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Discovery of benzoylpiperazines as a novel class of potent and selective GlyT1 inhibitors

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ABSTRACT

Screening of the Roche compound library led to the identification of the benzoylpiperazine **7** as a structurally novel GlyT1 inhibitor. The SAR which was developed in this series resulted in the discovery of highly potent compounds displaying excellent selectivity against the GlyT2 isoform, drug-like properties, and in vivo efficacy after oral administration.

Both clinical observations and preclinical studies suggest that hypofunction of *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 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 like **4**[9] and **5**,[10] have been described (Fig. 1). We have also contributed to this field and reported recently on the optimization of the non-sarcosine based spiropiperidine **6**.[11]

During our continued efforts to discover and develop structurally novel and selective GlyT1 inhibitors, the Roche compound collection was screened. This campaign led to the identification of the benzoylpiperazine hit **7** as a potent inhibitor of GlyT1 (15 nM), showing more than 300-fold selectivity against the type 2 isoform. **7** is characterized by the presence on the benzoyl moiety of a morpholine and a nitro group occupying positions 2 and 5, respectively.

In this letter, we describe the SAR studies obtained in this novel benzoylpiperazine class at positions 2, 5, and at the left-hand aromatic ring attached to the piperazine moiety (Fig. 2). We also report on the strategy we followed that led to the identification of highly potent and selective analogues displaying drug-like properties and in vivo efficacy after oral administration.

Our synthetic strategy[12] entailed mainly two straightforward and complementary approaches allowing for rapid modification of the three exit vectors around the central benzoylpiperazine core (Scheme 1). The first route that led to the amino analogues **13**, **15**–**18**, and **20**–**26** involved the reaction under thermal conditions of amines with the 2-halogen-substituted benzoyl piperazine precursors **67a**–**d** prepared under standard amide coupling conditions

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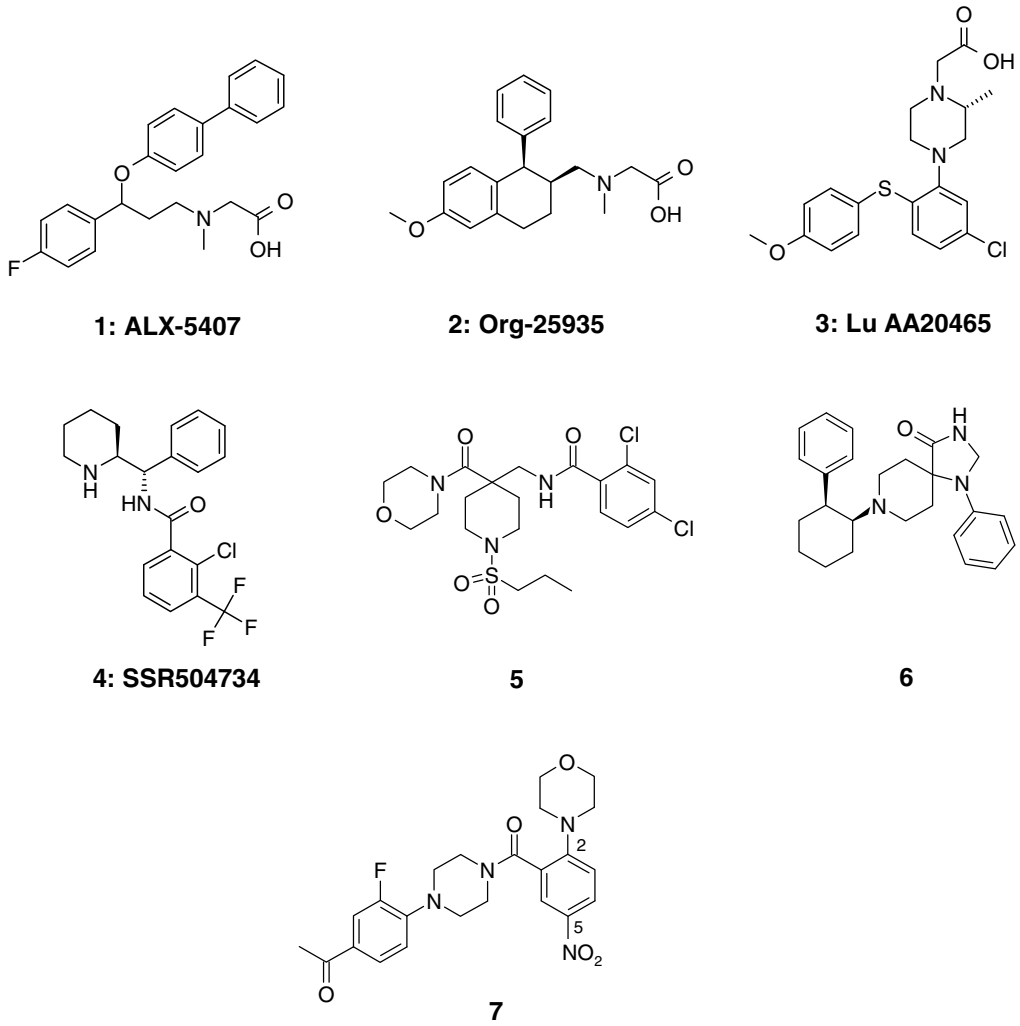


