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From pyrroles to pyrrolo[1,2-*a*]pyrazinones: A new class of mGluR1 antagonists

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Abstract—Exploiting the SAR of the known pyrrole derivatives, a new class of mGluR1 antagonists was developed through a cyclization of the C-2 position on the pyrrole N-1 nitrogen. The resulting pyrrolo[1,2-*a*]pyrazinones are potent and noncompetitive antagonists.

Glutamate is a key neurotransmitter in the central nervous system and it exerts its activity through ionotropic (NMDA, AMPA, and kainate) and metabotropic receptors (mGluRs).[1,2] The former are ligand-gated cation channels, while the latter belong to the C family of G-protein-coupled receptors (GPCRs) and are characterized by a large amino-terminal domain where the agonists bind. The ability of these GPCRs to interact with a large number of key effectors within the cell provided a variety of targets to medicinal chemists who developed different series of molecules able to interact with these receptors.[3] To date, eight mGluR subtypes and multiple splice variants have been identified and named mGluR1–8 according to the succession of the molecular cloning.These receptors are divided into three main groups on the basis of sequence similarity, pharmacology, and transduction mechanisms: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR6, mGluR7, and mGluR8). Recent molecular modeling studies as well as receptor models based on crystallographic data shed light on the basis of the interactions between agonists and antagonists with these receptors.[4–6]

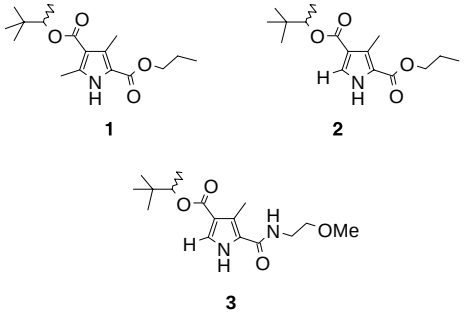

Figure 1. Previously described mGluR1 pyrrole antagonists.

Our interest in this area was mainly devoted to group I, and in particular to the mGluR1 receptor subtype where potent and selective molecules (Fig. 1, **1**–**3**) were described.[7–9]

In this paper, we would like to report a substantial modification to the pyrrole scaffold which led to the identification of a new and selective class of mGluR1 noncompetitive antagonists.

As discussed in the previously published papers, the C-2 position was quite tolerant to substitutions from a SAR point of view. Moreover, N-alkylation with reasonably small substituents was tolerated with no major impact on the potency of the compounds.

Keywords: mGluR1; Pyrrole; Metabotropic; Excitatory amino acids; Antagonist.
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C-2 amide introduction (**3**) led to an improved pharmacokinetic (PK) profile of the class, but still a few derivatives of the amide series showed a relatively high plasmatic clearance. This problem might be due to possible metabolic reactions occuring at the C-2 side chain or to the specific recognition of the 'amino-acidic moiety' formed by the pyrrole nitrogen and C2 carboxy derivative.

In order to investigate this working hypothesis, the synthesis of 'constrained' system was undertaken as depicted in Figure 2 and the class of pyrrolo[1,2-*a*]pyrazinones of general formula **4** was therefore identified as a possible target.

The desired derivatives of class **4** were accordingly prepared following different attempts as it will be exemplified in the different synthetic schemes below reported.

The first route explored involved the reaction of the starting pyrroles with an iodoacetonitrile in DMF at room temperature.[10] The yield was almost quantitative and the following reduction of the cyano group[11] produced the desired compound by cyclization even if the yield were not optimal (20%) (Scheme 1).

This was due to the opened intermediate which was not able to undergo cyclization under the reaction conditions. Nonetheless, once identified, the open intermediate **7** was isolated and underwent complete cyclization after appropriate heating under basic conditions as reported in Scheme 2.[12]

Intermediate **4a** proved to be useful for array exploration. Actually, the use of NaH in DMF at 0 °C with the appropriate alkyl halides gave good to acceptable yields of the desired products. Potency results are reported in Table 1 and discussed afterwards.

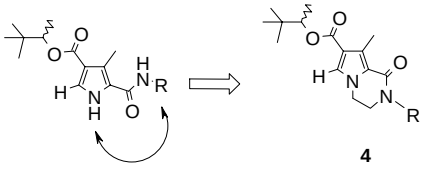
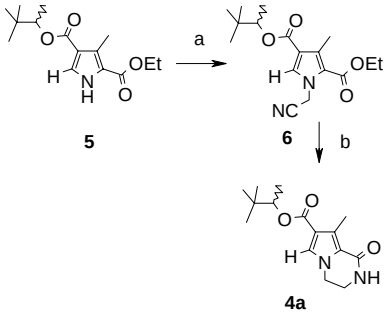
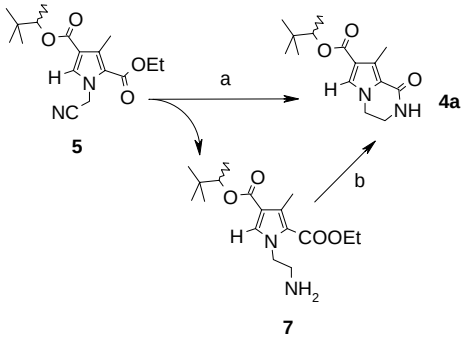


Figure 2. Proposed working hypothesis on the pyrrole scaffold.



