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Optimization of Novel Aza-benzimidazolone mGluR2 PAMs with Respect to LLE and PK Properties and Mitigation of CYP TDI

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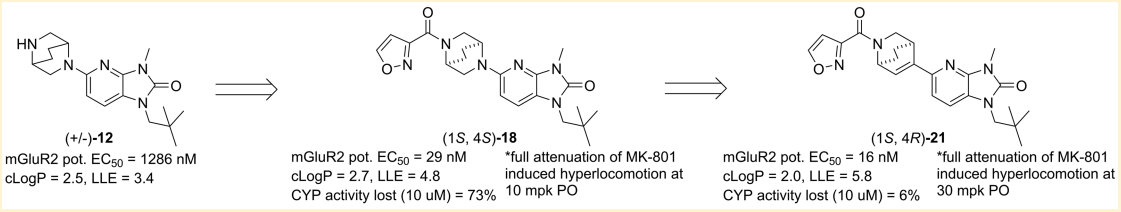
Supporting Information



ABSTRACT: Investigation of a novel amino-aza-benzimidazolone structural class of positive allosteric modulators (PAMs) of metabotropic glutamate receptor 2 (mGluR2) identified [2.2.2]-bicyclic amine **12** as an intriguing lead structure due to its promising physicochemical properties and lipophilic ligand efficiency (LLE). Further optimization led to chiral amide **18**, which exhibited strong *in vitro* activity and attractive pharmacokinetic (PK) properties. Hypothesis-driven target design identified compound **21** as a potent, highly selective, orally bioavailable mGluR2 PAM, which addressed a CYP time-dependent inhibition (TDI) liability of **18**, while maintaining excellent drug-like properties with robust *in vivo* activity in a clinically validated model of antipsychotic potential.

KEYWORDS: *Schizophrenia, metabotropic glutamate receptor, positive allosteric modulator, time-dependent inhibition*

Schizophrenia is a chronic and debilitating disease affecting 1% of the world's population.[1−3] Current treatments primarily include atypical antipsychotics such as Olanzapine and Risperidone. These therapeutics target the dopamine D2 and serotonin 5HT2A receptor pathways and are effective at combating the positive symptoms of the disorder (hallucinations, delusions). However, they are far less successful at treating the negative symptoms (emotional blunting, social withdrawal) and offer no efficacy against the characteristic cognitive deficits.[4] In addition, atypical antipsychotics have been associated with dose-limiting side effects (i.e., weight gain, hyperglycemia, diabetes, sedation, and various dyskinesias[5]), which have contributed to compliance issues and increased risk of relapse. Furthermore, the failure of a significant percentage of patients to respond to these treatments suggests that other neurotransmitters play a critical role in schizophrenic pathology. Therefore, therapeutic agents targeting alternative neurotransmitters with novel modes of action may ultimately prove more effective at addressing this unmet medical need.

L-Glutamate is the most abundant excitatory neurotransmitter in the mammalian CNS.[6] The "glutamate hypothesis" states that schizophrenic symptomology may be attributed to disrupted glutamate transmission in the forebrain (prefrontal cortex, hippocampus, striatum).[7] Metabotropic glutamate receptor 2 (mGluR2) is highly expressed primarily in the forebrain and is a presynaptic regulator of glutamate.[8] As such, it has been identified as a potential target for novel treatments and has been the focus of intense research over the past decade. Pioneering work by Lilly led to nonselective mGluR2/3 orthosteric agonist prodrug LY2140023 (**1**, Figure 1a), which demonstrated robust efficacy in preclinical indicators of antipsychotic potential as well as promising scores against positive and negative symptoms in a 4-week phase IIb study involving schizophrenic patients.[9] Disappointedly, it was

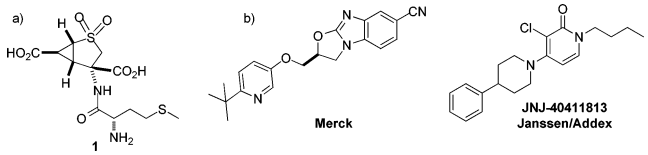


Figure 1. (a) mGluR2/3 orthosteric agonist prodrug (**1**). (b) Previously reported mGluR2 PAMs.

