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Discovery of 1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamides as novel, allosteric mGluR5 antagonists

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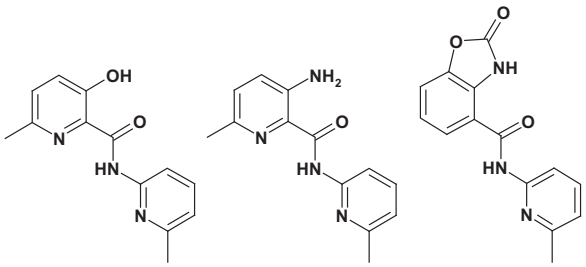
ABSTRACT

1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamides constitute a new series of allosteric mGluR5 antagonists. Variation of the substituents attached to the heterocyclic scaffold allowed to improve the physico-chemical parameters for optimization of the aqueous solubility while retaining high in vitro potency.

Glutamate is the predominant excitatory neurotransmitter in the mammalian brain and acts at several ionotropic (AMPA, kainate and NMDA) and metabotropic glutamate receptor (mGluR) subtypes. Whereas the ionotropic receptors mediate fast synaptic transmissions, their metabotropic counterparts work in a modulating fashion on synaptic signaling. The eight known mGluR subtypes are divided into three groups, based on their sequence similarities, effector coupling and agonist/antagonist selectivity. Group I comprises mGluR1 and mGluR5, both positively coupled to phosphoinositide hydrolysis via activation of phospholipase C. Group II consists of mGluR2 and 3, both of them negatively coupled to cAMP production via adenylyl cyclase, and group III includes mGluR4, 6, 7 and 8 which are also negatively coupled to cAMP production. mGlu5 receptors are strongly expressed in the striatum, hippocampus and cerebral cortex and to a lower extent in the olfactory bulb, hypothalamus and thalamus,[1] as well as in nociceptive neurons of the dorsal horn. In contrast to most of the ionotropic glutamate receptors, mGlu5 receptors are also widely found in peripheral tissue,[2] for example in peripheral nociceptors or along the gastric vagal afferents.[3] These broad localizations possibly turn mGlu5 receptors into a drug target for brain disorders as well as for some peripheral diseases. To date, mGluR5 antagonists have been clinically tested in Fragile X syndrome,[4] L-dopa induced dyskinesias in Parkinson's disease (PD-LID),[5] migraine[6], anxiety[7] and gastro-esophageal reflux disease (GERD).[8] Other indications considered for mGluR5 antagonists include depression,[9] chronic pain[10] and drug addiction.[11]

In the course of our mGluR5 drug discovery efforts we found by scaffold morphing of known mGluR5 antagonists[7] that 6-azaindole-7-arylcarboxamides (1*H*-pyrrolo[2,3-*c*]pyridine-7-arylcarboxamides) constitute an interesting class of potent mGluR5 antagonists, comprising derivatives with nanomolar potency. In



	I	II	III
Functional test IC_{50} (nM):	7	22	60

Chart 1. Known dipyridyl and benzoxazolone amides with functional data from literature.

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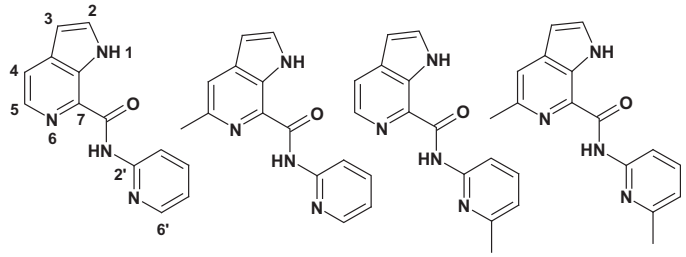
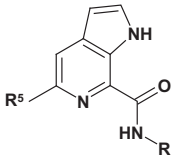
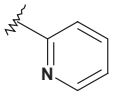
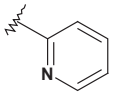
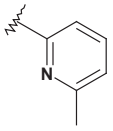
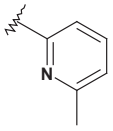
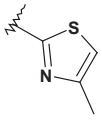
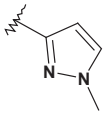
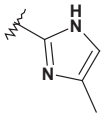


	1	2	3	4
Functional test IC_{50} (nM):	240	11	3100	13

Chart 2. 6-Azaindole amides as mGluR5 antagonists.

