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Discovery of benzoylisoindolines as a novel class of potent, selective and orally active GlyT1 inhibitors

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ABSTRACT

Benzoylisoindolines were discovered as a novel structural class of GlyT1 inhibitors. SAR studies and subsequent lead optimization efforts focused primarily on addressing hERG liability and on improving in vivo efficacy resulted in the identification of potent GlyT1 inhibitors displaying excellent selectivity and in vivo PD and PK profiles.

Both clinical observations and preclinical studies suggest that hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor is implicated in the pathophysiology of schizophrenia.[1] Thus, therapeutic intervention aiming at restoring NMDA receptor activity represents a promising novel strategy for the management of schizophrenia. As glycine is an obligatory co-agonist at the NMDA receptor complex,[2] one strategy to enhance NMDA receptor activity is to elevate extracellular levels of glycine in the brain through selective inhibition of glycine uptake mediated by the glycine transporter-1 (GlyT1) which is co-expressed with the NMDA receptor.[3] Strong support for this approach comes from clinical studies where glycine and D-serine (co-agonists at the glycine site of the NMDA receptor) and sarcosine (a prototypical weak GlyT1 inhibitor) improved positive, negative and cognitive symptoms in schizophrenic patients, when added to conventional therapy.[4] As a result, considerable efforts have been focused on the development of selective GlyT1 inhibitors.[5] The first examples reported were sarcosine derivatives including **1**,[6] **2**,[7] and **3**.[8] More recently, non amino-acid chemotypes[9] like **4**,[10] **5**,[11] and **6**,[12] have been described (Fig. 1). We have recently disclosed our lead optimisation effort in a benzoylpiperazine class[13] that led to the identification of RG1678 (**7**)[14] which is the first potent and selective GlyT1 inhibitor to demonstrate a beneficial effect in schizophrenic patients in a phase II clinical trial. Following the identification of RG1678, further medicinal chemistry effort at F. Hoffmann-La Roche concentrated on studying the structural diversity allowed at the western arylpiperazine site of RG1678. Towards this end, keeping the eastern 5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl moiety of RG1678 in place, a focused screen of cyclic amine systems selected from the Roche compound depository was performed.

This exercise led to the identification of 5-chloro-substituted-benzoylisoindoline compound **8** as a fairly potent GlyT1 inhibitor (135 nM) showing more than 200-fold selectivity against the type 2 isoform (Fig. 2a). Further characterization revealed that **8** possessed medium lipophilicity, excellent membrane permeability, medium to low in vitro clearance in mouse and human liver microsomes and no significant inhibition of the major drug metabolizing CYP450 enzymes. In addition, despite its low aqueous solubility in the lyophylisated solubility assay (LYSA),[15] **8** proved to be orally active (ID_{50} = 20 mg/kg) in the mouse L-687,414-induced hyperlocomotion assay, a novel and straightforward functional screening model recently introduced by us which allows the detection of the in vivo activity of GlyT1 inhibitors (Fig. 2b).[14] The promising in vitro and in vivo results obtained with benzoylisoindoline compound **8** prompted us to study in detail this novel class of GlyT1

