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Scaffold hopping from pyridones to imidazo[1,2-*a*]pyridines. New positive allosteric modulators of metabotropic glutamate 2 receptor

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The authors dedicate this Letter to the memory of Dr. Hassan Imogai, Addex Pharmaceuticals SA

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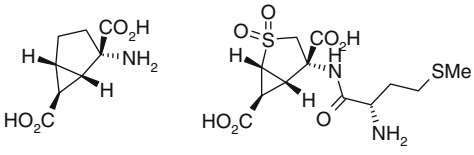
ABSTRACT

Imidazo[1,2-*a*]pyridines were identified via their shape and electrostatic similarity as novel positive allosteric modulators of the metabotropic glutamate 2 receptor. The subsequent synthesis and SAR are described. Potent, selective and metabolically stable compounds were found representing a promising avenue for current further studies.

The metabotropic glutamate type 2 receptor (mGluR2) is a G-protein coupled receptor (GPCR) expressed on presynaptic nerve terminals where it negatively modulates glutamate and GABA release.[1] Mixed mGluR2/mGluR3 agonists such as LY354740 (**1**) have shown activity in a range of preclinical animal models of anxiety and schizophrenia (see Fig. 1).[2,3] Early clinical work with LY354740 demonstrated activity in a CO_2 inhalation study suggesting the usefulness for the treatment of anxiety related disorders.[4] Subsequently, a related prodrug LY2140023 (**2**) demonstrated improvements in positive and negative symptoms in patients suffering from schizophrenia.[5] These molecules exhibit combined mGluR2/mGluR3 activity although there is evidence from knock-out studies that preclinical anti-psychotic effects may be mediated via the mGluR2 receptor.[6]

An alternative avenue for modulating GPCRs is to act via allosteric mechanisms, binding at a different site from the orthosteric agonist.[7] Positive allosteric modulators (PAMs) of mGluR2 have been claimed and reported, Figure 2.[8] PAMs may offer benefits over orthosteric agonists. The orthosteric site is highly conserved across the mGluR family therefore targeting alternative sites assists the identification of selective compounds.[9] Allosteric ligands will in general be more brain penetrant as they would not be amino acid analogues. The allosteric modulator exerts its effect when glutamate is present allowing the receptor to respond to physiological



1, LY354740 **2**, LY2140023

Figure 1. Structures of mixed mGluR2/3 agonists LY354740 and LY2140023.

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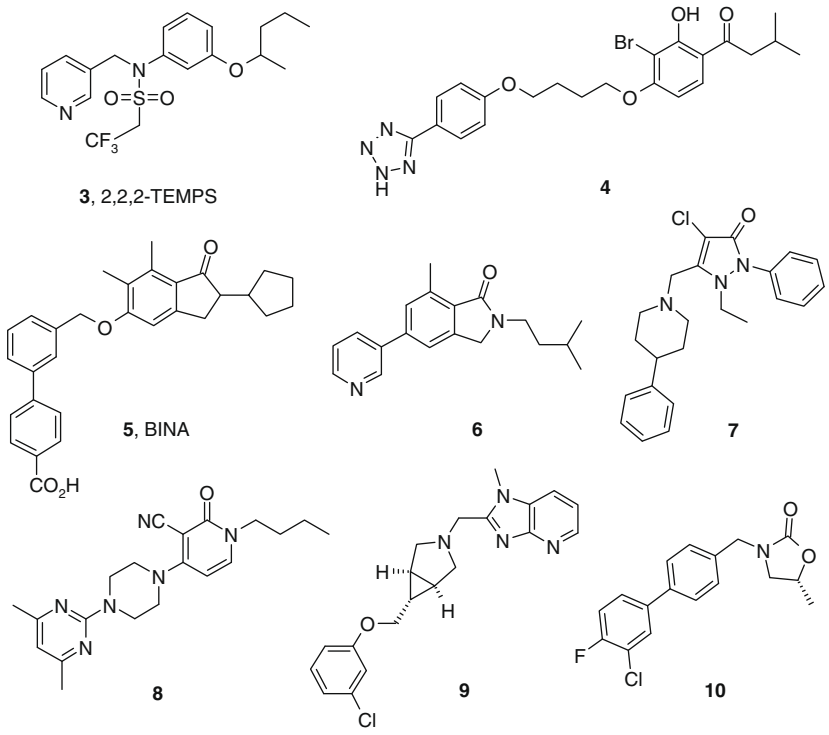