Figure 1. GlyT1 inhibitors.

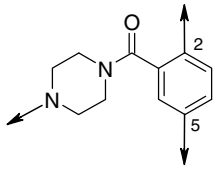


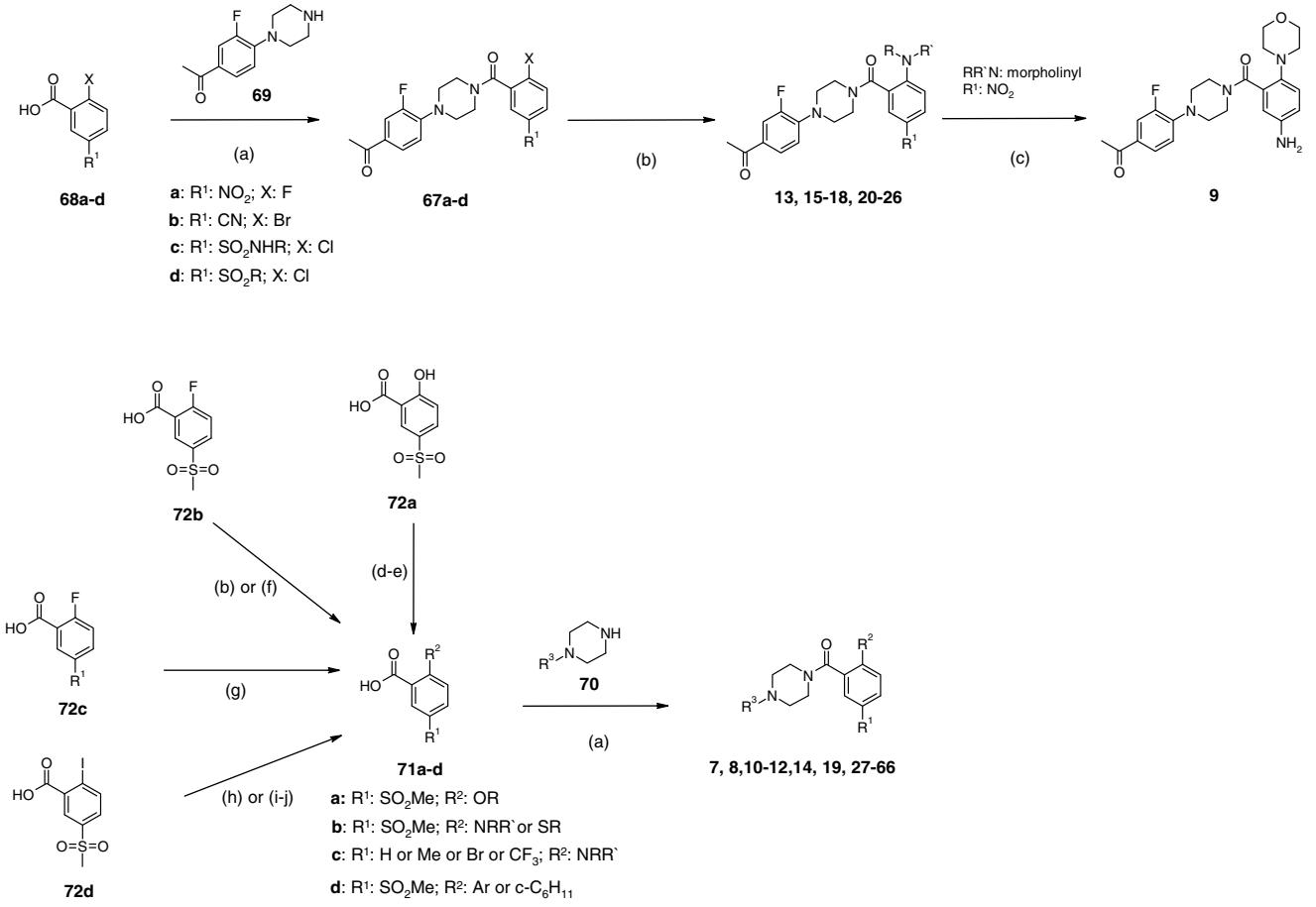
Figure 2. Core benzoylpiperazine structure and the three exit vectors explored.

