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Positive allosteric modulators for mGluR2 receptors: a medicinal chemistry perspective

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Abstract

This review summarizes drug discovery efforts on mGluR2 positive allosteric modulators (PAMs) from 2000 to 2013. Medicinal chemistry programs and the identified 21 chemotypes are analyzed and compared in terms of their biological activity and ligand efficiency. Comparative analysis of ligand efficiency metrics including ligand efficiency and lipophilic ligand efficiency allowed us to identify the most promising chemotypes. The perspective of their clinical development was evaluated in the light of recent human data.

Keywords

positive allosteric modulators, mGluR2 receptors, medicinal chemistry, ligand efficiency, clinical development

Introduction

Glutamate is the major excitatory neurotransmitter that plays a role in eliciting and modulating synaptic responses. These processes involve ionotropic (AMPA, NMDA, kainate) and metabotropic receptors. Up to now eight metabotropic glutamate (mGluR) receptors have been described and characterized [1] and were classified into three subgroups based on their similarity in sequence, signaling and pharmacology [2]. Most of the drug discovery interest has been focused to Group I and Group II targets that include mGluR1/mGluR5 and mGluR2/mGluR3 receptors, respectively. Inhibition of mGluR1 receptors has been connected to anxiolytic [3] and analgesic [4] effects. Negative modulation of mGluR5 receptors found to be beneficial in the animal models of anxiety, depression, Fragile-X and autism spectrum disorder (ASD) [5,6]. mGluR5 positive allosteric modulators (PAMs) are believed to be attractive as a potential pharmacotherapy of schizophrenia [7].

In addition to mGluR5 PAMs compounds targeting Group II receptors are also considered as a promising treatment option for schizophrenia. mGluR2 and mGluR3 receptors impact the glutamatergic transmission in certain brain areas implicated in the pathophysiology of schizophrenia. These neurobiological observations have been validated in the experimental models of schizophrenia indicating that Group II mGluR agonists are effective in a number of antipsychotic animal models [8-11]. One of the best characterized compounds from this class is the mGluR2/3 receptor agonists LY404039 that showed remarkable efficacy in animal models of schizophrenia [12] and anxiety [13]. The suboptimal pharmacokinetics of LY404039 prompted the Lilly research team developing its methionine amide prodrug LY2140023 that were found to be effective in a phase 2 study in schizophrenia patients [14, 15]. Although LY2140023 was less effective than the comparator olanzapine but its effect was separated from the placebo and more importantly no weight gain was observed during the treatment period. These promising results, however, were followed by two negative studies. The first one was claimed to be an inconclusive study since neither the effect of LY2140023 nor that of the active control olanzapine could be separated from placebo [16]. In the second negative study LY2140023 was tested against placebo and risperidone as an active control in two doses and two populations one of them preselected using genetic markers. Unlike the active comparator risperidone unfortunately LY2140023 did not show efficacy compared to placebo in either population or dose.

The relative contribution of mGluR2 and mGluR3 receptors in the antipsychotic pharmacology of mGluR2/3 agonists has yet to be fully elucidated. Due to the high level of conservation of the orthosteric (agonist) binding site of mGluRs, developing subtype-specific agonists has proven to be difficult. To date no agonist has been reported to discriminate between mGluR2 and mGluR3. However, in studies using transgenic mice lacking the mGluR2 or mGluR3 receptor, it has been shown that the antipsychotic effects of the mGluR2/3 receptor agonists in the PCP and amphetamine models of psychosis are mediated through the activation of mGluR2 and not of mGluR3 receptors [17,18].

One alternative approach to direct-acting selective mGluR2 receptor agonists is the use of subtype-selective positive allosteric modulators (PAMs). These ligands do not activate the mGluR2 receptor per se but act at an allosteric binding site on the receptor to potentiate glutamate-induced activation of this receptor. Since a potentiator with no inherent agonist activity would only function in the presence of the endogenous agonist, the receptor would not be activated continuously, avoiding receptor desensitization which often occurs after repeated dosing of orthosteric agonists [19-20]. In addition, the allosteric binding sites on glutamate receptors might sufficiently be different as to make subgroup selectivity achievable [21]. In fact, the preclinical proof of concept was achieved by LY487379, the first mGluR2 receptor–specific PAM [22] showing efficacy in animal models of schizophrenia [23, 24]. More recently the Addex-J&J team reported the first successful clinical proof of concept study with ADX-71149 (also known as JNJ-4041183). This phase 2a study was separated into A and B parts investigating ADX-71149 as monotherapy and adjunctive therapy, respectively. ADX-71149 was found to be safe and well-tolerated while in the part B setup demonstrated efficacy on residual negative symptoms [25].

The promising clinical results with the first mGluR2 PAM in man prompted us collecting recently published series of positive allosteric modulators for mGluR2 receptor with primary pharmacology data (general assay conditions are available as supplementary material) and review their potential in psychiatric indications.

Medicinal chemistry of mGlu2 positive allosteric modulators

mGluR2 positive allosteric modulators has been reviewed in 2005 [21] and 2009 [26]. Here we provide a comprehensive overview of mGluR2 PAMs published thirteen years up to 2013. Analyzing the major competitors on the field AstraZeneca, Janssen and Merck are the key players (Table 1) but pharma companies filed almost a constant amount of patent applications during the last five years (please note that data for 2013 is incomplete).

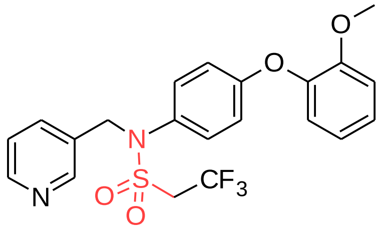
	2001	2004	2006	2007	2008	2009	2010	2011	2012	2013	Total
Lilly	1		2				1				4
Merck		1	3			3	3	5	7		22
AZ		1	2	5	5	1		1			15
Janssen			2	1	3	4	6		4		20
Pfizer				2	2	1					4
Sanofi					1	1		3			5
Abott					1			2			3
Organon								1			1
Sanford-Burnham								1			1
Taisho										2	2
Dainippon										1	1
Total	1	2	9	8	12	10	10	14	11	3	**78**

Table 1. Patent applications filed on mGlu2 positive allosteric modulators

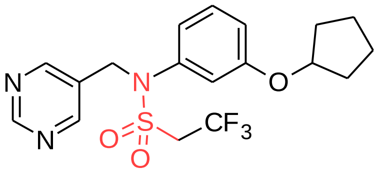
Here we present a comprehensive review of compound series reported as mGluR2 positive allosteric modulators. We discuss the series in compound families that helps to understand the structure-activity relationship and useful to identify key pharmacophore elements.

1. Sulfonamides

LY487379 (**1**) was the first reported highly active and selective mGluR2 positive allosteric modulator (Figure 1). It was identified by in-house high throughput screening (HTS) and subsequent medicinal chemistry optimization at Eli Lilly in the early 2000s [27]. Compound **1** is a potent mGluR2 PAM with an EC_{50} value of 270 nM in an mGluR FLIPR assay [28]. LY487379 was characterized in a series of in vivo pharmacological tests [28,29] and showed activity which suggested potential antipsychotic activity in humans. A series of compounds closely-related to LY487379 was also disclosed in a patent application from Merck [30]. This series of sulfonamide derivatives is exemplified by compound **2** showing an EC_{50} value of 840 nM in a GTPγS binding assay [31] (Figure 1).



1 (LY487379) Eli Lilly
EC_{50} = 270 nM (FLIPR) [28]

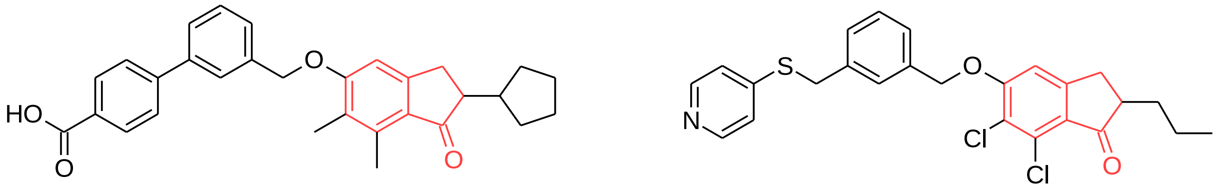


2 Merck
EC_{50} = 840 nM (GTPγS) [31]

Figure 1. mGluR2 PAM sulfonamides

2. Indanones

In 2004 researchers at Merck published two patent applications describing indanone derivatives. The first application disclosed indanones typically substituted with cyclopentyl at C-2, methyl or chloro at C-6 and C-7 and phenyl tertazoles and biaryl acids, as lipophilic end groups at C-5 [32]. Examples of this application indicated to have an EC_{50} value less than 10 μM in a GTPγS binding assay. Preferred compound possess an EC_{50} less than 1 μM, although no specific potency values are given. Compound **3**, also known as BINA [33] is a representative structure of this indanone series (**Figure 2**). BINA, together with LY487379, is among the first mGluR2 potentiators showing antipsychotic- and anxiolytic like effects in vivo [34,35]. Detailed SAR of this series is also published separately in two medicinal chemistry papers [33,36]. The second application from this series discloses closely-related indanones with 4-thiopyridine structure elements at C-6 [37], as exemplified with compound **4**. This compound is a potent mGluR2 PAM with an EC_{50} value of 225 nM in a GTPγS binding assay and significant effect in a ketamine-induced hyperlocomotion model in rats at the dose of 40 mg/kg, *i.p.* [36].



3 (BINA) Merck
EC_{50} = 111 nM (GTPγS) [33]

4 Merck
EC_{50} = 225 nM (GTPγS) [36]

Figure 2. mGluR2 PAM indanones

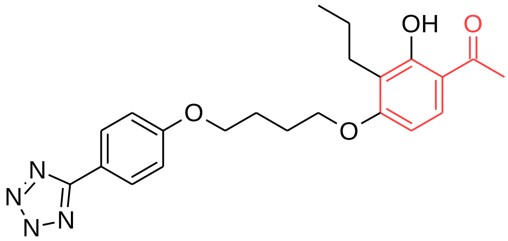
3. Arylketones

Researchers at Merck disclosed novel chemical entities showing significant activity on mGluR2 receptor in two patent applications published in 2002 and 2004, respectively [37,38] (**Figure 3)**. The first in a series of applications disclosed such arylketone derivatives where acetophenones were linked with an aryl ether linker to an acidic phenyl tetrazole scaffold. Representative compound **5**, identified by in-house high-throughput screening had an EC_{50} value of 328 nM and found to be selective over other mGluR receptors [39]. The structure–activity relationships (SAR) of these derivatives have been reported in a separate paper [40]. In the second patent application Merck disclosed acetophenone derivatives with improved brain penetration [38]. Potency and pharmacokinetic data of these derivatives have also been reported [41,42]. Compound **6**, bearing a coumarinone scaffold instead of phenyl tetrazole moiety showed improved brain/plasma ratio compared to the original HTS hit **5**, nevertheless, the mGluR2 affinity was slightly decreased (GTPγS EC_{50} = 1400 nM). Researchers at Lilly have also identified a closely-related series of arylketone derivatives using a benzyl ether linkage [43]. These compounds are dual-acting compounds; potentiators of mGluR2 and antagonists of leukotriene Cys-1 receptor. These derivatives are exemplified by compound **7** with an mGluR2 EC_{50} less than 350 nM and CysLT1 IC_{50} less than 150 nM in a FLIPR assay.