Figure 2. Reported mGluR2 positive allosteric modulators.

changes in endogenous agonist levels. In addition, it is expected that PAMs will not produce the same degree of receptor desensitization.[10] The first allosteric modulators of mGluR2 were a series of sulfonamides developed by Lilly that include the 2,2,2-TEMPS **3** which inhibited ketamine evoked norepinephrine release in rats.[11] BINA **5** has shown anxiolytic and antipsychotic effects in behavioral models in mice.[12] Finally, compound **10** was active in a methamphetamine induced hyperlocomotion model in mice.[8h]

In this Letter we present the discovery of imidazo[1,2-*a*]pyridines as a new series of mGluR2 PAMs. With the need to identify new hit matter for this target we applied computational techniques based on 3D shape and electrostatic similarity. Such approaches are well suited to scaffold hopping as similarity is assessed using properties important for biological recognition not the underlying atom connectivity. We demonstrate that examples from the imidazopyridine series, show good in vitro mGluR2 PAM activity, selectivity and metabolic stability.

An overlay hypothesis for mGluR2 PAMs **4**–**8** is shown in Figure 3. This was derived with flexible alignment in MOE, the MMFF94x force field, Born solvation, internal dielectric equal to 4 and all other settings as defaults.[13,14] We do not present a fully validated mGluR2 PAM pharmacophore here yet the plausible alignment serves to highlight shared features. Firstly, the molecules have a central scaffold with an often exocyclic H-bond acceptor, adjacent to which is a small substituent such as –Cl, –Br, –Me or –CN. Secondly, a larger lipophilic group is pendant from the scaffold, examples include isopentyl, cyclopentyl, phenyl and benzyl. Finally, there is a scaffold substituent with greater extent of structural variation, ranging from pyridyl and phenylpiperidine to larger and more flexible substituted ethers as in **4** and **5**. In summary, inspection of the molecules in Figure 2 and overlay in Figure 3 helped identify conserved features of mGluR2 PAM molecules and suggested that alternative scaffolds with suitable features and decoration would yield new hits.

Within our labs a process of scaffold hopping using annotated fragment databases and 3D shape and electrostatic similarity has been implemented.[15] In this project a similar approach was applied. Search queries were defined as scaffold fragments of molecules **6**–**8** with phenyl, ethyl and chloro decoration to mimic the complete molecules, see pyridone query in Figure 4. The search database was constructed from two sources: ideas from the project team and scaffolds generated in an automated fashion via fragmentation of in-house and external compound collections. Database fragments were capped in an analogous manner to the queries using phenyl, ethyl and chloro at each open valence. The database contained 115,647 fragments and 3D conformations were generated with Omega.[16] The lowest energy conformer was used

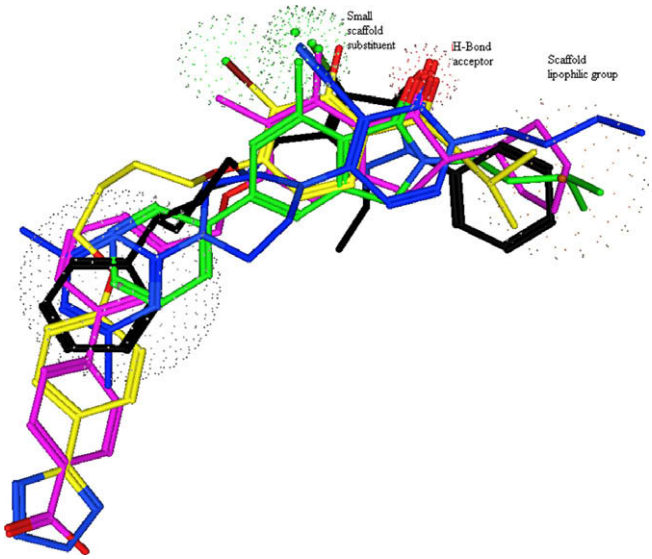


Figure 3. Overlay of molecules **4**–**8**. Selected conserved features are highlighted with dotted spheres, H-bond acceptor, small scaffold substituent and larger lipophilic scaffold group. Molecule color-coding: **4**—yellow, **5**—magenta, **6**—green, **7**—black, **8**—blue.