from the 2-halogen-benzoic acids **68a–d** and piperazine **69**. The second route that led to compounds **7**, **8**, **10–12**, **14**, **19**, and **27–66** consisted in coupling the aryl piperazine **70** with the appropriately functionalized benzoic acids **71a–d**. Well-established methods were used for the preparation of these acids from their precursors **72a–d** as indicated in Scheme 1: Mitsunobu alkylation for the 2-alkoxy-substituted acid **71a**, thermal conditions for the 2-alkylsulfanyl and 2-alkylamino-substituted acids **71b–c**, and Suzuki coupling for the 2-aryl- or 2-cycloalkyl-substituted acids **71d**.[13]

Starting from **7,** our first effort was aimed at identifying suitable groups in position 5 of the benzoyl ring to replace the nitro substituent: a moiety often causing safety concerns due to its well-documented mutagenic and carcinogenic potential.[15] Table 1 summarizes the in vitro potency at GlyT1 and selectivity against GlyT2 of analogues prepared. First, removal of the nitro group to give (**8**) resulted in the complete loss of GlyT1 activity. Similar detrimental effect was observed after its replacement with either electron-donating or neutral groups (**9–10**) as well as with lipophilic electron-withdrawing (EWG) groups (**11–12**).

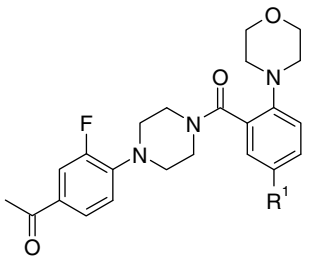
In contrast, in vitro potency recovered with the introduction of polar EWG groups (**13–16**). In particular, high activity was obtained with the methylsulfone (**14**), methylsulfonamide (**15**), and sulfonamide (**16**) derivatives, respectively, showing 70, 100, and 120 nM activity at GlyT1. Gratifyingly, the introduction of such groups simultaneously abolished the low micromolar activity at the GlyT2 isoform seen with the starting hit **7**. Introduction of larger substituents than methyl on the sulfonyl group (**17–18**) resulted in a severe drop in GlyT1 activity, which we postulate to be due to limited space available in this region of the receptor.