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subsequently discontinued due to a lack of efficacy in a 7-week double-blind study in phase III.[10]

Positive allosteric modulators (PAMs) offer an alternative approach toward mGluR2 activation with potentially significant advantages over orthosteric agonists.[11] As exemplified by Merck[12] and others[13,14] (Figure 1b), binding to the less homologous 7-transmembrane domain (7-TMD) leads to high subtype selectivity for mGluR2 and thus mitigation of mGluR3-mediated effects. This is significant, as previous studies in mouse models predictive of antipsychotic potential have shown that mGluR2, not mGluR3, mediates the actions of mGlu2/3 receptor dual agonists.[15,16] Furthermore, modulation restricts receptor activation only to relevant tissues in the presence of endogenous agonist (glutamate) and reduces the potential for tachyphylaxis, which has been reported with GPCR agonists upon chronic treatment.[17]

We have recently described a novel class of mGluR2 PAMs featuring aryl aza-benzimidazolones, culminating in the discovery of optimized compound **2** (Figure 2).[18] Here, we

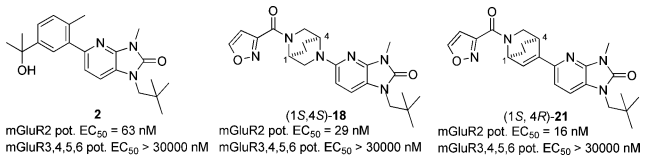
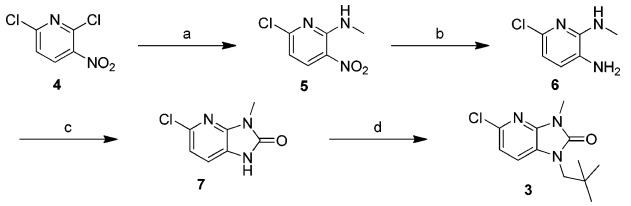


Figure 2. Aza-benzimidazolone mGluR2 PAMs **2**, **18**, and **21**.

report the development of *N*- and carbon (nonaryl)-linked aza-benzimidazolones, with leading exemplars being **18** and **21**, respectively. These compounds not only exhibit enhanced *in vitro* potency but also significant advancements in pharmacokinetic properties and *in vivo* efficacy. These data, along with key structure−activity relationship (SAR) findings, are detailed herein.

Pyridyl chloride **3** (Scheme 1) served as a common intermediate toward each of the aza-benzimidazolone chemo-

Scheme 1. Synthesis of Common Intermediate 3[a]

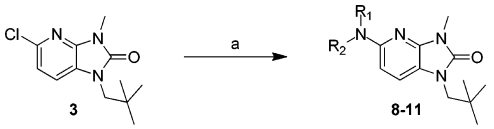


[a]Reagents and conditions: (a) $MeNH_2$, Na_2CO_3, EtOH, rt, 3 h, 82%; (b) $SnCl_2$, HCl, reflux, 18 h, 85%; (c) CDI, DMF, 80 °C, 18 h, 95%; (d) neopentyl iodide, Cs_2CO_3, NMP, 90 °C, 15 h, 78%.

types described in this work. The synthesis of **3** began with a regioselective chloride displacement of commercially available 2,6-dichloro-3-nitropyridine (**4**) with methylamine, furnishing **5**. This was subsequently treated with tin chloride and concentrated hydrochloric acid to give diamine **6**. Ring closure with CDI assembled aza-benzimidazolone **7**, which was then functionalized with neopentyl iodide under basic conditions, affording pyridyl chloride **3**.

Palladium catalysis proved to be critical in effecting the *N*-arylation of pyridyl chloride **3**, as thermally driven S_NAr reactions resulted in recovered starting material and/or significant decomposition (Scheme 2). Bis(tri-*tert*-

Scheme 2. Synthesis of Compounds 8-11[a]

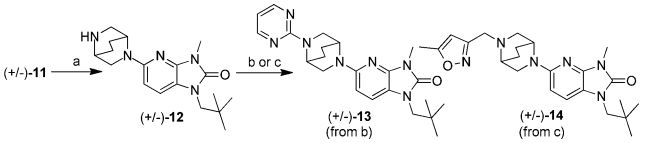


[a]Reagents and conditions: (a) amine, $Pd[P(t\text{-}Bu)_3]_2$, K_3PO_4, DMA, 100 °C, 18 h, 38−97%.

butylphosphine)palladium was found to be most effective in mediating the desired transformations as well as in minimizing undesired protodehalogenation.[19] Using readily available secondary amine building blocks, over 70 amino-aza-benzimidazolones were prepared, with key exemplars being compounds **8**−**11**.