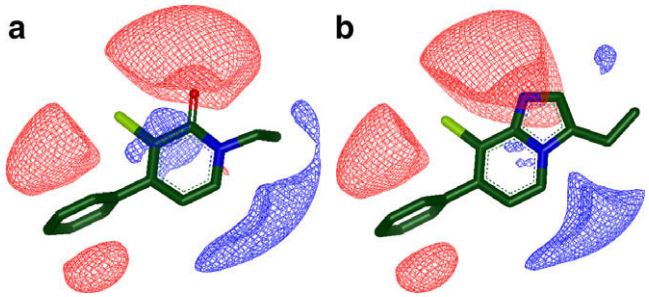


Figure 4. Electrostatic fields of (a) pyridone query and (b) imidazopyridine hit fragment. Negative field is red and positive blue.

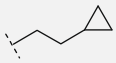
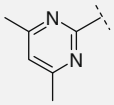
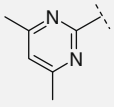
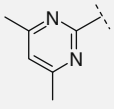
for each query whilst default settings generated multiple 3D conformers of each database fragment. Firstly, searches were performed with ROCS[17] using comboscore ranking to align and identify shape and feature similar database fragments. Subsequently the top 500 hits were re-ranked by their electrostatic field similarity to the query using EON.[18]

From the search using the pyridone query the imidazopyridine was identified among the best ranked hits. The Poisson–Boltzmann electrostatic Tanimoto similarity was 0.87. The query and hit are shown in Figure 4. Overall they have similar shape, size and distribution of substituent groups. The negative region of the carbonyl acceptor is well reproduced by the imidazo nitrogen. The phenyl groups are both twisted yielding very similar regions of negative charge above and below the ring. In addition the positive regions produced by –CH moieties on the scaffold are well matched. Before synthesis a virtual library of imidazopyridines was enumerated and target compounds including examples from Tables 1 and 2 with the best overall shape and feature similarity compared to molecule **8** were prioritized.

The synthesis of the final imidazo[1,2-*a*]pyridines[19] is depicted in Schemes 1 and 2. Microwave promoted thermal condensation of commercially available pyridine derivative **11** with an α-bromoaldehyde **12** afforded in moderate to good yields the 8-cyano-7-hydroxyimidazo[1,2-*a*]pyridines **13**. Subsequent reaction of **13** with $P(O)Cl_3$ led to the corresponding chloro derivatives **14** which were then transformed into the final compounds **16** by nucleophilic substitution of the chlorine atom with secondary amine **15** in the presence of diisopropylethylamine (DIPEA) under microwave irradiation (Scheme 1).

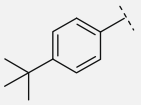
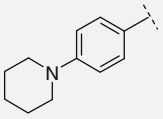
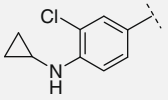
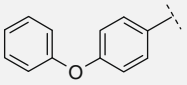
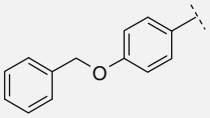
In the case of aryl substituted imidazo[1,2-*a*]pyridines **18** the target compounds were obtained by Suzuki coupling of the corresponding boronic esters **17** with the chloroimidazopyridine **14a**.

