Bioorganic & Medicinal Chemistry Letters 21 (2011) 2650–2654

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design and synthesis of substituted *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)-benzamides as positive allosteric modulators of the metabotropic glutamate receptor subtype 5

Mu-Fa Zou [a], Jianjing Cao [a], Alice L. Rodriguez [b], P. Jeffrey Conn [b], Amy Hauck Newman [a,*]

[a] Medicinal Chemistry Section, National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health, 333 Cassell Drive Baltimore, MD 21224, United States
[b] Department of Pharmacology, Vanderbilt Program in Drug Discovery, Vanderbilt University Medical Center, I215D Light Hall, 2215B Garland Avenue, Nashville, TN 37232-057, United States

ARTICLE INFO

Article history:
Received 17 September 2010
Revised 17 December 2010
Accepted 21 December 2010
Available online 28 December 2010

This manuscript is dedicated to Professor James M. Cook on the occasion of his 65th birthday

Keywords:
mGluR5
MPEP
CDPPB
Allosteric modulators

ABSTRACT

Based on SAR in the alkyne class of mGlu5 receptor negative allosteric modulators and a set of amide-based positive allosteric modulators, optimized substitution of the aryl 'b' ring was used to create substituted *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamides. Results from an mGlu5 receptor functional assay, using calcium fluorescence, revealed varying efficacies and potencies that provide evidence that subtle changes in compounds within a close structural class can have marked effects on functional activity including switches in modes of efficacy (i.e., negative to positive allosteric modulation).

Published by Elsevier Ltd.

Glutamate (L-Glutamic acid) is the major excitatory neurotransmitter within the mammalian central nervous system and regulates a variety of neuronal activities through ionotropic glutamate receptors and metabotropic glutamate receptors (mGlu receptors).[1] mGlu receptors are G protein-coupled receptors (GPCRs) that have been cloned, sequenced, and classified into Group I (mGlu1 and mGlu5 receptors), Group II (mGlu2 and mGlu3 receptors), or Group III (mGlu4, 6, 7, 8 receptors) based on sequence homology, pharmacology and 2nd messenger coupling.[1] The mGlu5 receptor is primarily located postsynaptically and is coupled with phospholipase C. Activation of mGlu5 receptor stimulates phospholipase C, which results in the hydrolysis of phosphoinositide and increases intracellular calcium concentrations.[1,2] The mGlu5 receptors have been targeted in the development of drugs to treat a variety of neurological and psychiatric illnesses, including anxiety, depression, pain, Parkinson's disease, schizophrenia and Fragile X syndrome.[2–8] Preclinical studies suggest that mGlu5 receptors may also play a role in drug abuse and addiction.[9] A large number of potent noncompetitive antagonists for mGlu5 receptor have been developed based on the structure of the leading compounds 2-methyl-6-(phenylethynyl)pyridine (MPEP, **1**, Fig. 1) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP). However, cross-target activity and in vivo metabolism may limit further development of these alkynes as medications.[10] In our attempts to design nonalkynyl mGlu5 receptor antagonists (negative allosteric modulators), several moderately active diarylamides were discovered (e.g., **2b**, in Fig. 1).[11] Based on the binding and functional data for amide-linked derivatives, we previously considered that the marked differences in functional potency as compared to binding affinities might be due to different conformational states of the mGlu5 receptor.[11a] The discovery of amide-linked positive allosteric modulators of mGlu5 receptor, such as 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide[12] (CDPPB; **3**, Fig. 1), provided further support of this idea. Thus, we hypothesized that the 'b' ring in our amide series primarily influences affinity at the mGlu5 receptor, whereas the 'a' ring determines efficacy that leads to potentiation rather than inhibition of glutamate stimulation.

In this study, we explore (i) the substituent effects at the 6-position of the pyridyl 'a' ring of the 3-CN, 5-F phenyl 'b' ring amide (Scheme 1, Table 1), and (ii) structural modifications of the 'b' ring of CDPPB by incorporating previously described[11b,c] and optimized substitutions of the 'b' ring (Schemes 2 and 3, Table 2). 1-(2-Chlorophenyl)-3-phenyl-1*H*-pyrazol-5-yl was used to replace the 'a' ring of CDPPB since a chloro substitution at

* Corresponding author.
E-mail address: anewman@intra.nida.nih.gov (A.H. Newman).