Table 1
Functional data and physico-chemical properties of 6-azaindole-7-carboxamides **1–7**

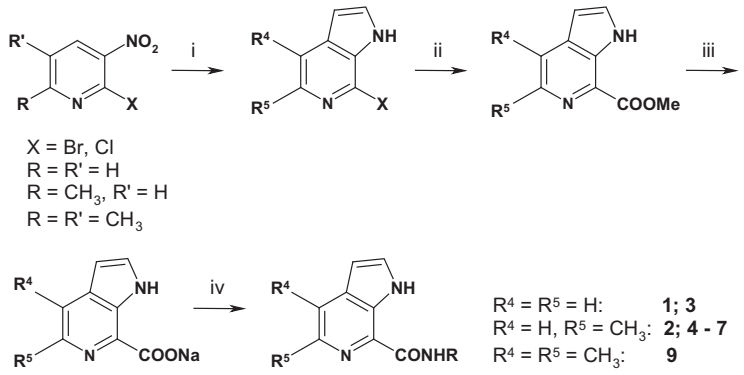


Compound	R^5	R	IC_{50}[a] (nM)	*c*log*P*[b]	log*P*[c]	pK_a[d]	M.P.[e]	Solubility[f]
1	H		240					4
2	CH_3		11 ± 1.7	2.186	4.2	3.5	222	<1
3	H		3100					8
4	CH_3		13 ± 3.8	2.685	5.3	4.5	179	<3
5	CH_3		4 ± 1.6	2.548	3.9	5.6	216	<1
6	CH_3		670 ± 210	1.533	2.9	4.1		18
7	CH_3		300 ± 21	1.781	3.1	7.6		52

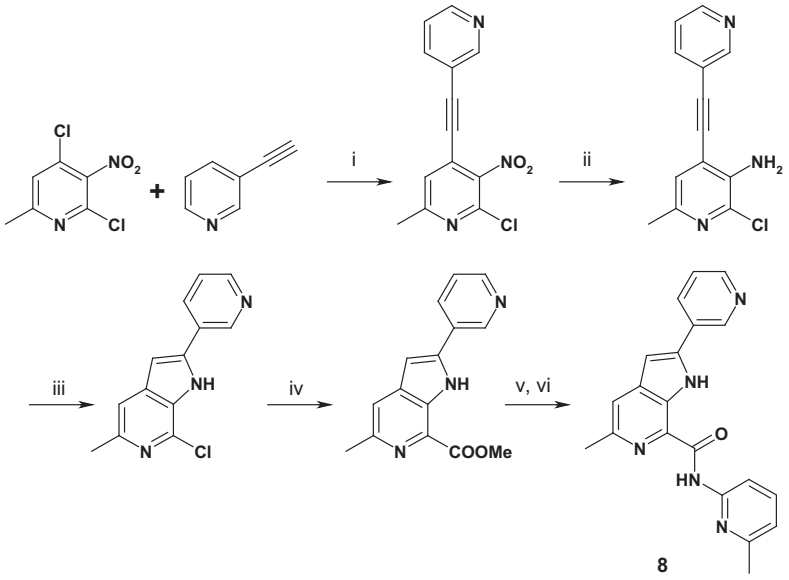
[a] Effect on glutamate induced $[Ca^{2+}]_i$ in L(tk$^-$)cells expressing human mGluR5a, using a fluorescence imaging plate reader (FLIPR)[23]; values are means ± S.E.M. of at least two independent experiments, or single determinations performed in duplicate.
[b] Calculated log*P* using the *c*log*P* program from BioByte (v. 4.71).
[c] Experimental log*P*.
[d] Experimental pK_a of the most basic center.
[e] Melting point (uncorrected) in °C.
[f] Equilibrium solubility (mg/l), measured at pH 6.8 using a shake-flask approach.

this letter we would like to report our key findings on this novel chemotype.

Several years ago Bonnefous et al.[12] reported the high potency of the hydroxy and aminopyridines I and II at rat mGlu5 receptors



Scheme 1. General access to the 6-azaindole-7-carboxamides **1**–**7** and **9**. (i) 3 equiv vinylmagnesium bromide, THF, −78 °C, 90 min (43–47%); (ii) CO (gas) 6 bar (for X=Br) or 55 bar (for X=Cl), MeOH/toluene, NEt_3, $PdCl_2dppf{\cdot}CH_2Cl_2$, 110 °C, 17 h (78–89%); (iii) 1 M NaOH, THF, 25 °C, 1–6 h (90–100%); (iv) RNH_2, TBTU, NMM, DMF, 25 °C, 12–24 h (24–63%).