Molecular properties as well as metabolic stability in rat and human liver microsomes for the most active nitro (**7**), nitrile (**13**), methylsulfone (**14**), and sulfonamides (**15–16**) analogues were measured (Table 2). All these derivatives possessed excellent membrane permeability as measured in the Pampa assay[16] and furthermore, the sulfone and sulfonamide derivatives (**14–16**) exhibited a much higher aqueous solubility (pH 6.5) compared to the nitro and nitrile analogues **7** and **13**. As expected, the two sulfonamides displayed the highest polar surface area (PSA) above 90 $Å^2$, raising concern regarding the ability of these two compounds to penetrate the central nervous system (CNS). Lower



Scheme 1. Synthesis of benzoylpiperazines **7–66**. Reagents and conditions: (a) TBTU, DIPEA, DMF, rt, 60–95%; (b) RR′NH, THF, 80 °C, 70–97%; (c) H_2 (1 atm), Pd/C, MeOH, rt, 80%; (d) MeOH, cat. H_2SO_4, reflux, 90%; (e) ROH, di-*tert*-butyl-azodicarboxylate, triphenylphosphine, THF, rt then NaOH, 50 °C, 95–100%; (f) RSH, Cs_2CO_3, DMA, 90 °C, 88%; (g) RR′NH, dioxane, sealed tube, 130 °C, 67–92%; (h) $ArB(OH)_2$, cat. $Pd(OAc)_2$, Na_2CO_3, H_2O, rt, 92–95%; (i) 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane, cat. $Pd(dppf)Cl_2$, KOH, dioxane, 80 °C, 57%; (j) Pd/C, ammonium formate, MeOH, reflux, 80%.

Table 1
In vitro inhibitory activity of **7–18** at GlyT1 and GlyT2[a]



Compound	R^1	GlyT1 EC_{50}[b] (μM)	GlyT2 EC_{50}[b] (μM)	Selectivity[c]
7	NO_2	0.015	4.8	320
8	H	>30	nd	
9	NH_2	>30	>30	
10	CH_3	>30	>30	
11	Br	>30	5.1	<0.2
12	CF_3	26.0	11.0	0.4
13	CN	0.18	13	72
14	SO_2Me	0.07	>30	>417
15	SO_2NHMe	0.1	>30	>300
16	SO_2NH_2	0.12	>30	>250
17	SO_2n-Pr	1.6	>30	
18	SO_2CH_2Ph	>30	>30	

[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[14a] or hGlyT2[14b] cDNAs.
[c] Ratio of the EC_{50} (μM) values GlyT2/GlyT1.

Table 2
Molecular properties and microsomal clearances for **7**, **13–16**

Compound	Pampa, Pe[a]	Solubility[b]	PSA[c]	CLint[d] (rat microsomes)	CLint[d] (human microsomes)
7	4.7	9	92	106	35
13	6.1	<1	73	53	31
14	3.1	30	82	40	26
15	5.3	30	94	106	43
16	3.3	308	105	nd	31

[a] Pe: permeation constant (10^{-6} cm/s).[16]
[b] Solubility (μg/mL) measured in a lyophilization solubility assay.[17]
[c] PSA: polar surface area calculated with Moloc.[18]
[d] CLint: intrinsic clearance (μL/min/mg protein).

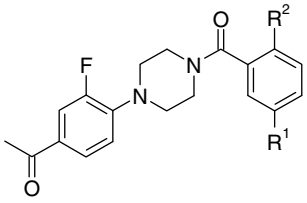
and more favorable PSA values were obtained for the nitrile (**13**) and the methylsulfone (**14**) derivatives. Finally, encouraging microsomal stability data were obtained for the methylsulfone analogue **14** showing a medium in vitro clearance in both the rat and human species. Altogether, these results demonstrate that among the groups tested at position 5, the methylsulfone function offers the best opportunity to generate compounds having CNS drug-like properties, and as a result constitutes our preferred motif at this position. Pleasingly, in a CEREP selectivity screen performed against a panel of 80 targets including transmembrane and soluble receptors, enzymes, ion channels, and monoamine transporters,[19] the methylsulfone compound **14** exhibited a highly selective profile (< 20% inhibition at 10 μM was measured for all targets).