0960-894X/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2010.12.110

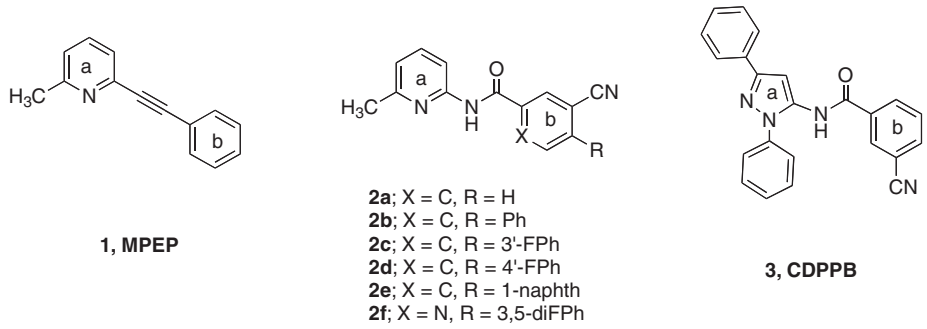
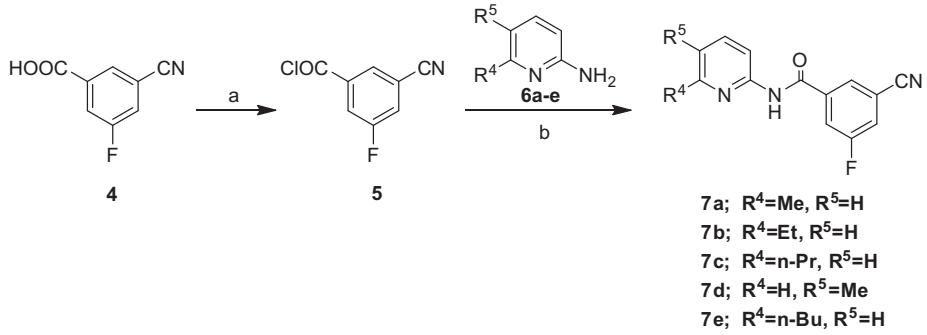
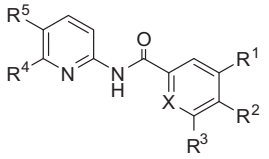


Figure 1. Structures of mGlu5 receptor allosteric modulators.



Scheme 1. Synthesis of (6-substituted pyridine-2-yl)benzamides. Reagents and conditions: (a) $SOCl_2$, reflux, 2 h; (b) 5- or 6-substituted 2-aminopyridines (**6a**–**e**), Et_3N, CH_2Cl_2, rt, 1 h.

Table 1
In vitro data for amide-linked mGlu5 receptor antagonists



Compd	X	R^1	R^2	R^3	R^4	R^5	*c* Log *P*[f]	mGluR5 binding (K_i, nM)[a]	mGluR5 function IC_{50} (nM) (Ca^{+2} flux)
2a[d,e]	C	CN	H	H	Me	H	2.1	330 ± 20[c,d]	490 ± 94
2b[e]	C	CN	Ph	H	Me	H	4.0	9.8 ± 2.1 [b]	13.7 ± 2.54
2c[e]	C	CN	3′FPh	H	Me	H	4.1	22 ± 5.3 [b]	25.3 ± 1.90
2d[e]	C	CN	4′FPh	H	Me	H	4.1	134 ± 31[c]	4.57 ± 0.38
2e[e]	C	CN	1-Naphth	H	Me	H	5.1	72 ± 12[c]	640 ± 32.2
2f[e]	N	H	3,5-DiFPh	H	Me	H	3.8	43 ± 10	98.1 ± 18.9
7a	C	CN	H	F	Me	H	2.2	65.5 ± 20[c]	21.7 ± 5.41
7b	C	CN	H	F	Et	H	2.8	762 ± 177[c]	169 ± 21.7
7c	C	CN	H	F	*n*-Pr	H	3.3	325 ± 62[c]	165 ± 21.7
7d	C	CN	H	F	H	Me	2.2	2831 ± 567[c]	4170 ± 528
7e	C	CN	H	F	*n*-Bu	H	3.8	1054 ± 262[c]	1550 ± 146
1, MPEP[c]	—	—	—	—	—	—	3.8	13 ± 1	3.54 ± 1.39

[a] Data provided by NIMH-PDSP.
[b] Cloned.[15]
[c] Rat brain (http://pdsp.med.unc.edu).
[d] Compound previously reported.[11a]
[e] Compound and data reported previously.[11b,c]
[f] Determined using Sybyl 7.2.3, Tripos Inc.

that position was reported to increase mGlu5 receptor binding affinity of CDPPB.[13]

Synthesis of the N-(5- or 6-substituted pyridin-2-yl)-3-cyano-5-fluorobenzamides **7** started from 3-cyano-5-fluorobenzoic acid **4** (Scheme 1). The acid **4** was first converted to the corresponding acid chloride **5** followed by reaction with 2-aminopyridines **6** to give the benzamides **7(a–e)** in good yields.

Synthesis of substituted *N*-[1-(2-chlorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]benzs amide **19** is shown in Scheme 2. The preparation of 1-(2-chlorophenyl)-3-phenyl-5-amino-1*H*-pyrazol **10** was achieved according to a literature procedure.[13] Benzylic protection of both the OH and COOH groups in compound **11** gave intermediate **12**. Cyanation of **12** with $Zn(CN)_2$ in the presence of $Pd(PPh_3)_4$ catalyst gave intermediate **13**. Hydrolysis of **13** under basic conditions resulted in selective deprotection to give the carboxylic acid **14**. The free acid **14** was protected as the ethyl ester **15** via its acid chloride. Pd/C catalyzed hydrogenation successfully deprotected **15,** followed by treatment with trifluoromethanesulfonic