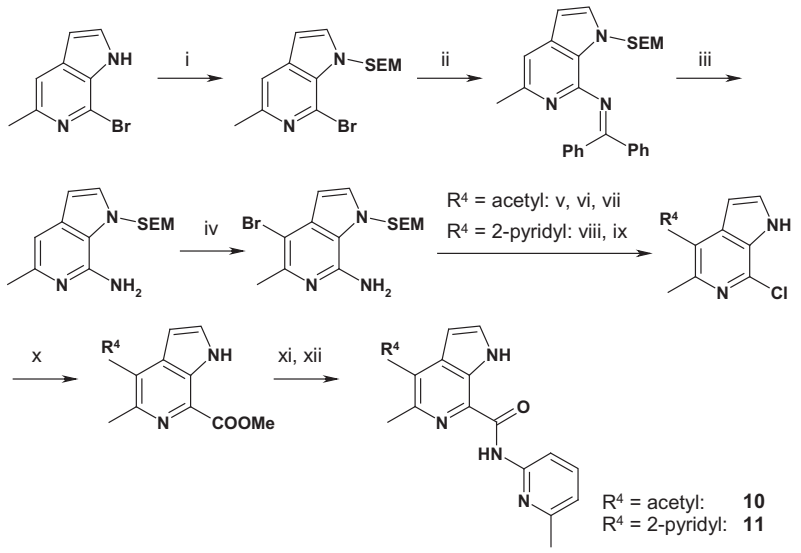
Scheme 2. Preparation of **8**. (i) $PdCl_2(PPh_3)_2$, CuI, NEt_3, DMF, 100 °C, 90 min (27%); (ii) Fe powder, NH_4Cl, $EtOH/H_2O$, 85 °C, 24 h (89%); (iii) CuI, DMF, 110 °C, 60 h, (74%); (iv) CO (gas) 55 bar, MeOH/toluene, NEt_3, $PdCl_2dppf{\cdot}CH_2Cl_2$, 110 °C, 48 h (74%); (v) 1 M NaOH, THF, 50 °C, 21 h (91%); (vi) 6-methyl-pyridine-2-yl-amine, TBTU, NMM, DMF, 90 °C (microwave reactor), 1 h (43%).

in a cellular Ca-assay (Chart 1). Soon thereafter Ceccarelli et al.[13] described a series of bicyclic bisaryl amides displaying allosteric negative modulation of mGlu5 receptors, with the benzoxazolone III as the most potent compound of the examples given. The N-atom of the five membered ring carries a hydrogen atom in the same position as the OH-group of compound I and the amino group of compound II, all three forming an intramolecular hydrogen bond to the carbonyl group.

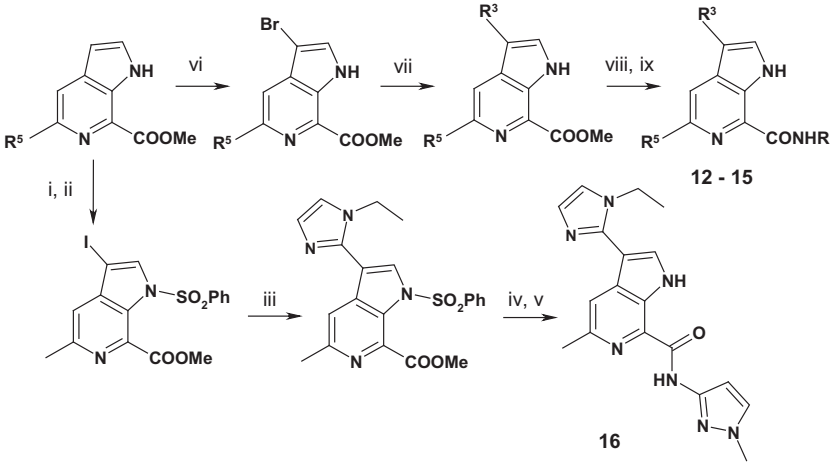
Since phenolic OH- and anilinic NH-groups are often causative for unfavorable pharmacokinetic behavior or toxic metabolism of a compound, we thought to mask those groups in I and II by incorporating them in an annelated pyrrole ring, similar to the situation in compound III. This concept[14] gave rise to the hitherto unknown 6-azaindole carboxamides **1**–**4** which indeed inhibited glutamate evoked Ca signals in a cell line transfected with the human mGlu5a receptor (Chart 2 and Table 1). A binding experiment with the same cell line using [^{3}H]ABP688 as radioligand[15] showed that **4** is a high affinity ligand at the well characterized allosteric binding site located in the transmembrane region of mGluR5[16] with a K_i value of 43 nM.