Next, SAR exploration at position 2 of the benzoyl ring in hit **7** and compound **14** was conducted (Table 3). Deletion of the morpholine unit (**19**) as well as its replacement with smaller alkyl-substituted amino groups (**20**–**22**) resulted in inactive or weakly active analogues. Pleasingly, a dramatic improvement in activity was seen by increasing the size of the alkylamino substituent as seen with the isopropyl (**23**), cyclohexyl (**24**), and piperidinyl (**25**) derivatives, which were found to display 1–2 nM activity at GlyT1. An abrupt drop of activity was, however, observed upon introduction of more extended substituents like the cyclohexylmethyl group (**26**), suggesting that substituents at position 2 fit in a size limited pocket of the GlyT1 receptor. Further SAR exploration revealed to our delight that activity was in fact not restricted to the presence of an alkylamino residue at this position and that, on the contrary, great latitude for variation was possible. Indeed, low nanomolar GlyT1 activity was also obtained with analogues carrying a wide array of structurally diverse substituents like alkoxy groups (**27**-**29**), alkylsulfanyl groups (**30**), and aromatic groups (**31**–**32**). All these derivatives, in addition, displayed excellent selectivity versus the GlyT2 isoform.

Finally, SAR around the left-hand aromatic system was explored (Table 4). A rapid scanning of electron-donating (–OMe), electron neutral (–Me), and EWG groups (–Cl and –CF_3) at the *ortho*, meta, and *para* positions of the aromatic ring (**33**–**44**) revealed that best activity was reached with the presence of an EWG group in *para* position, as exemplified with the 4-trifluoromethyl-substituted derivative **44**: 100 nM. In fact, further exploration showed that a variety of EWGs were allowed at this position. Indeed, not only lipophilic groups, but also moderately or strongly polar substituents were tolerated such as the cyano (**45**) or the methylsulfone group (**46**). Keeping these preferred motifs in place, a significant improvement in GlyT1 potency was measured upon the introduction of an additional EWG like fluorine, or cyano group at either the *ortho* or *meta* position as observed with compounds **47**–**51**. Interestingly, the replacement of the aromatic nucleus with heteroaromatic systems as exemplified with pyridine derivatives **52** and 5**3** was well tolerated. With all active derivatives, good to excellent selectivity against the GlyT2 isoform was seen (Table 4).

Having established a preliminary SAR at the three exit vectors around the central benzoylpiperazine core, the next step consisted in combining some of the preferred groups identified at the left-hand side as well as at position 2 on the right-hand benzoyl moiety, while keeping position 5 occupied with the favored methylsulfone group. This approach led to the identification of a number of highly potent GlyT1 inhibitors (Table 5), displaying no activity at the GlyT2 isoform (data not shown). Gratifyingly, the great structural diversity seen previously at position 2 was also observed with compounds **54**–**60** incorporating the 4-CF_3-phenyl group at the left-hand side. Indeed, low nanomolar activity was obtained with the alkylamino (**54**–**55**), the alkoxy (**56**–**57**), the aromatic (**58**–**59**), and the cycloalkyl (**60**) derivatives. In view of their favorable pharmacological activities in vitro, these compounds were assessed for solubility and metabolic stability. Interestingly, as seen in Table 5, the isopropyloxy and cyclopropylmethylenoxy derivatives **56** and **57** exhibited good aqueous solubility (pH 6.5) and excellent metabolic stability in mouse and human liver microsomes. Much less favorable results were obtained with the corresponding alkylamino, aromatic, and cycloalkyl compounds (**54**–**55**, **58**–**60**), which exhibited, in general, low solubility and medium microsomal clearance, a result likely due to the higher lipophilicity of these analogues compared to the alkoxy derivatives (see *c*log*P*, Table 5). Moreover, the positive influence of alkoxy groups on physico-chemical and metabolic properties was also observed when more polar left-hand aromatic rings than the 4-CF_3-phenyl group were in place. Indeed, for example, the cyclopropylmethylenoxy derivatives **62** and **65** incorporating, respectively, the cyano and methylsulfone-substituted