TFA-mediated deprotection of compound **11** procured racemic intermediate **12** (Scheme 3). The versatile terminal

Scheme 3. Synthesis of Compounds 12−14[a]

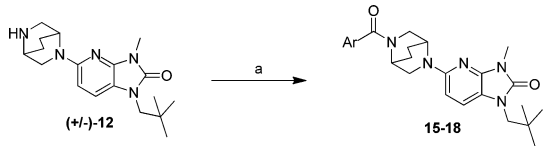


[a]Reagents and conditions: (a) TFA, DCM, rt, 30 min, 98%; (b) 2-chloropyrimidine, Cs_2CO_3, THF, rt, 18 h, 34%; (c) 5-methylisoxazole-3-carbaldehyde, NMP, rt, 30 min, then $NaBH(OAc)_3$, rt, 18 h, 41%.

amine functionality of **12** allowed for the subsequent synthesis of a broad range of analogues. For example, *N*-aryl analogues exemplified by **13** were investigated. In this case, S_NAr displacement with chloropyrimidine under basic conditions generated the targeted compound. A one-carbon "spacer" between the piperazine and aromatic group was incorporated through reductive alkylation chemistry, providing compounds such as isoxazole **14**.

Amide derivatives were also of interest. To this end, acid chloride or carboxylic acid monomers served as effective building blocks to generate compounds **15**−**18** through standard coupling conditions (Scheme 4).

Scheme 4. Synthesis of Compounds 15−18[a]



[a]Reagents and conditions: acid chloride, TEA, DMF, rt, 3 h; or carboxylic acid, EDC, HOBT, TEA, DMF, rt, 18 h, 52−82%.

In the synthesis of compound (1*S*, 4*R*)-**21**, chiral bicyclic piperidinone **19**[20] was converted to the corresponding vinyl triflate using Comins' reagent (Scheme 5). Palladium-catalyzed, *in situ* boronic ester formation followed by Suzuki coupling with intermediate **3** furnished **20**. Oxidative removal of the *para*-methoxyphenyl group and subsequent HATU-mediated amidation completed the synthesis of compound **21**.

With a broad range of chemotypes in hand, *in vitro* profiling leveraged a fluorescent imaging plate reader (FLIPR) assay using a Chinese hamster ovary (CHO) cell line coexpressing recombinant human mGluR2 and a promiscuous G-protein,

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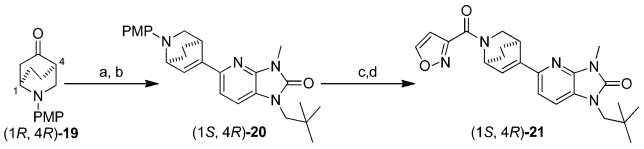
Scheme 5. Synthesis of Compound 21[a]

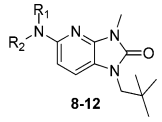


[a]Reagents and conditions: (a) Comins' reagent, NaHMDS, THF, 0 °C, 60 min, 98%; (b) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)$, 1,4-dioxane, 60 °C, 18 h, then **3**, Cs_2CO_3, H_2O, $Pd[P(t\text{-}Bu)_3]_2$, 60 °C, 4.5 h, 59%; (c) H_5IO_6, H_2SO_4, 50 °C, 18 h, 29%; (d) isoxazole-3-carboxylic acid, HATU, DIPEA, CH_3CN, rt, 10 min, 80%.

Gα16. Functional activity was provided as the EC_{50} for potentiating a submaximal concentration (EC_{20}) of glutamate.

Key *in vitro* data for representative *N*-aryl compounds is summarized in Table 1. Racemic decahydroquinoline **8**[21]

Table 1. Functional Activity of mGluR2 PAMs 8−12

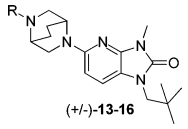


compd	R_1R_2N-	mGluR2 pot. EC_{50} (nM) (%max)	cLogP	LLE
(+/-)-**8**		2200 (77%)	5.0	0.7
9		332 (60%)	5.4	1.1
10		430 (87%)	4.3	2.0
(+/-)-**11**		125 (70%)	4.5	2.4
(+/-)-**12**		1286 (71%)	2.5	3.4

demonstrated modest mGluR2 PAM activity and poor lipophilic ligand efficiency (LLE).[22] While tetrahydroquinoline **9** featured a nearly seven-fold increase in potency relative to early lead **8**, its increased cLogP[23] resulted in only a modest increase in LLE. In contrast, truncation afforded piperidine **10**, which exhibited significant improvements in physicochemical properties and LLE relative to both **8** and **9**. Incorporation of a [2.2.2]-bicyclic piperazine framework led to **11** and **12**. Bicyclic piperazine **12**, while three-fold less potent than piperidine **10**, was regarded as a superior lead due to its reduced cLogP and marked increase in LLE. Importantly, all compounds were inactive against other mGlu receptors (mGluR3,4,5,6 pot. EC_{50} > 30000 nM), highlighting the exquisite subtype selectivity of these PAMs.