In a second application [44], consisting of 155 specific examples, a benzhydril linkage is used. The preferred compound is **8**, possesses an mGluR2 EC_{50} less than 100 nM and CysLT1 IC_{50} less than 750 nM in a FLIPR assay. Compound **8**, also known as LY2300559 had been in Phase

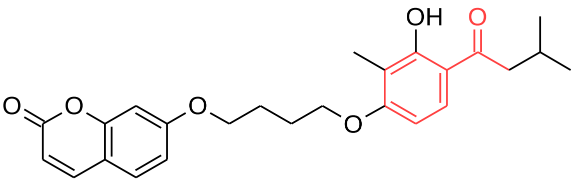
II development for migraine prophylaxis but the study was terminated due to transaminase elevations [45].

In a third application novel arylketone derivatives containing an imidazole carboxamide function have been disclosed [46]. These derivatives are exemplified with compound **9**, as a potent mGluR2 PAM with an EC_{50} value of 26 nM in FLIPR assay. A detailed in vivo profile of this compound, also known as THIIC, was given in a separate literature [47].



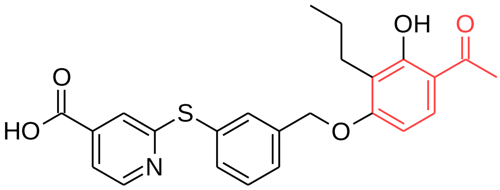
5 Merck

EC_{50} = 348 nM (GTPγS)



6 Merck

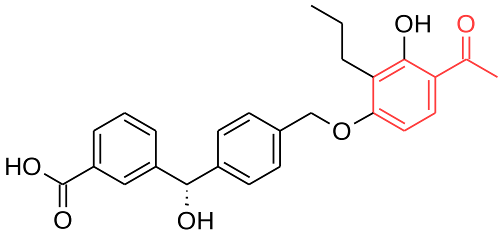
EC_{50} = 1400 nM (GTPγS)



7 Eli Lilly

mGluR2 EC_{50} < 350 nM (FLIPR)

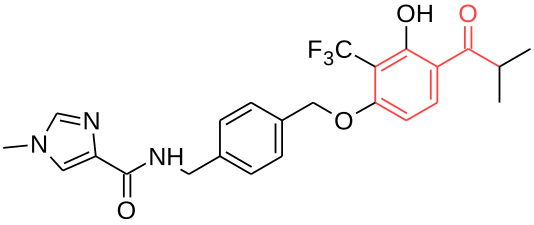
CysLT1 IC_{50} < 150 nM



8 (LY2300559) Eli Lilly

mGluR2 EC_{50} < 100 nM (FLIPR)

CysLT1 IC_{50} < 750 nM



9 (THIIC) Eli Lilly

mGluR2 EC_{50} = 26 nM (FLIPR)

Figure 3. mGluR2 PAM arylketones

4. Pyridones

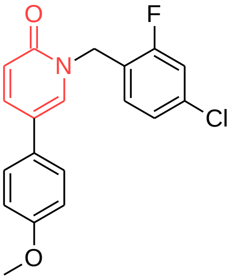
Janssen Pharmaceutical and partner Addex Therapeutics have filed 10 patent applications disclosing pyridones (unsubstituted, 3-cyano and 3-chloro pyridones) chemotypes.

In their initial case, consisting of around 370 examples, discloses N-benzyl pyridones substituted at C-4 or C-5 with aryl moieties [48]. Exemplified compounds have different substitution pattern around the benzylic and aryl groups. Preferred compounds possess EC_{50} values less than 1 µM in a GTPγS binding assay, including compound **10** (**Figure 4**). Detailed SAR of this chemotype has been reported in a separate paper [49]. Compound **10** displayed good brain levels after *i.p.* administration and comparable activity to a reference PAM, LY487379, in the in vivo Phencyclidine-Induced Hyperlocomotion (PCP-HL) assay. Janssen/Addex identified the important role of the cyano substituent at position 3 on the pyridine core. Thus, in 2006 and 2007 four patent applications have been published disclosing these 3-cyanopyridone derivatives [50,51,52,53].

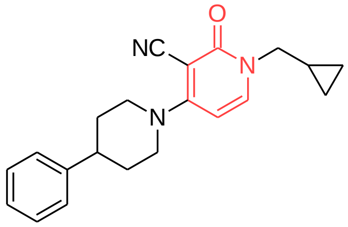
In the first application examples of pyridones substituted at N-1 by a lipophilic alkyl chain and substituted at C-4 by an aryl or N-linked heterocycles, often substituted at position 4 with an aryl ring are described. The preferred example of this application is compound **11**, with an EC_{50} value of 320 nM in a GTPγS binding assay [50]. A detailed pharmacological profile of compound **11**, also known as JNJ40068782 and its radioligand [^{3}H]JNJ40068782 has been recently reported in literature [54]. The compound has influenced rat sleep-wake organization by decreasing rapid eye movement sleep with a lowest active dose of 3 mg/kg *p.o.* In addition, JNJ-40068782 also reversed PCP-HL with an ED_{50} of 5.7 mg/kg *s.c.* in mice.

In the second case nine examples of pyridones substituted at C-4 by 4-phenyl piperidines are described. These compounds are exemplified by compound **12** showing an EC_{50} value of 174 nM in a GTPγS binding assay [51]. In the other two cases of 3-cyanipyridones C-4 biaryl ethers are disclosed. Examples of these applications are compounds **13** [52] and **14** [53] with EC_{50} values of 138 nM and 282 nm, respectively. By parallel filings Janssen/Addex demonstrated the equipotency of the chloro- and cyano substituent at position 3 on the pyridone scaffold (compound **15**, **16** and **17**) [55,56,57].

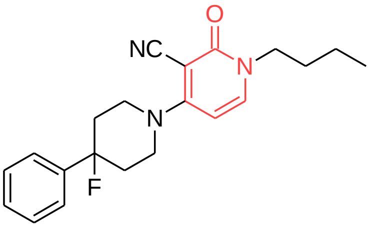
In 2010 further two patent applications were disclosed in the field of 3-chloro pyridones. In the first case 3-azabyciclo[3.1.0.]hexyl side chain is used at C-4 position. A preferred compound of this invention is **18** with an EC_{50} value of 89 nM [58]. The second application discloses indole and benzomorpholine heterocycles, as lipophilic side chains. These derivatives are exemplified by **19** showing an EC_{50} value of 76 nM [59].



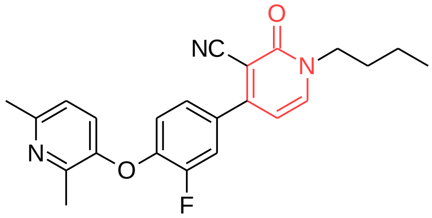
10 Janssen/Addex



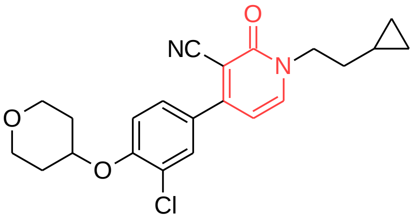
11 (JNJ40068782) Janssen/Addex
EC_{50} = 320 nM (GTPγS)



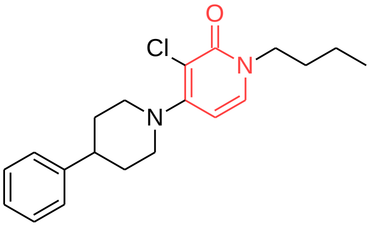
12 Janssen/Addex
EC_{50} = 174 nM (GTPγS)



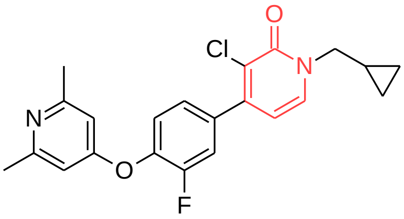
13 Janssen/Addex
EC_{50} = 138 nM (GTPγS)



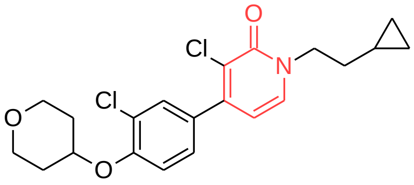
14 Janssen/Addex
EC_{50} = 282 nM (GTPγS)



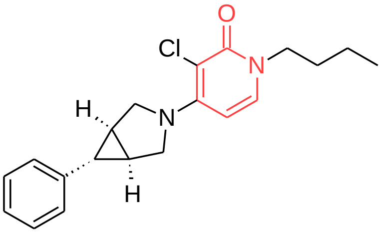
15 Janssen/Addex
EC_{50} = 182 nM (GTPγS)



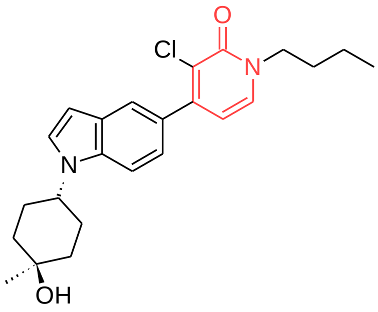
16 Janssen/Addex
EC_{50} = 182 nM (GTPγS)



17 Janssen/Addex
EC_{50} = 275 nM (GTPγS)



18 Janssen/Addex
EC_{50} = 89 nM (GTPγS)



19 Janssen/Addex
EC_{50} = 76 nM (GTPγS)

Figure 4. mGluR2 PAM pyridones

5. Isoindolones

Researchers at AstraZeneca/NPS pharmaceuticals disclosed numerous isoindolone derivatives as novel scaffold showing significant activity as mGluR2 potentiators (**Figure 5**). The first disclosure in 2006 [60] included isoindolones typically substituted with a 4-trifluoromethoxybenzyl group at N-1, a chloro or methyl substituent at C-7 and a heterocycle linked to the central scaffold. Among the preferred seven examples compound **20** is the most potent one with an EC_{50} value of 40 nM in a GTPγS binding assay. Further optimization of this scaffold was based primarily on the modification of the N-1 position. The second narrower application covering 19 compounds substituted with 4-phenoxybenzyl group at N-1 and a heteroaryl ring at C-5. These compounds showed EC_{50} values less than 10 µM in a FLIPR or GTPγS binding assay, as compound **21** [61]. In parallel with this application AstraZeneca covered the analogues of the previously reported compounds [60] exemplified with **20.** The first set of compounds use a piperidine methyl moiety at N-1, while the other set use substitutedoxadiazoles at C-5 coupled directly to the isoindolone core. Compounds **22** and **23** are the most potent ones among the 33 examples with EC_{50} values of 28 nM and 75 nM, respectively [62]. Oxadiazole derivatives were further optimized by AstraZeneca and two patent applications filed in 2008 describing isomeric oxadiazoles [63,64]. In these focused applications (20 examples) hERG and solubility data are also presented for selected compounds (see compounds **24** and **25** in **Figure 5**). Interestingly, in 2011, AstraZeneca filed a patent application claiming the preparation and polymorphs of compound **25** [65].