The construction of the 6-azaindole scaffold was based on the Bartoli reaction[17] with 3-nitro-pyridine derivatives[18] (Scheme 1, step i). The halogen atom in position 2 of the pyridine ring allowed the introduction of a carboxymethyl group in position 7 of the 6-azaindole scaffold by Pd-catalyzed carbonylation in methanol.[18] Saponification of the methyl ester and condensation of the sodium carboxylate with the appropriate amine provided the 6-azaindole-7-carboxamides.[19]

A comparison of the activity of **1** and **2** reveals the crucial role of the methyl group in position 5 of the azaindole scaffold for high potency. In contrast, the methyl group in position 6′ of the pyridyl ring is either detrimental (cf. **1** and **3**) or, if the 5-methyl group is installed, does not contribute to potency (cf. **2** and **4**). All these compounds and also the highly potent bioisosteric thiazole analog **5** displayed only marginal aqueous solubility at neutral pH, a consequence of several factors: the compounds are basically nonelectrolytes, as the pK_a value of the most basic center, the amidic pyridine or thiazole ring, is in the range of 3.5–5.6; the compounds are rather lipophilic, as shown by the octanol/water partition coefficient log$P$ which varies from 3.9 to 5.3. Furthermore, the compounds have a pronounced crystallinity,[20] as demonstrated by the high melting points and suggested by their planar conformations which may strengthen crystal packing.[21] The planar conformations are supported by the underestimation of log$P$ by the



Scheme 3. Preparation of the 4-substituted compounds **10** and **11**. Preparation of starting material according to Scheme 1; (i) SEMCl, NaH, DMF/DMSO 5:1, 25 °C, 2 h (94%); (ii) benzhydrylideneamine, $Pd(OAc)_2$, BINAP, Cs_2CO_3, THF, 70 °C, 50 h (65%); (iii) $NH_2OH{\cdot}HCl$, NaOAc, THF/H_2O, 60 °C, 10 min (65%); (iv) $Py{\cdot}HBr{\cdot}Br_2$, $CHCl_3$, 25 °C, 4 h (99%); (v) 1-ethoxyvinyltri-*n*-butyltin, $PdCl_2dppf{\cdot}CH_2Cl_2$, dioxane, 120 °C, 22 h (59%); (vi) removal of SEM: HCl concn, −30 °C 75 min; 2 M NaOH, 75 min (71%); (vii) *t*-butyl nitrite, $CuCl_2$, CH_3CN, 65 °C, 10 min (7%); (viii) 2-tributylstannanyl-pyridine, $PdCl_2dppf{\cdot}CH_2Cl_2$, dioxane, 100 °C, 28 h (65%); (ix) $NaNO_2$, HCl concn, 25 °C, 3 h (32%); (x) CO (gas), 55 bar, MeOH/toluene, NEt_3, $PdCl_2dppf{\cdot}CH_2Cl_2$, 110 °C, 72 h (57–62%); (xi) 1 M NaOH, THF, 25 °C, 1 h; (xii) 6-methyl-pyridine-2-yl-amine, TBTU, NMM, DMF, 90 °C, 1 h (microwave reactor) (56–61% for 2 steps).



