Journal of Medicinal Chemistry

Article

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Imidazo[1,2-*a*]pyridines: Orally Active Positive Allosteric Modulators of the Metabotropic Glutamate 2 Receptor

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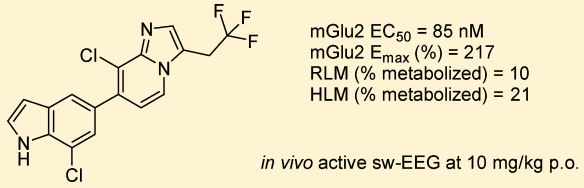
Supporting Information

ABSTRACT: Advanced leads of an imidazopyridine series of positive allosteric modulators of the metabotropic glutamate 2 (mGlu2) receptor are reported. The optimization of in vitro ADMET and in vivo pharmacokinetic properties led to the identification of **27o**. With good potency and selectivity for the mGlu2 receptor, **27o** affected sleep−wake architecture in rats after oral treatment, which we have previously shown to be indicative of mGlu2 receptor-mediated central activity.



INTRODUCTION

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and modulates a range of physiological and behavioral processes via ionotropic or metabotropic glutamate (mGlu) receptors.[1] There are eight known mGlu receptor subtypes, part of the class C family of G-protein-coupled receptors (GPCRs), of which the mGlu2 receptor received particular interest because of a strong belief in the potential of this receptor as a drug target. Expressed on presynaptic nerve terminals, the mGlu2 receptor negatively modulates glutamate and GABA release.[2] The expression pattern of the mGlu2 receptor in the prefrontal cortex, hippocampus, and amygdala supports a role for mGlu2 in psychiatric disorders.[3−5] Therefore, it is expected that schizophrenia-like symptoms arising from increased glutamate transmission in the forebrain could be treated by stimulating mGlu2 receptors and thereby reducing glutamate levels.[6] Indeed, treatment with LY2140023 {(1*R*,4*S*,5*S*,6*S*)-2-thiabicylo[3.1.0]-hexane-4,6-dicarboxylic acid,4-[(2*S*)-2-amino-4-(methylthio)-1-oxobutyl]amino-,2,2-dioxide monohydrate} (Figure 1), the prodrug of the mixed mGlu2/3 receptor agonist LY404039 [(−)-(1*R*,4*S*,5*S*,6*S*)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid], demonstrated improvements in positive and negative symptoms in a phase IIb trial in schizophrenic patients.[7] Furthermore, anxiolytic efficacy of LY354740 [(1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate] was confirmed in a CO_2 inhalation study by reduction in number and severity of panic symptoms in patients with DSM-IV panic disorder.[8] Multiple preclinical studies have reported efficacy of mGlu2 receptor activation in animal models of disorders such as anxiety/stress and depression.[9,10]

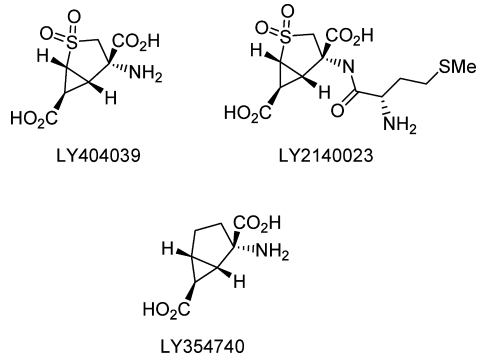


Figure 1. Selected mixed mGlu2/3 orthosteric agonists.

The constrained glutamate agonists LY2140023 and LY354740 bind at the orthosteric site, and their activity in reducing REM sleep is believed to be mGlu2 receptor mediated.[11,12] Allosteric activation of mGlu2 receptor with positive allosteric modulators (PAMs) may offer several advantages to the constrained glutamate analogues LY404039 and LY354740 that bind at the orthosteric site: these ligands are not based on an amino acid structure that is generally detrimental for CNS penetration; they avoid the conserved mGlu receptor orthosteric binding site and offer improved selectivity; they may be less liable to cause receptor desensitization;[13,14] they only act in the presence of endogenous glutamate, thereby responding to physiological fluctuations in activity.

Received: November 21, 2011
Published: February 21, 2012

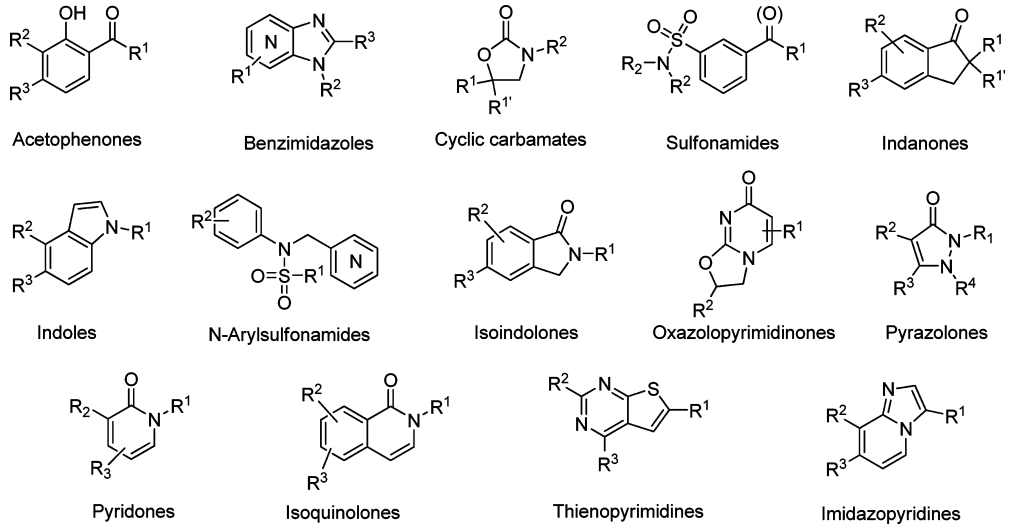


Figure 2. Known mGlu2 potentiator chemotypes.

Over recent years, the number of reported mGlu2 receptor PAM chemical series has increased significantly (Figure 2).[15]

Here we report the identification and subsequent optimization of advanced leads within an imidazopyridine series of mGlu2 receptor PAMs. This series was identified via its shape and electrostatic similarity to a pyridone scaffold that was also pursued within the program.[16−19] Compound **1** was among the best leads that were identified from our previous exploration (Figure 3). The trifluoroethyl group was proven to be crucial to

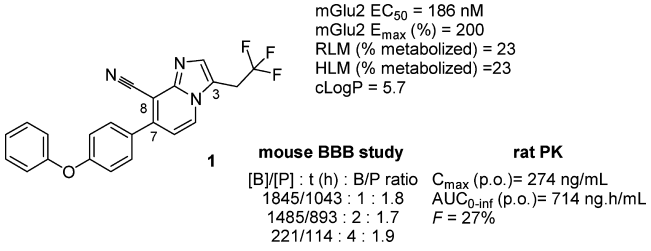


Figure 3. Lead compound **1** resulting from previous hit exploration studies. RLM and HLM refer to percent of compound metabolized after 15 min of incubation of a 5 μM concentration in rat and human liver microsomes, respectively. For the mouse BBB study, male Swiss SPF mice were dosed subcutaneously at 10 mg/kg. Compound was formulated in 20% CD: [B], brain levels in ng/g; [P] plasma levels in ng/mL; *B*/*P*, brain to plasma ratio. For the rat PK study Sprague−Dawley rats were dosed orally (po) at 10 mg/kg and intravenously (iv) at 1.25 mg/kg. Compound was formulated in 20% CD: AUC, area under curve; *F*, oral bioavailability.

combine both good activity and metabolic stability in a region of the molecule where lipophilic aliphatic groups were preferred for activity. Besides good primary activity and microsomal stability, the molecule did not exhibit significant interaction with cytochrome P450 enzymes (3A4, 2C9, 2D6, 1A2, 2C19 inhibition less than 19% at 10 μM) or binding inhibition of ion channels (hERG, Ca^{2+}, and Na^{+}, all with IC_{50} > 10 μM). At 3 μM, it did result in 46% inhibition of hERG channel activity in our patch clamp electrophysiology assay. While brain penetration was good, with a 10 mg/kg subcutaneous (sc) dose in mice resulting in relatively high absolute levels of 1845 ng/g in the brain at 1 h, **1** displayed poor oral pharmacokinetics (PK) following a 10 mg/kg dose in rat. The C_{max} and AUC_{0-inf} were low, 274 ng/mL and 714 ng·h/mL, respectively, as was the corresponding oral bioavailability (27%). Since the high lipophilicity of **1** (calculated log *P* of 5.7) was likely detrimental for the oral PK, the exploration of **1** described herein focused on small modifications at the 7 and 8 positions with the aim of reducing lipophilicity and overall aromaticity.

