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Phenylethynyl-pyrrolo[1,2-*a*]pyrazine: A new potent and selective tool in the mGluR5 antagonists arena

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Abstract—The synthesis and the structure activity of a new series of pyrrolo[1,2-*a*]pyrazine is reported. These molecules are potent and selective non-competitive mGluR5 antagonists and may shed new light on the pattern of substitution tolerated by this receptor.

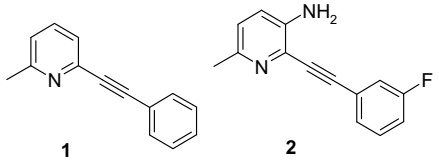
Glutamate is the main neurotransmitter within the central nervous system (CNS) and it operates through different receptors. Some are ion channels (NMDA, AMPA, and kainate receptors), while others are a peculiar family of 7-Transmembrane (7-TM) G-protein-coupled receptors (GPCRs), the metabotropic receptors (mGluRs).[1] Based on sequence homology, functional coupling, and pharmacology, mGluRs are classified as belonging to groups I, II, or III.[2,3] Group I receptors are primarily localized postsynaptically and consist of subtype 1 (mGluR1) and subtype 5 (mGluR5), which exhibit different patterns of expression in the CNS.

The activation of the mGluR5 receptor is linked to the stimulation of phospholipase C (PLC), leading to phosphoinositide (PI) hydrolysis and ultimately to an increase of intracellular levels of Ca^{2+}.

One of the best known non-competitive antagonists is surely represented by 6-methyl-2-(phenylethynyl)-pyridine[4] (MPEP; **1**, Fig. 1), and by its close analogs, like **2**.[5,6] The modulation of mGluR5 receptor through this type of derivatives has wide potential therapeutic applications in a variety of CNS disorders.[7–11]

A number of different reviews have been recently published on ligands acting on this family[12,13] and it is evident that one of the most recurring structural motifs in the field of mGluR5 non-competitive antagonists is the acetylene linker,[14–16] despite the fact that the triple bond has sometime been suspiciously considered by some medicinal chemists because of its potential liabilities (e.g., phototoxicity or bio-activation potential). This acetylene linker is also a key feature of a new high affinity radioligand prepared for Positron Emission Tomography (PET) recently disclosed.[17] In this manuscript, the identification of an alternative scaffold to the pyridine MPEP nucleus is reported together with the associated exploration which allows some further consideration of the space available into the mGluR5 allosteric pocket.

Considering the relatively limited solubility of derivative **1** and its activity on some monoaminergic transporters,[18] the identification of alternative and highly selective scaffolds was considered a priority in GSK to further validate in vivo a number of the potential



1 2

Figure 1. mGluR5 non-competitive antagonists. MPEP (**1**), and its close analog amino derivative from Addex Pharmaceuticals (**2**).

Keywords: mGluR5; Metabotropic; 7-TM; Receptor; Antagonists.
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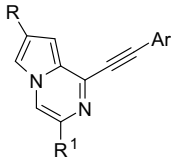
therapeutic applications claimed for the mGluR5 antagonists. Among the different approaches used to achieve this target (ranging from HTS campaign to rational drug design), the introduction of a novel ring attached to the ethynyl moiety is described here.

Each of the new chemical entities (NCE) prepared was tested for agonism and antagonists in a Fluorescent Imaging Plate Reader (FLIPR™) functional screen.[19] Selectivity assays over mGluR1 and over representative of group II and III mGluRs were performed on the most interesting NCEs. Among the different alternative nuclei identified, the exploration of the pyrrolo[1,2-*a*]pyrazine scaffold is reported here as this template resulted of particular interest: actually, the non-decorated derivative **3** (Table 1) showed a potency comparable to MPEP (**1**) in the same assay. The compound was completely selective over mGluR1 and over group II and III mGluRs. Before starting an investment of chemical resources on this template, its overall selectivity profile was checked too. Compound **3** was therefore submitted to a CEREP High-Throughput Profiling over 50 receptors (test concentration 1 μM), including Noradrenaline (NE) and Dopamine (DE) transporters showing no unwanted activities. The introduction of a methyl group in *meta* position on the phenyl ring (**4**) lead to an almost 10-fold increase in potency, leading to sub-nanomolar potency.