Table 1
Functional activity and metabolic stability in rat (RLM) and human liver microsomes (HLM) of representative mGluR2 PAMs (general structure **16**)[a]

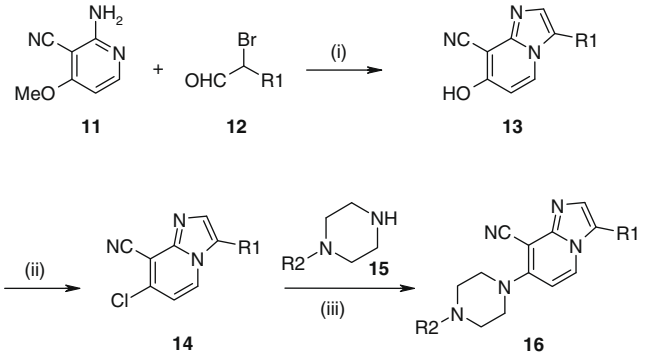
Compds	R^1-	R^2-	mGluR2 pEC_{50}[a]	mGluR2 E_{MAX}[a] (%)	RLM[b,c] (%)	HLM[b,c] (%)
3	—	—	7.51	124	nd	nd
5	—	—	7.56	213	nd	nd
8	—	—	6.20	235	nd	nd
16a			6.01	241	88	71
16b			<5.5	73	nd	nd
16c			<5.5	214	nd	nd
16d			<5.5	248	nd	nd
16e			5.96	229	nd	57
16f			6.07	231	26	32
16g			5.64	142	nd	70
16h			6.19	179	nd	70
16i			6.35	128	nd	57

[a] Values are means of three experiments.
[b] RLM and HLM data refer to % of compound metabolized after 15 min at 5 μM concentration.
[c] nd: not determined.

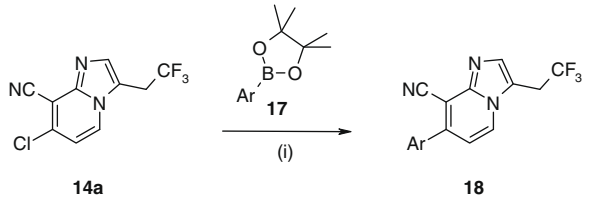
Table 2
Functional activity and metabolic stability in rat (RLM) and human liver microsomes (HLM) of representative mGluR2 PAMs (general structure **18**)[a]

Compds	R^1-	Ar-	mGluR2 pEC_{50}[a]	mGluR2 E_{MAX}[a] (%)	RLM[b,c] (%)	HLM[b,c] (%)
18a			6.35	272	21	32
18b			6.63	123	nd	nd
18c			6.85	187	38	28
18d			6.73	200	23	23
18e			6.80	222	nd	nd

[a] Values are means of three experiments.
[b] RLM and HLM data refer to % of compound metabolized after 15 min at 5 μM concentration.
[c] nd: not determined.



Scheme 1. Reagents and conditions: (i) EtOH, μW, 150 °C, 40 min, 50–82%; (ii) $P(O)Cl_3$, μW, 150 °C, 15 min, 70–85%; (iii) DIPEA, CH_3CN, mW, 180 °C, 15 min, 67–97%.



Scheme 2. Reagents and conditions: (i) $Pd(PPh_3)_4$, $NaHCO_3$ (aq)/1,4-dioxane, 150 °C, 15 min 71–88%.

The functional activity[20] and microsomal stability data for a set of selected imidazo[1,2-*a*]pyridines are listed in Tables 1 and 2. Two activity data are reported for each molecule: the maximum % effect increase in glutamate response (E_{MAX}) and the pEC_{50} for the modulatory effect.