CHEMISTRY

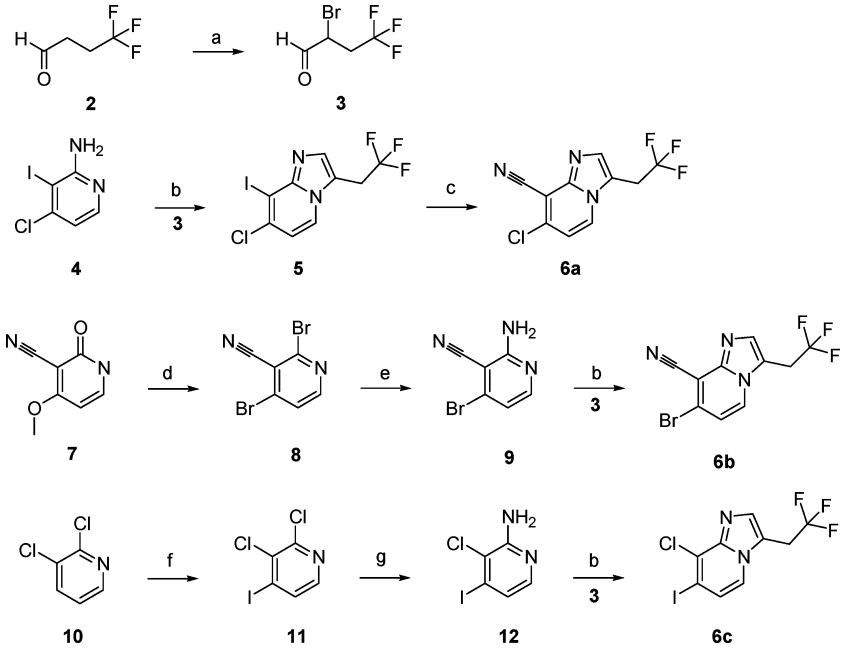
The synthesis of the imidazo[1,2-*a*]pyridine derivatives is outlined in Schemes 1−4. The key intermediates **6a−c** were prepared as shown in Scheme 1. Treatment of aldehyde **2** with bromine in 1,4-dioxane provided the α-bromoaldehyde derivative **3**. Subsequent cyclization of **3** with 2-amino-4-chloro-3-iodopyridine **4**[20] under microwave heating conditions afforded the 7-chloro-8-iodoimidazo[1,2-*a*]pyridine **5** in good yield. Compound **5** was then transformed into the 7-chloro-8-cyanoimidazo[1,2-*a*]pyridine **6a** by treatment with CuCN in acetonitrile under microwave irradiation.

A different reaction pathway was followed for the synthesis of the analogous intermediate **6b**. In this case, the reaction of commercially available 3-cyano-5-methoxy-2-pyridone **7** with $POBr_3$ under thermal conditions led to the corresponding dibromopyridine **8** which was further reacted with ammonia to give a 1:2 mixture of the desired 2-aminopyridine **9** and the corresponding 4-aminopyridine regioisomer. Both regioisomers were separated by their different solubility in CH_2Cl_2.[21] The final cyclization of intermediate **9** with α-bromoaldehyde **3** used the same conditions described for the preparation of **5** and afforded the 7-bromo-8-cyanoimidazo[1,2-*a*]pyridine **6b**. The synthesis of the scaffold **6c** started with treatment of the commercially available 2,3-dichloropyridine **10** with BuLi in the presence of 2,2,6,6-tetramethylpiperidine in Et_2O and used iodine as the electrophile to afford **11** in good yield. Similar to the intermediate **8** previously described, compound **11** underwent nucleophilic substitution with ammonia to yield a 1:1 mixture of the desired 2-amino-3-chloro-4-iodopyridine **12** and the corresponding 4-amino-2,3-dichloropyridine; both were separated by reverse phase HPLC. Finally, the microwave promoted thermal condensation of derivative **12** with the aldehyde **3** led to the 7-iodo-8-chloroimidazo[1,2-*a*]pyridine **6c**.

The synthesis of the arylboronic esters **13a−f** is depicted in Scheme 2. Mitsunobu reaction of the commercially available

dx.doi.org/10.1021/jm201561r | J. Med. Chem. 2012, 55, 2688−2701

Scheme 1. Synthesis of the 7-Haloimidazo[1,2-*a*]pyridines 6a−c[a]



[a]Reagents and conditions: (a) Br_2, 1,4-dioxane, 0 °C; (b) EtOH, 150 °C, 50 min, microwave; (c) CuCN, CH_3CN, 160 °C, 30 min, microwave; (d) $POBr_3$, CH_3CN, 60 °C, 16 h; (e) NH_4OH, THF, 100 °C, 1 h; (f) *n*-BuLi, 2,2,6,6-tetramethylpiperidine, Et_2O, −78 °C, 45 min; then I_2, THF, −78 °C to rt; (g) NH_4OH, THF, 150 °C, 24 h.

4-bromo-2-chlorophenol **14** with 4-hydroxytetrahydropyrane in the presence of polymer supported triphenylphosphine afforded the ether **15**. Reductive amination of the aniline **16** with 4-tetrahydropyranone or cyclohexanedione monoethylene acetal gave the corresponding intermediates **17** and **18** in moderate to good yields. Treatment of compound **18** with *p*-toluensulfonic acid (PTSA) in a mixture of acetone and water under microwave irradiation followed by reduction with $NaBH_4$ in MeOH afforded a mixture of the trans amino alcohol **19** and the corresponding cis isomer, both separated by flash column chromatography. The palladium-catalyzed coupling reaction of the aryl bromides **15**, **17**, and **19**−**22** with bis(pinacolato)-diboron afforded the arylboronic esters **13a**−**f**.[22]

The synthesis of indolylpinacolboronates **13g**−**l** is illustrated in Scheme 3. The N-substituted indole bromides **24a**−**c** were obtained by alkylation of commercially available 5-bromoindole **23a** or 7-chloro-5-bromoindole[23] **23b** with the corresponding alkyl halides in DMF in the presence of NaH. **24d** was commercially available. Additionally, treatment of **23a** with toluene-4-sulfonic acid 1,4-dioxaspiro[4.5]dec-8-yl ester[24] in DMSO under basic conditions followed by deprotection of the ketone with PTSA under microwave irradiation afforded **25**. Reduction of the latter compound with $NaBH_4$ in MeOH gave mainly the *trans*-cyclohexanol isomer **26**. The final palladium-catalyzed coupling reaction of the indole bromides **23b**, **24a**−**d**, and **26** with bis(pinacolate)diboron gave the targeted boronate derivatives **13g**−**l**.

The target compounds **27a**−**p**[25] were obtained by microwave assisted Suzuki coupling of the 7-haloimidazo[1,2-*a*]pyridines **6a**−**c** with the corresponding boronic esters **13a**−**l**.

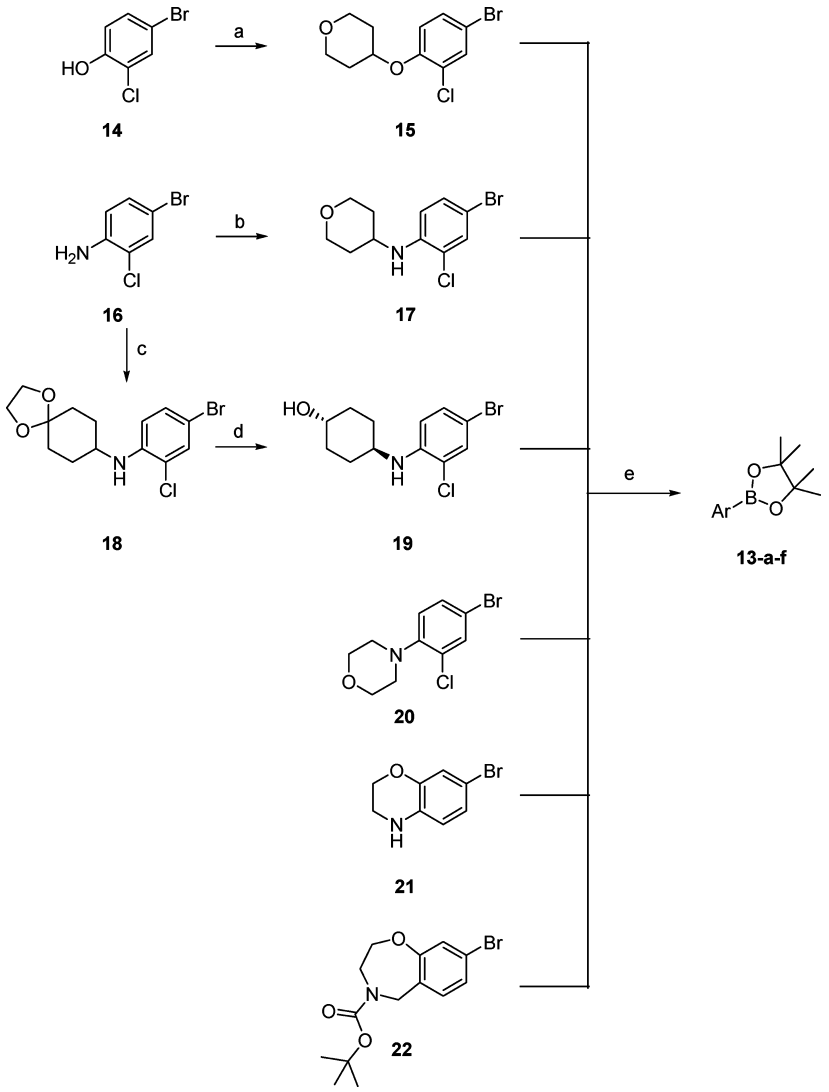
RESULTS AND DISCUSSION

The functional activity[26] of the imidazo[1,2-*a*]pyridines **1** and **27a**−**p** was measured on the human mGlu2 receptor. The human receptor has 97% sequence identity with the rat mGlu2 receptor.[27] Repeated GTPγS screens performed in our group with both human and rat mGlu2 receptor have shown excellent correlation for activity data between the two species.[28] Functional activity and microsomal stability data for imidazo-[1,2-*a*]pyridines **1** and **27a**−**p** are listed in Table 1. Aromaticity and lipophilicity were reduced by replacing the distal phenyl in **1** with tetrahydropyranyl in **27a**. The 2 log unit reduction in clogP was accompanied by a 3-fold drop in EC_{50}. Replacement of the ether linker in **27a** with secondary aniline in **27b** maintained the lower log *P* and resulted in a comparable EC_{50} but an increased maximal glutamate effect (E_{max} = 173% for **27a** compared to E_{max} = 307% for **27b**). The morpholine derivative **27c** replaced the secondary aniline, resulting in decreased activity (EC_{50} = 2140 compared to EC_{50} = 710 nM). The same decreasing trend in activity was observed with the phenoxazine analogue **27d**. The corresponding ring-expanded version, benzoxazepine derivative **27e**, was weakly active (E_{max} = 105%), suggesting that this structural modification or the inclusion of a basic center[29] was not well tolerated for potency.