The *para* position, on the other side, resulted to be quite sensitive to electron-withdrawing (EWG) groups and to steric hindrance; while the introduction of a Fluorine (**5**) led to a 10-fold decrease in potency, the substitution with a Chlorine (**6**) or a Bromine (**7**) led to poor or complete loss of activity, respectively. The presence of the hydroxyl derivative (**8**), even if in *meta* position, was also detrimental. This effect might be associated to the presence of a hydrogen donor (HD) group not tolerated by the receptor. The detrimental effect onto this scaffold of EWG systems was also evident replacing the phenyl ring with a pyrimidine one (**9**) and, probably reinforced by the steric clashes, with an isoquinolinyl moiety (**10**). Working on the pyrrolo[1,2-*a*]pyrazine scaffold, the introduction of a moderately EWG group like the trifluoromethyl derivative in position 7 (**12**) was relatively well tolerated and helped to demonstrate, like in the MPEP series, the positive role of the methyl group in position 3 (**11**) on the potency at the mGluR5 receptor. In the same position 7, the slightly more EWG cyano group (**13**) was, on the other hand, very well tolerated leading to almost nanomolar potency. It was therefore hypothesized that the EWG detrimental effect on the scaffold might have been mitigated by the relative hydrophilicity of the CN group.

To test this hypothesis, different amides were prepared (**14**–**16**). In this case, a reduction of potency was ob-

Table 1. Potency values for selected NCEs on h-mGluR5 receptor



Compound	R^1	R	Ar	pIC_{50}
1		Not applicable		8.0
2		Not applicable		7.5
3	CH_3	H	Ph	8.6
4	CH_3	H	3-Me-Ph	9.4
5	CH_3	H	4-F-Ph	7.8
6	CH_3	H	4-Cl-Ph	6.2
7	CH_3	H	4-Br-Ph	<4.9
8	CH_3	H	3-OH-Ph	6.5
9	CH_3	H	5-Pyrimidinyl	5.7
10	CH_3	H	4-Isoquinolinyl	<4.9
11	H	CF_3	Ph	6.8
12	CH_3	CF_3	Ph	7.4
13	CH_3	CN	Ph	8.9
14	CH_3	(4-Methyl-1-piperazinyl) carbonyl	Ph	7.0
15	CH_3	1-Pyrrolidinyl carbonyl	Ph	7.1
16	CH_3	4-Morpholinyl carbonyl	Ph	7.8
17	CH_3	CH_3	Ph	7.3
18	CH_3	COOEt	Ph	8.0
19	CH_3	3-Methyl-1,2,4-oxadiazol-5-yl	Ph	8.2
20	CH_3	CONHMe	Ph	6.9
21	CH_3	1-Piperidinyl methyl	Ph	6.8
22	CH_3	(4-Methyl-1-piperazinyl) methyl	Ph	6.3
23	CH_3	4-Acetyl-1-piperazinyl) methyl	Ph	6.5
24	CH_3	(3-Oxo-1-piperazinyl) methyl	Ph	6.7

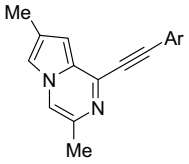
IC_{50}s are geometric means of at least three independent experiments.
The standard deviation is ±0.3.

served, but this effect might have been also due to the limited space available in this region of the receptor. Actually, among the three amides, the more hydrophilic (but not basic) morpholinyl derivative **16** was the best tolerated. To continue the work around this hypothesis, the introduction of an almost neutral methyl group (**17**) resulted in a comparable potency to the $-CF_3$ derivative **12**, while the bulkier but more hydrophilic COOEt derivative **18** increased the potency again, even if not reaching the values of the cyano derivative. As the bulkiness of the amides (**14**–**16**) was spaced by one carbon (the carbonyl group) from the scaffold, the introduction of a sterically hindered, but hydrophilic group directly linked to the template was attempted. The results achieved by the oxadiazole (**19**) seem to strengthen the hypothesis that hydrophilic and moderately hindered derivatives are well tolerated in this region of the receptor. As it happened on the aromatic ring for the phenolic derivative **8**, the presence of a hydrogen donor (HD) group (or of an acidic proton) directly linked to the template (**20**) resulted in a loss of potency. This was also observed with the introduction of basic moieties (**21**–**24**) independently of their pK_b or steric hindrance.

The new scaffold also provided advantages in terms of solubility. When measured at pH 7.4, derivative **1** showed in our conditions an average solubility – measured as a free base – of 70 μg/mL; under the same conditions, derivatives **3** and **21** were endowed (as free base) of a solubility of 165 and 100 μg/mL, respectively.