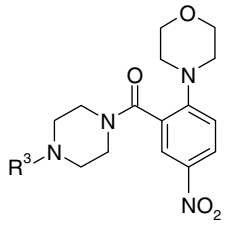
Table 3
In vitro inhibitory activity of **19**–**32** at GlyT1 and GlyT2[a]



Compound	R^1	R^2	GlyT1 EC_{50}[b] (μM)	GlyT2 EC_{50}[b] (μM)
19	NO_2	H	32	24.5
20	NO_2	NH_2	>10	3.3
21	NO_2	NHMe	1.9	1.4
22	NO_2	NMe_2	0.5	2.0
23	NO_2	NH-*i*-Pr	0.002	10
24	NO_2	NH-*c*-C_6H_{11}	0.002	8.5
25	NO_2	Piperidin-yl	0.001	4.0
26	NO_2	NH-CH_2-*c*-C_6H_{11}	>10	nd
27	SO_2Me	O-*i*-Pr	0.039	>30
28	SO_2Me	O-*i*-Bu	0.009	>30
29	SO_2Me	O-CH_2-*c*-Pr	0.015	>30
30	SO_2Me	S-*i*-Pr	0.015	>30
31	SO_2Me	Ph	0.069	>30
32	SO_2Me	3-F-Ph	0.016	>30

[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[14a] or hGlyT2[14b] cDNAs.

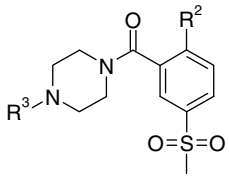
Table 4
In vitro inhibitory activity of **33**–**53** at GlyT1 and GlyT2[a]



Compound	R^3	GlyT1 EC_{50}[b] (μM)	GlyT2 EC_{50}[b] (μM)
33	2-OMe-Ph	>10	13.4
34	2-Me-Ph	>10	14.2
35	2-Cl-Ph	1.4	11.2
36	2-CF_3-Ph	7.1	>30
37	3-OMe-Ph	0.53	8.3
38	3-Me-Ph	1.1	4.0
39	3-Cl-Ph	0.7	3.1
40	3-CF_3-Ph	0.4	0.3
41	4-OMe-Ph	1.3	11.4
42	4-Me-Ph	2.9	7.7
43	4-Cl-Ph	0.31	1.17
44	4-CF_3-Ph	0.1	3.3
45	4-CN-Ph	0.078	1.1
46	4-SO_2Me	0.11	2.1
47	2-F, 4-CN-Ph	0.03	4.3
48	2-F, 4-SO_2Me	0.04	>30
49	2-CN, 4-CF_3-Ph	0.015	>30
50	2-F, 4-CF_3-Ph	0.041	29
51	3-F, 4-CF_3-Ph	0.037	15
52	5-CF_3, 6-Cl-2-Py	0.033	24
53	3-Cl, 5-CF_3-2-Py	0.047	>30

[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[14a] or hGlyT2[14b] cDNAs.

Table 5
In vitro inhibitory activity at GlyT1, molecular properties, and microsomal clearances of **54**–**66**



Compound	R^3	R^2	GlyT1 EC_{50}[a,b] (μM)	*clog P*	Solubility[c] (μg/mL)	CLint[d] (mouse microsomes)	CLint[d] (human microsomes)
54	4-CF_3-Ph	Morpholinyl	0.045	1.97	3	15	10
55	4-CF_3-Ph	Piperidin-yl	0.075	3.5	<1	125	12
56	4-CF_3-Ph	O-*i*-Pr	0.082	2.8	62	0	0
57	4-CF_3-Ph	O-CH_2-*c*-Pr	0.04	2.97	15	1	6
58	4-CF_3-Ph	Ph	0.031	3.79	<1	9	12
59	4-CF_3-Ph	4-F-Ph	0.029	3.95	<1	5	12
60	4-CF_3-Ph	-*c*-C_6H_{11}	0.025	4.52	<1	11	10
61	2-F, 4-CN-Ph	Piperidin-yl	0.012	2.36	14	33	16
62	**2-F, 4-CN-Ph**	**O-CH_2-*c*-Pr**	**0.016**	**1.83**	**31**	**9**	**4**
63	2-F, 4-CN-Ph	Ph	0.02	2.64	<1	124	5
64	2-F, 4-SO_2Me	Piperidin-yl	0.046	1.35	5	53	29
65	2-F, 4-SO_2Me	O-CH_2-*c*-Pr	0.052	0.82	50	14	1
66	2-F, 4-SO_2Me	Ph	0.057	1.62	18	90	0