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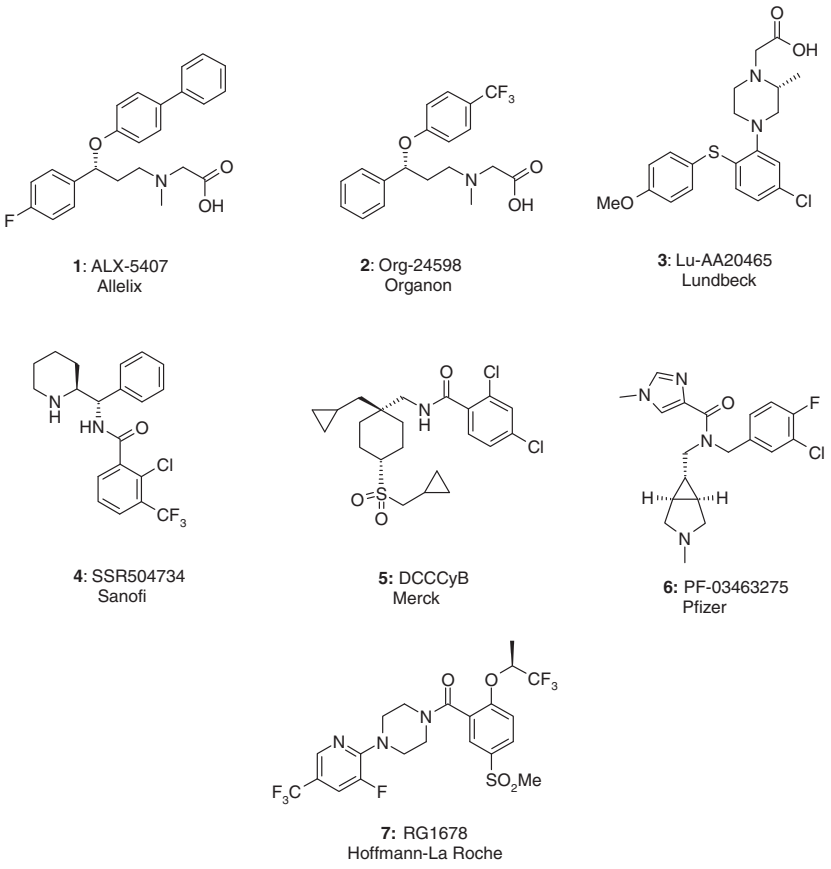


Figure 1. A selection of published GlyT1 inhibitors.

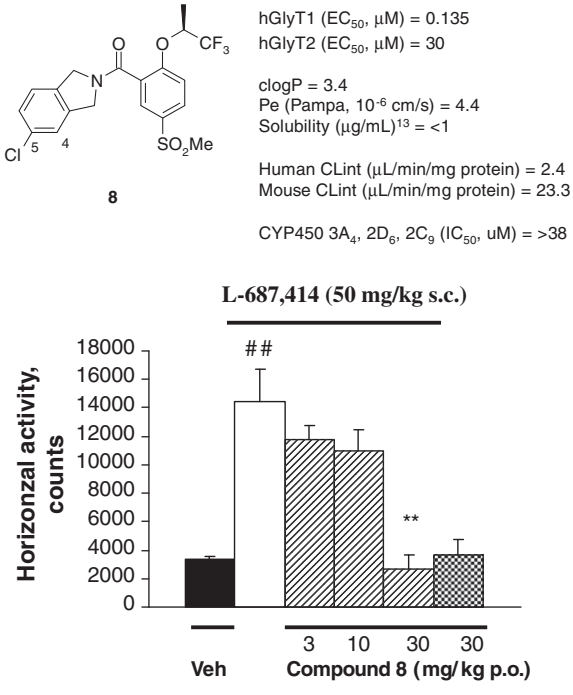
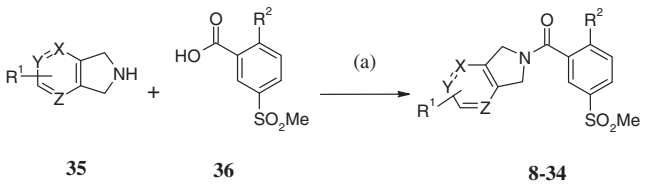


Figure 2. (a) Structure of benzoylisoindoline hit **8** and some key in vitro characteristics; (b) Dose-dependent inhibition of L-687,414-induced hyperlocomotion by **8** in mice. The data represent mean horizontal activity counts per group recorded over a 60-min time period; error bars indicate S.E.M. (n = 8 per group). ##, p <0.01 versus vehicle (Veh) alone; **, p <0.01 versus L-687,414 alone.