Conformational restriction of the anilinic nitrogen in molecules **27b**−**d** via the introduction of an indole proved to be an excellent modification for obtaining compounds with both good mGlu2 PAM receptor potentiating activity and moderate to good microsomal stability (**27f**−**i**). The indole nitrogen was substituted with small aliphatic groups such as methyl (**27f**) and cyclopropylmethyl (**27g**) which resulted in an increased activity of 230 and 190 nM, respectively. Reducing log *P* via the use of the tetrahydropyran in **27h** and 4-hydroxycyclohexyl in **27i** resulted in a drop in EC_{50} (501 and 330 nM) but good potentiation of the maximal glutamate effect (442% and 237%, respectively) and excellent metabolic stability, particularly for **27i**, 4% and 15% metabolized in human and rat liver microsomes. Chlorine decoration at the 7 position on the indole was well tolerated and led to increased activity compared to the unsubstituted indoles, as exemplified

dx.doi.org/10.1021/jm201561r | *J. Med. Chem.* 2012, 55, 2688−2701

Scheme 2. Synthesis of the Arylboronic Esters 13a–f[a]



[a]Reagents and conditions: (a) 4-hydroxytetrahydropyrane, di-*tert*-butyl azodicarboxylate, polymer-supported PPh_3, CH_2Cl_2, rt, 2 h; (b) 4-tetrahydropyranone, $NaBH(OAc)_3$, 1,2-dichloroethane, molecular sieves, rt, 72 h; (c) cyclohexanedione monoethylene acetal, $NaBH(OAc)_3$, 1,2-dichloroethane, AcOH, rt, 24 h; (d) (i) PTSA, H_2O, acetone, 100 °C, 15 min, microwave; (ii) $NaBH_4$, MeOH, −78 °C to rt, 24 h; (e) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, 1,4-dioxane, 150 °C, 10–30 min, microwave, or 95 °C, 24 h.

by **27f** and **27k** (230 and 120 nM) and **27g** and **27l** (190 and 110 nM). This was, however, at the cost of increased clogP and unfavorable rat microsomal stability. For instance, **27k** and **27l** were metabolized 62% and 74%, respectively, compared to 55% and 40% for **27f** and **27g**.

Modification of cyano for chloro at the 8 position of the scaffold was also performed as part of the SAR exploration. An approximate 2-fold increase in potency was observed with the chloroimidazopyridine **27m** compared to the cyano equivalent **27i** (330 nM for **27i** vs 160 nM for **27m**). This also led to a corresponding 0.9 log unit increase in clogP (4.0 for **27i** vs 4.9 for **27m**). The unrestricted aniline **27n** contained equivalent decoration to indole **27m**. The EC_{50} and E_{max} were comparable for both molecules, and good metabolic stability was also seen in each case. The indole substituted chloroimidazopyridine **27o** was the most potent compound prepared and showed an EC_{50} of 85 nM with an E_{max} of 217%. Despite the increased clogP of 5.4, **27o** was also among the most stable representatives of this series. Comparing the replacement of the cyano group for chloro in the analogous molecules **27j** and **27o** suggests that the chlorine improved functional activity (EC_{50} of 320 and 85 nM, respectively). In addition, the indole moiety seems to be a consistently good moiety for conferring appropriate mGlu2 PAM receptor activity along with microsomal stability.

The selectivity of **27m** and **27o** versus other receptors in the mGlu receptor family was evaluated with use of Ca^{2+} assays for human mGlu1, mGlu3, mGlu5, mGlu7, and mGlu8 receptors (each expressed in HEK293 cells). Effects on the human mGlu4 and rat mGlu6 receptors, expressed in L929 or CHO cells, were assessed in [^{35}S]GTPγS functional assays. Neither **27m** nor **27o** showed significant agonist or antagonist activities at 10 μM against any of the mGlu receptors, with the exception of **27m**, which displayed weak mGlu7 receptor agonistic activity with an EC_{50} of 5.2 μM.

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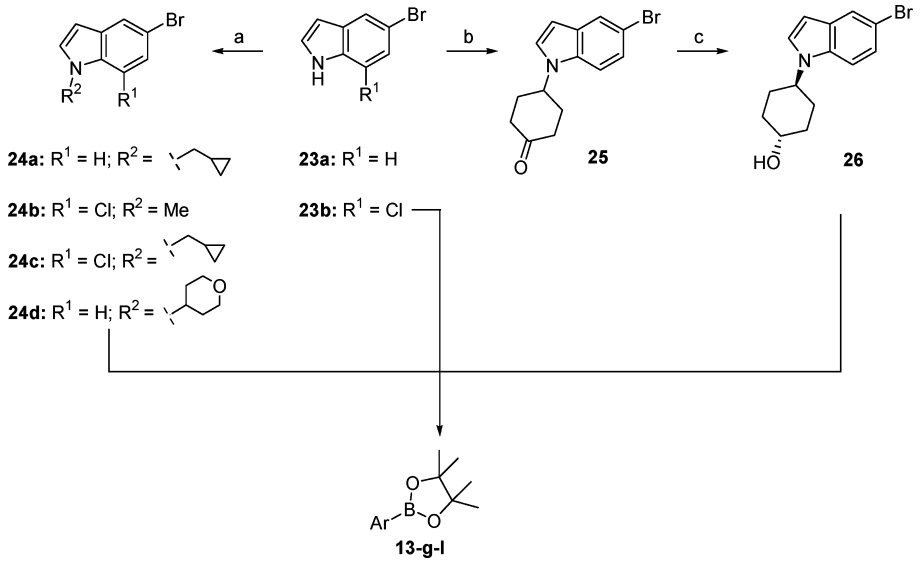
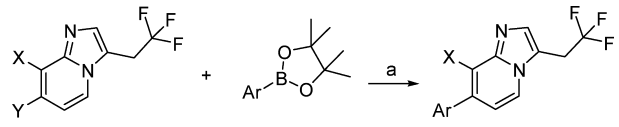
Scheme 3. Synthesis of the Indolylpinacolboronates 13g–l[a]



[a]Reagents and conditions: (a) R^2Cl or R^2Br, NaH, DMF, 0 °C to rt; (b) (i) toluene-4-sulfonic acid 1,4-dioxaspiro[4.5]dec-8-yl ester, KOH, DMSO, rt, 16 h, then 55 °C, 16 h; (ii) PTSA, water, acetone, 100 °C, 15 min, microwave; (c) $NaBH_4$, MeOH, 0 °C to rt, 1 h; (d) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, 1,4-dioxane, 150 °C, 10–30 min, microwave, or 95 °C, 24 h.

Scheme 4. Synthesis of the 7-Arylimidazo[1,2-*a*]pyridines 27a–p[a]



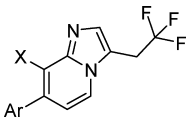
[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, 1,4-dioxane, sat. $NaHCO_3$, 150 °C, 10 min, microwave.

Given their reasonable primary activity and good metabolic stability, PK and brain penetration studies were performed on **27h** and **27i** (Tables 2 and 3). A bioavailability study with **27h**, dosed at10 mg/kg oral (po) and 2.5 mg/kg intravenous (iv), revealed a poor rodent PK profile, offering no significant improvement over **1**: C_{max} = 216 ng/mL, AUC_{0-inf} = 281 ng·h/mL, $t_{1/2}$ = 0.9 h, F = 15%, Cl = 5.0 L h^{-1} kg^{-1} (Table 2). Initial brain penetration at 1 h was reasonable, but the high clearance led to rapid decline in both plasma and brain, with a 10 mg/kg subcutaneous (sc) dose in mice resulting in 704 ng/g in brain and 932 ng/mL in plasma at 1 h (Table 3). Compound **27i** displayed better bioavailability compared to **1** and **27h** with C_{max} = 1062 ng/mL, AUC_{0-inf} = 7525 ng·h/mL, $t_{1/2}$ = 2.8 h, F = 50%, and Cl = 0.7 L h^{-1} kg^{-1}. However, brain penetration was lower, a 10 mg/kg (sc) dose in mice resulting in 322 ng/g in brain and 4174 ng/mL in plasma after 1 h (Table 3). Since compounds **27m**, **27n**, and **27o** from the 8-chloroimidazopyridines subseries also showed acceptable primary activity and metabolic stability, they were advanced further to assess their PK properties and brain penetration. Compound **27m** showed an excellent profile in the rat: C_{max} = 1142 ng/mL, AUC_{0-inf} = 10648 ng·h/mL, $t_{1/2}$ = 4.3 h, $F \approx$ 100%, and Cl = 0.9 L h^{-1} kg^{-1} (Table 2). Absolute levels in brain were reasonable (Table 3, 10 mg/kg (sc), rat), with 932 ng/g at 1 h, although the B/P ratio was low at 0.2. Comparing with the equivalent 8-cyanoimidazopyridine, **27i**, suggests that the presence of the chloro was beneficial for brain penetration without being detrimental to other PK parameters. A full bioavailability study was not performed for **27n**, but the brain and plasma levels were studied after a 10 mg/kg sc dose in rats, showing 1004 ng/g in brain and 2140 ng/mL in plasma after 1 h. Molecule **27o** was administered orally to rat and exhibited a fair oral PK profile, C_{max} = 534 ng/mL, AUC_{0-inf} = 1981 ng·h/mL, and $t_{1/2}$ = 2.0 h (Table 2). Brain penetration was also acceptable, with 538 ng/g in brain and 414 ng/mL in plasma after 1 h. Overall, the strategy to reduce log P in **27** led to better oral bioavailability than seen for **1**. However, more polar motifs introduced at position C_7 had a detrimental effect on brain penetration. Compound **27o** represented a compromise with high in vitro potency and better oral in vivo PK behavior.