Scheme 4. Synthesis of the 3-substituted 6-azaindole-7-carboxamides **12**–**16**. Preparation of starting materials according to Scheme 1; (i) NIS, dibenzoylperoxide, CH_2Cl_2, 25 °C, 1 h (95%); (ii) $ClSO_2Ph$, NaH, DMF, 25 °C, 2 h (42%); (iii) 1-ethyl-2-tributylstannanyl-1*H*-imidazole (prepared from 1-ethyl-1*H*-imidazole, *n*-BuLi, $ClSnBu_3$, THF, −78 °C), $PdCl_2dppf.CH_2Cl_2$, dioxane, 110 °C, 20 h (47%); (iv) 2.1 equiv 1 M NaOH, THF, 50 °C, 3 h (100%); (v) 1-methyl-1*H*-pyrazol-3-ylamine, TBTU, NMM, DMF, 25 °C, 16 h (54%); (vi) NBS, dibenzoylperoxide, CH_2Cl_2, 25 °C, 1 h (65–69%); (vii) R^3SnBu_3, $PdCl_2dppf.CH_2Cl_2$, dioxane, 110 °C, 20 h (27–41%); (viii) 1.1 equiv 2 M KOH, THF, 18 h, 50 °C (74–100%); (ix) RNH_2, TBTU, NMM, DMF, 25 °C, 16 h (27–76%).

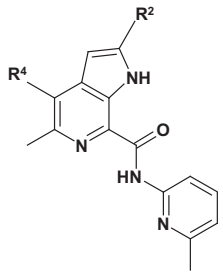
predicted *c*log*P* values, arguing for intramolecular H-bonds between the NH of the pyrrole ring and the carbonyl group, and between the amidic NH and N(6) of the azaindole scaffold. Poorly soluble compounds often lead to absorption problems[22] during pharmaco-kinetic and/or toxicological studies. Therefore we tried to optimize water solubility while keeping the potency at high level. As a cutoff for drugability of this chemotype we choose a solubility at pH 6.8 of 50 mg/l or higher.

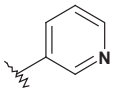
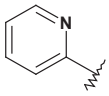
Increasing the polarity of the amide substituent by taking 1-methyl-pyrazol-3-yl or 4-methyl-1*H*-imidazol-2-yl in place of 2-pyridyl or 4-methyl-thiazol-2-yl resulted in compounds **6** and **7** which both showed higher solubility but unfortunately much lower potency than the pyridyl analogs **2** and **4** (Table 1). The slightly improved solubility of **6** (vs **5**) is likely due to its reduced lipophilicity whereas the more marked improvement with **7** can be attributed to a higher solvation energy, effected by protonation of the amidic imidazole residue ($pK_a = 7.6$). The structure activity relationship with respect to the amide group appeared to be rather steep because no further aromatic five membered ring could be identified as a replacement of the pyridine or thiazole amide substituent that was equally well tolerated by the mGlu5 receptor.

The 5-methylated 6-azaindole-7-carboxamide scaffold allows the attachment of substituents in position 2, 3 and 4, providing new opportunities for modulation of potency and solubility.

The synthetic approaches used to achieve substitution in these positions are outlined in Schemes 1–4.[19] For compound **8** the Cu-catalyzed internal cyclization of the appropriate ortho-amino-alkynyl pyridine was employed to get the 2-substituted 6-azaindole

Table 2
Functional data of the 2- and 4-substituted 6-azaindole-7-carboxamides **8**–**11**



Compound	R^2	R^4	IC_{50}[a] (nM)
8		H	47 ± 16
9	H	CH_3	2700 ± 200
10	H	Acetyl	540 ± 25
11	H		780 ± 35

[a] See legend Table 1.

scaffold[24] (Scheme 2, step iii). For compound **9**, bearing a methyl group in position 4, the sequence in Scheme 1 could be used, starting from the commercial 2-chloro-5,6-dimethyl-3-nitro-pyridine.

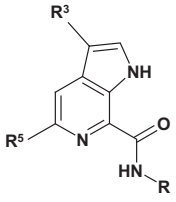
Preparation of compounds **10** and **11** made use of protecting group technology. Protecting the pyrrole N-atom by the 2-(trimethylsilyl)ethoxymethyl group (SEM) allowed the regioselective bromination of the 7-amino-6-azaindole scaffold in para-position of the amino group (Scheme 3, step iv). For **10** the bromine atom was replaced in a Stille reaction by the masked acetyl group (step v). Removal of SEM and Sandmeyer reaction (steps vi, vii) prepared the intermediate for carbonylation (step x) and subsequent transformation to **10** (steps xi, xii). An analog sequence was used for **11** after execution of the Stille reaction with 2-tributylstannanyl-pyridine (step viii).