The next step of the exploration was related to a more complete analysis of the aromatic region linked to the ethynyl group. As clearly reported in Table 2, the substitution of position 4 of the phenyl ring (**25**–**28**) was detrimental for potency (compared to **17**) and also the substitution in position 3 (**29**–**31**) was not very effective, with the only tolerated groups being represented by the $-CF_3$ (**29**) and the thienyl compound **31**, while the moderate basicity of the pyridine moiety (**30**) led to a sensible decrease of potency. A more extensive exploration was performed on the trifluoromethyl scaffold **12** and the results are reported in Tables 3 and 4. Also in this case, *meta* substitution (**32**–**37**) of the phenyl ring was

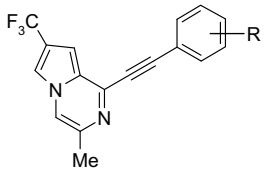
Table 2. Potency values for selected NCEs on h-mGluR5 receptor



Compound	Ar	pIC_{50}
25	4-CF_3	<4.8
26	4-Cl	<5.4
27	4-F	6.4
28	4-CN	<4.8
29	3- CF_3	6.8
30	3-Pyridyl	5.7
31	3-Thienyl	7.2

IC_{50}s are geometric means of at least three independent experiments. The standard deviation is ±0.3.

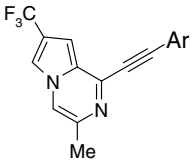
Table 3. Potency values for selected NCEs on h-mGluR5 receptor



Compound	R	pIC_{50}
12	H	7.4
32	3-OMe	7.1
33	3-CF_3	6.5
34	3-F	7.8
35	3-Cl	7.0
36	3-Br	7.6
37	3-CN	7.9
38	3-$NHSO_2CH_3$	<4.9
39	3-NHAc	6.1
40	3-COOH	<4.9
41	3-COO-*t*-Bu	<4.9
42	2-F	6.9
43	2-Cl	5.3
44	2-CF_3	<4.8
45	2,4-bis F	<4.8
46	4-F	7.0
47	4-Cl	5.7
48	4-CF_3	<4.8
49	4-CN	<4.8
50	4-NMe_2	<4.8
51	4-$NHSO_2CH_3$	<4.8

IC_{50}s are geometric means of at least three independent experiments. The standard deviation is ±0.3.

Table 4. Potency values for selected NCEs on h-mGluR5 receptor



Compound	Ar	pIC_{50}
52	4-Pyridyl	7.1
53	2-Pyridyl	7.3
54	3-Pyridyl	6.3
55	1-Methyl-imidazol-5-yl	<4.9
56	3-Furyl	7.3
57	2-Thienyl	7.2
58	3-Thienyl	8.0
59	3-(1*H*-Pyrazol-4-yl)phenyl	<4.9
60	3-(4-Isoxazolyl)phenyl	6.1
61	3-(1-Methyl-1*H*-pyrazol-4-yl) phenyl	<4.9
62	3-(3,5-Dimethyl-4-isoxazolyl) phenyl	<4.9
63	3-(3-Furanyl)phenyl	5.0
64	3-(3-Thienyl)phenyl	5.3

IC_{50}s are geometric means of at least three independent experiments. The standard deviation is ±0.3.

favoured over *para*-substituted analogs (**46**–**51**) with the caveat that acidic or bulky groups were not tolerated in this region (**38**–**41**).

The replacement of the phenyl ring (**12**) with different heterocycles (**52**–**58**) was generally tolerated with the

exception of more basic/polar substitution (**55**). The 3-thienyl derivative (**58**), in particular, reached remarkable levels of potency keeping unchanged its original selectivity profile.

The attempt to exploit the 'favoured' *meta* position of the phenyl ring to achieve higher potency values or to introduce groups that might have potentially led to more soluble derivatives gave poor results when different heterocycles were inserted in this region (**60–64**).

As this result was not related to the level of basicity/acidity of the aromatic residues used, it might be correlated to a possible steric clash of this region of the scaffold within the mGluR5 receptor as previously observed with the introduction of the bulky *tert*-butyl ester **41** in the same region.

Finally, to rapidly complete the exploration of position 7 of the pyrrolo[1,2-*a*]pyrazine in combination with the pattern of substitution on the aromatic ring attached to the ethynyl moiety in terms of potency at the mGluR5 receptor, a small combinatorial exploration was performed and the results are reported in Table 5, highlighting the discovery of some very potent nanomolar and sub-nanomolar derivatives. Derivative **71**, when submitted to an in-house profiling over 70 receptors (test concentration 1 μM), confirmed complete selectivity at the desired target for this template, with no activity on the other mGluRs tested. More importantly, the potency results achieved were not only limited to the smaller and more hydrophilic substituents present in position 7 (CN, COOEt), but also confirmed the results already observed with the more hindered 4-morpholinylcarbonyl substituent.