Compounds **13**−**16** were among the initial set of derivatives from piperazine lead compound **12** (Table 2). *N*-Aryl compounds such as **13** displayed attractive *in vitro* potency but limited LLE due to high cLogP relative to parent compound **12**. Homologated analogues such as **14** generally featured lower cLogPs relative to **13**, but were less active and thus had comparable LLEs. Despite being three-fold less potent relative to benzamide **15**, pyridyl amide **16** emerged as a new lead compound due to a significant reduction in cLogP as well as a superior LLE.

Table 2. Derivatization of [2.2.2]-Bicyclic Piperazine 12



compd	R	mGluR2 pot. EC_{50} (nM) (%max)	cLogP	LLE
(+/-)-**13**		37 (65%)	4.1	3.3
(+/-)-**14**		149 (74%)	3.6	3.2
(+/-)-**15**		36 (71%)	3.7	3.7
(+/-)-**16**		115 (74%)	2.6	4.3

The improved physicochemical properties of pyridyl amide **16** were reflected in high aqueous solubility (183 μM) at neutral pH (Table 3). Its pharmacokinetic profile relative to

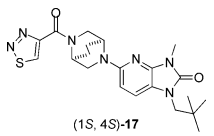
Table 3. Rat PK Properties of Compounds 13−16

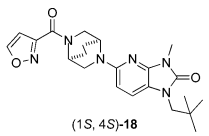
		IV (2 mpk)[a]			PO (10 mpk)[b]	
compd	sol. (μM)[c]	$T_{1/2}$ (h)	CL (mL/min/kg)	CL/f_u	AUC (μM·h)	F (%)
(±)-**13**	18	n/a	n/a	n/a	3.9	n/a
(±)-**14**	186	n/a	n/a	n/a	2.0	n/a
(±)-**15**	66	1.2	69	35	2.0	10
(±)-**16**	183	0.5	50	2.9	18	73

[a]Vehicle = DMSO. [b]Vehicle = 20% Vit E/TPGS. [c]pH = 7.

compounds **13**−**15** was likewise encouraging, with attractive rat oral bioavailability (AUC = 18 μM·h, F = 73%) as well as clearance adjusted for fraction unbound (CL/f_u = 2.9).

The promising data for pyridyl amide **16** triggered a focused follow-up library involving parent compound **12** and heteroaryl-functionalized carboxylic acid monomers. Over 100 heteroaryl-amides were synthesized, with the two most intriguing being thiadiazole **17** and isoxazole **18** (Figure 3).





29 nM (72%)	mGluR2 pot. EC_{50} (%max)	29 nM (78%)
637 nM (49%)	agonism EC_{50} (%max)	668 nM (35%)
26	glutamate shift (1 μM)	12
>30000 nM	mGluR3,4,5, 6 pot. EC50	>30000 nM
2.2 / 5.3	cLogP / LLE	2.7 / 4.8
116	sol. (μM)[a]	125
1.1	P-gp B/A:A/B	1.5
30 x 10^{-6} cm/sec	P_{app} (rat)	31 x 10^{-6} cm/sec

Figure 3. Profiles of chiral mGluR2 PAMs **17** and **18** ([a]pH = 7).

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The (1*S*,4*S*)-eutomers of **17** and **18** each exhibited a 4-fold improvement in FLIPR potency relative to pyridyl amide **16** without compromising physicochemical properties. While modest agonism was observed for **17** (EC_{50} = 637 nM) and **18** (EC_{50} = 668 nM), the percent activation relative to maximum response of glutamate was less than 50%. In conjunction with the primary FLIPR EC_{50} data, the synergistic effect of these mGluR2 PAMs was assessed by their ability to "left-shift" glutamate's dose response curve. The "glutamate shifts" at 1 μM concentrations of aza-benzimidazolones **17** and **18** were measured to be 26- and 12-fold, respectively.

