CHAPTER SIX

mGluR2 Activators and mGluR5 Blockers Advancing in the Clinic for Major CNS Disorders

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Contents

1. INTRODUCTION

Metabotropic glutamate receptors (mGluRs) are membrane-type receptors for glutamate, which is the major excitatory neurotransmitter in the brain. They belong to the Class C G-protein coupled receptor and consist of a family of eight receptor subtypes, as summarized in Table 6.1. Each receptor subtype has a unique pharmacological profile and their therapeutic potential as drug targets is predicted mainly based on their respective localization in the central and peripheral nervous systems.[1,2] Beyond the classical approach targeting the orthosteric binding site of these receptors, the development of allosteric modulators represents an emerging class of

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Table 6.1 mGluR subtypes: function and signaling pathway

Receptor class	Subtype	Function	Signaling
Group I	mGluR1 mGluR5	Excitatory	Gq/G_{11}; ↑PLC
Group II	mGluR2 mGluR3	Inhibitory	Gq/G_{11}; ↑PLC
Group III	mGluR4 mGluR6 mGluR7 mGluR8	Inhibitory	Gi/G_0; ↓AC

PLC, phospholipase C; AC, adenylyl cyclase.

orally available small molecules offering greater selectivity and better modulatory control at disease mediating receptors.[3,4] This approach has been successively applied to mGluRs and extensively reviewed.[5,6] The mGluR2 activators and mGluR5 blockers are the first drug targets that have demonstrated clinical proof-of-concept in patients suffering from major CNS disorders, such as schizophrenia and anxiety, Parkinson's disease levodopa-induced dyskinesia (PD-LID), fragile X syndrome (FXS), and major depressive disorders. This review focuses on the drug discovery effort and clinical status of mGluR2 activators acting at orthosteric or allosteric binding sites, and negative allosteric modulators (NAMs) of mGluR5.

2. DISCOVERY AND DEVELOPMENT OF MGLUR2 ACTIVATORS

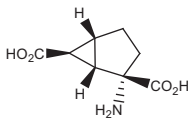
2.1. Localization and functions of mGluR2

Both mGluR2 and mGluR3 receptors are coupled to Gi/Go proteins, and their activation inhibits cAMP formation (Table 6.1).[7] Both receptors share ~70% sequence homology, highly conserved for the ligand binding site and most of the mGluR2 agonists identified so far were dual mGluR2/mGluR3 (mGluR2/3) activators. mGluR2 is exquisitely localized in neurons, specifically in the preterminal region of axons, while mGluR3 is located both pre- and postsynaptically, and in glial cells.[8] Presynaptic mGluR2/3 receptors are either activated by an excess of

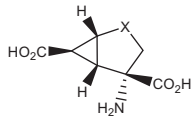
glutamate or by its release from astrocytes through the cystine–glutamate membrane antiporter.[9] mGluR2 is highly expressed in limbic-related regions, making its ligands promising therapeutic agents for neuropsychiatric disorders.[10] Recently, an mGluR2-5-HT_{2A} receptor complex has been characterized,[11] postulated to be the target of antipsychotic drugs acting as 5-HT_2R blocker and/or mGluR2 activators.[12] Site-directed mutagenesis studies have clarified the molecular interaction of mGluR2 orthosteric agonists (and antagonists) with the active site[13] as well as mGluR2 PAM (and NAMs) with the seven-transmembrane domain.[14,15]

2.2. mGluR2 orthosteric agonists

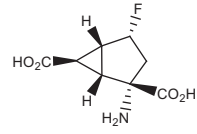
Since the identification of the conformationally constrained bicyclo[3.1.0] alkane-based glutamate mGluR2/3 agonist LY354740 (**1**, eglumetad) in 1997, Lilly scientists have dedicated intensive efforts to delineate this unique chemotype into numerous nanomolar dual mGluR2/3 agonists, represented by LY379268 (**2**), LY389795 (**3**), and LY459477 (**4**),[16] as well as novel mGluR2 agonist/mGluR3 antagonist compounds, such as LY541850 (**5**).[17,18] All these compounds display 100- to >600-fold selectivity versus the other mGluR subtypes.



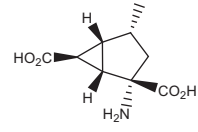
1, LY354740



2, LY379268 (X=O)
3, LY389795 (X=S)

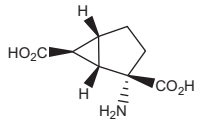


4, LY459477

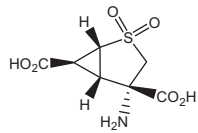


5, LY541850

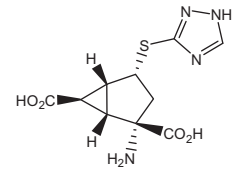
Peptidyl prodrugs have been developed in order to improve oral absorption and brain penetration, providing the first development candidates LY544344 (**6**, talaglumetad)[19] and LY2140023 (**8**, pomaglumetad), prodrug of LY404039 (**7**, hmGluR2/mGluR3 EC_{50} = 23/48 nM).[20] Lilly scientists have pursued their pioneering discovery efforts leading to the first selective mGluR2 agonists **9** (LY2812223; hmGluR2 EC_{50} = 23 nM, hmGluR3 EC_{50} > 30 μM, calcium mobilization assay). LY2812223 has demonstrated *in vivo* efficacy in rodent models of schizophrenia, bipolar disorders, anxiety, and depression.[21] Its L-alanine prodrug LY2979165 (**10**) has been reported to be orally absorbed via the intestinal absorption transporter PepT1 and is effectively hydrolyzed in the human intestine and liver.[21,22]



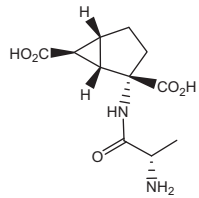
1, LY354740



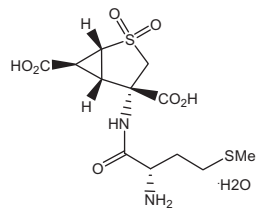
7, LY404039



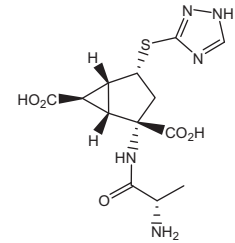
9, LY2812223



6, LY544344



8, LY2140023



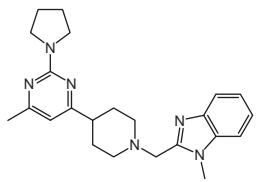
10, LY2979165

2.3. mGluR2 positive allosteric modulators

Two major reviews have reported the large chemical diversity of mGluR2 positive allosteric modulators (PAMs) based on the initial discovery of the first modulators in the early 2000s.[23,24] New structural enrichment has been recently disclosed and described hereafter.