In another narrower case of 55 examples, isoindolones with a substituted alkyl or cycloalkyl substituent at N-1 and a 3-pyridyl or a phenyl ring substituted with 3-methanesulfonamidophenyl at C-5 are disclosed [66]. These compounds are indicated to have mGluR2 EC_{50} values less than 10 µM in a FLIPR or GTPγS binding assay, although no specific potency values are given, including compound **26**. In 2008 another patent application was filed by AstraZeneca describing also 3-methanesulfonamidophenyl derivatives equipped with a 4-azaisoindolone core [67]. In this focused application that discloses 20 examples potency values of 3 compounds are given. Among these the most potent compound, **27**, showed an EC_{50} value of 160 nM. In another patent application of this series by AstraZeneca isoindolone hydrazides are disclosed [68]. The same substitution pattern can be seen in this application, exemplified with compound **28**, which showed an EC_{50} value of 24 nM when tested for allosteric activation of human mGluR2 receptors expressed in CHO cells in a GTPγS assay.

The last disclosure in this series by AstraZeneca included an isoxazole amide linked to the isoindolone scaffold at C-5 [69]. In this focused application hERG and solubility data are also presented for all 21 examples. The preferred compound is **29**, being the most potent with an EC_{50} value of 36 nM and other parameters are also remarkable (hERG IC_{50} > 33 µM, solubility = 11.2 µM) (**Figure 5**).

Researchers at Abbott have also filed 3 patent applications in the field of isoindolones (**Figure 6**). The first application discloses dual mGluR2 potentiators and 5-HT2A antagonists [70]. These dual acting isoindolone derivatives substituted with small alkyl groups at N-1 and aryl substituted pyrazol methyl ether at C-5, as exemplified with compound **30**. Preferred compounds of this application have EC_{50} values less than 100 nM for mGluR2 potentiation in a FLIPR assay and K_i values less than 100 nM as antagonists in a binding assay, but no specific potency values are given. These dual-acting compounds may represent a new strategy based on the direct and functional interaction of the mGluR2 and 5-HT2A receptors. It has been shown that mGluR2 and 5-HT2A receptors form functional heterodimers and that mGluR2 activation causes suppression of 5-HT2A-mediated signaling events [71,72]. Moreover, the responses elicited by hallucinogenic and non-hallucinogenic 5-HT2A agonists seem to differ in the intracellular signaling pathways involved [73,74] and mGluR2 activation might suppress the hallucinogenic pathway [71]. Interestingly, preliminary pharmacogenetic analysis of subjects treated with orthosteric mGluR2/3 agonist LY2140023 revealed a strong correlation between treatment response and 5-HT2A genotype of the patients [75].

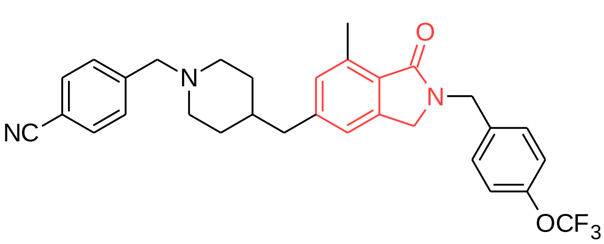
Based on these observations it is assumed that potentiation of endogenous mGluR2 activity with subtype-selective positive allosteric modulators would specifically augment the suppression of hallucinogenic 5-HT2A signaling and thus might offer an effective therapy for schizophrenia by attenuation of cortical overexcitation.

In the second application Abbott disclosed isoindolone derivatives substituted with a 3-pyridil at C-5 linked by a methyloxy- or a methylamino spacer [76]. Preferred compounds have EC_{50} values less than 0.5 µM, such as compound **31**.

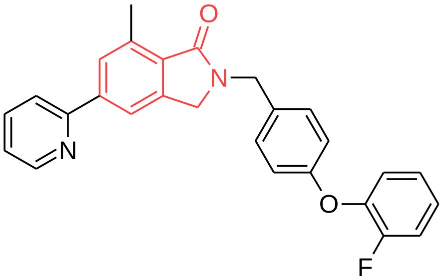
In the last application by Abbott [77] both isoindolones and isoquinolones are disclosed, in which a heterocyclic substituent is linked to the bicyclic core by a direct bond, methylene, oxygen or nitrogen spacer. Compounds from both chemotypes can be found within the six most active examples (EC_{50} less than 0.5 µM in a FLIPR assay) given (**Figure 6**, compound **32**).

In 2011, Organon also disclosed a series of isoindolone derivatives with different lipophilic side chains at C-5 position [78], suggesting that this part of the molecule is considerably variable. In this application 124 compounds are exemplified, of which 122 are isoindolone derivatives (2 are isoquinolinones). Preferred compounds have EC_{50} values less than 1 µM, such as compound **33**.

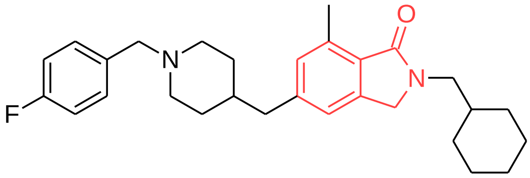
Researchers at the Sanford-Burham Medical Research Institute introduced some further analogs of isoindolones with modified lipophilic side chain at C-5 position [79]. The application also covers isoquinolinones, benzisothiazolones and benzisoxazolones, among which isoindolones were found to be the most potent. The representative compound of this invention is **34**, with an EC_{50} value of 50 nM in a rat thallium flux assay (**Figure 6**). Detailed SAR around these chemotypes was given in a separate literature [80]. Compound **34**, a close analogue of BINA, was shown to dose-dependently decrease nicotine self-administration in rats after oral administration. These data suggest the potential utility of mGluR2 PAMs for the treatment of nicotine dependence in humans.



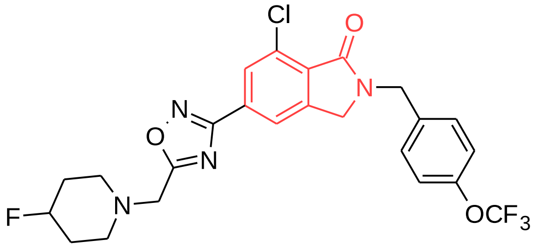
20 AstraZeneca/NPS
EC_{50} = 40 nM (GTPγS)



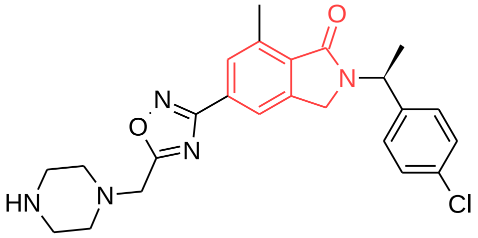
21 AstraZeneca/NPS



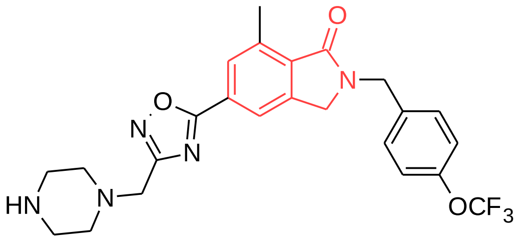
22 AstraZeneca/NPS
EC_{50} = 28 nM (GTPγS)



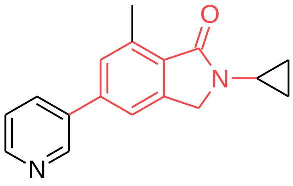
23 AstraZeneca/NPS
EC_{50} = 75 nM (GTPγS)



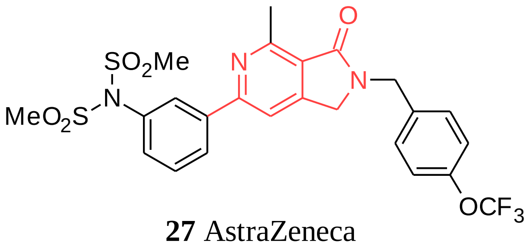
24 AstraZeneca
EC_{50} = 48 nM (GTPγS)



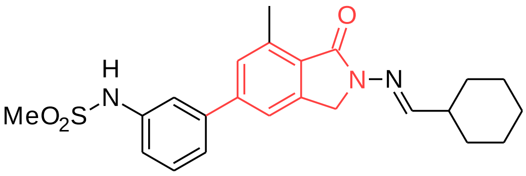
25 AstraZeneca
EC_{50} = 231 nM (GTPγS)



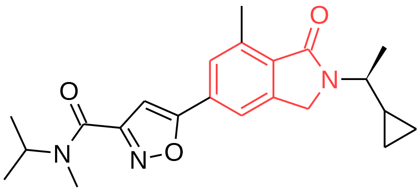
26 AstraZeneca/NPS



27 AstraZeneca
EC_{50} = 160 nM (GTPγS)

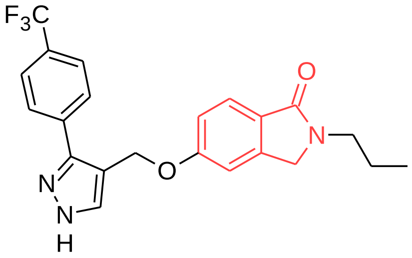


28 AstraZeneca
EC_{50} = 24 nM (GTPγS)

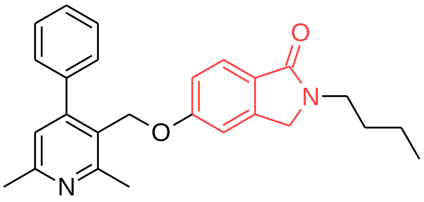


29 AstraZeneca
EC_{50} = 36 nM (GTPγS)

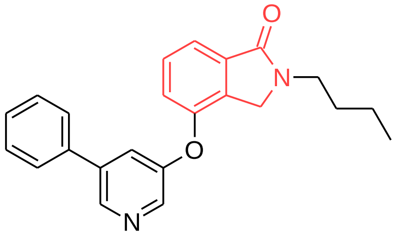
Figure 5. mGluR2 PAM isoindolones



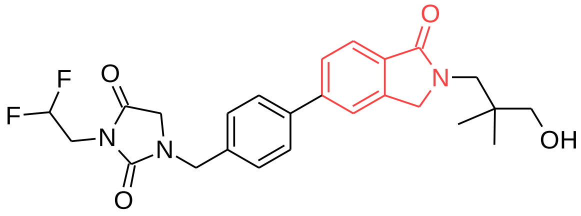
30 Abbott GmbH
mGluR2 $EC_{50} < 100$ nM (FLIPR)
5-HT_{2A} $K_i < 100$ nM