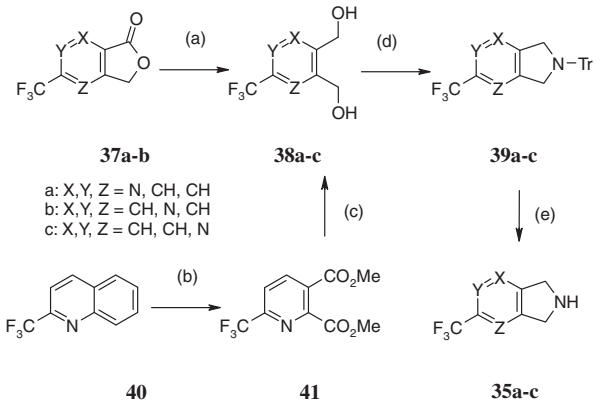
inhibitors.[16] In this Letter, we report on the SAR results and on our lead optimization effort that led to the identification of the potent, selective and orally active GlyT1 inhibitors **19**, **25** and **27**.

Benzoylisoindoline derivatives **8**–**34**[16] were synthesized under standard amide coupling conditions from isoindolines **35** and benzoic acids **36**[13,14,16] (Scheme 1).

The novel isoindoline building blocks **35a**–**k** were prepared following the synthetic routes depicted in Schemes 2 and 3. Trifluoromethyl-substituted dihydro-pyrrolo pyridines **35a**–**c** (Scheme 2) were obtained upon acidic cleavage of trityl protected precursors **39a**–**c**, themselves prepared from diols **38a**–**c** after a bis-chlorination or -mesylation followed by cyclization in the presence of tritylamine. Diols **38a**–**b** were obtained by reducing known lactones **37a**–**b**[17] and diol **38c** was synthesized after reduction of di-methyl ester **41**, itself prepared by oxidation of trifluoromethylquinoline **40** in the presence of ruthenium chloride and periodic acid as described by Lee and co-workers.[18]



Scheme 1. Synthesis of benzoylisoindolines **8**–**34**. Reagents and conditions: (a) TBTU, DIPEA, DMF, rt, 60–95%.



Scheme 2. Synthesis of isoindoline intermediates **35a–c**. Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 74–97%; (b) $RuCl_3{\cdot}H_2O$, HIO_4, H_2O, CH_3CN, CCl_4, rt then Cs_2CO_3, MeI, rt, 28%; (c) $NaBH_4$, $CaCl_2$, MeOH, 0 °C to rt, 63%; (d) $SOCl_2$, CH_2Cl_2, 0 °C to rt (for **38a–b**) or MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (for **38c**) then $TrNH_2$, DIPEA, DMF, 60 °C, 36–51%; (e) TFA, MeOH, $CHCl_3$, rt, 50–90%.

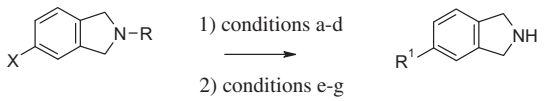
Isoindolines **35d–k** carrying aryl, heteroaryl, cyclic amino or tetrahydropyranyl moieties in position 5, were prepared from protected 5-bromo or 5-iodo substituted isoindolines **42** under Suzuki, Buchwald–Hartwig and Stille conditions (scheme 3).

Our first effort aimed at establishing the SAR at positions 5 and 4 of the western aromatic moiety (Table 1). Starting from **8**, deletion of the 5-chloro group leading to compound **9** resulted in a severe decrease of GlyT1 affinity (2.54 μM). In contrast, a significant improvement of activity was observed upon replacing the 5-chloro substituent with larger electron withdrawing or neutral groups as seen with the trifluoromethyl (**10**) and phenyl (**11**) derivatives, both showing a GlyT1 activity in the low nanomolar range (21 and 13 nM). Much weaker potencies were however measured with analogues carrying electron donating groups such as methoxy (**12**, 180 nM), pyrrolidinyl (**13**, 180 nM) and morpholinyl (**14**, 275 nM). A further reduced activity was observed with compounds bearing a basic nitrogen containing group as exemplified with the *N*-methylpiperazinyl derivative **15** (2.08 μM). At the position 4 of the isoindoline core, a rapid scanning revealed that substituents were always poorly tolerated. For example, methyl (**16**), methoxy (**17**) and nitrile (**18**) analogues showed GlyT1 affinities only in the micromolar or high nanomolar range. The two highly potent analogues **10** and **11** were selected for further evaluation. Both compounds exhibited excellent selectivity versus the GlyT2 isoform (like all active analogues in this series), good membrane permeability, and medium to low in vitro clearances in mouse, rat and human liver microsomes (data not shown).