2.3.1 Benzimidazoles

Researchers from Pfizer have described the optimization of benzimidazole derivatives, such as compound **11** (rmGluR2 $EC_{50} = 4790$ nM), identified from an HTS campaign. Exhibiting D_2R-antagonism off-target activities, a subsequent optimization led to the selective azabenzimidazole **12** ($EC_{50} = 35$ nM), which demonstrated oral bioavailability in rats ($F = 50\%$; 3 mg/kg, p.o.) and efficacy in psychosis mice models (minimum effective dose (MED) ranging from 10 to 17.8 mg/kg, s.c.).[25] A similar strategy was independently reported leading to piperazine **13** (GSK1331258; $EC_{50} = 79$ nM).[26]



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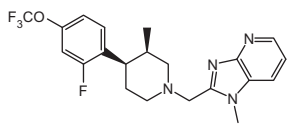

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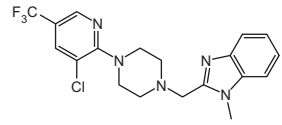
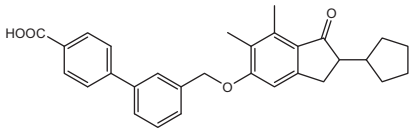


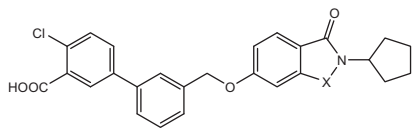
13 GSK1331258

2.3.2 Indanone and isosteres

The improved potency and PK properties of the historical mGluR2 PAM biphenylindanone A (**14**, BINA) via modification of the indanone core has been recently disclosed, as shown in compounds **15** and **16** (rmGluR2, $EC_{50} = 50$ and 170 nM, respectively; thallium flux assay).[27,28] In particular, **16** exhibited oral bioavailability ($F = 86\%$) and high brain/plasma ratio of 4.8 (10 mg/kg, p.o.) and demonstrated efficacy in a rat cocaine self-administration model (MED = 20 mg/kg, p.o.).[29]



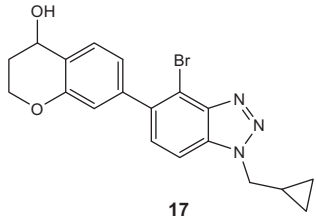
14 BINA



15 X = CH_2
16 X = S

2.3.3 Benzotriazoles, benzimidazolones, and benzothiazolones

N-cyclopropylmethylene-halobenzotriazole series has been broadly exemplified[30,31] yielding potent derivatives, like the direct-branched aryl **17** ($EC_{50} = 8$ nM) or pyridyloxy derivative **18**, being the most active compound within this series ($EC_{50} = 3$ nM).



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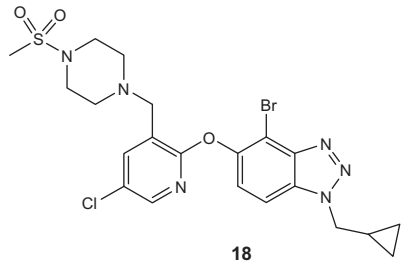
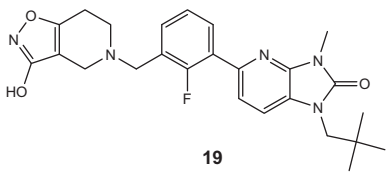


18

A potent *N*-alkylated azabenzimidazolone series has been reported, in which the methyl-*tert*-butyl group was recognized as a privileged substituent, represented by compound **19** ($EC_{50} = 11$ nM).[32] An optimization of this template led to additional cores, such as diazasulfone **20**, being the most potent mGluR2 PAM reported to date in a calcium mobilization assay ($EC_{50} = 0.5$ nM).[33]



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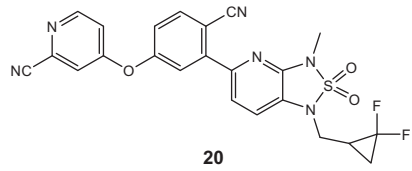
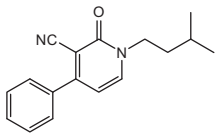


20

2.3.4 Pyridones and azolopyridines

Since the first disclosure of novel pyridone-based mGluR2 PAM chemical series in 2006,[34] scientists at Addex Therapeutics pursued their efforts around the 1,4-disubstituted pyridine HTS hit **21** ($EC_{50} = 8\ \mu M$, [^{35}S] GTPγS assay). This compound showed an adequate overlap with the reported mGluR2 PAM 3D-pharmacophore,[35] and therefore allowed subsequent identification of more potent compounds, such as the compound **22** ($EC_{50} = 42$ nM). The more soluble pyridyl representative **23** ($EC_{50} = 316$ nM) displayed a full selectivity over other mGluR subtypes, an improved hERG channel interaction (21% inhibition at 3 μM) and brain exposure. Compound **23** demonstrated inhibition of REM sleep in a rat sleep-wave EEG model at 10 mg/kg (s.c.).



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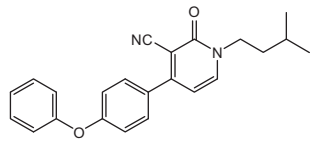

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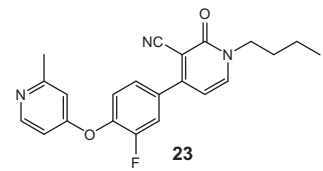
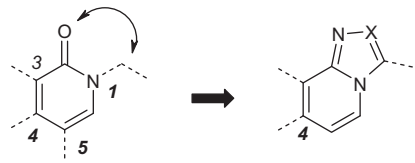


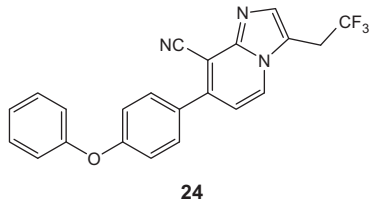
23

The recently disclosed imidazopyridine series is the result of a scaffold hopping exercise on the 1,4-pyridone series (chemotype **B**).[36] Since compound **24** ($EC_{50} = 186$ nM) had poor oral bioavailability, it was further optimized into indole derivative **25** ($EC_{50} = 85$ nM), exhibiting an improved oral pharmacokinetic profile and brain penetration.[37] Compound **25** showed modulation of REM sleep in a rat sleep–wake EEG model at 10 mg/kg orally, consistent with mGluR2 receptor activation.[38]



A

B (X=CH)
C (X=N)



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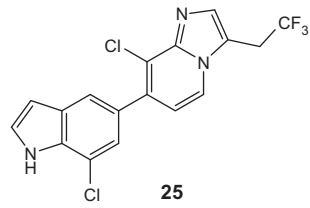
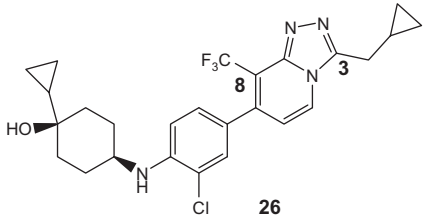
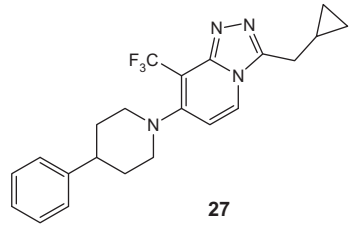