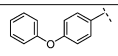
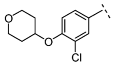
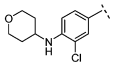
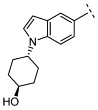
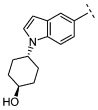
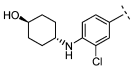
We have recently reported that mGlu2 receptor activation with agonist LY354740[30] and/or PAM BINA {[[1,1′-biphenyl]-4-carboxylic acid, 3′-[[(2-cyclopentyl-2,3-dihydro-6,7-dimethyl-1-oxo-1*H*-inden-5-yl)oxy]methyl], potassium salt}[31] showed common and synergistic changes of REM sleep variables in a rat sleep–wake electroencephalogram (sw-EEG) model.[32] Given the favorable brain exposure following oral administration, the effects of **27o** on sw-EEG architecture in rats were studied after oral treatment. Relative to control, acute oral administration of **27o** at a dose of 10 mg/kg exerted significant effect in suppressing REM sleep during the first 2 h (−57%, p < 0.05) without clear effects on the other sleep–wake stages (Figure 4). No additional effects were observed on other vigilance states. REM sleep reduction was accompanied by a slight increase of REM sleep onset latency (bottom right panel). Closer inspection of sleep–wake architecture indicated that reduction in REM sleep time was derived from a reduction in both number of periods and their mean duration. Overall, **27o** had no major effect on total time spent in different vigilance states,[33a] sleep variables,[33b] and total number of transitions from sleep states toward waking.[33c] Overall, oral

dx.doi.org/10.1021/jm201561r | J. Med. Chem. 2012, 55, 2688–2701

Table 1. Functional Activity and Metabolic Stability in Rat (RLM) and Human (HLM) Microsomes of Representative mGlu2 Receptor PAMs 1 and 27a−p



1, 27a-p

Compd	X	Ar	clogP	mGluR2 EC_{50} (nM)[a]	mGluR2 E_{max}(%)[a]	HLM[b] (%)	RLM[b] (%)
1	CN		5.7	186	200	23	23
27a	CN		3.7	617	173	29	50
27b	CN		3.7	710	307	21	36
27c	CN		3.9	2,140	167	--	--
27d	CN		3.1	1,660	232	45	100
27e	CN		2.7	ND[c]	105	--	--
27f	CN		4.0	230	154	28	55
27g	CN		5.0	190	230	24	40
27h	CN		3.7	501	442	23	28
27i	CN		4.0	330	237	4	15
27j	CN		4.4	320	277	35	49
27k	CN		4.8	120	184	51	62
27l	CN		5.7	110	200	19	74
27m	Cl		4.9	160	244	14	8
27n	Cl		5.0	150	293	16	15
27o	Cl		5.4	85	217	10	21
27p	Cl		6.7	250	193	1	70

[a]Values are the mean of three experiments. Only differences in EC_{50} up to 0.6 log units (SD < 0.5) were considered as reproducible and were maintained. [b]HLM and RLM data refer to percent of compound metabolized after 15 min of incubation in microsomes at 5 μM. [c]ND: not determined.

treatment with **27o** revealed a fingerprint consistent with changes in sleep variables known to be associated with mGlu2 receptor activation.[22]

CONCLUSION

In summary, the optimization of a series of imidazopyridines in search of mGlu2 receptor PAM compounds with a more optimal oral PK profile has been reported. Compound **27o** was identified showing good potency and selectivity for the mGlu2 receptor as well as an improved oral PK profile compared to the initial lead **1**. The mGlu2 receptor PAM **27o** modulated REM sleep variables in a rat sleep model, a mechanism of action that is consistent with mGlu2 receptor activation, in accordance with previous work from our laboratories. Further investigation of this advance lead is ongoing and will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck). Flash column chromatography was performed on silica gel, particle size 60 Å, mesh of 230−400 (Merck), under standard techniques. Microwave assisted reactions were performed in a single-mode reactor: Biotage Initiator Sixty microwave reactor (Biotage) or in a multimode reactor: MicroSYNTH Labstation (Milestone, Inc.). Nuclear magnetic resonance (NMR) spectra were recorded with either a Bruker DPX-400 or a Bruker AV-500 spectrometer (broaduker AG) with standard pulse sequences operating at 400 and 500 MHz, respectively, using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (δ = 0). Coupling constants are reported in hertz. Splitting patterns are defined by s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). Liquid chromatography combined with mass spectrometry (LC−MS) was performed on a HP 1100 HPLC system (Agilent Technologies) comprising a quaternary or binary pump with degasser, an autosampler, a column oven, a diode array detector (DAD), and a column. Flow from the column was split to a MS spectrometer. The MS detector was configured with either an electrospray ionization source or an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. Data acquisition was performed with MassLynx-Openlynx software or with Chemsation-Agilent data browser software. Gas chromatography combined with mass spectrometry (GC−MS) was performed using a 6890 series gas chromatograph (Agilent Technologies) system comprising a 7683 series injector and autosampler, a column oven, and a J&W HP-5MS coupled to a 5973N MSD mass selective detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source/chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 14.29 scans/s. The source temperature was maintained at 230 °C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software. Melting point (Mp) values are peak values and were obtained with experimental uncertainties that are commonly associated with this analytical method. Melting points were determined in open capillary tubes on a Mettler FP62 apparatus with a temperature gradient of 10 °C/min. Maximum temperature was 300 °C.

Purities of all new compounds were determined by analytical RP-HPLC using the area percentage method on the UV trace recorded at a wavelength of 254 nm and were found to have ≥95% purity unless otherwise specified.

2-Bromo-4,4,4-trifluorobutyraldehyde (3). Bromine (2.04 mL, 39.66 mmol) was added dropwise to a solution of 4,4,4-trifluorobutyraldehyde (**2**, 5g, 39.66 mmol) in 1,4-dioxane (2.2 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C, and then the mixture was allowed to warm to room temperature and stirred for a further 10 min. The mixture was cooled to 0 °C and carefully quenched with a $NaHCO_3$ saturated solution. Et_2O was added and the organic phase was separated, dried (Na_2SO_4) and the solvent

dx.doi.org/10.1021/jm201561r | J. Med. Chem. 2012, 55, 2688−2701

Table 2. In Vivo PK Data for mGlu2 Receptor PAMs in Rats after Oral and Intravenous Administration[a]

compd	po dose (mg/kg)	iv dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-inf} (ng·h/mL)	$t_{1/2}$ (h)	F (%)	Cl (L h^{-1} kg^{-1})
1	10	1.25	274 ± 191	0.5	714 ± 624	2.1 ± 0.2	27	3.4 ± 0.5
27h	10	2.5	216 ± 114	0.5	281 ± 288	0.92 ± 0.39	15	5.0 ± 0.7
27i	10	2.5	1062 ± 242	1.7	7525 ± 3561	2.8 ± 0.39	50	0.7 ± 0.2
27m	10	2.5	1142 ± 148	3.3	10648 ± 2621	4.3 ± 1.6	100	0.9 ± 0.1
27o	10		534 ± 96	0.8	1981 ± 355	2.0 ± 0.4		ND

[a]Compounds formulated in 20% HP-β-CD at pH 4. Data are expressed as the geometric mean values of at least two runs ± the standard error of the mean (SEM).

Table 3. Brain and Plasma Levels for mGlu2 Receptor PAMs[a]

		time point		
compd		1 h	2 h	4 h
1[b]	[B]	1845 ± 21	1530 ± 205	221 ± 15
	[P]	1043 ± 95	893 ± 144	114 ± 36
	B/*P*	1.8	1.7	1.9
27h[b]	[B]	704 ± 141	50 ± 8	n.m.
	[P]	932 ± 196	95 ± 32	n.m.
	B/*P*	0.8	0.5	
27i[b]	[B]	322 ± 49	469 ± 156	280 ± 35
	[P]	4174 ± 101	4495 ± 523	3861 ± 101
	B/*P*	0.1	0.1	0.1
27m[c]	[B]	932 ± 27	1042 ± 68	843 ± 85
	[P]	3806 ± 908	3728 ± 358	1949 ± 157
	B/*P*	0.2	0.3	0.4
27n[c]	[B]	1004 ± 493	1220 ± 30	485 ± 159
	[P]	2140 ± 944	1276 ± 102	708 ± 187
	B/*P*	0.5	1.0	0.7
27o[d]	[B]	538 ± 54	441 ± 133	126 ± 8
	[P]	414 ± 33	364 ± 126	168 ± 9
	B/*P*	1.3	1.2	0.8

[a][B]: brain levels in ng/g. [P]: plasma levels in ng/mL. Compounds formulated in 20% HP-β-CD at pH 4. Data are expressed as the geometric mean values of at least two runs ± the standard error of the mean (SEM). n.m.: not measurable. [b]Study in male Swiss SPF mice dosed sc at 10 mg/kg. [c]Study in male Sprague–Dawley rats dosed sc at 10 mg/kg. [d]Study in male Sprague–Dawley rats dosed po at 10 mg/kg.

evaporated in vacuo to yield compound **3** as a pale orange oil (8 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58–2.75 (m, 1H), 3.20 (s, 1H), 3.37–3.56 (m, 1H), 9.46 (s, 1H).

7-Chloro-3-(2,2,2-trifluoroethyl)-8-iodoimidazo[1,2-*a*]-pyridine (5). To a mixture of 2-amino-4-chloro-3-iodopyridine (**4**, 0.7 g, 2.71 mmol) in EtOH (5 mL) was added **3** (1.11 g, 5.42 mmol) at room temperature. The mixture was heated at 150 °C for 50 min under microwave irradiation. The mixture was cooled to room temperature, and the volatiles were evaporated in vacuo. The resulting residue was treated with Et_2O to afford **5** as a white solid (0.91 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.31 (q, J = 10.87 Hz, 2H), 7.53 (d, J = 7.40 Hz, 1H), 7.98 (s, 1H), 8.82 (d, J = 7.40 Hz, 1H). LC–MS: m/z 360.1 $[M + H]^+$.

