Bioorganic & Medicinal Chemistry Letters 26 (2016) 2289–2292

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Re-exploration of the $mGlu_1$ PAM Ro 07-11401 scaffold: Discovery of analogs with improved CNS penetration despite steep SAR

Pedro M. Garcia-Barrantes [a], Hyekyung P. Cho [a,b], Tahj M. Starr [a], Anna L. Blobaum [a], Colleen M. Niswender [a,b,c], P. Jeffrey Conn [a,b,c], Craig W. Lindsley [a,b,d,*]

[a] Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, TN 37232, USA
[b] Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA
[c] Vanderbilt Kennedy Center, Vanderbilt University, Nashville, TN 37232, USA
[d] Department of Chemistry, Vanderbilt University, Nashville, TN 37232, USA

ARTICLE INFO

Article history:
Received 4 March 2016
Revised 11 March 2016
Accepted 12 March 2016
Available online 14 March 2016

Keywords:
$mGlu_1$
Metabotropic glutamate receptor
Positive allosteric modulator (PAM)
Schizophrenia
Structure–Activity Relationship (SAR)

ABSTRACT

This letter describes the re-exploration of the $mGlu_1$ PAM Ro 07-11401 scaffold through a multi-dimensional, iterative parallel synthesis approach. Unlike recent series of $mGlu_1$ PAMs with robust SAR, the SAR around the Ro 07-11401 structure was incredibly steep (only ~6 of 200 analogs displayed $mGlu_1$ PAM activity), and reminiscent of the CPPHA $mGlu_5$ PAM scaffold. Despite the steep SAR, two new thiazole derivatives were discovered with improved in vitro DMPK profiles and ~3- to 4-fold improvement in CNS exposure (K_ps 1.01–1.19); albeit, with a ~3-fold diminution in $mGlu_1$ PAM potency, yet comparable efficacy (~5-fold leftward shift of the glutamate concentration–response curve at 10 μM). Thus, this effort has provided additional CNS penetrant $mGlu_1$ PAM tools in a different chemotype than the VU0486321 scaffold. These compounds will permit a better understanding of the pharmacology and therapeutic potential of selective $mGlu_1$ activation, while highlighting the steep SAR challenges that can often be encountered in GPCR allosteric modulator discovery.

Efforts towards the development of positive allosteric modulators (PAMs) of the metabotropic glutamate receptor subtype 1 ($mGlu_1$) were pioneered by Knoflach and co-workers at Roche, resulting in **1**–**4** (Fig. 1).[1–3] These small molecule PAMs, coupled with data generated with negative allosteric modulators (NAMs) of $mGlu_1$,[4,5] highlighted issues with species differences due to a single amino acid in rat versus human $mGlu_1$,[6,7] and thus **4**, a PAM active on both human and rat $mGlu_1$, emerged as a valuable tool compound, despite modest CNS penetration (K_p = 0.29 and high protein binding (f_u < 0.01). For over a decade, **4** was the only in vivo tool compound to study selective $mGlu_1$ activation.[8–11] Based on recent genetic data implicating *GRM1* in schizophrenia,[12–14] coupled with data showing that the adverse effect liabilities of group I metabotropic glutamate receptors (mGluRs) are mediated by $mGlu_5$ and not $mGlu_1$,[15] our lab has launched a program to develop the next generation of $mGlu_1$ PAMs.[14–18] In the past year, we have reported on the discovery and optimization of novel $mGlu_1$ PAMs **5**–**7** with improved potency (EC_{50}s < 20 nM), DMPK profiles (f_us > 2.0% unbound) and CNS penetration (K_ps > 1) to afford new avenues for target validation and to assess the therapeutic potential of selective $mGlu_1$ activation.[14–18]

Previously, revisiting the $mGlu_4$ PAM (−)-PHCCC scaffold led to the discovery of improved tool compounds.[19] Therefore, over a decade after its discovery, we felt it was prudent to revisit the Ro 07-11401 scaffold in an effort to develop an in vivo tool compound within this series with improved disposition to account for any chemotype or ligand-biased pharmacology and expand the repertoire of validation tools for $mGlu_1$.

In our functional assays, Ro 07-11401 (**4**) was an equipotent $mGlu_1$ PAM on both rat (EC_{50} = 276.5 nM, pEC_{50} = 6.56 ± 0.08, 109 ± 3% Glu Max) and human (EC_{50} = 246.0 nM, pEC_{50} = 6.61 ± 0.08, 96 ± 3% Glu Max), but with a modest disposition profile (vide infra).[14–18] Thus, we pursued a multi-dimensional optimization plan (Fig. 2) to explore SAR around **4** in an attempt to improve disposition by identifying replacements for the weakly basic oxadiazole (effectively neutral with the pendant CF_3 moiety) with analogs **9** and the lipophilic 9*H*-xanthene moiety in analogs **8**. Once identified, optimal moieties would then be combined.