In addition, fully in agreement with their increased GlyT1 affinities compared to the initial hit compound **8**, analogues **10** and **11** demonstrated an improved in vivo potency in the L-687,414-induced hyperlocomotion assay with an ID_{50} reaching 2 mg/kg for **10** and 6 mg/kg for **11** after po administration (Table 1).

In a single dose PK experiment performed in rat, the most in vivo active compound **10** exhibited low systemic clearance (1.7 mL/min/kg), medium volume of distribution (2.9 L/kg) and good brain penetration (brain/plasma = 1). However, **10** showed a fairly low oral bioavailability of 23%, a result we attributed to its low aqueous solubility (1 μg/mL) and hence limited absorption. Further profiling of **10** and **11** in our battery of in vitro safety tests revealed, in addition, that both compounds had significant inhibitory activities at the hERG potassium channel of 59% and 67%, respectively, at a concentration of 10 μM (Table 1).

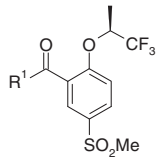
Therefore, starting from leads **10** and **11**, our next step aimed firstly at improving the oral in vivo potency of our compounds by increasing the solubility and secondly, at minimizing the hERG inhibitory activity. We reasoned that both objectives could be achieved simultaneously by designing compounds having decreased lipophilicities. Towards this end, a nitrogen atom insertion scan was performed on the western aromatic ring of compound **10** and on the 5-phenyl group of **11**. This approach delivered the dihydro-pyrrolo-pyridines: **19**, **20**, **21** and the 2- and 4-pyridines **22** and **23** (Table 1). From this novel set of compounds which exhibited, as expected, a reduced *c* log *P* (in the range of 2.2–3.3) and an increased aqueous solubility (25–470 μg/mL), only dihydropyrrolo-pyridine **19** and 4-pyridine **23** showed good affinities at GlyT1 of 50 and 17 nM, respectively. In the L-687,414 assay, both compounds, as hoped, exhibited an improved in vivo efficacy over their respective parent molecules **10** and **11**. The improvement was much more pronounced for **19** for which an ID_{50} of 0.4 mg/kg after oral dosing was reached. Pyridine **23** achieved a more moderate but still favorable potency having an ID_{50} of 3 mg/kg. Regarding hERG activity, again, the best results were obtained with compound **19** for which only a 12% block was measured at 10 μM, thus representing a fivefold reduction in hERG affinity over parent compound **10**. Pyridine **23** showed only a slight decrease of hERG potency with a measured 58% block at 10 μM compared to 67% for **11**. Reasoning that the pronounced aromatic character of the western part was possibly contributing to the hERG activity of **23**,[19] subsequent lead optimisation efforts focused on preparing analogues incorporating a saturated heterocyclic system on the isoindoline moiety such as the 2- and 4-tetrahydropyranyl (THP) group (compounds **24** and **25**, respectively). This strategy proved