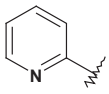
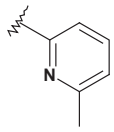
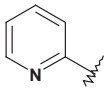
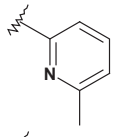
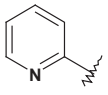
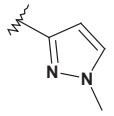
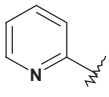
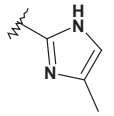
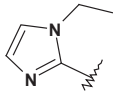
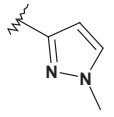
Substitution in position 3 (compounds **12 –16**) was easily achieved by iodination or bromination of position 3 of the 6-azaindole scaffold (Scheme 4, step i or vi) followed by Pd-catalyzed coupling reaction with the appropriate aryl stannane (step iii or vii).

Compound **8**, bearing a 3-pyridyl residue in position 2 and the 6′-methyl pyridine as amide substituent, displayed good potency (Table 2). Its solubility at pH 6.8, however, was still below the limit of detection. Compounds **9**, **10** and **11** with the same amide substituent and with methyl, acetyl or 2-pyridyl in position 4, respectively, had no improved physico-chemical profile (data not shown) compared to **4**, but were of significantly lower potency (Table 2).

Position 3 of the 6-azaindole scaffold was explored by a range of substituents. It was found that decent activity was only obtained when the heteroatoms of the 3-substituents were placed in well defined positions. Thus, among the different pyridine regioisomers the 2-pyridyl substituent, as exemplified in compound **12**, turned out to be the best. As expected, the analog derivative **13**, carrying

Table 3
Functional data and physico-chemical properties of the 3-substituted 6-azaindole-7-carboxamides **12**–**16**



Compound	R^3	R^5	R	IC_{50}[a] (nM)	*c*log *P*[b]	log *P*[c]	pK_a[d]	M.P.[e]	Solubility[f]
12		H		540					
13		CH_3		31 ± 11	3.303	4.7	4.5	217	<1
14		CH_3		65 ± 11	2.152	3.7	4.6	216	5
15		CH_3		240 ± 36	2.399	3.3	6.9	222	8
16		CH_3		54 ± 15	2.024	2.9	7.2	167	184

[a–f] See legend Table 1.

a methyl group in position 5 of the 6-azaindole scaffold, was even more potent. Solubility, however, was still below the limit of detection, in line with the unfavorable physico-chemical parameters (Table 3). Changing the amide substituent to 1-methyl pyrazole or 4-methyl-1*H*-imidazole (in analogy to **6** and **7**, respectively) gave compounds **14** and **15**, both showing slightly improved solubility (Table 3) compared to **13**, consistent with the fairly lower lipophilicity of **14** ($\log P = 3.7$) and the higher pK_a of 6.9 for **15**.

The finding that an acceptor atom within the 3-substituent is well tolerated by the receptor if this atom is located beneath the connection to the azaindole scaffold suggested the possibility for imidazolyl groups as substituents in position 3. Hence, the combination of 1-ethyl-imidazol-2-yl in position 3 with 1-methyl-pyrazol-3-yl as amide group in **16** resulted in good potency and a strongly enhanced solubility of 184 mg/l at pH 6.8. Evaluation of the three aforementioned physico-chemical parameters revealed drug-like values for **16**, with a $\log P$ of 2.9, a pK_a of 7.2 (corresponding to about 72% of protonation at pH 6.8) and a more moderate melting point of 167 °C. In an in vitro paradigm using rat liver microsomes **16** displayed low to medium intrinsic clearance, qualifying the compound for a pharmacokinetic experiment in animals. To this end, **16** was administered intravenously at 1 mg/kg in rats, using a cassette model with co-application of five other compounds. Compound **16** was found to have a short plasma half life of one hour and a moderate to high in vivo clearance of 53 ml/min/kg which is close to the rat hepatic blood flow of about 56 ml/min/kg.[25] Despite an acceptable ratio of brain to blood concentration of 0.34 after one hour, the short sojourn in blood disfavored this compound for further investigations. Whether combinations of substituents in position 2 or 3 of the 6-azaindole scaffold with appropriate amide groups can be found, conveying a more favorable pharmacokinetic profile while retaining good potency, remains to be seen.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.053.

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