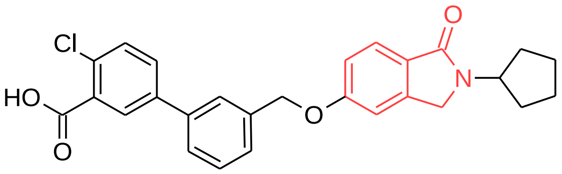
31 Abbott GmbH
$EC_{50} < 0.5$ µM (FLIPR)



32 Abbott GmbH
$EC_{50} < 0.5$ µM (FLIPR)



33 Organon



34 Sanford-Burham Medical Research Institute
$EC_{50} = 50$ nM (thallium flux)

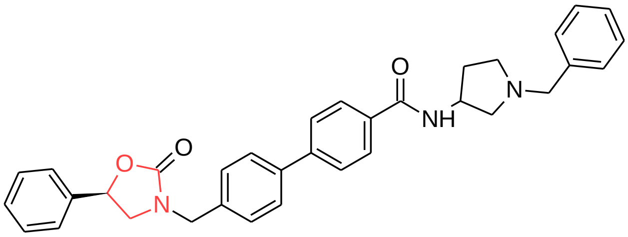
Figure 6. mGluR2 PAM isoindolones (continued)

6. Oxazole derivatives

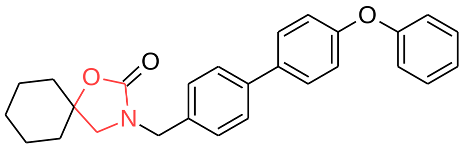
6.1. Oxazolidinones

The first oxazolidinone derivatives as mGluR2 potentiators were reported by AstaZeneca/NPS in 2007 [81]. This application exemplifies 125 N-benzylic oxazolidinones substituted with an aryl group at C-5 position, where the R configuration seems to be largely preferred. Specific potency values for 5 compounds are given, among which the most potent one is compound **35** with an EC_{50} value of 12 nM in a GTPγS binding assay (**Figure 7**). Optimization of this scaffold was based primarily on the modification of substituents at C-5. Thus, the second application from AstraZeneca discloses spirocyclic oxazolidinones [82]. Preferred compounds contain a cyclohexyl spirocycle as exemplified with compound **36**, as the most potent one (GTPγS EC_{50} = 14 nM). In 2009 researchers at Pfizer also disclosed oxazolidinone derivatives with methyl substituent at C-5 of the N-benzylic oxazolidinone

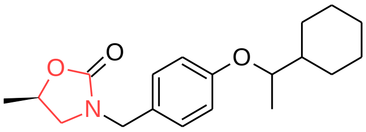
core [83]. The invention also prefers the R configuration at C-5. Potency values are given for all synthesized 318 examples, among which compound **37** proved to be the most potent with an EC_{50} value of 4.96 nM in a FLIPR assay. Detailed SAR around this chemotype started from a HTS hit was given in a separate literature [84]. Modification of the alkylether moiety of **37** led to a series of biaryl analogs with improved physical properties, such as compound **38** (FLIPR EC_{50} = 30 nM). This compound was found to be active in an in vivo methamphetamine-induced hyperlocomotion model in mice at a minimally effective dose (MED) of 10 mg/kg *s.c* [84].
Scientists at Merck have also published a series of oxazolidinones in 2009 [85]. Compounds of this invention have a smaller lipophilic side chain (aryl or benzyl) at N-3 but with large lipophilic substituents at C-5. A representative example from this series is compound **39** with EC_{50} value of 82 nM in a FLIPR assay. The hit-to-lead optimization of this oxazolidinone series is reported in a separate literature [86]. Compound **39** was shown to be brain penetrant and able to attenuate ketamine-induced psychomotor activity in rats similar to an mGluR2/3 agonist, an assay sensitive to clinically therapeutic antipsychotics (**Figure 7**).



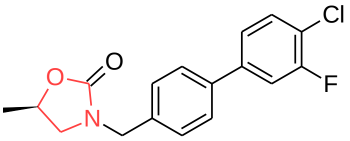
35 AstraZeneca/NPS
EC_{50} = 12 nM (GTPγS)



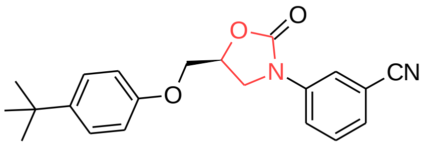
36 AstraZeneca/NPS
EC_{50} = 12 nM (GTPγS)



37 Pfizer
EC_{50} = 4.96 nM (FLIPR)



38 Pfizer
EC_{50} = 30 nM (FLIPR) [84]



39 Merck
EC_{50} = 82 nM (FLIPR)

Figure 7. mGluR2 PAM oxazoles: oxazolidinones

6.2. Oxazolobenzimidazoles

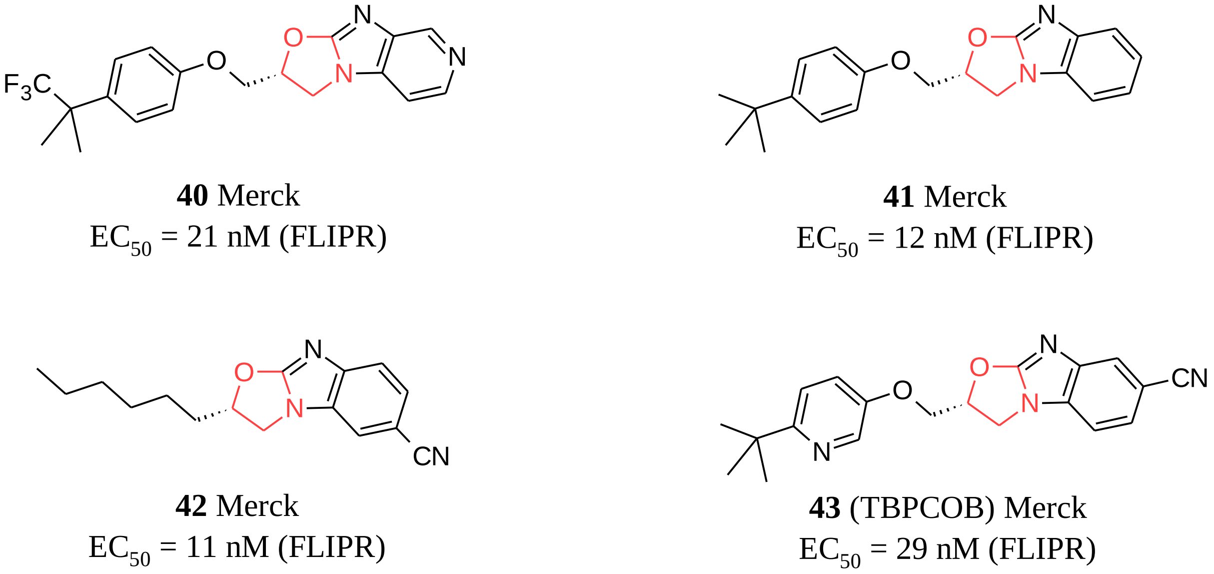
In 2009 HTS-derived lead oxazolidinone was transformed into a novel series of oxazolobenzimidazoles by Merck (**Figure 8**). In this year two patent applications were filed

[87,88]. Preferred compounds are substituted with heteroaryloxymethyl- or aryloxymethyl groups at C-2, where the R configuration seems to be largely preferred and small substituents at C-8 (cyano substitution is preferred). Representative examples of this invention are compound **40** [87] and **41** [88], with EC_{50} values of 21 nM and 12 nM, respectively. In 2010 Merck disclosed another oxazolobenzimidazole derivatives substituted with aliphatic groups at C-2 [89]. Compound **42** is a representative from this invention with an EC_{50} value of 11 nM.

Detailed SAR and pharmacological investigation of oxazolobenzimidazoles are described in a separate publication [90].

Optimization of the oxazolidinone through physical and pharmacokinetic properties led to the identification of potent and orally bioavailable compounds, such as compound **43**, also known as TBPCOB.

TBPCOB was shown to have robust activity in a PCP-HL model in rat, an assay responsive to clinical antipsychotic treatments for schizophrenia (**Figure 8**).



40 Merck
EC_{50} = 21 nM (FLIPR)

41 Merck
EC_{50} = 12 nM (FLIPR)

42 Merck
EC_{50} = 11 nM (FLIPR)

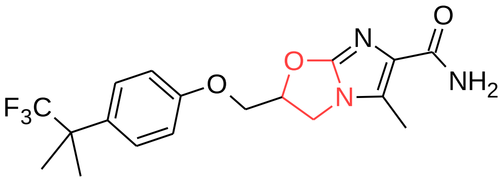
43 (TBPCOB) Merck
EC_{50} = 29 nM (FLIPR)

Figure 8. mGluR2 PAM oxazoles: oxazolobenzimidazoles

6.3. Imidazooxazoles

Very recently, researchers at Taisho have published a series of imidazooxazoles structurally related to previously reported oxazolidinones/oxazolobenzimidazoles [91] (**Figure 9**).

The representative compound is **44**, which potentiated ligand stimulation at rat and human mGluR2 receptors expressed in CHO cells with respective EC_{50} values of 215 and 317 nM in a GTPγS binding assay. It significantly attenuated methamphetamine-induced hyperlocomotion when administered to male Wistar rats at 30 mg/kg *p.o.* at 120 min before administration of methamphetamine (1 mg/kg *s.c.*).



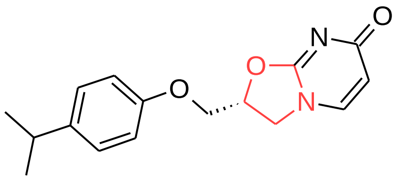
44 Taisho

EC_{50} = 215 nM (GTPγS)

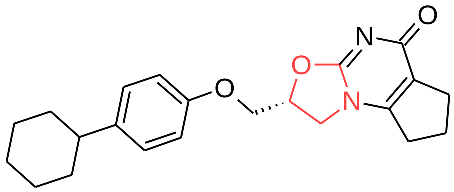
Figure 9. mGluR2 PAM oxazoles: imidazooxazoles

6.5. Oxazolopyrimidones

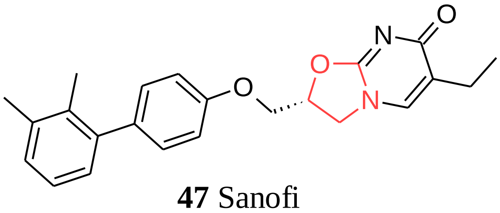
Scientists at Sanofi have also been active in the search of new mGluR2 PAMs from the year of 2008 to 2011. In this four year period 5 patent applications have been published, describing oxazolopyrimidones, structurally related to previously reported oxazolidinones/oxazolobenzimidazoles (**Figure 10**). The first application discloses oxazolopyrimidone derivatives, substituted with alkyl substituted aryloxymethyl groups at C-2, where the R configuration also largely preferred [92]. Exemplified compounds showed EC_{50} values between 0.5 nM and 3 µM in a FLIPR assay, but no specific data are given, as in case of compound **45**. The second case describes tricyclic oxazolopyrimidones, as exemplified with compound **46**, with EC_{50} values between 0.5 nM and 3 µM [93]. In 2011 Sanofi published three new patent applications describing the close analogues of the previously reported dihydro oxazolopyrimidinones [94,95,96]. These compounds have favorable pharmacological properties as previously reported derivatives, as mGluR2 PAM potency and ADME properties. The first new application discloses *para*-biphenyloxymethyl derivatives [94]. The preferred compound of this invention is **47**, having an ethyl side chain at C-5. This compound is a potent mGluR2 PAM with an EC_{50} value of 19 nM in a FLIPR assay. In the second case benzocycloalkyloxymethyl derivatives were used at C-2 [95]. These analogues showed improved potency, as exemplified with compound **48**. The last application discloses aryloxymethyl derivatives at C-2 [96]. Preferred compounds have EC_{50} values between 1 and 100 nM, as compound **49**.