25



26

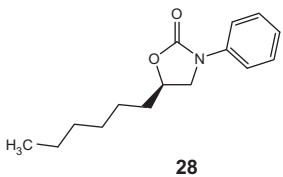


27

The triazolo[4,3:a]pyridine series (chemotype **C**) was exemplified in several patent applications with compounds demonstrated efficacy in different models of psychosis,[39,40] illustrated by compounds **26** and **27** ($EC_{50} = 1.6$ and 16.2 nM, respectively). Phenyl-piperidine **27** exhibited efficacy in PCP-induced hyperlocomotion in mice ($ED_{50} = 5.4$ mg/kg) and conditioned avoidance response in rats ($ED_{50} = 16.3$ mg/kg, p.o.).[41]

2.3.5 Oxazolidinones

The oxazolidinone derivative **28** ($EC_{50} = 450$ nM) was identified in an HTS calcium mobilization assay on hmGluR2 cell lines. Further optimization led to the identification of the benzonitrile **29** ($EC_{50} = 82$ nM) exhibiting moderate-to-high dog clearance (17.7 ml/min/kg), brain penetration in rat (CSF/plasma unbound ratio of 1), and a clean selectivity profile over other mGluR subtypes, D_2 and 5-HT_{2A} receptors. Compound **29** demonstrated efficacy in the ketamine-induced locomotor activity at 100 mg/kg after i.p. administration.[42]



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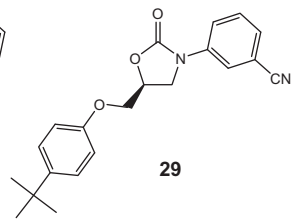

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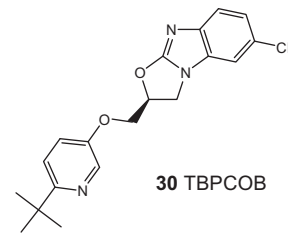


30 TBPCOB

The fusion of the oxazolidinone and the cyano-phenyl rings led to the discovery of the oxazolobenzimidazole series. The resulting *ter*-butyl-pyridyloxymethyl-cyano-oxazolobenzimidazole **30** combined high potency (hmGluR2 $EC_{50} = 29$ nM, rmGluR2 $EC_{50} = 42$ nM) and improved solubility and selectivity over mGluR, D_2, and 5-HT_{2A} receptors. Compound **30** demonstrated brain exposure and robust efficacy in a PCP-induced hyperlocomotion model in rats (MED = 30 mg/kg, p.o.).[43]

2.4. Clinical trials

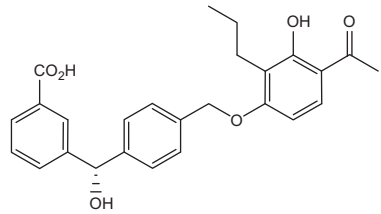
Today, several mGluR2 activators have successfully reached clinical development phases for the treatment of severe CNS disorders, including schizophrenia and anxiety (see Table 6.2).[10,50,51] LY2140023 (**8**)[20] is the first mGluR2/3 agonist demonstrating its tolerability and significant improvement of positive and negative symptoms of schizophrenia in patients in a Phase IIa trial.[44] However, a second Phase II study proved inconclusive due to lack of separation from placebo of both **8** and olanzapine.[52] LY2140023 has now reached Phase III clinical stage while being further investigated in additional Phase II studies.[53] Preclinical[54,55] and clinical[56] evidence also supports a significant benefit of mGluR2 activators on working memory processes and cognitive symptoms in schizophrenia. More recently, two additional specific mGluR2 activators LY2979165 (**10**)[45] and ADX71149/JNJ40411813 (undisclosed structure) have reached Phases I and IIa, respectively, for psychiatric disorders.[46]

Table 6.2 mGluR2 activators in Phase I and Phase II trials

Compound	MoA	Indications	Clinical status
LY2140023 (**8**)	mGluR2/3 agonist	Schizophrenia	Phase II/III[44]
LY2979165 (**10**)	mGluR2 agonist	Bipolar disorders	Phase I[45]
ADX71149/JNJ40411813	mGluR2 PAM	Schizophrenia	Phase II[46]
LY544344 (**6**)	mGluR2/3 agonist	Generalized anxiety disorders	Phase II[47,48]
LY2300559 (**31**)	mGluR2 agonist/CysLT1 antagonist	Migraine	Phase II[49]

LY544344 **6** has demonstrated clinical improvement in patients with generalized anxiety disorder.[47,48] LY354740 **1** has failed to reach clinical significance compared to placebo in a double-blind clinical trial in patients with panic disorder.[57] In a separate study, LY354740 has, however, demonstrated anxiolytic-like effect in the fear-potentiated startle paradigm.[58]

LY2300559 (**31**), a dual mGluR2 PAM ($EC_{50} = 50$ nM) and cysteinyl-leukotriene 1 (CysLT1) antagonist ($K_b = 22$ nM),[59,60] has entered a Phase II placebo-controlled proof-of-concept study in patients with migraine. Despite its low brain-to-plasma ratio of 0.01, **31** has demonstrated efficacy in a preclinical rodent model of migraine and was reported to be well tolerated in rat and dog toxicological studies.[49]



31

3. DRUG DISCOVERY AND DEVELOPMENT OF MGLUR5 NAMS

3.1. Localization and functions of mGluR5

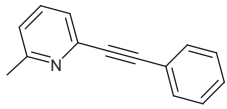
mGluR5 is coupled to Gq/G_{11} protein (Table 6.1), is localized postsynaptically, and is highly expressed in the hippocampus, corpus striatum, cerebral cortex, and in basal ganglia,[5,61] a key region for motor control.[62] In addition, cross talk between mGluR5, dopamine D_2 receptors, and adenosine A_{2A} receptors, which are all highly expressed in the striatum, is hypothesized to play a role in the motor dysfunction observed in Parkinson's disease.[63]

3.2. Alkyne-based mGluR5 negative allosteric modulators

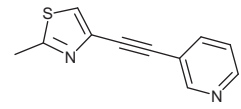
Many examples of mGluR5 NAMs have been reported in recent reviews[64,65] since the discovery of the diarylalkynes MPEP **32** and MTEP **33**. Potent mGluR5 modulators have been discovered through extensive exploration of the SAR in these narrow series.[66] Unless otherwise noted, biological activities reported in this section have been

demonstrated using a calcium mobilization assay (FLIPR) using a human mGluR5 clone.