7-Chloro-3-(2,2,2-trifluoroethyl)-8-cyanoimidazo[1,2-*a*]-pyridine (6a). To a mixture of **5** (3.65 g, 8.1 mmol) in MeCN (5 mL) was added CuCN (1.16 g, 12.96 mmol) at room temperature. The mixture was heated at 160 °C for 30 min under microwave irradiation. The mixture was cooled to room temperature, and the solvents were evapotated in vacuo. The residue thus obtained was treated with a mixture of EtOAc/THF and washed first with an aqueous solution of NH_4OH and then with an aqueous saturated solution of NH_4Cl and brine. The organic layer was then dried over Na_2SO_4, and the solvents were evaporated in vacuo. The resulting residue was triturated with diisopropyl ether to give **6a** as a pale brown solid (2.1 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.30 (q, J = 10.87 Hz, 2H), 7.43 (d, J = 7.40 Hz, 1H), 7.79 (s, 1H), 8.95 (d, J = 7.40 Hz, 1H). LC–MS: m/z 260 $[M + H]^+$.

2,4-Dibromonicotinonitrile (8). To a solution of 3-cyano-4-methoxy-2-pyridone (**7**, 25 g, 166.5 mmol) in MeCN (670 mL) was added $POBr_3$ (95.5 g, 333 mmol), and the reaction mixture was stirred at 80 °C for 16 h. Then water (500 mL) and brine (500 mL) were carefully added to the reaction mixture. The resulting solution was extracted with EtOAc (3 × 500 mL). The combined organic extracts were then washed with an aqueous $NaHCO_3$ saturated solution. The organic layer was separated, and the aqueous one was then extracted with EtOAc (2 × 500 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated until dryness. The solid residue was treated with diisopropyl ether, and the resulting solid was filtered off and dried in a vacuum oven to yield **8** as a white solid (33.8 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 5.5 Hz, 1H), 8.42 (d, J = 5.3 Hz, 1H). GC–MS (EI/CI): m/z 262 $[M]^+$.

2-Amino-4-bromonicotinonitrile (9). To a solution of **8** (32 g, 122.2 mmol) in THF (200 mL) was added aqueous ammonia (200 mL), and the reaction mixture was heated at 100 °C for 1 h in a sealed tube. Then the mixture was cooled, washed with water (500 mL), and extracted with EtOAc (3 × 500 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated until dryness. The crude product was dissolved with CH_2Cl_2 and the resulting solid (4-amino-2-bromonicotinonitrile, undesired regioisomer) filtered off. The filtrate was collected and evaporated until dryness, affording **9** as a pale yellow solid (6.7 g, 27%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.97 (d, J = 5.2 Hz, 1H), 7.25 (broad s, 2H), 8.06 (d, J = 5.2 Hz, 1H). LC–MS: m/z 198 $[M + H]^+$.

7-Bromo-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (6b). To a solution of **9** (2 g, 10.1 mmol) in EtOH (10 mL) was added **3** (2.9 g, 14.1 mmol), and the reaction mixture was stirred at 150 °C for 50 min under microwave irradiation. The volatiles were evaporated in vacuo, and the residue thus obtained was diluted with EtOAc (100 mL) and washed consecutively with water (100 mL) and HCl, 1 M (100 mL). The aqueous layers were extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated until dryness. The resulting residue was triturated with Et_2O and the solid filtered off and dried in a vacuum oven to give **6b** as a pale yellow solid (1.5 g, 49%). Mp 207.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.29 (q, J = 10.9 Hz, 2 H), 7.51 (d, J = 7.4 Hz, 1 H), 7.76 (s, 1 H), 8.86 (d, J = 7.2 Hz, 1 H). LC–MS: m/z 306 $[M + H]^+$.

2,3-Dichloro-4-iodopyridine (11). To a solution of *n*-BuLi (111.4 mL, 278.4 mmol, 2.5 M in hexanes) in dry Et_2O (600 mL), 2,2,6,6-tetramethylpiperidine (47.4 mL, 278.4 mmol) was added dropwise at −78 °C under N_2 atmosphere. The resulting reaction mixture was stirred at −78 °C for 10 min, and then a solution of **11** (40 g, 270.3 mmol) in dry THF (280 mL) was added dropwise. The mixture was stirred at −78 °C for 45 min, and then a solution of I_2 (100.8 g, 397.3 mmol) in dry THF (240 mL) was added. The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was quenched with an aqueous $Na_2S_2O_3$ saturated solution and extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with an aqueous $NaHCO_3$ saturated solution. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue thus obtained was triturated with Et_2O to yield compound **11** as a white solid (59.1 g, 80%). Mp 113.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 5.09 Hz, 1H), 7.90 (d, J = 4.86 Hz, 1H). GC–MS (EI/CI): m/z 273 $[M]^+$.

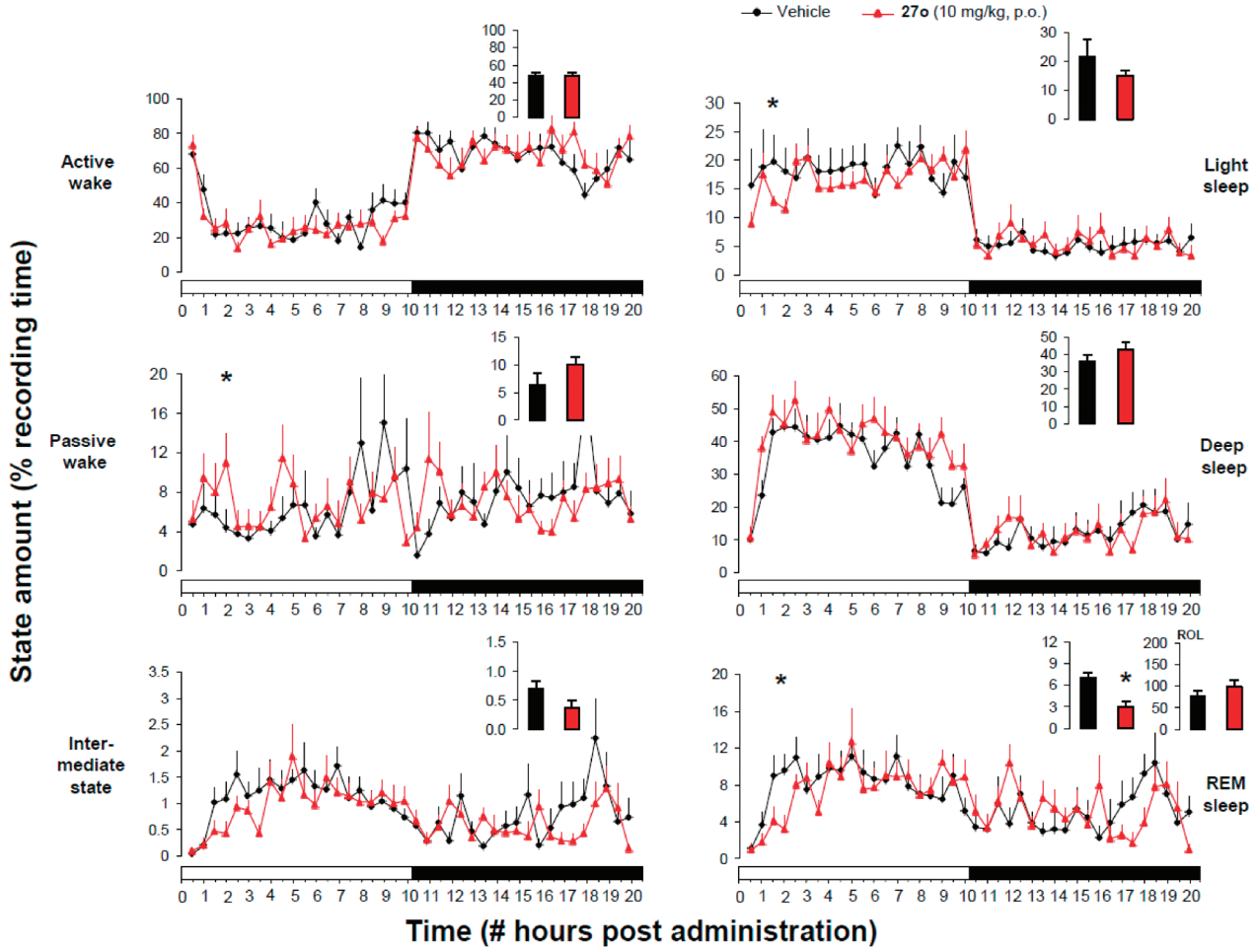


Figure 4. Effects of oral administration of mGlu2 receptor PAM **27o** (10 mg/kg) or vehicle (20% CD + 2H2T) on sleep−wake organization in rats during 20 consecutive hours. Mean percentage of occurrence per 30 min period is indicated for each sleep−wake state. Dark area indicates dark period. Small bar charts indicate amounts of vigilance states in minutes (plus SEM) during the first 2 h postadministration. For REM sleep, the REM sleep onset latency (ROL) is indicated additionally in the small bottom right panel. $n = 8$ for each group. ∗ indicates $p < 0.05$, Wilcoxon−Mann−Whitney rank sum tests compared to vehicle values.

2-Amino-3-chloro-4-iodopyridine (12). A mixture of **11** (6 g, 21.9 mmol) and NH_4OH (80 mL) in THF (40 mL) was stirred at 130 °C (oil bath temperature) for 12 h in a Parr reactor. The mixture was cooled to room temperature, and CH_2Cl_2 was added. The organic layer was separated, washed with brine, dried (Na_2SO_4), and filtered. Then the solvent was evaporated in vacuo and the residue thus obtained was purified by flash chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 2/98) to yield compound **12** as a pale yellow solid (1.48 g, 26%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 4.91 Hz, 1H), 7.80 (broad s, 2H), 7.90 (d, J = 4.91 Hz, 1H). LC−MS: m/z 255 $[M + H]^+$.