Based on data from our previous hit **8**[8f] we initially decided to use different phenylpiperazinyl and pyrimidylpiperazinyl groups to study the influence of substitution on the imidazole ring of the bicyclic imidazopyridine core (Table 1). Thus lipophilic alkyl and aryl groups such as *n*-propyl (**16a**, **16d** and **16h**), phenyl (**16b**), ethyl (**16c** and **16g**), cyclopropylethyl (**16e**) and 2,2,2-trifluoroethyl (**16f** and **16i**) were introduced. It was pleasing that amongst the first molecules synthesized with the new scaffold, mGluR2 PAM activity was found. This suggested that the scaffold replacement strategy was successful. However, not all combinations were well tolerated. The *n*-propyl group was active in compounds **16a** and **16h** yet **16d**, although delivering an increase in glutamate response, E_{MAX} 248%, did not have a pEC_{50} greater than the concentration limit. The highest pEC_{50} was observed for the more lipophilic groups as seen in the trend within the two subseries **16c–f** and **16g–i**.[21] The 2,2,2-trifluoroethyl was the most active group in combination with both pyrimidylpiperazinyl groups in compounds **16f** and **16i** with pEC_{50} values of 6.07 and 6.35, respectively. For compound **16c** having the less lipophilic ethyl residue a pEC_{50} could not be measured despite showing an increase in glutamate signal. In mGlu2 binding experiments **16f** displaced a tritiated analogue from the pyridone series with a pIC_{50} of 6.4 offering further experimental support for the scaffold hopping replacement of pyridone by imidazopyridine. Overall interesting functional activity was found in a similar range to the analogous pyridone **8**, pEC_{50} = 6.20 and E_{MAX} 235%. However, the compounds were less active than reference compounds **3** and **5** in the same assay, 7.51 and 7.56, respectively.

Some of the compounds shown in Table 1 were tested for single point microsomal stability in rat and human liver microsomes. Examples containing linear alkyl chains such as *n*-propyl **16a** suffered from extensive metabolism 88% and 71% metabolized after 15 min in rat and human liver microsomes, respectively. Compound **16f** with the 2,2,2-trifluoroethyl substituent was better, being 26% metabolized in rat and 32% in human microsomes.

With the aim of expanding the SAR and the hope of improving in vitro activity and metabolic stability, the amines present in the structures of **16a–i** were replaced by different substituted aryl groups leading to the arylimidazo[1,2-*a*]pyridines **18a–e** shown in Table 2. The 2,2,2-trifluoroethyl substituent on the imidazole

ring was fixed as it had delivered improved pEC_{50} activity and metabolic stability. In general a diverse range of substituents were well tolerated in the aromatic ring (chloro-, alkyl-, amino-, aryloxy-groups) and a good level of activity was retained. As observed in the case of the aminoimidazo[1,2-*a*]pyridines **16** the 2,2,2-trifluoroethyl substituent led to improved metabolic stability in both HLM and RLM (**18a** and **18c**,**d**). These compounds were more active than the examples in Table 1 and in all cases more active than the pyridone compound **8**. Increase in the E_{MAX} glutamate response was also good.

As mentioned earlier, one advantage of allosteric modulation is to facilitate the identification of selective compounds. To examine the selectivity of this new series, examples from both the aminoimidazo[1,2-*a*]pyridines **16** and arylimidazo[1,2-*a*]pyridines **18** were profiled in a panel of mGluR assays.[22] Examples such as **16f**, **16h** and **18d** showed no activity in either agonism or antagonism assays of mGluR1, mGluR3, mGluR4, mGluR5, mGluR6, mGluR7 or mGluR8 at 10 μM.

In summary, a series of imidazo[1,2-*a*]pyridines with mGluR2 PAM activity have been presented. The scaffold was identified via shape and electrostatic similarity to a known pyridone family previously reported by our team.[8f] Such approaches can be of value for providing new chemical series in medicinal chemistry programs. Incorporating side chains from our other pyridone series led to the rapid identification of hits. The reported compounds show comparable in vitro activity to reference compounds and examples displayed favorable metabolic stability. Imidazo[1,2-*a*]pyridines represent a promising avenue for current exploration.

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20. The effect of these compounds on the [^{35}S]-GTPγS binding induced by 4 μM glutamate (~EC_{20}) was characterized using a CHO cell line expressing the human mGluR2 receptor. See Ref. 19 for a detailed description of this assay.
21. The calculated *Alog P* for **16c–f** were 1.2, 1.6, 2.0 and 1.6, respectively, and 1.8, 2.2 and 2.2 for **16g–i**.
22. Compounds were tested for agonist or antagonist activity on mGlu receptors in fluorescent Ca^{2+} assays using HEK293 cells expressing human mGluR1, mGluR5, mGluR3, mGluR7 or mGluR8. Effects on the human mGluR4 and rat mGluR6, expressed in L929 or CHO cells, were assessed in [^{35}S]-GTPγS functional assays.