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Sarcosine based indandione hGlyT1 inhibitors

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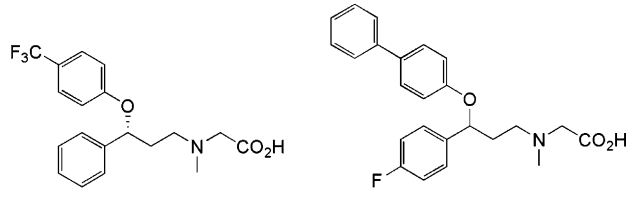
Abstract—A series of sarcosine based indandione hGlyT1 inhibitors has been developed. Optimization of substitution around the indandione and sarcosine moieties has led to highly potent inhibitors at hGlyT1, which show selectivity over a number of other receptors.

Hypoactivity of NMDA receptor mediated glutamatergic neurotransmission has been implicated in induction of negative symptoms of schizophrenia.[1] This is supported by the fact that competitive NMDA antagonists elicit psychotomimetic effects in humans.[2] As glycine is necessary as a co-agonist of glutamate at the NMDA receptor,[3] elevating synaptic levels of glycine by inhibition of the glycine reuptake system should lead to enhanced NMDA receptor function. Indeed, inhibitors of the GlyT1 glycine transporter[4] such as NFPS[5] and Org 24598[6] (Fig. 1) have been shown to elevate glycine levels in the CNS and reverse PCP-induced behaviour,[7] suggesting such compounds may have a role in treating the negative symptoms of schizophrenia.

In-house screening and pharmacophores developed from published hGlyT1 inhibitors[5,6,8] suggested that indandione-type molecules bearing a pendant sarcosine moiety might lead to a new series of hGlyT1 antagonists. The chemistry and structure–activity relationships (SARs) of this new series are described in this communication.

Initial chemistry efforts focussed on discovering the optimum chain length between commercially available 2-phenylindan-1,3-dione and sarcosine moieties. The indandione (**1**) was readily alkylated with a dibromoalkane (Scheme 1) or allyl bromide (Scheme 2; 4,5,6, X = H). Sarcosine *tert*-butyl ester was then appended by nucleophilic displacement or by reductive amination of the aldehyde formed by ozonolysis of the allyl adduct. Acid cleavage of the *tert*-butyl ester gave the amino acid salt of the desired compound (**2**).

Synthesis of substituted indandiones (**5** and **7**) started from commercially available substituted 1,2-diacids (**3**) or anhydrides (**4**). 3,4-Dichloro-5-methoxy phthalic acid[10] was readily available by oxidation of 2-propyl-5-methoxy-5,6-dichloroindanone.[12] Reaction of the anhydrides (**4**) with either phenyl or 4-fluorophenyl acetic acid in acetic anhydride, followed by sodium hydroxide as previously reported,[10] gave poor results. This could be improved to afford an almost quantitative yield, by replacing aqueous sodium hydroxide with sodium methoxide in methanol, as reported by He et al.[11]



Org 24598 **NFPS**

Figure 1. Sarcosine containing GlyT1 inhibitors.