As representative of this structural class, neither **17** nor **18** was a P-gp substrate in rat or human. Furthermore, both compounds featured excellent cell permeability, as reflected in P_{app} values exceeding 30 × 10^{-6} cm/sec.

While (1*S*, 4*S*)-amino-aza-benzimidazolones **17** and **18** were largely indistinguishable in terms of their respective *in vitro* profiles, investigation of their pharmacokinetic properties ultimately provided differentiation (Table 4). In particular, **17**

Table 4. Rat PK Properties of Chiral Compounds 17 and 18

		IV[a]			PO[b]	
compd	species	$T_{1/2}$ (h)	CL (mL/min/kg)	CL/f_u	AUC (μM·h)	*F* (%)
17	rat	n/a	n/a	n/a	13	n/a
17	dog	2.5	14	n/a	n/a	n/a
18	rat	2.3	28	4.7	14	72
18	dog	12	7.0	0.9	1.3	24

[a]Vehicle = DMSO; dose = 2 mpk (rat), 0.5 mpk (dog). [b]Vehicle = 20% Vit E/TPGS; dose =10 mpk (rat), 1.0 mpk (dog).

featured moderate clearance (CL = 14 mL/min/kg) and a short half-life ($T_{1/2}$ = 2.5 h) in dog. Metabolite ID studies in liver microsomes highlighted the thiadiazole moiety as a potential hotspot for oxidative metabolism. In contrast, **18** showed no turnover in liver microsomes (CL_{int} < 55 mL/min/kg), and this increased metabolic stability was reflected in outstanding clearance adjusted for fraction unbound ($CL/f_u \approx 1$) and a long half-life (12 h) in dog. With **18** also exhibiting strong rat pharmacokinetics (CL/f_u = 4.7, F = 72%), standard allometric scaling predicted its human PK to have a total clearance of 3−9 mL/min/kg with a half-life of 11−18 h. This pharmacokinetic profile would be supportive of once-daily dosing.

The oral bioavailability of chiral aza-benzimidazolone **18** allowed for the use of oral dosing in assessing its efficacy in a rat behavioral model of antipsychotic activity. Clinically approved typical and atypical antipsychotics, mGluR2/3 agonists, and previously reported mGluR2 PAMs have been found to inhibit hyperlocomotive effects in rats produced by psychostimulants (i.e., PCP, MK-801). As such, this assay has been considered predictive of antipsychotic potential.[12,24] Gratifyingly, **18** fully inhibited MK-801-induced rat hyperlocomotion at both 10 and 30 mpk doses relative to the vehicle-treated group (Figure 4a). Following behavioral testing, plasma and CSF samples were collected from a subset of rodents, with the latter used to approximate brain free drug levels. The plasma and CSF levels at 10 mpk were measured to be 3.2 μM and 73 nM, respectively. With the rat FLIPR EC_{50} of **18** measured to be 75 nM, the *in vitro*−*in vivo* correlation (IVIVC) was excellent. Furthermore, given the exposure required for full efficacy, **18** stands as one of the most efficacious orally dosed mGluR2

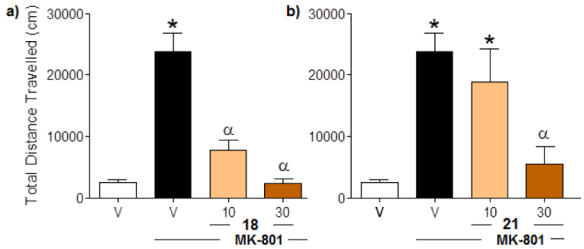

Figure 4. Rat locomotor response to MK-801 (0.23 mpk, sc) as a function of oral dosing (10, 30 mpk) of compound **18** (a) and compound **21** (b). *Significant increase from vehicle−vehicle group. [α]Significant decrease from vehicle-MK-801 group.

PAM's to date in a rodent model applicable to clinically proven antipsychotics.[12−14,18,25−30]

Unfortunately, despite these advancements, further profiling revealed that **18** was a potent time-dependent inhibitor (TDI) of CYP 3A4 (K_i = 540 nM, k_{inact} = 0.064 min^{-1}). This was viewed as a significant liability, especially due to the fact that oxidative metabolism of **18** was mediated primarily by CYP 3A4 enzymes in human liver microsomes. As a result, the clinical drug−drug interaction (DDI) potential was regarded as high, and further progression of isoxazole **18** was discontinued.