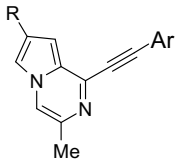
To further explore this area and to complete the exploration of the level of tolerance of mGluR5 receptor versus the increase of steric bulk of amide moieties in position 7 of the pyrrolo[1,2-*a*]pyrazine scaffold, a small array was prepared keeping fixed the thienyl portion. The results of this exploration are reported in Table 6 (derivatives **98–105**) and are in agreement with the results of the previous small exploration (**14–16**). This area of the scaffold seems to have a steric clash with the mGluR5 receptor even when a smaller 3-thienyl derivative is attached on the template. In particular, while derivative **104** and **105** are not dramatically different from derivative **14–16**, the increased bulkiness of the other groups (s, **98–99**) led to a greater reduction in potency.

All the NCEs described in this manuscript were prepared in accordance to the general Scheme 1.

The pyrrolo[2,1-*c*][1,4]oxazin-1-one **I**[20] was transformed into the corresponding pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one **II** with acetic acid and ammonium acetate. Functional group interconversion with phosphorous oxychloride allowed the preparation of the versatile intermediate **III** which was coupled under microwave (MW) conditions with appropriately substituted aryl acetylenes in good yields. The ethoxy carbonyl derivative **III** proved to be very versatile; it could be hydrolyzed to the corresponding carboxylic acid intermediate **V**, allowing the synthesis of differently substituted amides **VI**. When the amide was a primary one, it could be transformed into the corresponding nitrile **VII** through reaction with phosphorous oxychloride and subsequently converted to the final products using palladium coupling reactions.

Again, the COOEt derivative **III** could be directly transformed into the oxadiazolyl derivative and coupled with the acetylenic derivative to give derivative **19**. Furthermore, direct reduction of the same ester with lithium aluminum hydride led to the primary alcohol **VIII**. This intermediate was coupled to give the desired ethynyl derivatives **IX** and then transformed into the desired amino derivatives using a 'one pot' reaction exploiting supported reagents.

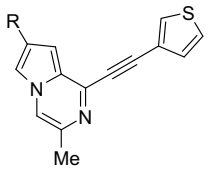
Table 5. Potency values for selected NCEs on h-mGluR5 receptor



Compound	R	Ar	pIC_{50}
65	CN	2-F-phenyl	8.5
66	CN	3-F-phenyl	9.1
67	CN	3-CF_3-phenyl	7.8
68	CN	3-Thienyl	9.4
69	COOEt	3-Cl-phenyl	7.7
70	COOEt	3-CF_3-phenyl	6.7
71	COOEt	3-CN-phenyl	8.5
72	COOEt	4-CN-phenyl	<4.8
73	COOEt	4-CF_3-phenyl	<4.8
74	COOEt	4-Cl-phenyl	<4.8
75	COOEt	4-F-phenyl	6.4
76	COOEt	2-F-phenyl	6.5
77	COOEt	3-Thienyl	8.1
78	COOEt	3-Pyridyl	5.8
79	$CONH_2$	2-F-phenyl	6.3
80	$CONH_2$	3-CF_3-phenyl	7.1
81	$CONH_2$	3-Thienyl	7.3
82	CONHMe	2-F-phenyl	5.8
83	CONHMe	3-F-phenyl	7.0
84	CONHMe	3-CF_3-phenyl	6.7
85	CONHMe	3-Thienyl	7.3
86	1-Pyrrolidinyl carbonyl	2-F-phenyl	6.6
87	1-Pyrrolidinyl carbonyl	3-F-phenyl	7.7
88	1-Pyrrolidinyl carbonyl	3-CF_3-phenyl	6.8
89	1-Pyrrolidinyl carbonyl	3-Thienyl	7.7
90	4-Morpholinyl carbonyl	2-F-phenyl	6.9
91	4-Morpholinyl carbonyl	3-F-phenyl	7.7
92	4-Morpholinyl carbonyl	3-CF_3-phenyl	7.9
93	4-Morpholinyl carbonyl	3-Thienyl	8.0
94	(4-Methyl-1-piperazinyl) carbonyl	2-F-phenyl	5.9
95	(4-Methyl-1-piperazinyl) carbonyl	3-F-phenyl	6.7
96	(4-Methyl-1-piperazinyl) carbonyl	3-CF_3-phenyl	6.6
97	(4-Methyl-1-piperazinyl) carbonyl	3-Thienyl	6.8