Keywords: Sarcosine; Indandione; GlyT1 inhibitors; Selectivity; Potent.
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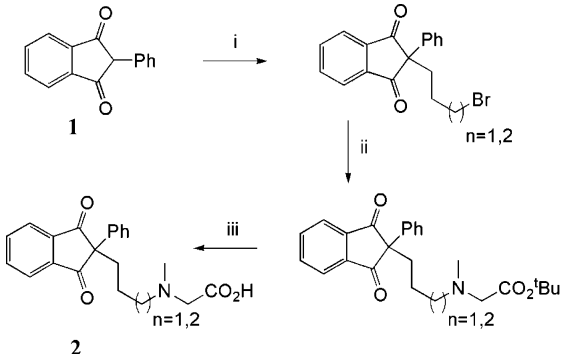
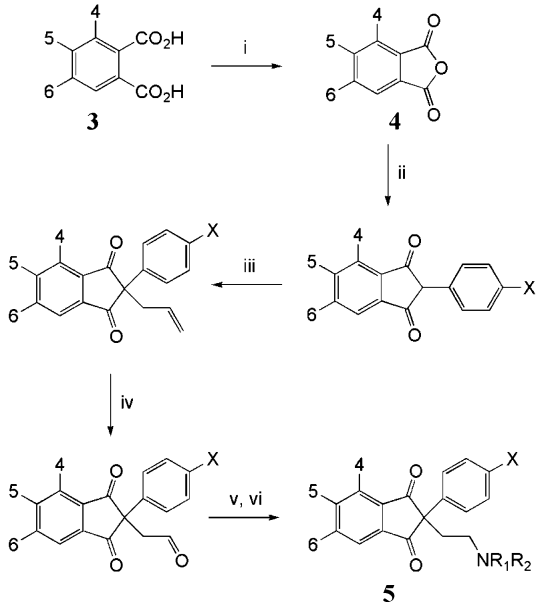


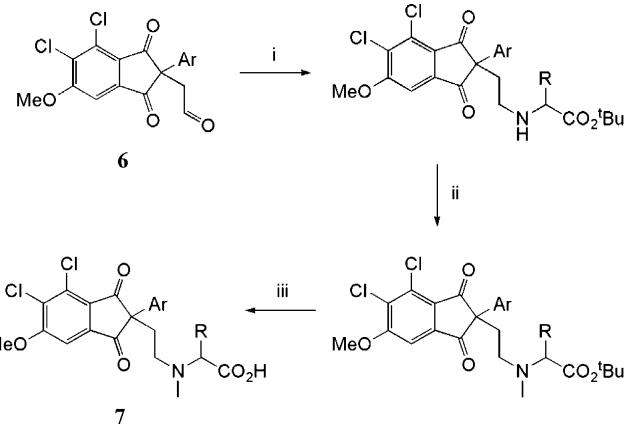
Scheme 1. Reagents and conditions: (i) 1,3-dibromopropane or 1,4-dibromobutane, K_2CO_3, acetone, 24 h, 60 °C, 80–95% yield; (ii) sarcosine *tert*-butyl ester hydrochloride, K_2CO_3, acetone, 72 h, 60 °C, 80% yield; (iii) TFA, DCM, 18 h, rt, 70–75% yield.



Scheme 2. Reagents and conditions: (i) Ac_2O, 1 h, reflux, 90% yield; (ii) 4-fluorophenyl or phenylacetic acid, Ac_2O, Et_3N, reflux, 1.5 h, then NaOMe, MeOH, reflux, 0.75 h, 90–98% yield; (iii) allyl bromide, K_2CO_3, acetone, 18 h, rt, quantitative; (iv) O_3, MeOH, DCM, −78 °C, 0.5 h, DMS, rt, 18 h, 80% yield; (v) amino acid *tert*-butyl ester, $NaBH(OAc)_3$, DCM, rt, 18 h, 90% yield; (vi) TFA, DCM, 18 h, rt, 70–75% yield.

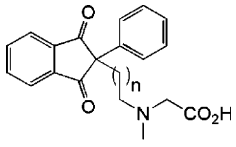
Aldehyde **6** was formed by allylation and ozonolysis as previously described. Substituted sarcosine derivatives were formed by reductive amination of **6** with the relevant amino acid *tert*-butyl ester. Where the substituted *N*-methyl amino acid fragment was not available, the primary amino acid ester was used, followed by reductive methylation with formaldehyde (Scheme 3).

In the case of compound **7d**, only the methyl ester of *iso*-butyric acid was available, so final hydrolysis was via 1 M sulfuric acid in 1,4-dioxane at elevated temperature. Compound **7f** was formed using *O*-*t*-butyl-protected serine *t*-butyl ester; hence, a final treatment with trifluoroacetic acid unmasked both acid and hydroxyl group.