[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.[14a]
[c] Solubility (μg/mL) measured in a lyophilization solubility assay.[17]
[d] CLint: intrinsic clearance (μL/min/mg protein).

aromatic rings consistently exhibited higher solubility and metabolic stability than the corresponding piperidinyl and phenyl analogues **61**, **64** and **63**, **66**.

Among the compounds prepared at this stage, the cyclopropylmethylenoxy analogue **62** attracted our most attention since it demonstrated particularly good in vitro potency at GlyT1 (16 nM), no activity at the GlyT2 isoform up to the highest concentration tested (30 μM), good physical properties with moderate lipophilicity: *clog P* = 1.83, good aqueous solubility: 31 μg/mL (pH 6.5), high membrane permeability: Pe (Pampa): 3.2, and good mouse and human microsomal stability.

Consequently, **62** was selected for further evaluation. An in vivo pharmacokinetic study in mouse (Table 6) revealed that **62**, as expected based on its in vitro profile, exhibited low clearance, good plasma exposure, excellent oral bioavailability, and moderate plasma protein binding (PPB). Despite demonstrating a relatively low brain/plasma ratio, **62** could achieve nevertheless a robust exposure in the brain, with a C_{max} of 373 ng/g at the dose of 10 mg/kg (po), above its inhibitory activity at the GlyT1 transporter.

These favorable data prompted us to evaluate the effect of compound **62** on the extracellular level of glycine in mouse striatum (Fig. 3). We were delighted to observe that **62** produced at the dose of 10 mg/kg administrated orally, a robust and sustained increase of glycine levels: 2.3-fold over basal level at 40 min and 1.7-fold at 140 min. Encouraged by this result, further in vitro profiling in safety assays was performed.

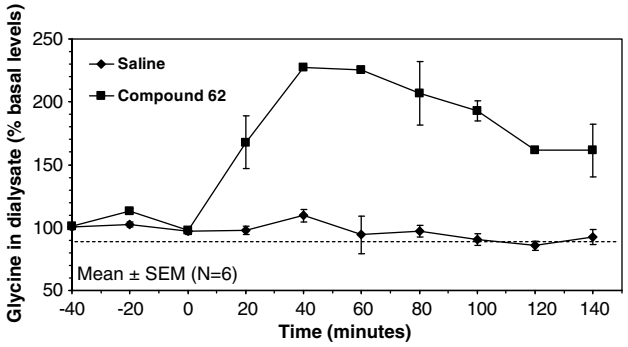


Figure 3. Effect of **62** on the extracellular glycine levels in mouse striatum at 10 mg/kg po.

Table 6
Pharmacokinetics properties of **62** in mouse

Parameter	Value[a]
Iv dose (2 mg/kg)	
CL (mL/min/kg)	9.5
V_{ss} (L/kg)	2.8
Po dose (10 mg/kg)	
Bioavailability *F* (%)	100
*T*1/2 (h)	5.8
C_{max} plasma (ng/mL)	3875
C_{max} brain (ng/g)	373
B/P	0.1
PPB (% unbound)	12

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

Compound **62** (like all compounds tested in this series) exhibited no significant inhibition of the major drug metabolizing CYP450 enzymes (3A4, 2D6, 2C9, 2C19, 1A2; IC_{50} > 29.1 μM). However, **62** was found to exhibit a fairly high activity at the hERG potassium channel with an IC_{50} of 0.6 μM measured in a patch-clamp assay.[20]