Scheme 1. Reagents and conditions: (a) ICH_2CN, NaH, DMF, from 0 °C to rt, 48 h; (b) $NaBH_4$, $CoCl_2$, MeOH, rt.



Scheme 2. Reagents and conditions: (a) $CoCl_2$ (2 equiv), $NaBH_4$ (5 equiv), MeOH, rt (1 h); (b) EtONa (1 equiv), EtOH, 60 °C (8 h).

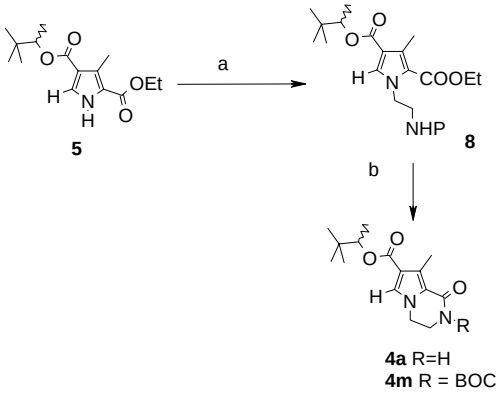
Table 1. Potency values of the pyrrole derivatives on r-mGluR1a-CHO cells using the CDP–DAG accumulation method[7]

Compound	R	Alkylation yield (%)	pIC_{50}
4a	H	—	N.A.
4b	$CH_2CH{=}CH_2$	78	7.7
4c	$CH_2CH_2CH_3$	79	7.4
4d	CH_2Ph	88	6.6
4e	CH_2CHF_2	83	7.6
4f	$(CH_2)_3NPht$	55	7.8
4g	CH_2CH_2OMe	79	6.6
4h	CH_2CH_2F	87	7.7
4i	$CH_2cC_3H_5$	74	7.7
4l	$(CH_2)_2N(CH_2)_2O$	19	5.5
4m	$(CH_2)_2NHBoc$	—	6.4

IC_{50}s were measured from at least six-point inhibition curves and are geometric means of at least three independent experiments. The standard error of the mean was less than 0.05.
N.A. = not active up to 100 μM.

In order to improve the overall yield of intermediate **4a** and therefore allow a wider medicinal chemistry exploration, different cyclization attempts were tried as depicted in Scheme 3.

Different nitrogen-protecting groups were experimented (phtalimido (Pht), Fmoc, Boc, and $COCF_3$) in conjunction with different leaving groups (Br, I or mesylate).



Scheme 3. Reagents and conditions: (a) NaH, DMF, from 0 °C to 80 °C; XCH_2CH_2NHP, where X can be Br, Cl, OMs and the protecting group P was alternatively Pht, Boc, $COCF_3$; (b) HCOOH deprotection and rt cyclization or direct cyclization, DMF, 60 °C.

The best match to achieve the desired alkylation results was obtained using the *N*-Boc mesylate in DMF at 80 degrees.

The intermediate **8** was obtained in good yield[13] and could then be deprotected (formic acid, 18 h, rt quantitative yield) and cyclized (to give **4a**) or directly cyclized giving the Boc-protected intermediate **4m**.

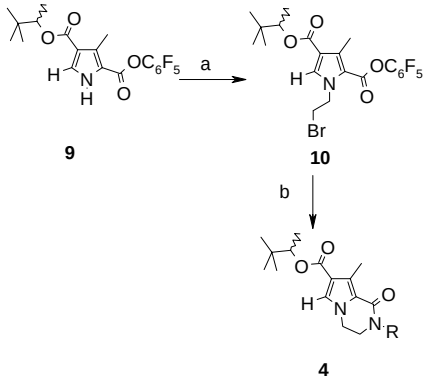
As an alternative strategy, to allow a wider exploration for products that could not be obtained for alkylation of intermediate **4a**, other different routes were also devised.

Among the different attempts, C2 amidation and subsequent cyclization on pyrrole nitrogen was followed as reported in Scheme 4. Unfortunately, the conversion to the desired bromide intermediate and the following cyclization was not as effective as desired.[14]

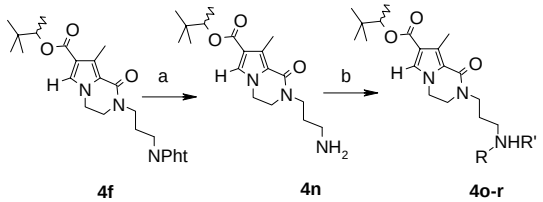
Nonetheless, this route proved to be very useful in the preparation of the compound which could not be easily obtained following simple alkylation of intermediate **4a**.

In order to achieve the maximum preliminary exploration around this new scaffold, the phthalimido compound **4f** was deprotected to the amino derivative (in quantitative yield) using hydrazine and was further functionalized as depicted in Scheme 5.[15] Potency results are reported in Table 2.