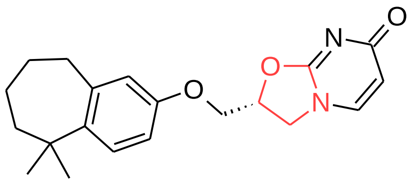
45 Sanofi
EC_{50} = 0.5 nM - 3μM (FLIPR)



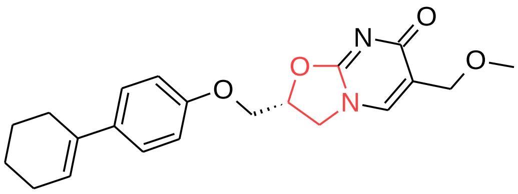
46 Sanofi
EC_{50} = 0.5 nM - 3μM (FLIPR)



47 Sanofi
EC_{50} = 19 nM (FLIPR)



48 Sanofi
EC_{50} = 11 nM (FLIPR)



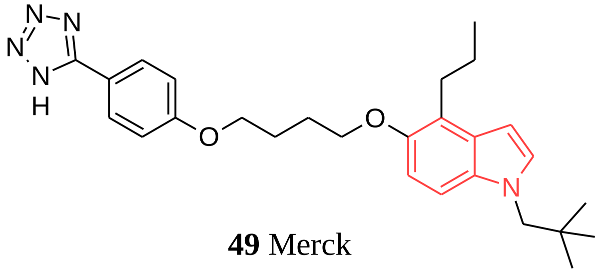
49 Sanofi
EC_{50} = 1 - 100 nM (FLIPR)

Figure 10. mGluR2 PAM oxazolopyrimidones

7. Benzazoles

7.1. Indoles

The first application, describing benzazole derivatives was published by Merck in 2006 [97]. The invention includes indoles, benzotriazoles, benzisoxazoles and indazoles. Preferred compounds of this application have EC_{50} values less than 1 μM, but no specific data is given. The structure–activity relationships of these derivatives have been reported in a separate paper [98]. The most promising compound, **49**, was identified starting from a hit compound, **3**, identified by a HTS screening campaign [39,40] (**Figure 11**). This compound is an mGluR2-selective PAM that is moderately brain penetrant (B/P = 0.16), has acceptable rat PK, and most importantly, significantly attenuated ketamine-induced hyperactivity at 40 mg/kg *i.p.* dose in rats.



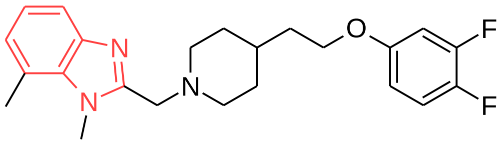
49 Merck

EC_{50} = 559 nM (GTPγS) [98]

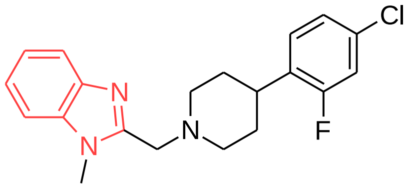
Figure 11. mGluR2 PAM benzazoles: indoles

7.2. Benzimidazoles

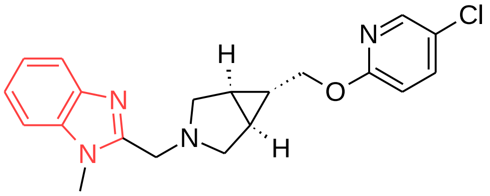
Benzimidazole derivatives as mGluR2 potentiators have been developed by researchers at AstraZeneca/NPS and Pfizer in 2007 and 2008 (**Figure 12**). In this two year period 5 patent applications have been published, describing benzimidazoles with different lipophilic side chains at C-2. The first application by AstraZeneca/NPS covers 117 benzimidazole examples, substituted typically with an aryloxyalkyl piperidine or piperazine moiety at C-2 through a methylene linker [99]. The most potent compound, **50**, has an EC_{50} value of 57 nM in a GTPγS assay. Pfizer also disclosed similar benzoimidazoles, in these cases aryl piperidine [100] and aryl [3.1.0.]azabicyclic ring systems [101] were used as lipophilic side chains at C-2, as exemplified with compound **51** (FLIPR EC_{50} = 7 nM) and **52** (FLIPR EC_{50} = 26 nM). These lipophilic side chains were also used and covered by Pfizer in two separate patent applications describing azabenzimidazoles. Compounds **53** [102] and **54** [103] are preferred examples with EC_{50} values of 27 nM and 36.9 nM, respectively. Detailed SAR and rat pharmacokinetic properties of azabicyclic derivatives are described in a separate publication [104].



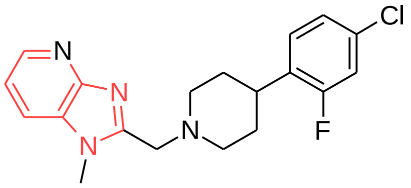
50 Pfizer
EC_{50} = 57 nM (FLIPR)



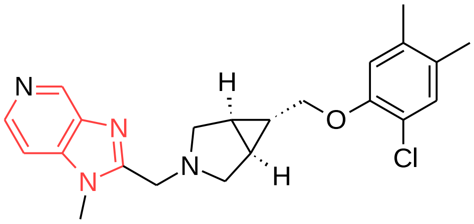
51 Pfizer
EC_{50} = 7 nM (FLIPR)



52 Pfizer
EC_{50} = 26 nM (FLIPR)



53 Pfizer
EC_{50} = 27 nM (FLIPR)

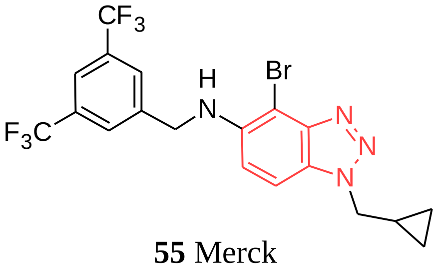


54 Pfizer
EC_{50} = 36.9 nM (FLIPR)

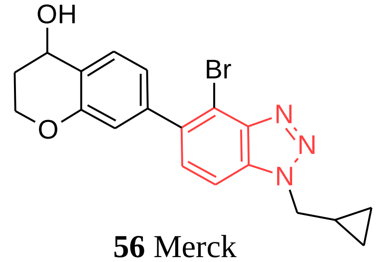
Figure 12. mGluR2 PAM benzazoles: benzimidazoles

7.3. Benzotriazoles

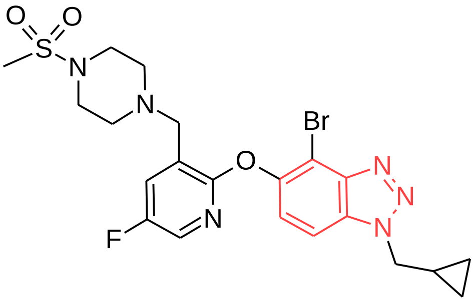
Benzotriazole derivatives have been published by Merck in eight patent applications as mGluR2 potentiators (**Figure 13**). The initiate series describes 1,2,3-benzotriazoles, substituted with benzyl amines or benzamides at C-5; halogen, methyl and cyano groups at C-4 and alkyl or cycloalkyl moieties at N-1 [105]. Compound **55** is the most potent example of this application with an EC_{50} value of 15 nM in a FLIPR assay. The second application discloses arylbenzotriazoles [106]. Preferred compounds contains aryl or heteroaryl substituents at C-5, bromo or chloro substituent at C-4 and tert-butylmethyl and cyclopropylmethyl groups at N-1 as exemplified with compound **56** as the most potent (FLIPR EC_{50} = 8 nM) derivative. Another series, called benzotriazole-ethers are reported in two patent applications [107,108] in 2011 and 2012. The first series [107] describes 1,2,3-benzotriazoles substituted with aryl or heteroaryl ethers at C-5 with the same preferred substituents at C-4 and N-1 as previously reported [105, 106]. Compound **57** in **Figure 13** is reported as the most potent one (FLIPR EC_{50} = 2 nM). The second application discloses 424 examples with alkylether substituents at C-5 [108]. Compound **58** is a preferred example with an EC_{50} value of 3.5 nM. In 2012 four new benzotriazole derivatives were published by Merck. These applications seem to be the result of the optimization program of Merck, focusing the lipophilic side chain at C-5. 4-aminomethylphenyl- and 4-aminomethylpyridin-3-yl [109], 4-hydroxymethylphenyl- [110], cyclohexenyl- [111] and alkynyl- [112] substituents at C-5 of the benzotriazole core were identified as potent mGluR2 PAMs. Compounds **59**, **60**, **61** and **62** are the most potent representatives from these new series (**Figure 13**).



