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Phenyl ureas of creatinine as mGluR5 antagonists. A structure–activity relationship study of fenobam analogues

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Abstract—Fenobam (**1**) was developed by McNeil Laboratories as an anxiolytic agent with an unknown molecular target in the late 1970s. In a recent publication, it was revealed that fenobam is a non-competitive mGluR5 antagonist. Herein, we present the structure–activity relationship of fenobam and its analogues and similarities between the SAR of mGluR5 antagonism and the SAR of CNS properties originally reported by McNeil are discussed.

The metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors that play important roles in modulating neuronal signalling in the central nervous system.[1] Eight subtypes have been identified and these are divided into three different groups depending on sequence similarities, second messenger coupling and pharmacology: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3) and group III (mGluR4 and mGluR6-8).[2] Preclinical data support the use of mGluR5 antagonists in the treatment of various neurological, psychiatric and pain disorders[3–6] and gastro-esophageal reflux disease.[7]

Fenobam (**1**) (Fig. 1) was developed by McNeil as an anxiolytic agent with an unknown molecular target in the late 1970s.[8,9] According to the literature, fenobam showed poor efficacy in the clinical trials with high variability in plasma exposure and lack of correlation between dose, plasma levels and clinical response.[8] The in vitro clearance of fenobam was found to be moderate (approx. 50 μL/min/mg in both human and rat liver microsomes) but Wu et al. reported that metabolism was more extensive in vivo than in vitro in rat.[10] Porter et al. recently published their finding that fenobam is a non-competitive mGluR5 antagonist.[11] This prompted us to report our own work on fenobam.

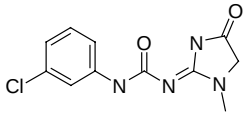

Figure 1. Fenobam (**1**).

We identified fenobam as a mGluR5 antagonist (FLIPR IC_{50} 0.33 μM, binding IC_{50} 0.46 μM) by a high throughput screening of the AstraZeneca compound collection. A follow-up programme was initiated to synthesize analogues, both compounds exemplified in the McNeil publications[9,12,13] and new compounds, in order to develop a structure–activity relationship and try to improve the potency.

The fenobam structure is a simple 3-chlorophenyl urea of the commercially available heterocycle creatinine. The creatinine analogues (starting materials for **12**–**23**) were synthesized from the corresponding N-alkylated

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amino acid or proline (compounds **17**–**23**) and cyanamide,[14] and the ureas were then synthesized by reaction with the appropriate aryl isocyanate as described for fenobam.[9] The heterocyclic ring used as starting material for compound **27** was made according to a literature protocol.[15]

Replacement of the chloro substituent on the phenyl ring (**2**–**6**) (Table 1) with other substituents did not improve the potency, though the 3-methyl (**3**) and the 3-bromo (**5**) analogues were in about the same potency range. The compound with an unsubstituted phenyl ring (**7**) was only a weak antagonist. An alkyl chain was not tolerated as an aryl substitute (**8**) and thienyl (**9**) was found to be comparable to the unsubstituted phenyl. The methyl pyridyl analogues (**10** and **11**) gave compounds with IC_{50} on a micromolar level. The small structural changes on the creatinine-based ureas in entry **12**–**17** (Table 1) were tolerated and the *N*-ethyl analogue (**13**) was slightly more potent than fenobam in both FLIPR and binding (FLIPR IC_{50} 0.25 μM, binding IC_{50} 0.18 μM). Increasing steric bulk deteriorated the potency, like when R^2 was butyl (**15**) and when R^1 was phenyl (**16**). Formation of a five-membered ring of the substituents R^1 and R^2 afforded a less potent compound for the 3-chlorophenyl derivative (**17**) but resulted in similar potency for the unsubstituted phenyl (**18**) (cf. compound **7**). Different substituent pattern on the phenyl ring gave inactive compounds (**19**–**24**). This is interesting to compare with the data from Rasmussen et al. for the 1-methylpyrrolidine-2-imine series[13] where other disubstitution patterns than 2,6-substitution resulted in less potent compounds concerning CNS properties like antianxiety and anticonvulsive activities. Accordingly, a mere 2-substitution at the phenyl ring also resulted in less potent compounds concerning CNS activities.

Replacement of the urea with an amide (Fig. 2) gave one weak antagonist (**25**) (FLIPR IC_{50} 2.3 μM) and one inactive compound (**26**), depending on linker length.

The isomer of fenobam with the carbonyl group in the other position on the heterocyclic ring (**27**) (Table 2) was inactive as well as the 3-chlorophenyl urea of *N*-methyl imidazole (**28**).

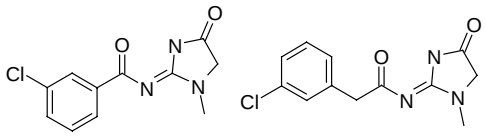
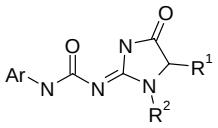


Figure 2. Amides (**25**) and (**26**).