In studies designed to understand the SAR associated with this TDI liability, it was found that a 10 μM concentration of racemic piperidine derivative **22** exhibited an order-of-magnitude reduction in CYP 3A4 inhibition relative to **18** (Figure 5). This suggested that the anilinic nitrogen of **18** was

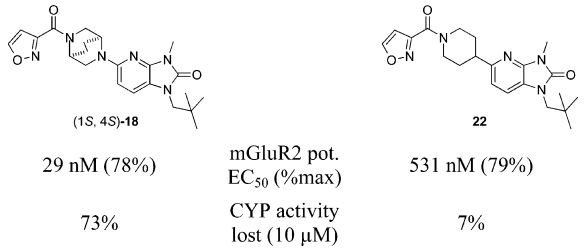

Figure 5. Potency vs CYP 3A4 TDI of **18** and **22**.

the most likely root cause of the TDI, presumably by forming a reactive nitroso metabolite.[31] While **22** was an encouraging novel lead compound, its modest mGluR2 potency (FLIPR EC_{50} = 531 nM) needed to be significantly improved in order to advance this modified chemotype.

Ultimately, and unsurprisingly, reincorporation of the [2.2.2]-bicyclic framework in addition to a potency-enhancing endocyclic olefin[32] provided the necessary enhancement in mGluR2 activity. The (1*S*,4*R*)-eutomer of aza-benzimidazolone **21** featured not only a significant mitigation of CYP 3A4 TDI but also higher *in vitro* potency than **18** (Figure 6). Compound **21** exhibited an extended half-life in both rat and dog (10 and 16 h, respectively), which was primarily driven by metabolic protection through elevated plasma protein-binding. Importantly, the styrenyl-like olefin was derisked in an AMES assay, as no genotoxicity was observed in the presence or absence of S9 liver fraction.

Chiral aza-benzimidazolone **21** demonstrated full attenuation of MK-801-induced rat hyperlocomotive effects (Figure 4b) at a 30 mpk po dose (CSF = 61 nM). As with amino-aza-benzimidazolone **18**, **21** was inactive against other mGluRs as well as targets that could produce a positive response in this

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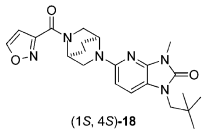
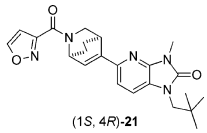


(1S, 4S)-18



(1S, 4R)-21

(1S, 4S)-18		(1S, 4R)-21
29 nM (78%)	mGluR2 pot. EC_{50} (%max)	16 nM (78%)
>30000 nM	mGluR3,4,5,6 pot. EC_{50}	>30000 nM
73%	CYP activity lost (10 μM)	6%
2.7 / 4.8	cLogP / LLE	2.0 / 5.8
6%, 8%	f_u (rat, dog)	2%, 2%
4.7, 0.9	CL/f_u (rat, dog)	17, 4.7
2.3 h, 12 h	$T_{1/2}$ (rat, dog)	10 h, 16 h

Figure 6. Profiles of mGluR2 PAMs **18** and **21**.

behavioral model (dopamine D2, serotonin 5-HT2A, or phosphodiesterase 10 receptors).

In summary, new chemotypes based on an aza-benzimidazolone pharmacophore have been discovered.[33,34] Target design guided by physical property indicators such as LLE led to the prioritization of a [2.2.2]-bicyclic piperazine series. Exemplar **18** featured advancements in pharmacokinetics across multiple species as well as full efficacy in a rat hyperlocomotion model at low-micromolar plasma exposure. The primary structural feature associated with time-dependent inhibition of CYP 3A4 was identified through SAR studies. Hypothesis-driven target design subsequently led to optimized aza-benzimidazolone **21**, which mitigated the TDI liability of **18** while preserving its otherwise attractive profile. With robust *in vivo* efficacy, exquisite subtype selectivity and drug-like properties, **21** stands as a novel tool compound to assess the viability of mGluR2 PAM's as therapeutics for the treatment of schizophrenia.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00459.

Experimental details of chemical synthesis, characterization, and *in vitro* screening of all compounds (PDF)

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■ ABBREVIATIONS

mGluR2, metabotropic glutamate receptor 2; PAM, positive allosteric modulator; pot, potentiation; LLE, lipophilic ligand efficiency; TDI, time-dependent inhibition; $T_{1/2}$, half-life; sol, solubility; f_u, fraction unbound (%); P-gp, *p*-glycoprotein; CYP, cytochrome P450; DDI, drug−drug interaction; IVIVC, *in vitro*−*in vivo* correlation

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