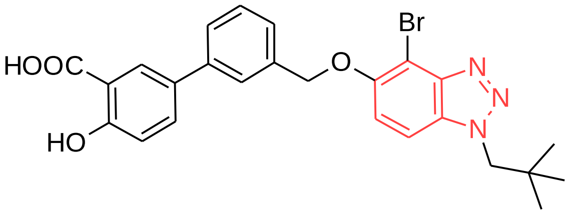
55 Merck
EC_{50} = 15 nM (FLIPR)



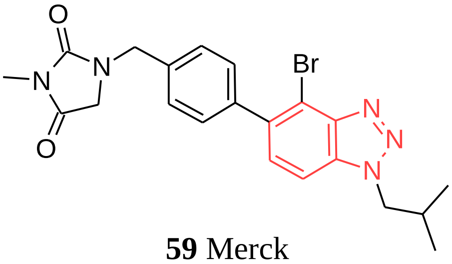
56 Merck
EC_{50} = 8 nM (FLIPR)



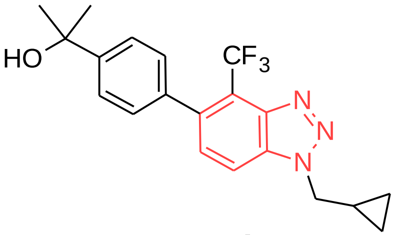
57 Merck
EC_{50} = 2 nM (FLIPR)



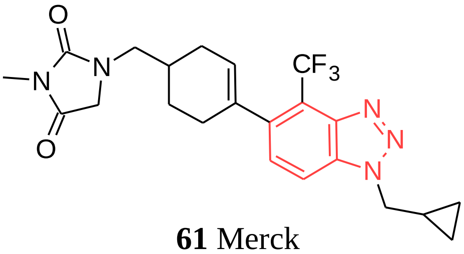
58 Merck
EC_{50} = 3.5 nM (FLIPR)



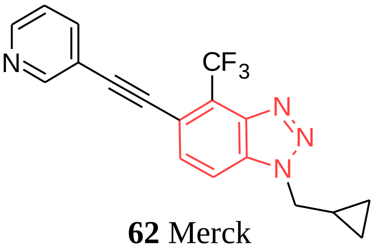
59 Merck
EC_{50} = 3 nM (FLIPR)



60 Merck
EC_{50} = 2.1 nM (FLIPR)



61 Merck
EC_{50} = 15 nM (FLIPR)



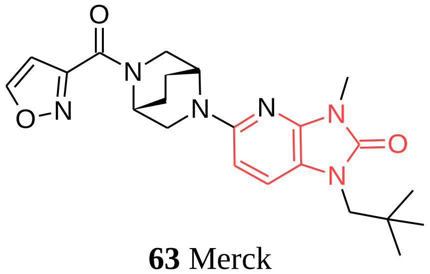
62 Merck
EC_{50} = 4.8 nM (FLIPR)

Figure 13. mGluR2 PAM benzazoles: benzotriazoles

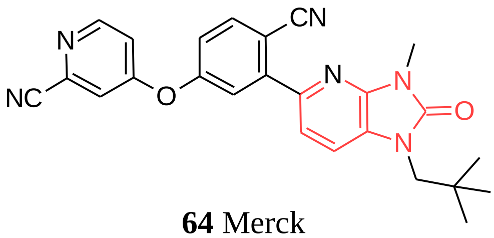
8. Benzazolones

8.1. Benzimidazolones

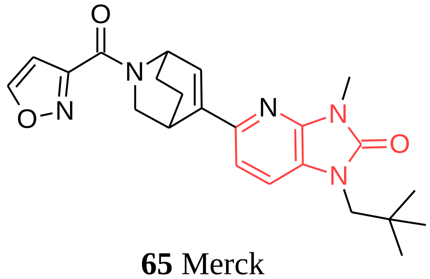
In 2011 and 2012 researchers at Merck have published four new patent applications describing benzimidazolones and the analogue 3-methyl-imidazopyridin-2-one derivatives; structurally related to previously reported benzotriazoles (**Figure 14**). The initiate application discloses aminosubstituted imidazopyridinones [113]. Preferred aminosubstituents at C-5 of the core are piperidines and piperazines as in the case of the most potent example, **63** (FLIPR EC_{50} = 29 nM). Aryl and heteroaryl derivatives at C-5 of imidazopyridinones have disclosed in a separate application [114]. This application covers 523 examples generally with EC_{50} values less than 3 µM in a FLIPR assay as represented by the most potent compound, **64** (FLIPR EC_{50} = 8 nM), in **Figure 14**. Another series of imidazopyridinones have been published in 2012 [115]. This application discloses aminoalkyl or alkyl substituents at C-5 and large lipophilic substituents at N-1, preferably tert-butylmethy- and 2,2-difluorocyclopropylmethyl groups, as exemplified by compound **65** with an EC_{50} value of 16 nM in a FLIPR assay.
The last patent application from this series was published in 2012 describing benzimidazolones [116]. Preferred substituents were chosen from the previously reported [114] lipophilic side chains at C-5. Compounds of this invention are reported to have EC_{50} values less than 10 µM in a FLIPR assay. Compound **66** is the most potent one (FLIPR EC_{50} = 40 nM) exemplified in this patent application (**Figure 14**).



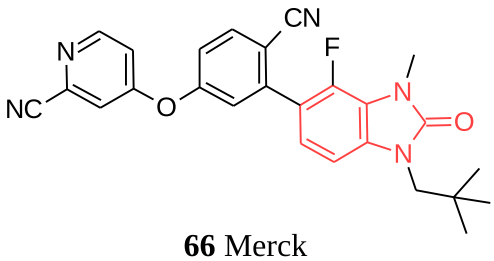
63 Merck
EC_{50} = 29 nM (FLIPR)



64 Merck
EC_{50} = 8 nM (FLIPR)



65 Merck
EC_{50} = 16 nM (FLIPR)

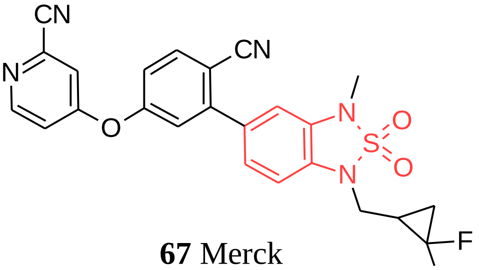


66 Merck
EC_{50} = 40 nM (FLIPR)

Figure 14. mGluR2 PAM benzazolones: benzimidazolones

8.2. Benzothiadiazole-dioxides

1,3-dihydro-2,1,3-benzothiadiazole-2,2-dioxides, structurally related to the benzimidazolone/3-methyl-imidazopyridin-2-one series have also been published by Merck in 2011 [117] exemplified by compounds substituted with aryl or heteroaryl groups at C-5 and lipophilic substituents (preferably 2,2-difluorocyclopropylmethyl) at N-1. Preferred examples show EC_{50} values less than 1.5 µM in both FLIPR and GTPγS assays. Compound **67** is one of the most potent ones (FLIPR EC_{50} = 0.8 nM) exemplified in this patent application in **Figure 15**.

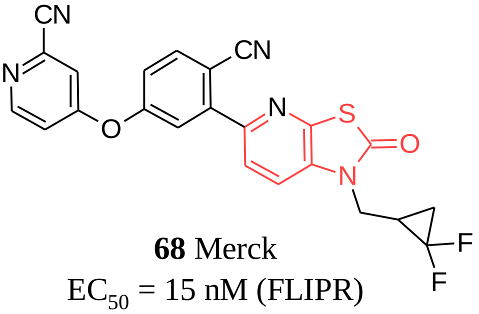


67 Merck
EC_{50} = 0.8 nM (FLIPR)

Figure 15. mGluR2 PAM benzazolones: benzothiadiazole-dioxides

8.3. Benzothiazolones

Benzothiazolone derivatives with the previously reported [117] lipophilic side chains at C-5 of the central core were published separately by Merck in 2011 [118]. Preferred examples show EC_{50} values less than 3 μM. Compound **68** in **Figure 16** is the representative example in this application with an EC_{50} value of 15 nM in a FLIPR assay.

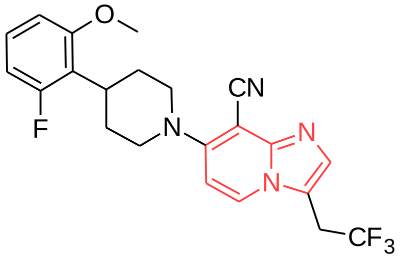


68 Merck
EC_{50} = 15 nM (FLIPR)

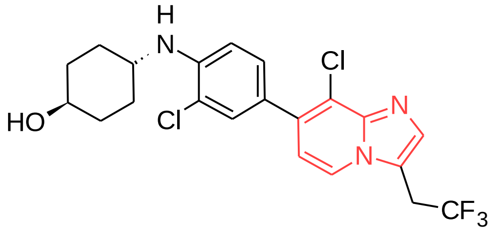
Figure 16. mGluR2 PAM benzazolones: benzothiazolones

9. Imidazopyridines

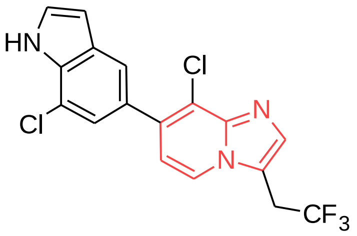
Janssen has discovered an interesting series of imidazopyridines as mGluR2 potentiators based on the bioisosteric replacement of the previously reported pyridone core [119]. The first patent application is the combination of the imidazopyridine core and the previously reported lipophilic side chains at C-7 [120]. Preferred compounds are amino- and arylimidazopyridines, exemplified with compound **69** and **70**, with EC_{50} values of 10 nM and 150 nM, respectively (**Figure 17**). In a second application, indole- and benzoxazine derivatives at C-7 of the imidazopyridine core were described [121]. Compound **71** is a representative example in this application. Detailed SAR and optimization of the imidazopyridine series with a more optimal oral PK profile has been reported in a separate paper [122]. Compound **71** was identified showing good potency (GTPγS EC_{50} = 85 nM) and good selectivity for the mGluR2 receptor, as well and with an improved oral PK profile. Compound **71** also modulated REM sleep variables in a rat sleep model, a mechanism of action that is consistent with mGluR2 receptor activation.



69 Janssen/Addex
EC$_{50}$ = 10 nM (GTPγS)



70 Janssen/Addex
EC$_{50}$ = 150 nM (GTPγS)



71 Janssen/Addex
EC$_{50}$ = 85 nM (GTPγS) [122]

Figure 17. mGluR2 PAM imidazopyridines

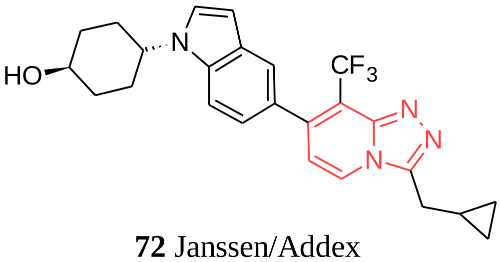
10. Triazolopyridines

A series of triazolopyridines closely-related to imidazopyridine derivatives were also disclosed in several patent applications from Janssen/Addex (**Figure 18**). The initial series discloses triazolopyridines, substituted with heterobicyclic rings at C-7 and alkyl side chains at C3, as commonly used lipophilic moieties at this region [123]. Detailed pharmacological data are given for some examples, as in the case of compound **72** in **Figure 18**. Compound **72** is a potent mGluR2 PAM with an EC$_{50}$ value of 11 nM in a GTPγS binding assay. Compound **72** was active in a PCP-HL assay in mice with an ED$_{50}$ value of 13.2 mg/kg *s.c.* and found to be also active in the conditioned avoidance response (CAR) test in rats (ED$_{50}$ = 20 mg/kg, *s.c.*, ED$_{50}$ < 40 mg/kg, *i.p.*).