In summary, we report here on the discovery of benzoylpiperazines as a novel chemotype of GlyT1 inhibitors. Starting from the chemically tractable HTS hit **7**, rapid exploration of SAR accompanied by the early assessment of molecular property and metabolic stability of the synthesized derivatives allowed the prompt identification of a highly promising sub-series in which the nitro and morpholine residues in **7** are replaced, respectively, by a methylsulfone and an alkoxy group. Within this 'alkoxy-methylsulfone-benzoylpiperazine' sub-series, highly potent and selective GlyT1 inhibitors were identified, which as seen with representative compound **62** demonstrated drug-like properties and in vivo efficacy after oral administration. Results from our subsequent lead optimization work in this sub-series, which was mainly focused on the improvement of brain penetration/in vivo activity as well as of hERG selectivity, will be reported in due course.

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13. All intermediates and final compounds were characterized by ^{1}H NMR (300 MHz) and mass spectroscopy. The following data were obtained for compounds **56**, **57**, and **62**. Compound **56**: ^{1}H NMR ($CDCl_3$): 1.31 (m, 6H), 3.06 (s, 3H), 3.21 (m, 2H), 3.36 (m, 4H), 3.96 (m, 2H), 4.71 (septuplet, J = 6.0, 1H), 6.94 (d, J = 8.6, 2H), 7.04 (d, J = 8.8, 1H), 7.48 (d, J = 8.6, 2H), 7.86 (d, J = 2.3, 1H), 7.93 (dd, J = 2.3, J = 8.8, 1H); MS: m/z (%): 471.2 (100%, M+H$^+$). Compound **57**: ^{1}H NMR ($CDCl_3$): 0.34 (m, 2H), 0.62 (m, 2H), 1.26 (m, 1H), 3.06 (s, 3H), 3.22–3.55 (m, 6H), 3.85–4.12 (m, 4H), 6.94 (d, J = 8.7, 2H), 7.03 (d, J = 8.7, 1H), 7.51 (d, J = 8.7, 2H), 7.88 (d, J = 2.1, 1H), 7.94 (dd, J = 2.1, J = 8.7, 1H); MS: m/z (%): 483.5 (100%, M+H$^+$). Compound **62**: ^{1}H NMR ($CDCl_3$): 0.36 (m, 2H), 0.65 (m, 2H), 1.26 (m, 1H), 3.06 (s, 3H), 3.07–3.55 (m, 6H), 3.85–4.05 (m, 4H), 6.92 (t, J = 8.5, 1H), 7.02 (d, J = 8.7, 1H), 7.31 (dd, J = 1.9, J = 12.4, 1H), 7.39 (d, J = 8.3, 1H), 7.88 (d, J = 2.3, 1H), 7.94 (dd, J = 2.3, J = 8.7, 1H); MS: m/z (%): 458.5 (100%, M+H$^+$).
14. (a) Ceccarelli, S. M.; Pinard, E.; Stalder, H.; WO Patent 2005040166, 2005; *Chem. Abstr.* **2005**, *142*, 447121; Compound **6** used as positive comparator displayed an EC_{50} of 26 nM.; (b) Same conditions as described for the hGlyT1 assay (see Ref. 14a) with slight modifications: conc. [^{3}H]-glycine: 200 nM, cold glycine not present.
15. For a review, see Purohit, V.; Basu, A. K. *Chem. Res. Toxicol.* **2000**, *13*, 673.
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17. Compound initially in DMSO solution is lyophilized, then dissolved in 0.05 M phosphate buffer (pH 6.5), stirred for 1 h, and shaken for 2 h. After one night, the solution is filtered and the filtrate is analyzed by direct UV measurement or by HPLC-UV.
18. Gerber Molecular Design, Amden, Switzerland, http://www.moloc.ch.
19. The panel consisted in targets included in the standard CEREP high throughput profile screen complemented with enzymes (phosphodiesterases, kinases, MAO-A, COMT, acetylcholineesterase). http://www.cerep.fr.
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