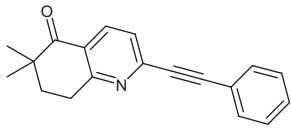
Dihydroquinolinone MRZ-8676 (**34**, $IC_{50} = 20$ nM) has been reported to demonstrate activity in a rat model of L-dopa-induced dyskinesia (MED = 8.33 mg/kg, p.o.), and no tolerance was observed after repeat dosing (6 days) at 75 mg/kg.[67] The imidazolyl derivative CTEP (**35**) is another potent and selective mGluR5 NAM ($IC_{50} = 11.4$ nM) and demonstrated efficacy in the Vogel conflict drinking rat model (MED = 0.3 mg/kg, p.o.).[68]



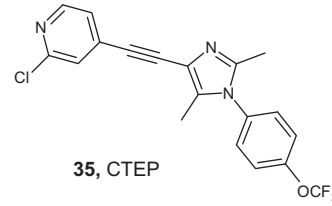
32, MPEP



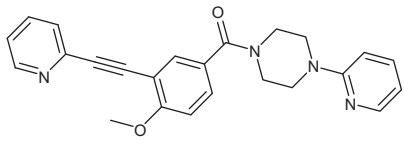
33, MTEP



34, MRZ8676



35, CTEP



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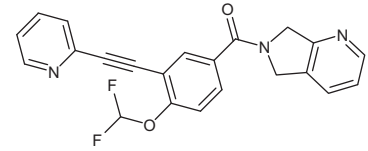
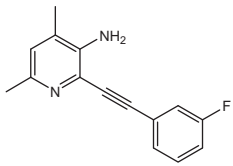


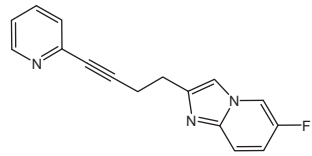
37, WYE304529

Further exploration around ethynylbenzamide **36** ($IC_{50} = 8.0$ nM)[69] led to pyrido-isoindoline **37** (WYE304529/GRN529). Compound **37** displayed improved potency ($IC_{50} = 3.1$ nM), above 1000-fold selectivity versus mGluR1, and dose-dependent efficacy in a wide range of rodent models of anxiety, depression, and pain.[70,71] Since the initial discovery of the Addex clinical candidate ADX10059 (**38**, raseglurant), intensive efforts led to the identification of the ethynylpyridine development candidate ADX48621 (**39**, dipraglurant; rmGluR5, $IC_{50} = 21$ nM).[64] ADX48621 has demonstrated antiparkinsonian activity in two preclinical models: the haloperidol-induced catalepsy in rats (ED50 = 2.8 mg/kg, p.o.) and the MPTP-treated macaque model (MED = 10 mg/kg, p.o.).[72] Another mGluR5 NAM clinical candidate, mavoglurant **40** (AFQ056, Novartis Pharmaceuticals), was able to restore the prepulse inhibition of startle

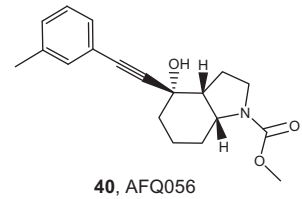
response in Fmr1 KO mice, confirming the interest of this molecule in FXS.[73]



38, ADX10059



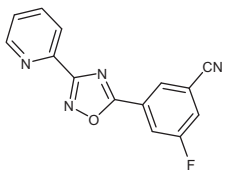
39, ADX48621



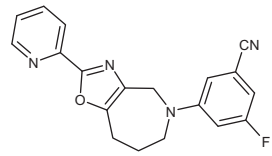
40, AFQ056

3.3. Non alkyne-based mGluR5 chemotypes

Bioisosteric replacement of the ethynyl bond, which keeps the molecular topology and the established SAR within the alkyne series, is exhibited by compounds such as 1,2,4-oxadiazole **41** (VU0285683) and the carboxamide **44** derivatives. As illustrated, many combinations preserved the 3-cyano-5-fluorophenyl moiety which can be considered as a privileged fragment.



41, VU0285683



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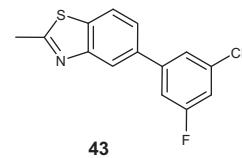

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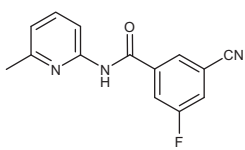
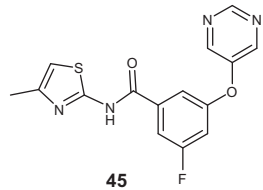


44



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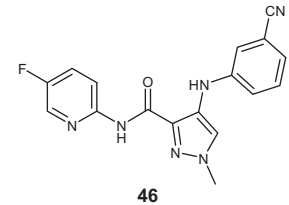

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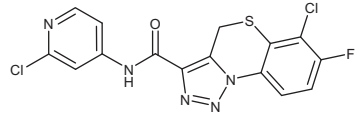
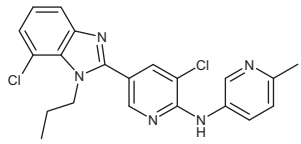


47

A series of tetrahydro-oxazolopyridines have been optimized leading to the identification of the azepine **42** ($IC_{50} = 16$ nM). Unfortunately, its short half-life in rat and monkey precluded further development.[74] Alternative heteroaryl ring systems were identified, such as the 2-methylbenzothiazole **43** ($IC_{50} = 61$ nM).[75] Carboxamide **44** (rmGluR5, $IC_{50} = 24$ nM) demonstrated

efficacy in anxiety models similar to MTEP.[76] Compound **45** ($IC_{50}=25$ nM)[77] or pyrazole **46** ($IC_{50}=6.9$ nM)[78] showed efficacy in the marble burying mouse model. A novel constrained tricyclic series has been reported, illustrated by compound **47**, with subnanomolar activity ($pIC_{50}=9.1$).[79]

Another interesting set of potent mGluR5 NAM has been recently disclosed. Benzimidazol-3-yl pyridine **48** ($IC_{50}=24$ nM) showed oral efficacy in the anxiety fear-potentiated startle rat model (MED = 1 mg/kg).[80] Pyridinyl derivative **49** ($IC_{50}=17$ nM) exhibited moderate exposure after oral dosing due to extensive hepatic metabolism.[81] The piperidino-tetrazole **50** ($pIC_{50}=6.7$) resulted from a hit to lead campaign starting from a 3,5-oxadiazole hit.[82] Interestingly, *S*-enantiomers generally exhibited better potency.[83]



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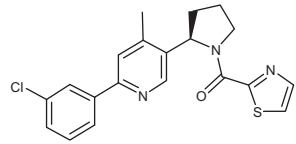

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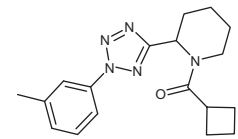

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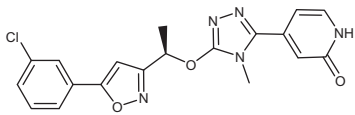

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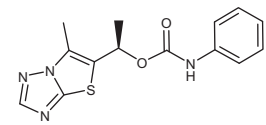
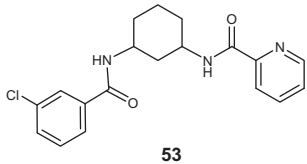
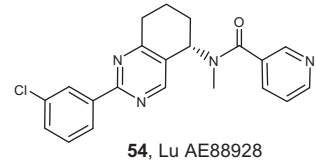


52, GSK2210875



53



54, Lu AE88928

A number of related series where the heterocyclic spacer can be replaced by linear linkers have been extensively investigated, as illustrated methyloxy-triazole **51** ($IC_{50}=10$ nM)[84] or carbamate **52** (GSK2210875, $pIC_{50}=7.4$).[85] The tetrahydroquinazolinyl derivative **54** (LuAE88928, $IC_{50}=13$ nM), inspired from the cyclohexyldiamide **53** ($IC_{50}=10$ nM), has shown favorable PK profile and oral efficacy at 30 mg/kg in the Geller-Seifter conflict test.[86]

The mGluR5 NAM field of research is becoming mature, and the mining of a large collection of mGluR5 ligands and the recognition of their pharmacophoric patterns have been successfully applied to the discovery of novel chemotypes with several progressing into development.