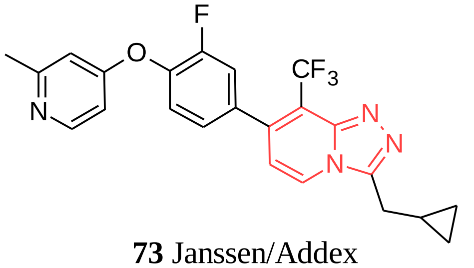
Aryl substituted derivatives at C-7 of the triazolopyridine core were published in a separate patent application [124]. Detailed in vivo data (PCP-HL, CAR and amphetamine-induced hyperlocomotion) were also given for some examples. Compound **73** is a representative example from this application (GTPγS EC$_{50}$ = 50 nM; Mice PCP-HL ED$_{50}$ = 18.7 mg/kg, *s.c.*; Rat CAR ED$_{50}$ = 21.4 mg/kg, *p.o.*; Amp.ind. HL ED$_{50}$ = 28.3 mg/kg).

In a third application amino substituted triazolopyridines were described [125]. Also in this case in vivo data are provided for some examples, such as compound **74** (GTPγS EC$_{50}$ = 17 nM; Mice PCP-HL ED$_{50}$ = 5.4 mg/kg, *s.c.*; Rat CAR ED$_{50}$ = 2.35 mg/kg, *s.c.*). The optimization of the triazolopyridine chemotype starting from the imidazopyridines is published in a separate paper in 2012 [126]. Compound **74**, also known as JNJ42153605 was identified as the most potent derivative, showing a central in vivo efficacy by inhibition of REM sleep state at a dose of 3 mg/kg *p.o.* in the rat sleep–wake EEG paradigm.

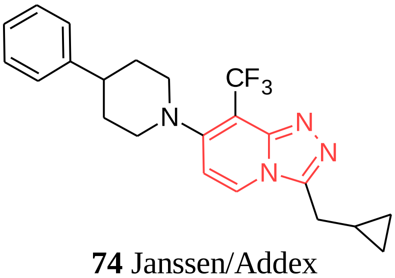
Further three patent applications from the triazolopyridine series were published in 2012 describing different aminomethyl substituents at C-7. Representative examples of these inventions are compounds **75** [127], **76** [128], and **77** [129] with EC_{50} values of 38 nM, 170 nM and 2.5 nM, respectively. In 2012 Janssen published a patent application claiming radiolabeled triazolopyridines as mGluR2 PET ligands [130] and the profile and properties of these ligands are also published in a separate paper [131].



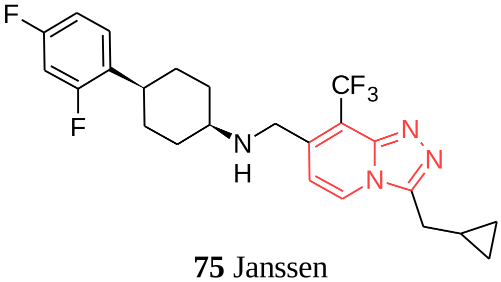
72 Janssen/Addex
EC_{50} = 11 nM (GTPγS)



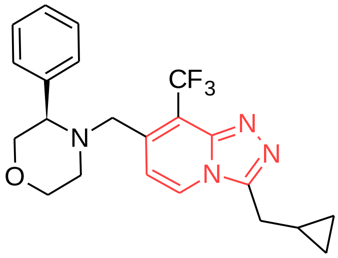
73 Janssen/Addex
EC_{50} = 50 nM (GTPγS)



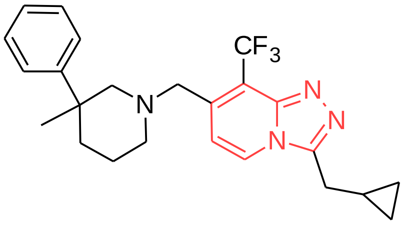
74 Janssen/Addex
EC_{50} = 17 nM (GTPγS)



75 Janssen
EC_{50} = 38 nM (GTPγS)



76 Janssen
EC_{50} = 170 nM (GTPγS)



77 Janssen
EC_{50} = 2.5 nM (GTPγS)

Figure 18. mGluR2 PAM triazolopyridines

11. Other scaffolds

11.1. Benzosulphonamides

A large series (124 examples) of benzosulphonamides was described by AstraZeneca/NPS as mGluR2 potentiators in 2004 [132]. Compounds exemplified in this application are benzoic acid ester derivatives at C-1, substituted typically with methyl and chloro substituent at C-2 and C-4. Compounds are indicated to have mGluR2 PAM EC_{50} values less than 10 µM, but no specific potency data are given. Compound **78** is a representative structure of the benzosulphonamide series (**Figure 19**).

11.2. Pyrazolones

In 2006 AstraZeneca/NPS have disclosed a novel chemical series in a large patent application [133]. This case discloses pyrazolone derivatives, substituted with a piperidine or piperazine at C-5 and a phenyl ring at C-2 as exemplified with compound **79**. Potency data are not provided (**Figure 19**).

11.3. Thienopyrimidines

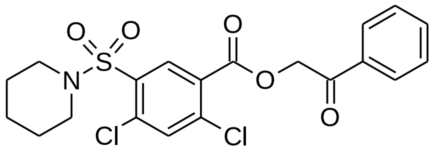
In 2004, Janssen/Addex published a patent application detailing 2,4-disubstituted thienopyrimidine derivatives as mGluR2 potentiators [134]. Compounds of this application are typically substituted with a methyl or propyl group at C-2 and a benzylamino group at C-4. Preferred compounds are noted to have EC_{50} values less than 10 µM in a GTPγS binding assay. A representative compound (**80**) from this application is shown in **Figure 19**.

11.4. Imidazolones

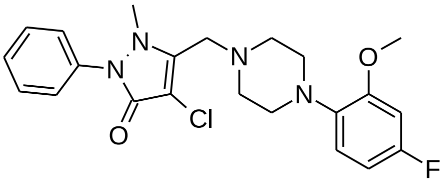
In 2013, a large series (188 examples) of imidazolones has been published by Taisho [135]. The substitution pattern around the imidazolone core are substituted phenyl at C-3, small substituents, preferably methyl at C-2 and lipophilic alkyl- and cycloalkyl at N-3. Potency data are given for all examples, among which compound **81** showed the best potency with an EC_{50} value of 2.7 nM in a GTPγS binding assay (**Figure 19**).

11.5. Dihydroimidazopyrazinones

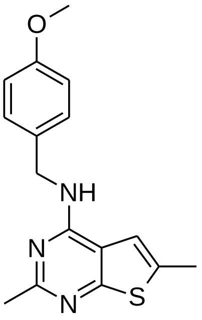
In 2013, Dainippon Sumitomo published a patent application describing dihydroimidazo pyrazinones [136]. Compounds of this application are typically substituted with a chloro at C-2, an aryl group at C-3 and alkyl- or cycloalkyl groups at N-1. An exemplified compound, **82**, showed positive modulator activity at human mGluR2 stably expressed in HEK cells by 63, 70 and 91% at 0.1, 1 and 10 µM, respectively (**Figure 19**).



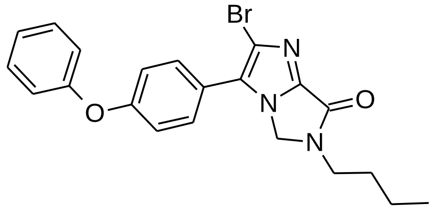
78 AstraZeneca/NPS
$EC_{50} < 10$ μM (GTPγS)



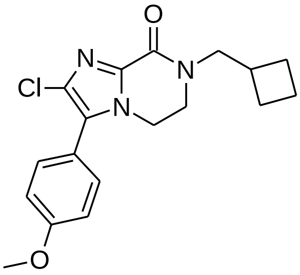
79 AstraZeneca/NPS



80 Janssen/Addex
$EC_{50} < 10$ μM (GTPγS)



81 Taisho
$EC_{50} = 2.7$ nM (GTPγS)



82 Dainippon Sumitomo

Figure 19. mGluR2 PAM benzosulphonamides, pyrazolones, thienopyrimidines, imidazolones and dihydroimidazopyrazolones

Conclusion

Collecting data on the medicinal chemistry of mGluR2 positive allosteric modulators we conclude that a number of chemotypes have been found. The compounds reported up to now show high efficacy on the target and some chemical series fulfill general drug likeness criteria. The evaluation of mGluR2 PAM compound classes was completed by the assessment of ligand efficiency analysis performed on compounds available from the Thomson Reuters Integrity database [137]. Ligand efficiency (LE) [138], ligand lipophilicity efficiency (LLE) [139] and ligand-efficiency-dependent lipophilicity (LELP) [140] values were calculated and compounds were depicted in the LE-LLE and LLE-LELP spaces.

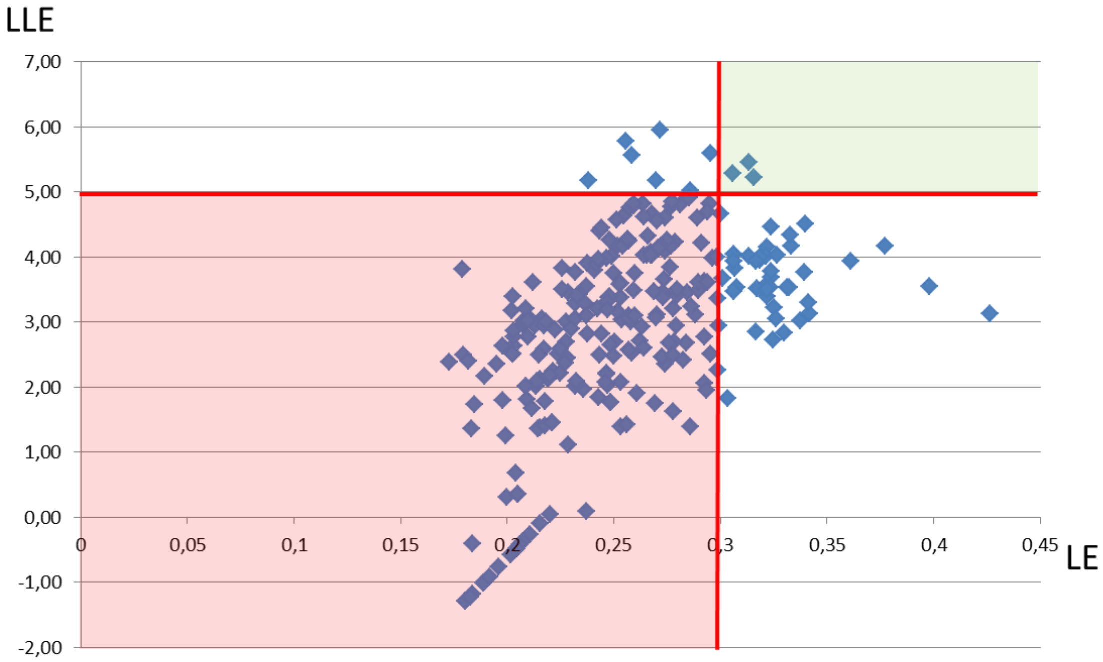
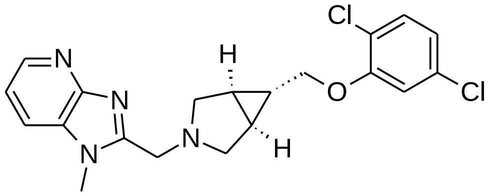
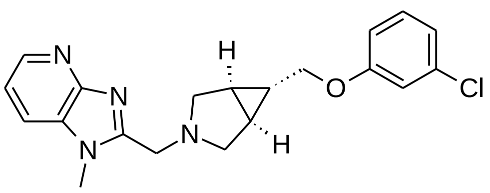


Figure 20. Ligand efficiency (LE) versus lipophilic ligand efficiency (LLE) plot for mGluR2 PAM compounds (n = 271;LE and LLE values were calculated from half-maximal effective concentration (EC50) values).