8-Chloro-7-iodo-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]-pyridine (6c). A suspension of **12** (0.51 g, 1.99 mmol) and **3** (0.82 g, 3.99 mmol) in EtOH (7 mL) was stirred at 150 °C for 30 min under microwave irradiation. The reaction mixture was cooled to room temperature, and the solvent was evaporated in vacuo. Then an aqueous $NaHCO_3$ saturated solution was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 6/94) to give **6c** as a yellow solid (0.5 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (q, J = 9.83 Hz, 2H), 7.26 (d, J = 7.20 Hz, 1H), 7.63 (s, 1H), 7.72 (d, J = 7.23 Hz, 1H). LC−MS: m/z 361 $[M + H]^+$.

4-(4-Bromo-2-chlorophenoxy)tetrahydropyrane (15). To a cooled suspension (0 °C) of 4-hydroxytetrahydropyrane (2.2 mL, 23.1 mmol), 4-bromo-2-chlorophenol (**14**, 4 g, 19.3 mmol), and polymer-supported PPh_3 (17.29 g, 39.6 mmol) in dry CH_2Cl_2 (250 mL) was added di-*tert*-butyl azodicarboxylate (6.65 g, 28.9 mmol) portionwise. The mixture was stirred at 0 °C for 5 min and at room temperature for 2 h. The resin was filtered off and washed with CH_2Cl_2 (2 × 100 mL). The combined filtrates were concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 2/98) to give **15** as a colorless oil (5.38 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79−1.89 (m, 2H), 1.96−2.05 (m, 2H), 3.59 (ddd, J = 11.4, 7.5, 3.7 Hz, 2H), 4.00 (ddd, J = 11.4, 7.2, 3.6 Hz, 2H), 4.51 (tt, J = 7.3, 3.7 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 7.30 (dd, J = 8.8, 2.3 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1 H). GC−MS (EI/CI): m/z 290 $[M]^+$.

(4-Bromo-2-chorophenyl)tetrahydropyranylamine (17). 4-Bromo-2-choroaniline **16** (4 g, 19.37 mmol) was added to a stirred solution of tetrahydropyranone (2.69 mL, 29.05 mmol), $NaBH(OAc)_3$ (6.12 g, 29.05 mmol), and 4 Å molecular sieves in dry CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 72 h and then filtered over a Celite pad. The filtrate was diluted with CH_2Cl_2 and washed with an aqueous $NaHCO_3$ saturated solution. The organic phase was dried (Na_2SO_4), filtered, and the volatiles were evaporated in vacuum. The resulting crude product was purified by column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 5/95) to yield **17** as a white solid (4.83 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49−1.60 (m, 2H), 1.98−2.07 (m, 2H), 3.45−3.56 (m, 3H), 4.01 (dt, J = 11.9, 3.9 Hz, 2H), 4.21 (broad d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.7 Hz, 1H), 7.21 (dd, J = 8.7, 2.3 Hz, 1H), 7.39 (d, J = 2.3 Hz, 1H). LC−MS: m/z 291 $[M + H]^+$.

dx.doi.org/10.1021/jm201561r | *J. Med. Chem.* 2012, 55, 2688−2701

4-Bromo-2-chlorophenyl-1,4-dioxaspiro[4.5]dec-8-ylamine (18). To a solution of **16** (12 g, 58.1 mmol) and cyclohexanedione monoethylene acetal (11.8 g, 75.6 mmol) in 1,2-dichloroethane (250 mL) and AcOH (5 mL) at room temperature was added $NaBH(OAc)_3$ (18.5 g, 87.2 mmol), and the mixture was stirred for 16 h. The mixture was then diluted with an aqueous saturated solution of $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, CH_2Cl_2 in heptane, 50/50 to 30/70) to yield **18** as a colorless oil (14.8 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53−1.72 (m, 4H), 1.76−1.85 (m, 2H), 1.97−2.09 (m, 2H), 3.31−3.43 (m, 1H), 3.96 (s, 4H), 4.22 (broad d, J = 7.2 Hz, 1H), 6.54 (d, J = 8.7 Hz, 1H), 7.20 (dd, J = 8.7, 2.3 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H). LC−MS: m/z 346 $[M + H]^+$.

4-(4-Bromo-2-chlorophenylamino)cyclohexanol (19). Compound **18** (14.8 g, 42.7 mmol) was suspended in water (15 mL) and acetone (30 mL), and then then *p*-toluensulfonic acid (0.41 g, 2.14 mmol) was added. The mixture was stirred at 100 °C for 15 min under microwave irradiation. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (60 mL) and washed with an aqueous saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 03/97), affording 10.5 g (80%) of the corresponding cyclohexanone derivative. The resulting product was dissolved in MeOH (40 mL) and cooled to −78 °C. Then $NaBH_4$ (1.16 g, 30.5 mmol) was added portionwise. The mixture was stirred at the same temperature for 10 min and then warmed to room temperature and stirred for 16 h. The solvent was concentrated in vacuo. The residue thus obtained was dissolved in CH_2Cl_2 (100 mL), diluted with an aqueous saturated solution of NH_4Cl (100 mL), and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and the volatiles were evaporated in vacuo. The crude product was purified by flash column chromatography (silica gel, 7 M MeOH−NH_3 in CH_2Cl_2, 0/100 to 05/95) to yield **19** as a colorless oil (3.7 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.35 (m, 2H), 1.36−1.51 (m, 3H), 1.97−2.20 (m, 4H), 3.19−3.33 (m, 1H), 3.65−3.77 (m, 1H), 4.12 (d, J = 7.6 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 7.20 (dd, J = 8.8, 2.3 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H). LC−MS: m/z 304 $[M + H]^+$.

5-Bromo-1-cyclopropylmethyl-1*H*-indole (24a). To a stirred solution of **23a** (1 g, 5.1 mmol) in DMF (10 mL) at 0 °C, NaH (0.3 g, 7.65 mmol, 60% in mineral oil) was added portionwise. The mixture was stirred at 0 °C for 20 min. Then 1-(bromomethyl)cyclopropane (0.083 g, 6.12 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and then stirred for 4 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in heptane, 0/100 to 06/94) to yield **24a** as a colorless oil (1.2 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.27−0.39 (m, 2H), 0.54−0.68 (m, 2H), 1.16−1.35 (m, 1H), 3.92 (d, J = 6.6 Hz, 2H), 6.42 (d, J = 3.2 Hz, 1H), 7.19 (d, J = 2.9 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.26 (dd, J = 8.7, 1.7 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H). LC−MS: m/z 250 $[M + H]^+$.

5-Bromo-7-chloro-1-methyl-1*H*-indole (24b). NaH (0.075 g, 1.95 mmol, 60% in mineral oil) was slowly added to a mixture of **23b** (0.3 g, 1.3 mmol) in DMF (4 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min, and then MeI (0.1 mL, 1.56 mmol) was added. The mixture was stirred at room temperature for 4 h. Then water and CH_2Cl_2 were added. The organic layer was separated, dried (Na_2SO_4), and the solvents were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in heptane, 1/4) to give **24b** as a colorless oil (0.345 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 3H), 6.39 (d, J = 3.2 Hz, 1H), 6.97 (d, J = 3.2 Hz, 1H), 7.23−7.26 (m, 1H), 7.60 (d, J = 1.8 Hz, 1H). GC−MS (EI/CI): m/z 244 $[M]^+$.

5-Bromo-7-chloro-1-cyclopropylmethyl-1*H*-indole (24c). Compound **24c** was prepared following the same reaction procedure as compound **24a**. Thus, starting from **23b** (0.7 g, 3.04 mmol) and bromomethylcyclopropane (0.49 g, 3.64 mmol), compound **24c** was obtained as a colorless oil (0.8 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29−0.42 (m, 2H), 0.52−0.65 (m, 2H), 1.28−1.38 (m, 1H), 4.36 (d, J = 6.9 Hz, 2H), 6.44 (d, J = 3.2 Hz, 1H), 7.15 (d, J = 3.2 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.63 (d, J = 1.8 Hz, 1H). GC−MS (EI/CI): m/z 283 $[M]^+$.

4-(5-Bromo-indol-1-yl)cyclohexanone (25). To a stirred suspension of **23a** (10.58 g, 54 mmol) and powdered KOH (16.54 g, 394.9 mmol) in DMSO (60 mL) was added a solution of toluene-4-sulfonic acid 1,4-dioxaspiro[4.5]dec-8-yl ester (25.31 g, 81 mmol) in DMSO (60 mL) dropwise over 2 h. The mixture was stirred at room temperature for 16 h and then at 55 °C for additional 16 h. The hot reaction mixture was poured into ice−water, and it was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the volatiles were evaporated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, CH_2Cl_2 in heptane, 0/100 to 50/50) to give 5-bromo-1-(1,4-dioxa-spiro[4.5]dec-8-yl]-1*H*-indole (8.27 g, 11.9 mmol) as a white solid. This compound was suspended in water (18 mL) and acetone (36 mL), and then *p*-toluensulfonic acid (22.61 mg, 0.11 mmol) was added at room temperature. The mixture was heated at 100 °C for 20 min under microwave irradiation. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (75 mL), and washed with an aqueous saturated solution of $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in heptane, 0/100 to 40/60) to yield **25** as a colorless oil (2.64 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (qd, J = 12.62, 5.20 Hz, 2H), 2.36−2.47 (m, 2H), 2.53−2.68 (m, 4H), 4.69 (tt, J = 11.81, 3.65 Hz, 1H), 6.48 (d, J = 3.18 Hz, 1H), 7.17 (d, J = 3.47 Hz, 1H), 7.24−7.34 (m, 2H) 7.76 (d, J = 1.44 Hz, 1H). GC−MS (EI/CI): m/z 291 $[M]^+$.