3.4. Clinical trials

3.4.1 Parkinson's disease

To date, two compounds have been reported to be in clinical development for Parkinson's disease levodopa-induced dyskinesia. AFQ056 **40** has shown activity in two randomized controlled clinical trials in PD patients with moderate-to-severe LID and severe LID on stable dopaminergic therapy.[87] Patients received 25–150 mg AFQ056 or placebo twice daily for 16 days. AFQ056-treated patients showed significant improvements in dyskinesia on day 16 versus placebo, but no significant changes were seen from baseline to day 16 in the Unified Parkinson's Disease Rating Scale (UPDRS Part III), suggesting that AFQ056 does not affect the antiparkinsonian activity of levodopa and does not improve or worsen motor signs in these patients.

Dipraglurant (Addex Therapeutics) has entered a double-blind, placebo-controlled randomized Phase IIa study in patients with moderate or severe PD-LID, and positive top line data have been reported.[88] Dipraglurant demonstrated a statistically significant reduction in LID severity with both 50- and 100-mg doses, without interfering with levodopa efficacy. During week 4, patients reported a reduction in daily off-time of 50 min, suggesting an effect on parkinsonian motor symptoms in addition to the observed reductions in LID. In a subset of patients, dipraglurant appears to have reduced dystonia severity in addition to chorea, the two major LID components.

The antidyskinetic effect observed with AFQ056 and ADX48621 have demonstrated that mGluR5 inhibition is one of the most promising potential treatments for LID and a clinically relevant therapeutic target.

3.4.2 Other CNS disorders

FXS is an X-linked condition associated with intellectual disability and behavioral problems. AFQ056 has recently demonstrated a beneficial effect on the behavioral symptoms of fully methylated FXS patients versus partially methylated patients in a crossover study of 30 male FXS patients.[89] RO4917523 (undisclosed structure; Roche) entered a Phase II clinical trial in early 2012.[90] STX107 (undisclosed structure; Seaside Therapeutics) has completed Phase I trials.[91]

RO4917523 is currently being studied in patients with major depressive disorders, who show inadequate response to ongoing antidepressant therapies. Phase II studies have been completed, but no data have yet been released.[92]

ADX10059 (**38**) has shown the first clinical evidence for analgesic effects of mGluR5 NAMs. Data from a proof-of-concept study in episodic migraine patients demonstrated a significant improvement following acute treatment of ADX10059.[93]

4. CONCLUSION

Tremendous progress has been made recently toward the development of mGluR2 activators and mGluR5 NAM drugs. These are the first two subtypes from the whole class of mGluR family to reach mid-stage clinical testing and demonstrate positive outcomes in patients suffering from severe disorders. The first group II mGluR2/3 orthosteric agonists have demonstrated proof-of concept in humans for psychiatric and anxiety disorders. In addition, for the first time, pure mGluR2 PAMs have entered Phase II clinical trials in schizophrenia patients. Within group I mGluRs, three mGluR5 NAMs have achieved Phase II human proof-of-concept in PD-LID, FXS, or major depressive disorders.[94] In light of the wide range of chemotypes reported during the past 2–3 years, it is likely that novel potent and selective mGluR2 PAMs and mGluR5 NAMs will advance into the clinic in the coming years.

REFERENCES

(1) Nicoletti, F.; Bockaert, J.; Collingridge, G.L.; Conn, P.J.; Ferraguti, F.; Schoepp, D.D.; Wroblewski, J.T.; Pin, J.P. *Neuropharmacology* **2011**, *60*, 1017.
(2) Niswender, C.M.; Conn, P.J. *Annu. Rev. Pharmacol. Toxicol.* **2010**, *50*, 295.
(3) Kenakin, T. *Trends Pharmacol. Sci.* **2007**, *28*, 407.
(4) Christopoulos, A.; Kenakin, T. *Pharmacol. Rev.* **2002**, *54*, 323.
(5) Urwyler, S. *Pharmacol. Rev.* **2011**, *63*, 59.
(6) Gregory, K.J.; Dong, E.N.; Meiler, J.; Jeffrey, C.P. *Neuropharmacology* **2011**, *60*, 66.
(7) Pin, J.P.; Duvoisin, R. *Neuropharmacology* **1995**, *34*, 1.
(8) Tamaru, Y.; Nomura, S.; Mizuno, N.; Shigemoto, R. *Neuroscience* **2001**, *106*, 481.
(9) Kalivas, P.W. *Nat. Rev. Neurosci.* **2009**, *10*, 561.
(10) Fell, M.J.; McKinzie, D.L.; Monn, J.A.; Svensson, K.A. *Neuropharmacology* **2012**, *62*, 1473.
(11) Prezeau, L.; Rives, M.L.; Comps-Agrar, L.; Maurel, D.; Kniazeff, J.; Pin, J.P. *Curr. Opin. Pharmacol.* **2010**, *10*, 6.
(12) Fribourg, M.; Moreno, J.L.; Holloway, T.; Provasi, D.; Baki, L.; Mahajan, R.; Park, G.; Adney, S.K.; Hatcher, C.; Eltit, J.M.; Ruta, J.D.; Albizu, L.; Li, Z.; Umali, A.; Shim, J.;