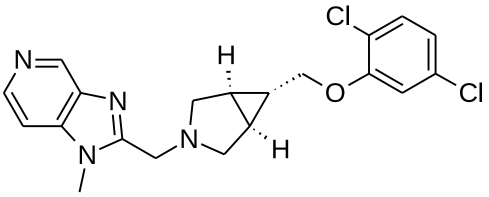
A recent analysis of compounds developed against a high number of drug target revealed that promising drug candidates have LE>0.3 and LLE>5 that defines a preferred region of the LE-LLE space [141]. Compounds located in this region have typically higher chance reaching the clinic than those fail to achieve these criteria. Furthermore the authors claimed that the percentage of compounds within this area indicates the chemical tractability of the drug target. Analyzing the mGluR2 PAMs in the LE-LLE space (Figure 20) we found that the majority of the compounds have both suboptimal LE and LLE values suggesting mGluR2 being a challenging target from medicinal chemistry point of view. It seems that reaching the LE criterion of 0.3 is somewhat easier than fulfilling LLE>5 indicating that the PAM site of mGluR2 is rather lipophilic. There were only three compounds in the most preferred region of the LE-LLE plot all claimed by Pfizer in 2007. These azabenzimidazoles are the results of a lead optimization program, starting from the original benzimidazole scaffold identified in an HTS campaign. Interestingly, introduction of pyridyl nitrogens could improve physicochemical and ADME properties and was also well tolerated for mGluR2 potency for 4-(compound 83 and 84) and 5-azabenzimidazoles (compound 85) (Figure 21) [103,104].



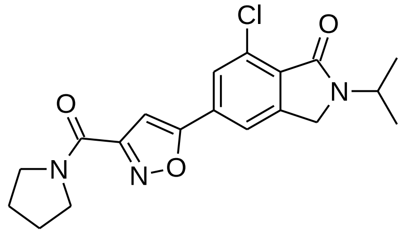
83 Pfizer
EC_{50} = 3-79.5 nM (FLIPR)



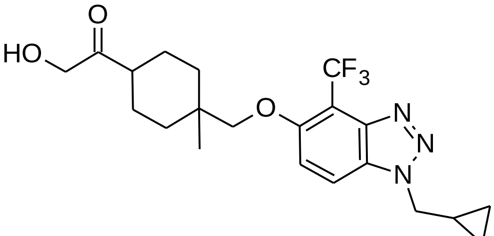
84 Pfizer
EC_{50} = 64 nM (FLIPR) [104]



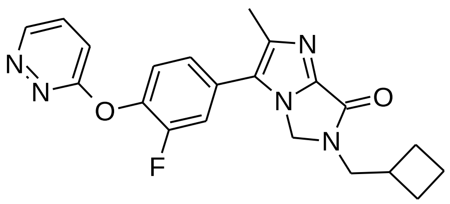
85 Pfizer
EC_{50} = 5.56-130 nM (FLIPR)



86 AstraZeneca
EC_{50} = 37 nM (GTPγS)



87 Merck
EC_{50} = 7 nM (FLIPR)



88 Taisho
EC_{50} = 15 nM (GTPγS)

Figure 21. The most promising mGluR2 positive allosteric modulators identified on the LE-LLE and the LLE-LELP plots.

Another analysis of drug discovery compounds from different development stages concluded that marketed drugs and Phase II compounds have typically LLE>5 and LELP<10 [142]. This observation was in line with a Pfizer study concluding that compounds having LELP>10 have much higher chance for attrition during clinical development [143].

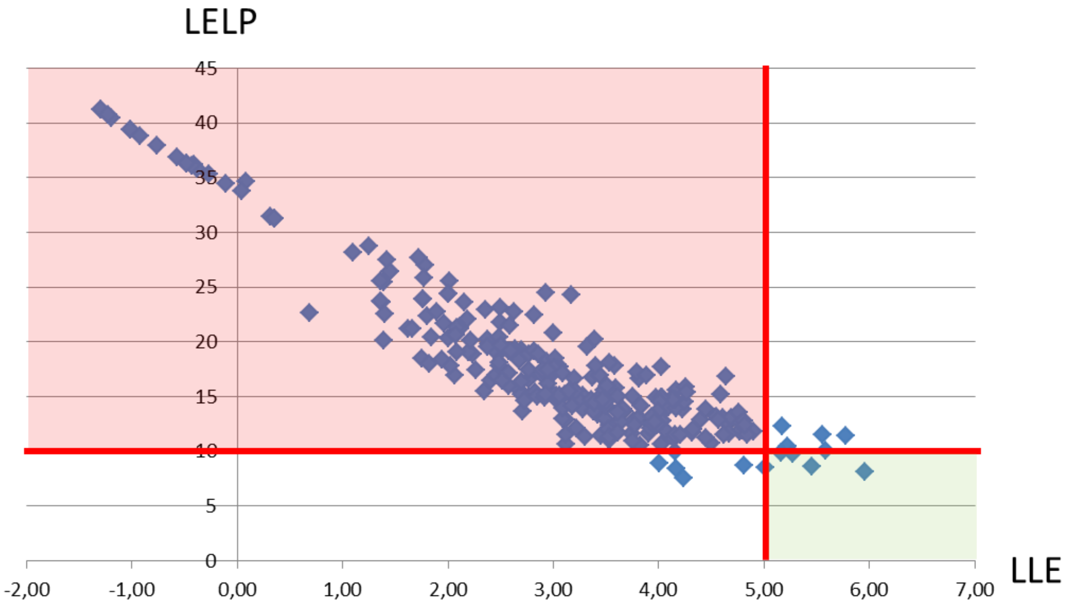


Figure 22. Ligand lipophilicity efficiency (LLE) [139] and ligand-efficiency-dependent lipophilicity (LELP) plot for mGluR2 PAM compounds (n = 271;LLE and LELP values were calculated from half-maximal effective concentration (EC_{50}) values).

The analysis of mGluR2 PAM compounds in the LLE-LELP space (Figure 22) revealed that the vast majority of published compounds fail to meet both LLE>5 and LELP<10 criteria. We identified only five compounds located in the desired area of the LLE-LELP plot (Figure 21). The most attractive series based on LELP-LLE values are described by Pfizer (compound 84 and 85 also favoured by the LE-LLE plot), AstraZeneca (compound 86), Merck (compound 87) and Taisho (compound 88). Isoindolone derivatives as mGluR2 ligands were first described by AstraZeneca. The hit to lead optimization around this scaffold resulted in 10 patent applications. Compound 86 is an example of the last disclosure [69] claiming 21 specific examples. With the combination of the earlier introduced and claimed less lipophilic end-groups, a successful effort was made to find the best quality compounds of this isoindolone class. Compound 87 from Merck Laboratories [106] is also a great example for balanced optimization of potency and ADME profile in the benzotriazole class claimed in 8 patent applications. Compound 88 from Taisho, an imidazolone derivative is a newly published [135] mGluR2 chemotype with attractive lipophilic efficiencies.

These analyses of available mGluR2 PAM compounds revealed that despite of the lipophilic character of the PAM binding site some of the compound series fulfill the ligand efficiency criteria of development candidates. These compound classes were identified by a number of pharmaceutical companies having the potential to push compounds from these series into clinical development.

Although the leading orthosteric agonist LY2140023 has failed to show robust efficacy in clinical trials several companies have still significant interest in the target. Activation of mGluR2 receptors could be achieved via allosteric modulation as has been demonstrated in preclinical functional studies. This approach might demonstrate considerable advantages over orthosteric activation. First, there is higher chance to achieve selectivity over mGluR3 receptors. Second, allosteric modulators are only effective in the presence of glutamate that would prevent receptor desensitization that is often the case with orthosteric agonists. Third, positive allosteric modulators might use different signaling pathways transforming mGluR2 receptors into its activated state. Utilizing the principles of functional selectivity several subtypes of positive allosteric modulators might be considered and tested in experimental disease models. Finally, positive modulators could realize their functional effects as pure PAMs but also as ago-PAMS when compounds show inherent agonistic activity over their allosteric modulatory effect. Although it is not clear whether pure PAMs or ago-PAMs are better in disease models, this phenomena together with the proposed functional selectivity represents further opportunities optimizing the molecular mechanism of action for targeted indications. Considering one of the major indications, schizophrenia the effect of PAMs is proposed to be mediated via the mGluR2-5HT2A functional heterodimer. It has been shown that mGluR2 activation causes suppression of 5-HT2A-mediated signaling events due to protein-protein interactions [71,72]. Moreover, the responses elicited by hallucinogenic and non-hallucinogenic 5-HT2A agonists seem to differ in the intracellular signaling pathways involved [73, 74] and mGluR2 activation might suppress the hallucinogenic pathway [71]. Interestingly, preliminary pharmacogenetic analysis of subjects treated with LY2140023 revealed a strong correlation between treatment response and 5-HT2A genotype of the patients [75]. Based on the above observations it is assumed that potentiation of endogenous mGluR2 activity with subtype-selective positive allosteric modulators would specifically augment the suppression of hallucinogenic 5-HT2A signaling and thus might offer an effective therapy for schizophrenia by attenuation of cortical overexcitation. Since mGluR2 PAMs might have diverse impact on the functional heterodimers this offers further opportunities for selecting allosteric modulators being most effective on heterodimers. Considering the multiple options in molecular mechanisms of action and the high number of chemotypes available we think that further research is needed to define the most effective approach against mGluR2 receptor related indications. We hypothesize that these indications might need different approaches that should be selected in preclinical disease models. This work of course implies the detailed in vitro functional characterization (functional activity in different paradigms, selectivity, receptor sensitization, signaling pathways, effect on heterodimers etc.) of a wide range of chemotypes including those actually investigated in clinical trials. We are more than confident that the publication of clinical data collected for ADX-71149 (JNJ-4041183) would facilitate further research on mGluR2 positive allosteric modulators. The community is looking forward to these data since positive results might encourage further companies pushing their mGluR2 PAM programs further in their clinical pipeline. In other scenarios, however, further research would clarify the impact of molecular mechanisms of activation in mGluR2 related indications.

Conflict of Interest

Declared none.

Acknowledgements

Declared none.

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