4-(5-Bromoindol-1-yl)cyclohexanol (26). NaH (0.54 g, 14.19 mmol, 60% in mineral oil) was added portionwise to a stirred solution of **25** (2.07 g, 7.09 mmol) in MeOH (50 mL) at 0 °C. The mixture was warmed to room temperature, and then it was stirred for 1 h. The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with an aqueous saturated solution of NH_4Cl (2 × 25 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and the solvents were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in heptane, 0/100 to 30/70) to yield **26** as a colorless oil (1.80 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43−2.30 (m, 9H), 3.72 (tt, J = 10.89, 4.02 Hz, 1H), 4.11−4.21 (m, 1H), 6.40−6.45 (m, 1H), 7.14 (d, J = 3.24 Hz, 1H), 7.18−7.28 (m, 2H), 7.71−7.75 (m, 1H). MS: m/z 293 $[M + H]^+$.

Synthesis of Pinacol Esters 13a−l. General Procedure A. 2-(3-Chloro-4-tetrahydropyran-4-yloxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13a). To a suspension of **15** (1.8 g, 6.17 mmol), bis(pinacolato)diborane (1.88 g, 7.4 mmol), and AcOK (1.81 g, 18.5 mmol) in a mixture of previously degassed 1,4-dioxane (8 mL) and DMF (1 mL) was added $PdCl_2$dppf (0.15 g, 0.18 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and then filtered through a Celite pad. The filtrate was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 in heptane, 0/100 to 100/0) to yield **13a** as a pale yellow oil (2 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ 1.33 (s, 12H), 1.81−1.90 (m, 2H), 1.97−2.06 (m, 2H), 3.61 (ddd, J = 11.34, 7.44, 3.47 Hz, 2H), 4.00 (td, J = 7.59, 3.61 Hz, 2H), 4.58−4.65 (m, 1H), 6.92 (d, J = 8.38 Hz, 1H), 7.63 (dd, J = 8.09, 1.44 Hz, 1H), 7.82 (d, J = 1.45 Hz, 1H).

General Procedure B. 1-Cyclopropylmethyl-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1*H*-indole (13g). Bis-(pinacolato)diboron (0.48 g, 9.64 mmol) and AcOK (0.41 g, 4.2 mmol)

were added to a solution of **24a** (1 g, 1.2 mmol) in 1,4-dioxane (8 mL). The resulting mixture was degassed, and then $PdCl_{2(}$dppf) (0.044 g, 0.06 mmol) was added. The reaction mixture was heated at 110 °C for 16 h in a sealed tube. After cooling to room temperature, the mixture was filtered through a Celite pad. The filtrate was diluted with water (25 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was separated, dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The crude product was purified by flash column chromatography (silica gel, MeOH in CH_2Cl_2, 0/100 to 10/90) to yield **13g** as an oil (0.21 g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.33−0.38 (m, 2H), 0.58−0.63 (m, 2H), 1.22−1.30 (m, 1H), 1.36 (s, 12H), 3.99 (d, J = 6.6 Hz, 2H), 6.51 (d, J = 3 0.2 Hz, 1H), 7.20 (d, J = 3.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 8.2, 0.7 Hz, 1H), 8.16 (broad s, 1H). LC−MS: m/z 298 $[M + H]^+$.

[2-Chloro-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenyl](tetrahydropyran-4-yl)amine (13b). Starting from compound **17** (3.66 g, 12.6 mmol) and following general procedure B, compound **13b** was obtained as a colorless oil (2.87 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 12H), 1.49−1.62 (m, 2H), 1.99−2.09 (m, 2H), 3.49−3.65 (m, 3H), 4.01 (dt, J = 11.8, 3.7 Hz, 2H), 4.48 (broad d, J = 7.9 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 7.55 (dd, J = 8.2, 0.8 Hz, 1H), 7.70 (d, J = 0.7 Hz, 1H). LC−MS: m/z 338 $[M + H]^+$.

4-[2-Chloro-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenylamino]cyclohexanol (13c). Starting from **19** (1.66 g, 5.45 mmol) and following general procedure B, compound **13c** was obtained as a white solid (1 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.38 (m, 14H), 1.39−1.52 (m, 3H), 1.96−2.20 (m, 4H), 3.29−3.41 (m, 1H), 3.66−3.76 (m, 1H), 4.36−4.43 (m, 1H), 6.62 (d, J = 8.1 Hz, 1H), 7.55 (dd, J = 8.1, 1.4 Hz, 1H), 7.68 (d, J = 1.4 Hz, 1H). LC−MS: m/z 352 $[M + H]^+$.

4-[2-Chloro-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenyl]morpholine (13d). Starting from commercially available **20** (1.99 g, 7.196 mmol) and following general procedure A, compound **13d** was obtained as a white solid (1.34 g, 58%). Mp 130.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 12 H), 3.07−3.13 (m, 4 H), 3.85−3.91 (m, 4 H), 7.01 (d, J = 7.9 Hz, 1 H), 7.65 (dd, J = 8.0, 1.5 Hz, 1 H), 7.80 (d, J = 1.4 Hz, 1 H). LC−MS: m/z 324 $[M + H]^+$

7-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-2*H*-benzo[1,4]oxazine (13e). Starting from commercially available **21** (0.6 g, 2.8 mmol) and following general procedure B, compound **13e** was obtain as a solid (0.55 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 12 H), 3.41−3.47 (m, 2 H), 3.95 (broad s, 1 H), 4.17−4.26 (m, 2 H), 6.56 (d, J = 8.1 Hz, 1 H), 7.19−7.25 (m, 2 H). LC−MS: m/z 262 $[M + H]^+$.

8-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-5*H*-benzo[*f*][1,4]oxazepine-4-carboxylic Acid *tert*-Butyl Ester (13f). Starting from commercially available **22** (0.492 g, 1.5 mmol) and following general procedure A, compound **13e** was obtained (0.396 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.34 (broad s, 12H), 1.40 (s, 9H), 3.79 (broad s, 2H), 3.97−4.07 (m, 2H), 4.42 (broad s, 1.4H), 4.49 (br s, 0.6H), 7.19 (d, J = 6.9 Hz, 0.7H), 7.32 (d, J = 6.6 Hz, 0.3H), 7.43−7.50 (m, 2H).

7-Chloro-1-methyl-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1*H*-indole (13). Starting from **24b** (0.35 g, 1.41 mmol) and following general procedure B, compound **13h** was obtained (0.13 g, 33%) as a white solid. Mp 169.4 °C. GC−MS (EI/CI): m/z 291 $[M]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 12 H), 4.14 (s, 3 H), 6.47 (d, J = 3.2 Hz, 1 H), 6.97 (d, J = 2.9 Hz, 1 H), 7.56 (s, 1 H), 7.98 (s, 1 H). LC−MS: m/z 292 $[M + H]^+$.

7-Chloro-1-cyclopropylmethyl-5-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-1*H*-indole (13i). Starting from **24c** (0.71 g, 2.48 mmol) and following general procedure A, compound **13i** was obtained (0.36 g, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.29−0.42 (m, 2H), 0.49−0.63 (m, 2H), 1.34−1.38 (m, 1H), 1.36 (s, 12H), 4.41 (d, J = 6.6 Hz, 2H), 6.52 (d, J = 2.3 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 7.58 (s, 1H), 8.01 (s, 1H). GC−MS (EI/CI): m/z 331 $[M]^+$.

1-(Tetrahydropyran-4-yl)-5-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-1*H*-indole (13j). Starting from **24d**[1] (0.38 g, 1.4 mmol) and following general procedure A, compound **13j** was obtained (0.31 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 12H), 1.99−2.18 (m, 4H), 3.58−3.67 (m, 2H), 4.12−4.19 (m, 2H), 4.44−4.54 (m, 1H), 6.55 (dd, J = 3.2, 0.5 Hz, 1H), 7.21 (d, J = 3.2 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.65 (dd, J = 8.3, 1.2 Hz, 1H), 8.17 (s, 1H). LC−MS: m/z 328 $[M + H]^+$.

7-Chloro-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1*H*-indole (13k). Starting from **23b** (1.5 g, 4.55 mmol) and following general procedure B, compound **13k** was obtained (0.95 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 6.61 (dd, J = 3.1, 2.2 Hz, 1H), 7.23−7.27 (m, 1H), 7.63 (s, 1H), 8.05 (s, 1H), 8.42 (broad s, 1H). LC−MS: m/z 277 $[M]^-$.

4-[5-(4,4,5,5-Tetramethyl[1,2,3]dioxaborolan-2-yl)indol-1-yl]cyclohexanol (13l). Starting from **26** (1.80 g, 6.11 mmol) and following general procedure A, compound **13l** was obtained as a yellow foam (1.35 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 1.48−1.69 (m, 3H), 1.74−1.90 (m, 2H), 2.11−2.21 (m, 4H), 3.78 (tt, J = 10.95, 3.96 Hz, 1H), 4.22−4.31 (m, 1H), 6.52 (d, J = 3.24 Hz, 1H), 7.16 (d, J = 3.24 Hz, 1H), 7.35 (d, J = 8.55 Hz, 1H), 7.64 (dd, J = 8.32, 0.92 Hz, 1H), 8.15 (s, 1H). LC−MS: m/z 341.21 $[M + H]^+$.

Synthesis of Final Compounds 27a−p. 7-[3-Chloro-4-(tetrahydropyran-4-yloxy)phenyl]-3-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridine-8-carbonitrile (27a). To a mixture of **6a** (0.20 g, 0.50 mmol) and **13a** (0.27 g, 0.81 mmol) in a saturated aqueous solution of $NaHCO_3$ (2 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.057 g, 0.051 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 20/80) to give **27a** as a white solid (0.080 g, 38%). Mp 232.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87−1.95 (m, 2H), 2.04−2.12 (m, 2H), 3.65 (ddd, J = 11.4, 7.4, 3.8 Hz, 2H), 3.80 (q, J = 10.0 Hz, 2H), 4.04 (ddd, J = 11.5, 7.4, 3.6 Hz, 2H), 4.68 (tt, J = 7.1, 3.5 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 7.64 (dd, J = 8.4, 2.3 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.80 (s, 1H), 8.22 (d, J = 7.2 Hz, 1H). LC−MS: m/z 425 $[M + H]^+$.