Fabiato, A.; MacKerell, A.D.; Brezina, V.; Sealfon, S.C.; Filizola, M.; Gonzalez-Maeso, J.; Logothetis, D.E. *Cell* **2011**, *147*, 1011.
(13) Lundstrom, L.; Kuhn, B.; Beck, J.; Borroni, E.; Wettstein, J.G.; Woltering, T.J.; Gatti, S. *ChemMedChem* **2009**, *4*, 1086.
(14) Peeters, L.; Lavreysen, H.; Masure, S.; Gabriëls, L.; Tresadern, G.; Cid, J.; Atack, J.R. *Curr. Neuropharmacol.* **2011**, *9*, 1.
(15) Lundstrom, L.; Bissantz, C.; Beck, J.; Wettstein, J.G.; Woltering, T.J.; Wichmann, J.; Gatti, S. *Br. J. Pharmacol.* **2011**, *164*(2b), 521.
(16) Wright, R.A.; Johnson, B.G.; Zhang, C.; Salhoff, C.; Kingston, A.E.; Calligaro, D.O.; Monn, J.A.; Schoepp, D.D.; Marek, G.J. *Neuropharmacology* **2012**, http://dx.doi.org/10.1016/j.neuropharm.2012.01.019.
(17) Ceolin, L.; Kantamneni, S.; Barker, G.R.; Hanna, L.; Murray, L.; Warburton, E.C.; Robinson, E.S.; Monn, J.A.; Fitzjohn, S.M.; Collingridge, G.L.; Bortolotto, Z.A.; Lodge, D. *J. Neurosci.* **2011**, *31*, 6721.
(18) Hanna, L.; Ceolin, L.; Lucas, S.; Monn, J.; Johnson, B.; Collingridge, G.; Bortolotto, Z.; Lodge, D. *Neuropharmacology* **2012**, http://dx.doi.org/10.1016/j.neuropharm.2012.02.023.
(19) Monn, J.A.; Massey, S.M.; Valli, M.J.; Henry, S.S.; Stephenson, G.A.; Bures, M.; Herin, M.; Catlow, J.; Giera, D.; Wright, R.A.; Johnson, B.G.; Andis, S.L.; Kingston, A.; Schoepp, D.D. *J. Med. Chem.* **2007**, *50*, 233.
(20) Mezler, M.; Geneste, H.; Gault, L.; Marek, G.J. *Curr. Opin. Investig. Drugs* **2010**, *11*, 833.
(21) Monn, J.; Prietto, L.; Tabaoda Martinez, L.; Montero Salgado, C.; Shaw, B. *Patent Application WO2011084437.* **2011.**
(22) Swanson, S. *AAPS Prodrug Symposium.* Oct2011 http://www.aaps.org/Meetings_and_Professional_Development/Past_Meetings/2011_AAPS_Annual_Meeting_and_Exposition/Thu_0930_147AB_Swanson.
(23) Trabanco, A.A.; Cid, J.M.; Lavreysen, H.; Macdonald, G.J.; Tresadern, G. *Curr. Med. Chem.* **2011**, *18*, 47.
(24) Fraley, M.E. *Expert Opin. Ther. Pat.* **2009**, *19*, 1259.
(25) Zhang, L.; Brodney, M.A.; Candler, J.; Doran, A.C.; Duplantier, A.J.; Efremov, I.V.; Evrard, E.; Kraus, K.; Ganong, A.H.; Haas, J.A.; Hanks, A.N.; Jenza, K.; Lazzaro, J.T.; Maklad, N.; McCarthy, S.A.; Qian, W.; Rogers, B.N.; Rottas, M.D.; Schmidt, C.J.; Siuciak, J.A.; Tingley, F.D., III; Zhang, A.Q. *J. Med. Chem.* **2011**, *54*, 1724.
(26) D'Alessandro, P.L.; Corti, C.; Roth, A.; Ugolini, A.; Sava, A.; Montanari, D.; Bianchi, F.; Garland, S.L.; Powney, B.; Koppe, E.L.; Rocheville, M.; Osborne, G.; Perez, P.; Delafuente, J.; DeLosFrailes, M.; Smith, P.W.; Branch, C.; Nash, D.; Watson, S.P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 759.
(27) Dhanya, R.P.; Sidique, S.; Sheffler, D.J.; Nickols, H.H.; Herath, A.; Yang, L.; Dahl, R.; Ardecky, R.; Semenova, S.; Markou, A.; Conn, P.J.; Cosford, N.D. *J. Med. Chem.* **2011**, *54*, 342.
(28) Cosford, N.D.; Panickar, D.R.; Sidique, S. *Patent Application WO 2011116356.* 2011.
(29) Jin, X.; Semenova, S.; Yang, L.; Ardecky, A.; Sheffler, D.J.; Dahl, R.; Conn, J.P.; Cosford, N.D.P.; Markou, M. *Neuropsychopharmacology* **2010**, *35*, **2012.**
(30) Beshore, D.C.; Dudkin, V.; Kuduk, S.D.; Skudlarek, J.W.; Wang, C. *Patent Application WO 2010141360.* **2010.**
(31) Dudkin, V.; Fraley, M.E.; Wang, C.; Garbaccio, R.M.; Beshore, D.C.; Kuduk, S.D.; Skudlarek, J.W. *Patent Application WO 2011022312.* **2011.**
(32) Arrington, K.L.; Dudkin, V.; Laytov, M.E.; Pero, J.E.; Reif, A.J. *Patent Application WO 2011156245.* **2011.**
(33) Layton, M.E.; Kelly, M.J.; Hartingh, T.J. *Patent Application WO 2011109277.* **2011.**