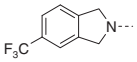
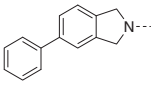
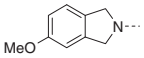
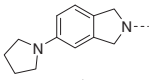
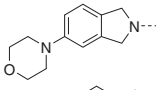
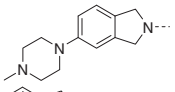
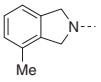
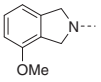
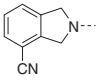
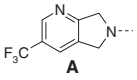
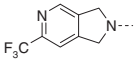
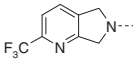
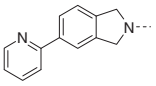
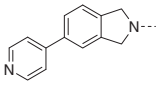
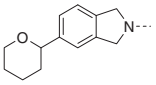
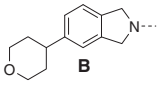


n°	35d	35e	35f	35g	35h	35i	35j	35k
R^1								
X	I	I	I	Br	Br	Br	Br	Br
R	Boc	Boc	Boc	Boc	Boc	Boc	Benzyl	Boc
Conditions	a, e	b, e	b, e	c, f	c, f	c, f	d, g	d, g, e
Yield from **42**	50%	69%	67%	75%	63%	71%	13%	64%

Scheme 3. Synthesis of isoindoline intermediates **35d–k**. Reagents and conditions: (a) $PhB(OH)_2$, K_2CO_3, cat. $Pd(PPh_3)_4$, DMF, 120 °C; (b) 2-or 4-tributylstannylpyridine, cat. Pd_2dba_3, cat. $AsPh_3$, CuI, DMF, 90 °C; (c) cyclic amine, cat. Pd_2dba_3, NaOtBu, 2-(dicyclohexylphosphino)biphenyl, toluene, 120 °C; (d) 2- or 4-dihydropyran-yl-tributylstanne, cat. $Pd_2dba_3{\cdot}CHCl_3$, cat. $AsPh_3$, cat. LiCl, DMF, 100 °C; (e) TFA, CH_2Cl_2, rt; (f) HCl in dioxane (4 N), dioxane, 90 °C; (g) cat Pd/C, ammonium formate, MeOH, 65 °C.

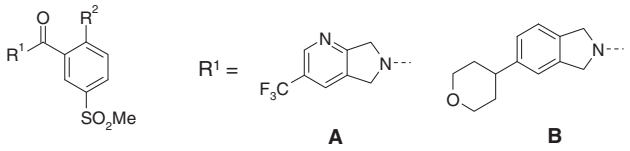
Table 1
In vitro and in vivo profiles of **9**–**25**



Compound	R1	GlyT1 EC_{50}[a,b] (μM)	GlyT2 EC_{50}[a,b] (μM)	*c* log *P*	Solubility[c] (μg/ml)	Pampa Pe[d]	Reversal of L-687, 414-induced hyperlocomotion in mouse ID_{50}[e] (mg/kg)	hERG % block at 10 μM[f]
9		2.54	>30	2.70	<1	0.8	—	—
10		0.021	>30	3.58	1	0.7	2	59
11		0.013	12	4.58	4	2.6	6	67
12		0.180	>30	2.62	46	2.7	—	—
13		0.180	14.3	2.98	<1	0.8	—	—
14		0.275	>30	2.15	355	4.3	—	—
15		2.08	>30	2.60	490	1.5	—	—
16		3.36	>30	3.20	73	4.2	—	—
17		1.94	>30	2.62	85	4.8	—	—
18		0.77	>30	2.13	259	0.8	—	—
19	 **A**	**0.050**	**>30**	**2.23**	**280**	**5**	**0.4**	**12**
20		0.132	>30	2.23	470	3.9	—	—
21		0.250	>30	2.23	429	5.5	—	—
22		0.084	>30	3.30	30	0.8	—	—
23		0.017	>30	3.09	25	4.2	3	58
24		0.205	>30	3.07	<1	0.9	—	—
25	 **B**	**0.014**	**>30**	**2.91**	**76**	**3.3**	**0.5**	**23**

[a] EC_{50} values are the average of at least two independent experiments.
[b] [^{3}H]-glycine uptake inhibition assay in cells transfected with hGlyT1[14] or hGlyT2[14] cDNAs.
[c] Solubility measured in a lyophilisation solubility assay (LYSA).[15]
[d] Pe: PAMPA permeation constant (10^{-6} cm/s) through artificial membranes.[22]
[e] Compound given orally, $n = 8$.
[f] Patch clamp assay, values are the average of at least two independent experiments.

