 3H), 0.80 (t, 3H). **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (t, 1H), 7.62–7.60 (m, 1H), 7.59–7.50 (m, 4H), 6.76–6.74 (m, 1H), 6.65 (s, 1H), 3.72 (br s, 4H), 3.51 (br s, 4H). **25**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, 1H), 7.63 (dd, 1H), 7.40 (d, 2H), 7.15 (d, 2H), 6.90 (dd, 1H), 6.44 (br s, 1H), 3.69–3.66 (m, 4H), 3.44–3.42 (m, 4H). **26**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, 1H), 7.63 (dd, 1H), 7.33 (d, 2H), 7.27 (d, 2H), 6.90 (dd, 1H), 6.39 (br s, 1H), 3.68–3.65 (m, 4H), 3.44–3.41 (m, 4H). **27**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.21 (t, 1H), 7.72–7.71 (m, 1H), 7.48–7.43 (m, 2H), 7.45–7.40 (m, 2H), 7.13–7.11 (m, 1H), 3.72 (br s, 4H), 3.23 (br s, 4H). **28**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.15 (s, 1H), 7.73–7.70 (m, 1H), 7.51–7.49 (m, 2H), 7.25–7.23 (m, 2H), 6.96–6.94 (m, 1H), 3.72 (br s, 4H), 3.23 (br s, 4H). **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.24 (m, 3H), 7.70 (dd, 1H), 7.62 (dd, 2H), 6.97 (dd, 1H), 6.80 (br s, 1H), 3.78–3.75 (m, 4H), 3.52–3.49 (m, 4H). **30**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.91 (s, 1H), 7.85–7.75 (m, 4H), 7.59–7.53 (m, 1H), 7.47–7.43 (m, 2H), 7.00 (br s, 1H), 3.75 (br s, 4H), 3.45 (br s, 4H). **31**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H), 7.60 (d, 1H), 6.87 (dd, 1H), 4.38 (d, 1H), 3.67–3.54 (m, 1H), 3.53–3.49 (m, 4H), 3.36–3.32 (m, 4H), 2.09–2.02 (m, 2H), 1.80–1.75 (m, 2H), 1.17–0.99 (m, 4H), 0.98–0.90 (m, 1H), 0.85 (s, 9H).

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