(34) Imogai, H.; Cid-Nuñez, J.M.; Duvey, G.; Boléa, C.M.; Nhem, V.; Finn, T.P.; Le Poul, E.C.; Rocher, J-.P.; Lutjens, R.J. *Patent Application WO 2006030032*. **2006.**
(35) Cid, J.M.; Duvey, G.; Tresadern, G.; Nhem, V.; Furnari, R.; Cluzeau, P.; Vega, J.A.; de Lucas, A.I.; Matesanz, E.; Alonso, J.M.; Linares, M.L.; Andres, J.I.; Poli, S.M.; Lutjens, R.; Himogai, H.; Rocher, J.P.; Macdonald, G.J.; Oehlrich, D.; Lavreysen, H.; Ahnaou, A.; Drinkenburg, W.; Mackie, C.; Trabanco, A.A. *J. Med. Chem*. **2012**, *55*, 2388.
(36) Tresadern, G.; Cid, J.M.; Macdonald, G.J.; Vega, J.A.; De Lucas, A.I.; García, A.; Matesanz, E.; Linares, M.L.; Oehlrich, D.; Lavreysen, H.; Biesmans, I.; Trabanco, A.A. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 175.
(37) Trabanco, A.A.; Tresadern, G.; Macdonald, G.J.; Vega, J.A.; de Lucas, A.I.; Matesanz, E.; Garcia, A.; Linares, M.L.; Alonso de Diego, S.A.; Alonso, J.M.; Oehlrich, D.; Ahnaou, A.; Drinkenburg, W.; Mackie, C.; Andres, J.I.; Lavreysen, H.; Cid, J.M. *J. Med. Chem*. **2012**, *55*, 2688.
(38) Ahnaou, A.; Dautzenberg, F.M.; Geys, H.; Imogai, H.; Gibelin, A.; Moechars, D.; Steckler, T.; Drinkenburg, W.H. *Eur. J. Pharmacol*. **2009**, *603*, 62.
(39) Cid-Nuñez, J.M.; De Lucas Olivares, A.I.; Trabanco-Suárez, A.A.; Macdonald, G.J. *Patent Application WO 2010130423*. **2010.**
(40) Cid-Nuñez, J.M.; Oehlrich, D.; Trabanco-Suárez, A.A.; Tresadern, G.J.; Vega Ramiro, J.A.; Macdonald, G.J. *Patent Application WO 2010130424*. **2010.**
(41) Trabanco, A.A.; Duvey, G.; Cid, J.M.; Macdonald, G.J.; Cluzeau, P.; Nhem, V.; Furnari, R.; Behaj, N.; Poulain, G.; Finn, T.; Lavreysen, H.; Poli, S.; Raux, A.; Thollon, Y.; Poirier, N.; D'Addona, D.; Andres, J.I.; Lutjens, R.; Le Poul, E.; Imogai, H.; Rocher, J.P. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 971.
(42) Brnardic, E.J.; Fraley, M.E.; Garbaccio, R.M.; Layton, M.E.; Sanders, J.M.; Culberson, C.; Jacobson, M.A.; Magliaro, B.C.; Hutson, P.H.; O'Brien, J.A.; Huszar, S.L.; Uslaner, J.M.; Fillgrove, K.L.; Tang, C.; Kuo, Y.; Sur, S.M.; Hartman, G.D. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 3129.
(43) Garbaccio, R.M.; Brnardic, E.J.; Fraley, M.E.; Hartman, G.D.; Hutson, P.H.; O'Brien, J.A.; Magliaro, B.C.; Uslaner, J.M.; Huszar, S.L.; Fillgrove, K.L.; Small, J.H.; Tang, C.; Kuo, Y.; Jacobson, M.A. *ACS Med. Chem. Lett*. **2010**, *1*, 406.
(44) Patil, S.T.; Zhang, L.; Martenyi, F.; Lowe, S.L.; Jackson, K.A.; Andreev, B.V.; Avedisova, A.S.; Bardenstein, L.M.; Gurovich, I.Y.; Morozova, M.A.; Mosolov, S.N.; Neznanov, N.G.; Reznik, A.M.; Smulevich, A.B.; Tochilov, V.A.; Johnson, B.G.; Monn, J.A.; Schoepp, D.D. *Nat. Med*. **2007**, *13*, 1102.
(45) http://clinicaltrials.gov/ct2/results?term=JNJ-40411813. NCT01248052.
(46) http://clinicaltrials.gov/ct2/results?term=JNJ-40411813. NCT01101659, NCT0135-8006, NCT01323205.
(47) Dunayevich, E.; Erickson, J.; Levine, L.; Landbloom, R.; Schoepp, D.D.; Tollefson, G.D. *Neuropsychopharmacology* **2008**, *33*, 1603.
(48) Michelson, D.; Levine, L.R.; Dellva, M.A.; Mesters, P.; Schoepp, D.D.; Dunayevich, E.; Tollefson, G.D. *Neuropharmacology* **2005**, *49*, 257.
(49) Johnson, M.P.; Schkeryantz, J.; Swanson, S.; Perkins, A.N.; Johnson, K.W. *Curr. Neuropharmacol*. **2011**, *9*, 1.
(50) Moghaddam, B.; Javitt, D. *Neuropsychopharmacology* **2012**, *37*, 4.
(51) Swanson, J.; Bures, M.; Johnson, M.P.; Linden, A.M.; Monn, J.A.; Schoepp, D.D. *Nat. Rev. Drug Discov*. **2005**, *4*, 131.
(52) Kinon, B.J.; Zhang, L.; Millen, B.A.; Osuntokun, O.O.; Williams, J.E.; Kollack-Walker, S.; Jackson, K.; Kryzhanovskaya, L.; Jarkova, N. *J. Clin. Psychopharmacol*. **2011**, *31*, 349.

(53) http://clinicaltrials.gov/ct2/results?term=LY2140023. NCT00845026, NCT01086748, NCT01052103, NCT01129674, NCT01125358, NCT01129674, NCT01487083, NCT01307800, NCT01328093, NCT01452919.
(54) Horiguchi, M.; Huang, M.; Meltzer, H.Y. *Psychopharmacology* **2011**, *217*, 13.
(55) Helton, D.R.; Tizzano, J.P.; Monn, J.A.; Schoepp, D.D.; Kallman, M.J. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 651.
(56) Nikiforuk, A.; Popik, P.; Drescher, K.U.; Van Gaalen, M.; Relo, A.L.; Mezler, M.; Marek, G.; Schoemaker, H.; Gross, G.; Bespalov, A. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 665.
(57) Bergink, V.; Westenberg, H.G. *Int. Clin. Psychopharmacol.* **2005**, *20*, 291.
(58) Grillon, C.; Cordova, J.; Levine, L.R.; Morgan, C.A., III *Psychopharmacology* **2003**, *168*, 446.
(59) http://clinical-trials.healia.com/doc/NCT01184508.
(60) Aicher, T.; Cortez, G.; Groendyke, T.; Khilevich, A.; Knolbelsdorf, J.; Magnus, N.; Marmsater, F.; Schkeryantz, J.; Tang, T. *Patent Application WO2006057870.* **2006.**
(61) Romano, C.; Sesma, M.A.; McDonald, C.T.; O'Malley, K.; van den Pol, A.N.; Olney, J.W. *J. Comp. Neurol.* **1995**, *355*, 455.
(62) Conn, P.J.; Battaglia, G.; Marino, M.J.; Nicoletti, F. *Nat. Rev. Neurosci.* **2005**, *6*, 787.
(63) Kniazeff, J.; Prezeau, L.; Rondard, P.; Pin, J.P.; Goudet, C. *Pharmacol. Ther.* **2011**, *130*, 9.
(64) Rocher, J.P.; Bonnet, B.; Bolea, C.; Lutjens, R.; Le Poul, E.; Poli, S.; Epping-Jordan, M.; Bessis, A.S.; Ludwig, B.; Mutel, V. *Curr. Top. Med. Chem.* **2011**, *11*, 680.
(65) Emmitte, K.A. *ACS Chem. Neurosci.* **2011**, *2*, 411.
(66) Alagille, D.; Dacosta, H.; Chen, Y.; Hemstapat, K.; Rodriguez, A.; Baldwin, R.M.; Conn, J.P.; Tamagnan, G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3243.
(67) Dekundy, A.; Gravius, A.; Hechenberger, M.; Pietraszek, M.; Nagel, J.; Tober, C.; van der Elst, M.; Mela, F.; Parsons, C.G.; Danysz, W. *J. Neural Transm.* **2011**, *118*, 1703.
(68) Lindemann, L.; Jaeschke, G.; Michalon, A.; Vieira, E.; Honer, M.; Spooren, W.; Porter, R.; Hartung, T.; Kolczewski, S.; Buttelmann, B.; Flament, C.; Diener, C.; Fischer, C.; Gatti, S.; Prinssen, E.P.; Parrott, N.; Hoffmann, G.; Wettstein, J.G. *J. Pharmacol. Exp. Ther.* **2011**, *339*, 474.
(69) Gilbert, A.M.; Bursavich, M.G.; Lombardi, S.; Adedoyin, A.; Dwyer, J.M.; Hughes, Z.; Kern, J.C.; Khawaja, X.; Rosenzweig-Lipson, S.; Moore, W.J.; Neal, S.J.; Olsen, M.; Rizzo, S.J.; Springer, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 195.
(70) Sperry, J.B.; Levent, M.; Varsolona, R.J.; Farr, R.M.; Ghosh, M.; Hoagland, S.M.; Rapisardi, V.; Fung, P.; Sarveiya, V.; Sutherland, K. ORGN-168*, 242nd ACS National Meeting, Denver, CO.* Aug **2011.**
(71) Hugues, Z.A.; Neal, S.J.; Smith, D.L.; Sukoff Rizzo, S.J.; Pulicicchio, C.M.; Lotarski, S.; Bryce, D.; Lu, S.; Dwyer, J.; Olsen, M.; Bender, C.N.; Kouranova, E.; Springer, D.; Li, D.; O'Neil, S.V.; Andree, T.H.; Whiteside, G.T.; Dunlop, J.; Brandonm, N.J.; Schechter, L.E.; Leonard, S.K.; Rosenzweig-Lipson, S.; Ring, R.H. *Curr. Neuropharmacol.* **2011**, *9*, 1.
(72) Hill, M.P.; Girard, F.; Keywood, C.; Poli, S.-M.; Le Poul, E.; Crossman, A.R.; Ravenscroft, P.; Li, Q.; Bezard, E.; Mutel, V. *Society for Neuroscience Meeting, San Diego.* Nov 2010 Poster 557.12/M18.
(73) Levenga, J.; Hayashi, S.; de Vrij, F.M.; Koekkoek, S.K.; van der Linde, H.C.; Nieuwenhuizen, I.; Song, C.; Buijsen, R.A.; Pop, A.S.; Gomezmancilla, B.; Nelson, D.L.; Willemsen, R.; Gasparini, F.; Oostra, B.A. *Neurobiol. Dis.* **2011**, *42*, 311.
(74) Burdi, D.F.; Hunt, R.; Fan, L.; Hu, T.; Wang, J.; Guo, Z.; Huang, Z.; Wu, C.; Hardy, L.; Detheux, M.; Orsini, M.A.; Quinton, M.S.; Lew, R.; Spear, K.Y. *J. Med. Chem.* **2010**, *53*, 7107.