The synthesis was straightforward (Scheme 1). A variety of commercially available 2-amino-4-substiuted oxazoles **10** were coupled under HATU conditions with a diverse array of carboxylic acids to provide analogs **8** in yields ranging from 18% to 54%. Sim-

* Corresponding author.
E-mail address: craig.lindsley@vanderbilt.edu (C.W. Lindsley).

http://dx.doi.org/10.1016/j.bmcl.2016.03.044
0960-894X/

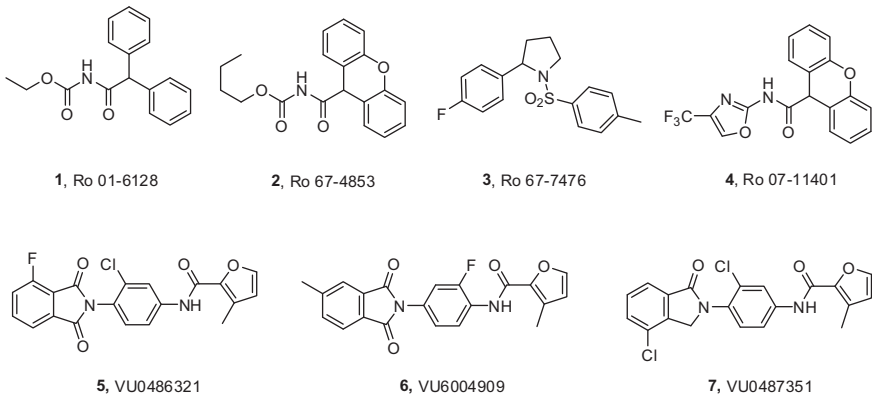


Figure 1. Structures of representative $mGlu_1$ PAMs **1**–**7**.

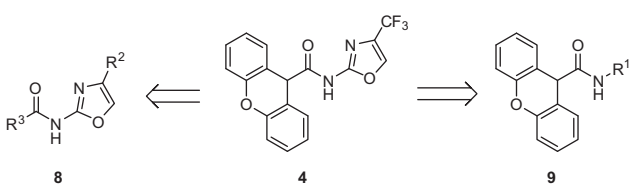
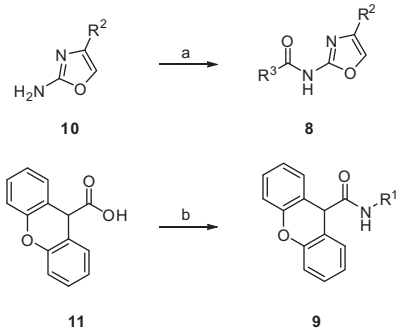


Figure 2. Chemical optimization plan to identify replacements for the lipophilic oxadiazole with analogs **9**, and the lipophilic 9*H*-xanthene with analogs **8**.

ilarly, the 9*H*-xanthene-9-carboxylic acid **11** was coupled under HATU conditions to a variety of 5- and 6-membered heterocyclic amines to deliver analogs **9** in 11–94% yields. For both series, many of the amines and acids coupled poorly due to a combination of steric and stereoelectronic effects, as well as a range of poor solubility.

In all, over 200 analogs of **8** and **9** were synthesized and triaged via a 10 μM single point screen on human $mGlu_1$, using an EC_{20} concentration of glutamate, prior to full concentration–response curves (CRCs) on both human and rat $mGlu_1$. Surprisingly, all analogs **8** (Fig. 3) were uniformly inactive $mGlu_1$ PAMs (no potentiation of an EC_{20} of glutamate at a concentration of 10 μM), indicating that the 9*H*-xanthene was a critical pharmacophore. The SAR was remarkably steep, and reminiscent of the steep SAR encountered with the non-MPEP, $mGlu_5$ PAM CPPHA,[20] wherein virtually any modification led to a complete loss of PAM activity. Obviously, these data cast doubt on the success of the campaign with analogs **9**, wherein the 9H-xanthene amide was held constant. While SAR once again was steep, active analogs did result (Table 1); however, functionalized pyrazoles, oxazoles, oxadiazoles, thiophenes, piperidines, azetidines, cycloalkyl, a structurally



Scheme 1. Reagents and conditions: (a) R^3CO_2H, DIEA, DMF, 60 °C, 18–54%; (b) H_2NR^1, HATU, DIEA, DCE, rt, 11–94%.

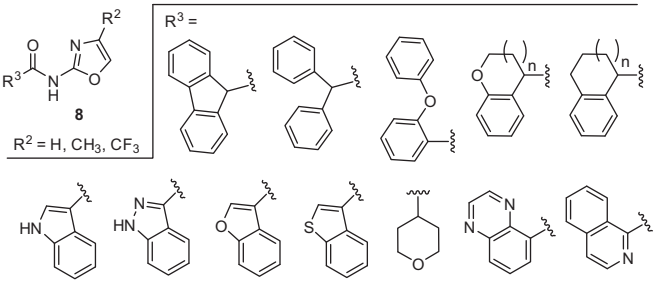
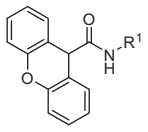
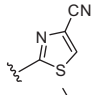
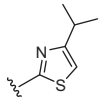
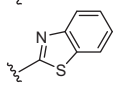
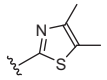


Figure 3. Representative 9*H*-xanthene amide replacement analogs **8** that are inactive $mGlu_1$ PAMs.

Table 1
Structures and activities for analogs **9**



Compd	R^1	$hmGlu_1$ EC_{50} (μM)[a] [% Glu Max ±SEM]	$mGlu_1$ pEC_{50} (±SEM)
9a		0.71 [110 ± 6]	6.14 ± 0.12
9b		0.90 [89 ± 3]	6.04 ± 0.07
9c		1.4 [75 ± 3]	5.85 + 0.07
9d		2.7 [101 ± 7]	5.57 + 0.11
9e		>10 [54 ± 7]	<5
9f		4.8 [96 ± 11]	5.32 ± 0.20
9g		>10 [68 ± 8]	<5
9h		1.7 [58 ± 3]	5.77 ± 0.11

[a] Calcium mobilization $mGlu_1$ assays, values are average of three ($n = 3$) independent experiments performed in triplicate.