Table 2
In vitro and in vivo profiles of **26**–**34**



Compound	R^1	R^2	GlyT1 EC_{50}[a,b] (μM)	GlyT2 EC_{50}[a,b] (μM)	*c* log *P*	Solubility[c] (μg/ml)	Pampa Pe[d]	Reversal of L-687,414-induced hyperlocomotion in mouse ID_{50}[e] (mg/kg)	hERG% block at 10 μM[f]
26	A		0.070	>30	1.97	114	4.1	1	10
27	B		**0.028**	**>30**	**2.65**	**191**	**4.2**	**0.5**	**10**
28	A		0.030	>30	2.59	445	5.5	—	37
29	A		0.111	>30	1.90	513	4.3	3	—
30	B		0.137	>30	2.59	334	4.1	—	—
31	A		0.805	>30	2.90	72	0.8	—	—
32	B		0.016	>30	3.76	15	1.4	0.3	36
33	A		0.030	>30	3.15	42	6.4	1	38
34	A		3.0	>30	0.73	495	0.9	—	—

[a] EC_{50} values are the average of at least two independent experiments.
[b] [^{3}H]-glycine uptake inhibition assay in cells transfected with hGlyT1[14] or hGlyT2[14] cDNAs.
[c] Solubility measured in a lyophilisation solubility assay (LYSA).[15]
[d] Pe: PAMPA permeation constant (10^{-6} cm/s) through artificial membranes.[22]
[e] Compound given orally, $n = 8$.
[f] Patch clamp assay, values are the average of at least two independent experiments.

successful since the 4-THP derivative **25**, displaying an excellent GlyT1 affinity (14 nM) showed more than twofold reduction in hERG activity (23% block at 10 μM) over the parent compound **23**. In addition, this compound exhibited an improved aqueous solubility (76 μg/mL) and an excellent in vivo potency with an ID_{50} of 0.5 mg/kg in the L-687,414-induced hyperlocomotion assay. In contrast to **25**, the 2-THP isomer **24** showed a fairly low GlyT1 activity (205 nM) and was therefore not profiled further.

In summary, from the SAR and optimisation studies performed on the western aromatic side of our benzoylisoindoline class, the dihydro-pyrrolo-pyridine fragment A and the 4-THP-isoindoline fragment B (see Table 1) emerged as two excellent scaffolds. Indeed, their combination with the 5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl moiety on the eastern side resulted in the two potent and selective GlyT1 inhibitors **19** and **25** showing balanced molecular properties, excellent in vitro selectivity and good in vivo potency. Keeping these two newly identified scaffolds in place, our next effort was directed at exploring the SAR at the position 2 of the eastern 5-methanesulfonyl-substituted-benzoyl moiety. Towards this end, a set of diverse substituents was evaluated including alkoxy groups of varied chain length and steric bulk, aromatic groups and amine systems. Results obtained with selected examples are presented in Table 2. With isopropoxy (**26** and **27**) and isobutyloxy (**28**) analogues, good to excellent GlyT1 affinities of respectively 70, 28 and 30 nM were obtained. As already observed in the parent benzoylpiperazine series from which RG1678 emerged,[13,14] more extended substituents such as the 3,3,3-trifluoro-propoxy (**29** and **30**) or benzyloxy (**31**) groups were less well tolerated. The attachment of fluoro-substituted phenyl groups delivered compounds with excellent activities as exemplified with compounds **32** (16 nM) and **33** (30 nM). Finally, an abrupt drop of GlyT1 activity was observed upon introduction of cyclic amine systems like the morpholine group (**34**). Among the set of potent GlyT1 compounds thus identified, the most favorable hERG profiles were obtained with the isopropoxy anologues **26** and **27** for which only a 10% block was measured at a concentration of 10 μM. The more extended isobutyloxy derivative **28** and the more lipophilic fluoro-substituted

Table 3
Pharmacokinetics properties of **19**, **25** and **27** in rat[a]

	Compound		
	19	**25**	**27**
iv dose (mg/kg)	2.0	2.2	1.7
CL (mL/min/kg)	1.7	21	22
V_{ss} (L/kg)	1.4	3.7	2.0
po dose (mg/kg)	2	6.8	5.7
Bioavailability F (%)	55	65	40
$T_{1/2}$ (h)	6.0	3.2	1.6
Brain/plasma	0.2	0.6	0.6

[a] Values are an average of two independent experiments.