(75) Lindsley, C.W.; Bates, B.S.; Menon, U.N.; Jadhav, S.B.; Kane, A.S.; Jones, C.K.; Rodriguez, A.L.; Conn, P.J.; Olsen, C.M.; Winder, D.G.; Emmitte, K.A. *ACS Chem. Neurosci.* **2011**, *2*, 471.
(76) Rodriguez, A.L.; Grier, M.D.; Jones, C.K.; Herman, E.J.; Kane, A.S.; Smith, R.L.; Williams, R.; Zhou, Y.; Marlo, J.E.; Days, E.L.; Blatt, T.N.; Jadhav, S.; Menon, U.N.; Vinson, P.N.; Rook, J.M.; Stauffer, S.R.; Niswender, C.M.; Lindsley, C.W.; Weaver, C.D.; Conn, P.J. *Mol. Pharm.* **2010**, *78*, 1105.
(77) Conn, P.J.; Lindsley, C.W.; Emmitte, K.A.; Weaver, C.D.; Rodriguez, A.L.; Felts, A.; Jones, C.K.; Bates, B.S. *Patent Application WO 2011035209.* **2011.**
(78) Kanuma, K.; Tamita, T.; Imura, K. *Patent Application WO 2009078432.* 2009.
(79) Bertani, B.; Cremonesi, S.; Garzya, V.; Micheli, F.; Rupcic, R.; Sabbatini, F.M. *Patent Application WO 2011151361.* **2011.**
(80) Carcache, D.; Vranesic, I.; Blanz, J.; Desrayaud, S.; Fendt, M.; Glatthar, R. *ACS Med. Chem. Lett.* **2011**, *2*, 58.
(81) Weiss, J.M.; Jimenez, H.N.; Li, G.; April, M.; Uberti, M.A.; Bacolod, M.D.; Brodbeck, R.M.; Doller, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4891.
(82) Wágner, G.; Wéber, C.; Nyéki, O.; Nógrádi, K.; Bielik, A.; Molnár, L.; Bobok, A.; Horváth, A.; Kiss, B.; Kolok, S.; Nagy, J.; Kurkó, D.; Gál, K.; Greiner, I.; Szombathelyi, Z.; Keseru, G.M.; Domány, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3737.
(83) Stauffer, S.R. *ACS Chem. Neurosci.* **2011**, *2*, 450.
(84) Isaac, M.; Slassi, A.; Edwards, L.; Dove, P.; Xin, T.; Stefanac, T. *Patent Application WO 2008/041075.* **2008.**
(85) Pilla, M.; Andreoli, M.; Tessari, M.; Delle-Fratte, S.; Roth, A.; Butler, S.; Brown, F.; Shah, P.; Betini, E.; Cavallini, P.; Benedetti, R.; Minick, D.; Smith, P.; Tehan, B.; D'Alessandro, P.; Lorthioir, O.; Ball, C.; Garzya, V.; Goodacre, C.; Watson, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7521.
(86) Li, G.; April, M.; Austin, J.; Zhou, H.; Pu, X.; Boyle, N.J.; Uberti, M.A.; Brodbeck, R.M.; Bacolod, M.D.; Smith, D.G.; Doller, D. *Curr. Neuropharmacol.* **2011**, *9*, 1.
(87) Berg, D.; Godau, J.; Trenkwalder, C.; Eggert, K.; Csoti, I.; Storch, A.; Huber, H.; Morelli-Canelo, M.; Stamelou, M.; Ries, V.; Wolz, M.; Schneider, C.; Di, P.T.; Gasparini, F.; Hariry, S.; Vandemeulebroecke, M.; Abi-Saab, W.; Cooke, K.; Johns, D.; Gomez-Mancilla, B. *Mov. Disord.* **2011**, *26*, 1243.
(88) http://www.addextherapeutics.com/rd/pipeline/dipra-ir/, Mar 21, **2012**.
(89) Jacquemont, S.; Curie, A.; des Portes, V.; Torrioli, M.G.; Berry-Kravis, E.; Hagerman, R.J.; Ramos, F.J.; Cornish, K.; He, Y.; Paulding, C.; Neri, G.; Chen, F.; Hadjikhani, N.; Martinet, D.; Meyer, J.; Beckmann, J.S.; Delange, K.; Brun, A.; Bussy, G.; Gasparini, F.; Hilse, T.; Floesser, A.; Branson, J.; Bilbe, G.; Johns, D.; Gomez-Mancilla, B. *Sci. Transl. Med.* **2011**, *3 64ra1.*
(90) http://www.roche-trials.com/trialDetailsGet.action?studyNumber=NP27936.
(91) http://clinicaltrials.gov/ct2/show/NCT01325740.
(92) http://clinicaltrials.gov/ct2/show/NCT01437657.
(93) Marin, J.C.; Goadsby, P.J. *Expert Opin. Investig. Drugs* **2010**, *19*, 555.
(94) Duncan, J.R.; Lawrence, A.J. *Pharmacol. Biochem. Behav.* **2012**, *100*, 811.