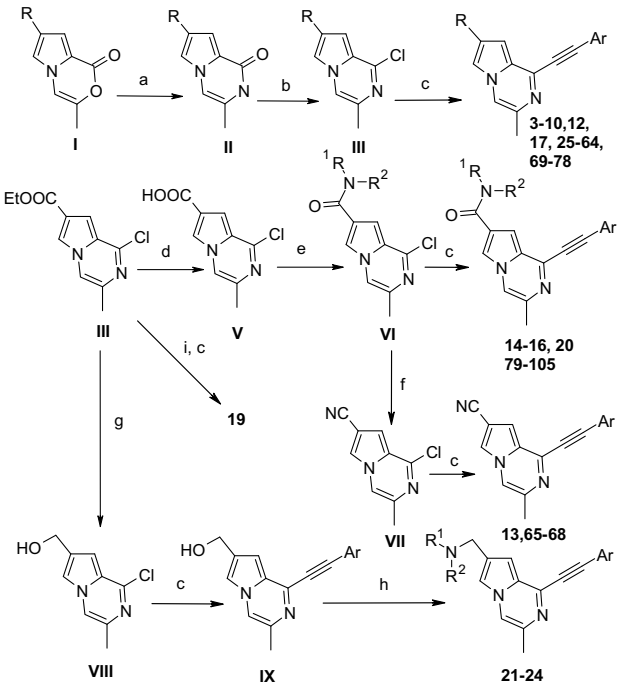
IC_{50}s are geometric means of at least three independent experiments. The standard deviation is ±0.3.

Table 6. Potency values for selected NCEs on h-mGluR5 receptor



Compound	R	pIC_{50}
98	(1*R*,4*S*)-2-azabicyclo[2.2.1]hept-2-yl carbonyl	6.2
99	[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl] carbonyl	5.4
100	(2,2-Dimethyl-1-pyrrolidinyl) carbonyl	5.9
101	(3,3-Difluoro-1-pyrrolidinyl) carbonyl	6.9
102	(2,5-Dimethyl-1-pyrrolidinyl) carbonyl	6.4
103	[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl] carbonyl	6.5
104	(2-Methyl-1-pyrrolidinyl) carbonyl	7.4
105	(2-Methyl-1-piperidinyl) carbonyl	7.0

IC_{50}s are geometric means of at least three independent experiments.
The standard deviation is ±0.3.



Scheme 1. General condition for the preparation of the NCEs previously described. Reagents and conditions: R = CF_3, Me, H, COOEt. (a) AcOH, NH_4OAc; 160 °C, 48 h; (b) $POCl_3$, reflux, 5 h; (c) CuI, $(PPh_3)_2PdCl_2$, HC≡CAr, DMF, TEA, 120 °C, MW, 0.5 h; when R = COOEt in intermediate **III**, then (d) NaOH, dioxane, H_2O, 95 °C MW, 0.2 h; (e) $R^1R^2NH_2$, DIPEA, HATU, DMF. rt, overnight. When intermediate **VI** has $R^1 = R^2 = H$, then (f) $POCl_3$, CH_3CN, reflux, 3 h; when R = COOEt in intermediate **III**, then (g) $LiAlH_4$, THF, from 0 °C–rt, 0.5 h; (h) supported PPh_3, CBr_4, CH_2Cl_2, rt, 2 h; followed by R^1R^2NH, DIPEA, DMF, rt overnight; (i) *N*-hydroxyethanimidamide, NaH, THF, rt, overnight.

In this case, also the purification from the excess of unreacted amines was performed through isocyanate resin scavengers.

In conclusion, the above reported exploration provided further structure activity information around the non-competitive binding site of the mGluR5 receptor. In particular, the tolerability of certain regions to steric bulk and hydrophilicity in position 7 of the new scaffold was established.

The exploration allowed the identification of compounds endowed with sub-nanomolar potency (**4**, **66** and **68**) and high selectivity versus both the mGluRs family and other receptors including monoaminergic transporters.

Finally, a number of derivatives with improved solubility and acceptable potency were also identified and helped to further validate the potential therapeutic applications of the mGluR5 antagonists as will be reported in due course.

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19. Activity is measured as the alteration of a glutamate induced increase in intracellular calcium which activates a fluorescent dye loaded into the cells. The fluorescence produced is measured by FLIPR™. Chinese Hamster Ovary cells transfected with the h-mGluR5 receptor under the control of the GeneSwitch™ Gene Expression apparatus were used.
20. Derivatives of general formula **I** reported in Scheme 1 were prepared from the corresponding 4-substituted 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone adding 1.2 equiv of 1-chloro-2-propanone and stirring the mixture in acetone in the presence of K_2CO_3 at room temperature for 20 h, followed by appropriate chromatographic separation (CyH-AcOEt from 90/10 to 80/20).