As reported above, the pyrrole class is surely endowed with great potency and selectivity for the mGluR1 receptor. The introduction of amides in C2 position



Scheme 4. Reagents and conditions: (a) $BrCH_2CH_2Br$, NaH, DMF; (b) RNH_2, DMF, rt, 1–24 h, rt.



Scheme 5. Reagents and conditions: (a) NH_2NH_2, THF 24 h; (b) RCOCl, Et_3N, THF.

Table 2. Potency values of the pyrrole derivatives on r-mGluR1a-CHO cells using the CDP–DAG accumulation method[7]

Compound	R	R′	2-steps yield (%)	pIC_{50}
4n	H	H	95	N.A.
4o	$COCH_3$	H	93	6.3
4p	CONHEt	H	38	6.4
4q	CO-4Py	H	51	6.4
4r	CO-4Py	Me	63	5.5

IC_{50}s were measured from at least six-point inhibition curves and are geometric means of at least three independent experiments. The standard error of the mean was less than 0.05.
N.A. = not active up to 100 μM.

(as exemplified by compound **3**) led to dramatic improvement in the PK profile of this series, leading to compounds showing very good bioavailability in different animal species. Nonetheless, a few examples of the amide series still showed an unexpectedly high clearance (Clb) when administered in vivo. This could obviously be due to different reasons and mainly to metabolic instability of the C2 lipophilic side chain. Another possibility could be linked to the specific recognition of the 'amino acidic' moiety masked within the 2 carboxy pyrrole structure. In order to prevent specific interactions with this moiety and to contemporary protect the side chain of the C2 amide with a forced conformation, the new class of pyrrolo[1,2-*a*]pyrazinones was developed.

As reported in Table 1, potency values for this new class of derivatives are generally comparable to the ones obtained with the corresponding noncyclized amides, confirming once again that the role of the nitrogen in the pyrrole scaffold is not critical for the interaction with the mGluR1 receptor.

Linear chains and chains substituted with fluorine atoms (**4e**, **4h**) to improve metabolic stability are well tolerated as well as the presence of slightly larger substituents like the cyclopropylmethyl one (**4i**). The introduction of a benzyl group (**4d**) leads to a tenfold decrease in potency as the introduction of the oxygen atom in compound **4g**. If the side chain is long enough, however, bulky and nonbasic group like the phthalimido derivative **4f** retains high potency. Once basicity is introduced, like in the morpholino derivative **4l**, as expected from previous SAR, a marked decrease in potency is observed.

Interestingly enough, like reported in Table 2, the introduction of a further amide moiety is sufficiently tolerated as far as potency is concerned and more importantly the moderate basicity of the 4-carboxypyridine substituent **4q** is tolerated too. This finding will be further explored with differently substituted pyridines to allow the generation of salts which might improve the solubility profile of this bis-amide class.

The selectivity profile of a few selected examples was tested versus mGluR2, mGluR4, and mGluR5, and no major difference was noticed with respect to the corresponding C2 amides. Further characterization is in progress on the most different chemotypes.

As far as the PK and metabolic profile of these derivatives are concerned, a detailed investigation both in vitro and in vivo in different animal species is currently in progress and will be reported in due course.

A new class of potent and selective mGluR1 noncompetitive antagonists derived from pyrrole scaffolds has been discovered. The possibility to introduce moderately basic substituents has been highlighted. Further studies on the overall profile of this new class are in progress.

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10. ICH_2CN was carefully added to a slurry of **5** and NaH in DMF at 0 °C; the reaction mixture was warmed up to rt and stirred for 48 h under nitrogen. The reaction was quenched with aq NH_4Cl, extracted with AcOEt, and the product was isolated through column chromatography.
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12. Compound **7** was dissolved in EtOH and 1.1 equiv of EtONa was added. The mixture was stirred at 60 °C for 8 h. The reaction was quenched with aq NH_4Cl, concentrated, and the desired product was extracted with AcOEt and purified through column chromatography.
13. Compound **5** was dissolved in DMF and NaH was carefully added at 0 °C under nitrogen. After 15 min, a solution of the alkylating agent in DMF was dropped into the slurry and the reaction mixture was warmed up to 80 °C untill completion of the reaction. The reaction was quenched with aq NH_4Cl, and the compound was extracted with AcOEt and subsequently purified by column chromatography. Formic acid deprotection at room temperature (10 equiv or more) was followed by in situ cyclization at rt.
14. Compound **9** was dissolved in DMF and NaH was carefully added at 0 °C under nitrogen. After 15 min, 1,2-dibromoethane was added and the mixture was stirred for 2 h; the appropriate amine was then added to the crude and the mixture was stirred up to 24 h. Products were isolated through column chromatograpy.
15. Compound **4f** was dissolved in THF and hydrazine was carefully added at 0 °C. The mixture was warmed up to rt and stirred for 24 h. The phthalidrazide was filtered and to the crude were added Et_3N and the appropriate acid chloride. The reaction mixture was stirred up to 24 h. Products were extracted into AcOEt and isolated through column chromatograpy.