Table 4
Effect of **19**, **25**, **32** on the extracellular glycine levels in rats striatum at 10 mg/kg po[a] and their plasma and brain exposures.

Compound	Max. fold inc. of glycine	Fold inc. of glycine at 3 h	Plasma[b] (ng/mL)	Brain[b] (ng/mL)	Brain[b]/GlyT1 EC_{50}
19	1.8	1.8	2500	500	20
25	2.1	2.0	480	274	39
27	1.9	1.5	279	159	13

[a] $n = 6$.
[b] Measured at 3 h post dosing.

phenyl compounds **32** and **33** showed more than threefold higher hERG activities.[20] Gratifyingly, in addition to their favorable hERG profiles, isopropoxy substituted compounds **26** and **27** exhibited good to excellent in vivo potencies with ID_{50} values of respectively 1 and 0.5 mg/kg after oral dosing.

The compounds showing the highest in vivo potencies: the dihydro-pyrrolo-pyridine **19** and the two THP-substituted derivatives **25** and **27** were selected for further evaluation. Pleasingly, in a CEREP selectivity screen performed against a panel of 92 targets including transmembrane and soluble receptors, enzymes, ion channels and monoamine transporters,[21] all three analogues demonstrated a highly selective profile (<20% inhibition at 10 μM measured for all targets). In single dose pharmacokinetic studies in rats (Table 3), **19** exhibited a low systemic clearance. In contrast, an intermediate clearance was measured for the THP derivatives **25** and **27**. These results correlated well with the intrinsic clearances measured in rat microsomes which were low for **19** (Cl_{int}: 1.9 μL/min/mg protein) and medium for **25** and **27** (13.9 and 18.9 μL/min/mg protein, respectively). The three compounds showed intermediate volumes of distribution and good oral bioavailabilities (40–65%). The brain penetration was good for **25** and **27** (brain/plasma: 0.6) and more moderate for **19** (brain/plasma: 0.2). The terminal half-lives for all three compounds were in the favorable range, although significantly shorter for the more rapidly cleared THP derivatives **25** and **27** (3.2 and 1.6 h, respectively) than for the dihydro-pyrrolo-pyridine **19** (6 h).

This favorable data prompted us to evaluate the effect of compounds **19**, **25** and **27** on the extracellular level of glycine in rat striatum in a microdialysis study (Table 4).

We were delighted to observe that, at an oral dose of 10 mg/kg, the three compounds produced a robust glycine increase in the range of 1.8 to 2.1-fold over basal levels. After 3 h, at which time the extracellular fluid sampling was stopped and the animal sacrificed, the PD effect remained strong for compounds **19** and **25** (1.8- and 2.0-fold, respectively), but was significantly diminished for **27** (1.5-fold), a result fully in agreement with the half-lives measured in plasma for the three compounds in PK studies (vide supra). The PD effect at 3 h post dosing correlated well with the brain level corrected by the in vitro GlyT1 potencies of the tested compounds (Table 4).

In summary, we report here on the discovery of benzoylisoindolines, a novel structural class of GlyT1 inhibitors originating from our previously reported benzoylpiperazine series. From the initial compound **8**, the SAR and the lead optimization effort, focused primarily on addressing the hERG liability and on improving in vivo efficacy resulted in the identification of potent GlyT1 inhibitors such as **19**, **25** and **27** displaying excellent overall in vitro and in vivo profiles.

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