Scheme 3. Reagents and conditions: (i) amino acid *tert*-butyl ester, $NaBH(OAc)_3$, DCM, rt, 18 h, 50–80% yield; (ii) HCHO, $NaBH_3CN$, MeCN, rt, 18 h, 40–85% yield; (iii) TFA, DCM, 18 h, rt, 70–75% yield.

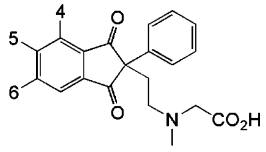
Table 1.



Compound	*n*	hGlyT1[a] IC_{50} (nM)
2a	3	13% at 3 μM
2b	2	2800
2c	1	103

Values represent geometric means of 3–6 determinations.
[a] Functional assay measuring inhibition of uptake of [^{14}C]glycine into human JAR cells expressing hGlyT1a.[9]

Table 2.

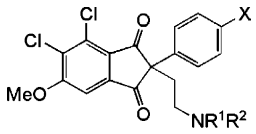


Compound	4	5	6	hGlyT1[a] IC_{50} (nM)
2c	H	H	H	103
5a	F	H	H	85
5b	H	Cl	H	28
5c	H	Cl	Cl	19
5d	Cl	Cl	OMe	1.9

Values represent geometric means of 3–6 determinations.
[a] Functional assay measuring inhibition of uptake of [^{14}C]glycine into human JAR cells expressing hGlyT1a.[9]

The initially unsubstituted compounds **2a**–**c** (Table 1) showed that a two carbon linker between the indandione and sarcosine was optimal for hGlyT1 potency. Substitution around compound **2c** was then explored (Table 2), showing that 4,5-dichloro-6-methoxy substitution

Table 3.



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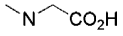
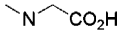
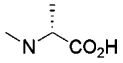
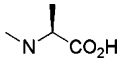
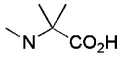
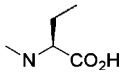
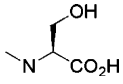
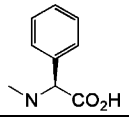
Compound	X	NR^1R^2	hGlyT1[a] IC_{50} (nM)
5d	H		1.9
7a	F		0.95
7b	H		19
7c	H		0.47
7d	F		38% at 3 μM
7e	F		6.4
7f	F		2.9
7g	H		1200
7h	F		1300

Values represent geometric means of 3–6 determinations.

[a] Functional assay measuring inhibition of uptake of [^{14}C]glycine into human JAR cells expressing hGlyT1a.[9]

of the indandione gave the very potent hGlyT1 inhibitor, **5d**. Incorporation of a 4-fluoro substituent on the pendant phenyl group (**7a**) gives a further modest improvement in potency (Table 3).

From investigation of substitution on sarcosine (Table 3) it became clear that there is significant steric intolerance around the amino acid, with cyclic substituents such as **7g** and larger groups (**7h**) having a detrimental effect on potency. Compound **7d** showed this area to be particularly sensitive as geminal substitution with two methyl groups abolishes all potency, whereas both methyl stereoisomers (**7b** and **7c**) show respectable IC_{50}'s. Compounds **7b** and **7c** also indicate the enantiospecificity of substitution; the (S) amino acid showing a 40-fold improvement in potency over (R).

The more potent compounds **5d**, **7a** and **7c** were counterscreened against a number of receptors implicated in schizophrenia, or which could lead to potential side effects.[13] These compounds showed little or no binding (>1000-fold selective) to hGlyT2,[9] $h5HT_{1A}$,[14] $h5HT_{2A}$,[15] hD_2[16] and hERG[17] making them selective tools for elucidating further the effects of hGlyT1 inhibition.

A novel series of sarcosine based indandione hGlyT1 inhibitors has been investigated. With suitable substitution around the indandione and on the amino acid, potent inhibitors have been discovered, with selectivity over a number of receptors. The SAR around the amino acid is extremely sensitive, showing stereochemical preference with small groups, leading to compound **7c**, with excellent potency at hGlyT1.

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