Table 1. Potency data for fenobam (**1**) and related creatinine ureas (**2**–**24**)



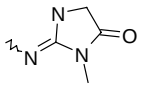
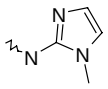
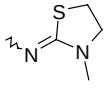
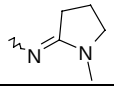
Compound	Ar	R^1	R^2	FLIPR IC_{50} (μM)[a]	Binding IC_{50} (μM)[b]
1[c]	3-Cl-Ph	H	Me	0.33	0.46
2	3-CN-Ph	H	Me	3.9	3.4
3[c]	3-Me-Ph	H	Me	0.55	nd
4[c]	3-MeO-Ph	H	Me	2.8	nd
5[c]	3-Br-Ph	H	Me	0.38	nd
6	3-CO_2Me-Ph	H	Me	>10	nd
7[c]	Ph	H	Me	4.9	nd
8	*n*-Hexyl	H	Me	>10	nd
9	2-Thienyl	H	Me	4.9	nd
10	5-Me-2-Pyridyl	H	Me	3.1	nd
11	3-Me-2-Pyridyl	H	Me	1.9	nd
12	3-Cl-Ph	Me	Me	0.49	1.3
13	3-Cl-Ph	H	Et	0.25	0.18
14	3-Cl-Ph	Me	Et	0.41	0.32
15	3-Cl-Ph	H	*n*-Butyl	0.68	1.3
16	3-Me-Ph	Ph	Me	1.4	>10
17	3-Cl-Ph	–$CH_2CH_2CH_2$–		0.80	1.6
18	Ph	–$CH_2CH_2CH_2$–		4.2	nd
19	4-Cl-Ph	–$CH_2CH_2CH_2$–		>10	nd
20	3-Cl, 4-Me-Ph	–$CH_2CH_2CH_2$–		>10	nd
21	2-Me-Ph	–$CH_2CH_2CH_2$–		>10	nd
22	2,5-Me_2-Ph	–$CH_2CH_2CH_2$–		>10	nd
23	2,3-Me_2-Ph	–$CH_2CH_2CH_2$–		>10	nd
24	3,5-Cl_2-Ph	H	Me	>10	nd

[a] Effect on glutamate induced $[Ca^{2+}]_i$ in a cell line expressing human mGluR5d (splice variant of mGluR5 with a truncated C-terminal domain) using a fluorescence imaging plate reader (FLIPR). Values are means of three experiments.

[b] Effect on [^{3}H]MPEP binding in rat brain membranes. Values are means of two experiments; nd = not determined.

[c] Mentioned in Ref. 9 among anxiolytic compounds but no biological data given.

Table 2. Potency data for 3-chlorophenyl ureas (**27**–**30**)

Compound	Structure	FLIPR IC_{50} (μM)[a]	Binding IC_{50} (μM)[b]
27[c]		>10	>10
28		>10	>10
29[d]		0.26	1.2
30[e]		0.62	2.0

[a] Effect on glutamate induced $[Ca^{2+}]_i$ in a cell line expressing human mGluR5d (splice variant of mGluR5 with a truncated C-terminal domain) using a fluorescence imaging plate reader (FLIPR). Values are means of three experiments.

[b] Effect on [^{3}H]MPEP binding in rat brain membranes. Values are means of two experiments.

[c] Mentioned in Ref. 9 among anxiolytic compounds but no biological data given.

[d] Mentioned in Ref. 12 among anticonvulsant compounds, but inactive. Not tested as an anxiolytic.

[e] Described in Ref. 13 to have anxiolytic activity.

The activities for compounds **29**[12] and **30**[13] are in agreement with the SAR for anxiolytic activity presented by Rasmussen et al. in the 1-methylpyrrolidine-2-imine series. Compound **30** was described to have anxiolytic activity, while compound **29** only was tested for anticonvulsant effect and was found to be inactive. The latter should rather have been tested for anxiolytic activity as well, following Rasmussen's SAR studies: *meta*-substituted phenylureas represent a favourable framework for anxiolytics and 2,6-disubstituted phenylureas for muscle-relaxant activity.[13] When assuming that only the anxiolytic activity is caused by mGluR5 antagonism, it was not surprising that xilobam (**31**)[13] (Fig. 3), a 2,6-disubstituted phenylurea with reported muscle-relaxant activity but inactive as an anxiolytic, did not show mGluR5 antagonism (FLIPR $IC_{50} > 10$ μM). Comparing compounds **1** and **27**–**30** suggests that the exocyclic imine double bond is crucial for the potency, that an endocyclic carbonyl group is not mandatory, but if present it has to be located appropriately and that it does not seem to make a drastic difference as to which of the heterocycles from creatinine, entry 29 or 30 is chosen as long as the phenylurea containes a 3-substituent. Altogether this gives a rather tight structure–activity relationship with only small changes tolerated in the molecule. Both the 3-substituted phenyl ring and the exocyclic imine double bond are important features for the mGluR5 potency and the creatinine ring tolerates only small alkyl substituents.

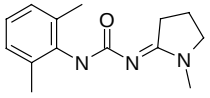


Figure 3. Xilobam (**31**).

The results presented herein in connection with literature data provide a clear indication that anxiolytic activity of fenobam analogues is mediated by mGluR5 antagonism, whereas the muscle-relaxant activity of 2,6-disubstituted species has to originate from a different mode of action. A correlation of CNS activity with the substitution pattern of the phenylurea unit as elaborated for the 1-methylpyrrolidine-2-imine series (like compound **30**) by Rasmussen et al. seems to represent a rather generally valid relationship as long as the heterocycle attached to the urea fulfils certain demands.

In summary, we have only been able to make small improvements in potency compared to fenobam, and we do not consider fenobam as a suitable chemical starting point for a drug-hunting project. However, the structure–activity relationship of fenobam and its analogues could be useful information for other lead-series concerning mGluR5.

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