7-[3-Chloro-4-(tetrahydropyran-4-ylamino)phenyl]-3-(2,2,2-trifluoroethyl)-8-cyanoimidazo[1,2-*a*]pyridine (27b). To a mixture of **6a** (0.25 g, 0.67 mmol) and **13b** (0.273 g, 0.81 mmol) in a saturated aqueous solution of $NaHCO_3$ (2 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.078 g, 0.067 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 10/90) to give **27b** as a white solid (0.068 g, 23%). Mp 230.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.61 (qd, J = 11.8, 4.3 Hz, 2H), 1.84−1.92 (m, 2H), 3.45 (td, J = 11.6, 1.7 Hz, 2H), 3.65−3.75 (m, 1H), 3.86−3.93 (m, 2H), 4.30 (q, J = 10.9 Hz, 2H), 5.49 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.60 (dd, J = 8.7, 2.3 Hz, 1H), 7.73 (s, 1H), 7.74 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 7.2 Hz, 1H). LC−MS: m/z 435 $[M + H]^+$.

7-(3-Chloro-4-morpholin-4-ylphenyl)-3-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridine-8-carbonitrile (27c). To a stirred suspension of **13d** (0.15 g, 0.38 mmol) and **6b** (0.12 g, 0.39 mmol) in a saturated aqueous solution of $NaHCO_3$ (0.5 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.022 g, 0.02 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 30/70) to give **27c** as a solid (0.10 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.14−3.19 (m, 4H), 3.80 (q, J = 10.0 Hz, 2H), 3.89−3.94 (m, 4H), 7.07 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H),

7.65 (dd, J = 8.1, 2.3 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.80 (s, 1H), 8.23 (d, J = 7.2 Hz, 1H). LC−MS: m/z 421 $[M + H]^+$.

7-(3,4-Dihydro-2*H*-benzo[1,4]oxazin-7-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (27d). To a stirred suspension of **13e** (0.18 g, 0.69 mmol) and **6a** (0.16 g, 0.62 mmol) in a saturated aqueous solution of $NaHCO_3$ (2 mL) and 1,4-dioxane (4 mL) was added $Pd(PPh_3)_4$ (0.036 g, 0.031 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, EtOAc in heptane, 0/100 to 20/80) to give the desired product **27d** as a yellow solid (0.11 mg, 50%). ^1H NMR (400 MHz, DMSO-d_6) δ 3.36−3.40 (m, 2H), 4.17 (broad t, J = 4.4 Hz, 2H), 4.28 (q, J = 10.9 Hz, 2H), 6.45−6.48 (m, 1H), 6.72 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.2, 2.2 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.70 (s, 1H), 8.80 (d, J = 7.4 Hz, 1H). LC−MS: m/z 359 $[M + H]^+$.

7-(2,3,4,5-Tetrahydro-benzo[*f*][1,4]oxazepin-8-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (27e). To a stirred suspension of **13f** (0.39 g, 0.58 mmol) and **6a** (0.12 g, 0.48 mmol) in a saturated aqueous solution of $NaHCO_3$ (0.9 mL) and 1,4-dioxane (2.5 mL) was added $Pd(PPh_3)_4$ (0.028 g, 0.024 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to ambient temperature and filtered through a Celite pad. The filtrate was diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 30/70) to give 40 mg (17%) of a Boc protected intermediate. This intermediate compound was taken up in CH_2Cl_2 (10 mL), and CF_3COOH (1 mL) was added to the mixture at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then the volatiles were evaporated in vacuo. The residue thus obtained was taken up in CH_2Cl_2 (20 mL), and it was washed with an aqueous $NaHCO_3$ saturated solution and brine. The organic layer was dried (Na_2SO_4), filtered, and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 20/80) to give **27e** as an orange oil (0.018 g, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.77 (broad s, 1H), 3.27−3.33 (m, 2H), 3.80 (q, J = 9.7 Hz, 2H), 4.07 (s, 2H), 4.12−4.17 (m, 2H), 7.08 (d, J = 7.2 Hz, 1H), 7.30−7.39 (m, 3H), 7.80 (s, 1H), 8.22 (d, J = 7.2 Hz, 1H). LC−MS: m/z 373 $[M + H]^+$.

7-(1-Methyl-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)imidazo-[1,2-*a*]pyridine-8-carbonitrile (27f). To a mixture of **6a** (0.25 g, 0.67 mmol) and commercially available 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (0.27 g, 0.81 mmol) in a saturated aqueous solution of $NaHCO_3$ (2 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.078 g, 0.067 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 10/90) to give **27f** as a yellow solid (0.025 g, 15%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.30−1.42 (m, 2H), 1.42−1.54 (m, 2H), 1.60 (broad s, 1H), 2.03−2.13 (m, 2H), 2.14−2.25 (m, 2H), 3.34−3.46 (m, 1H), 3.70−3.78 (m, 1H), 3.77 (q, J = 9.9 Hz, 2H), 4.51 (broad d, J = 7.6 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.59 (dd, J = 8.6, 2.3 Hz, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.75 (s, 1H), 8.16 (d, J = 7.4 Hz, 1H). LC−MS: m/z 355 $[M + H]^+$.

7-(1-Cyclopropylmethyl-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridine-8-carbonitrile (27g). To a mixture of **6b** (0.12 g, 0.39 mmol) and **13g** (0.14 g, 0.47 mmol) in a saturated aqueous solution of $NaHCO_3$ (1 mL) and 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (0.023 g, 0.02 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 10/90) to give **27g** as a yellow solid (0.079 g, 51%). Mp 117.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.34−0.47 (m, 2H), 0.60−0.74 (m, 2H), 1.24−1.37 (m, 1H), 3.79 (q, J = 9.8 Hz, 2H), 4.04 (d, J = 6.9 Hz, 2H), 6.62 (d, J = 3.2 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 3.2 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 8.6, 1.8 Hz, 1H), 7.76 (s, 1H), 7.97−7.99 (m, 1H), 8.19 (d, J = 7.4 Hz, 1H). LC−MS: m/z 395 $[M + H]^+$.

7-[1-(Tetrahydropyran-4-yl)-1*H*-indol-5-yl]-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (27h). To a mixture of **6b** (0.20 g, 0.50 mmol) and **13g** (0.18 g, 0.55 mmol) in a saturated aqueous solution of $NaHCO_3$ (2 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.057 g, 0.05 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 20/80) to give **27h** as a yellow solid (0.08 g, 38%). Mp 232.9 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 1.96 (dd, J = 12.4, 2.3 Hz, 2H), 2.07 (qd, J = 12.1, 4.3 Hz, 2H), 3.58−3.65 (m, 2H), 4.04 (dd, J = 11.3, 4.0 Hz, 2H), 4.33 (q, J = 10.9 Hz, 2H), 4.76 (tt, J = 11.6, 4.0 Hz, 1H), 6.65 (d, J = 3.2 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.54 (dd, J = 8.7, 1.7 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 7.76 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 1.4 Hz, 1H), 8.90 (d, J = 7.2 Hz, 1H). LC−MS: m/z 425 $[M + H]^+$.

7-[1-(4-Hydroxycyclohexyl)-1*H*-indol-5-yl]-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (27i). To a mixture of **6a** (0.20 g, 0.77 mmol) and **13l** (0.31 g, 0.92 mmol) in a saturated aqueous solution of $NaHCO_3$ (2 mL) and 1,4-dioxane (6 mL) was added $Pd(PPh_3)_4$ (0.045 g, 0.038 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 10/90) to give **27i** as a yellow solid (0.240 g, 71%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.54−1.69 (m, 3H), 1.82−1.94 (m, 2H), 2.16−2.25 (m, 4H), 3.79 (q, J = 10.1 Hz, 2H), 3.77−3.87 (m, 1H), 4.31 (tt, J = 12.0, 3.5 Hz, 1H), 6.63 (d, J = 3.5 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 3.5 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.56 (dd, J = 8.7, 2.0 Hz, 1H), 7.76 (s, 1H), 7.98 (d, J = 1.2 Hz, 1H), 8.20 (d, J = 7.2 Hz, 1H). LC−MS: m/z 439 $[M + H]^+$.

7-(7-Chloro-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)imidazo-[1,2-*a*]pyridine-8-carbonitrile (27j). To a mixture of **6b** (0.11 g, 0.34 mmol) and **13k** (0.11 g, 0.38 mmol) in a saturated aqueous solution of $NaHCO_3$ (3 mL) and 1,4-dioxane (3 mL) was added $Pd(PPh_3)_4$ (0.020 g, 0.017 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 30/70) to give the desired product **27j** (0.090 g, 69%) as a pale yellow solid (0.090 g, 69%). ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (q, J = 10.0 Hz, 2H), 6.72 (dd, J = 3.0, 2.2 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.38 (t, J = 2.7 Hz, 1H), 7.50 (d, J = 1.4 Hz, 1H), 7.79 (s, 1H), 7.93 (d, J = 0.9 Hz, 1H), 8.22 (d, J = 7.2 Hz, 1H), 8.72 (broad s, 1H). LC−MS: m/z 375 $[M + H]^+$.

7-(7-Chloro-1-methyl-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridine-8-carbonitrile (27k). To a mixture of **6b** (0.15 g, 0.32 mmol) and **13h** (0.11 g, 0.38 mmol) in a saturated aqueous solution of $NaHCO_3$ (0.5 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 30/70) to give **27k** as a pale yellow solid (0.035 g, 28%). Mp 172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (q, J = 9.8 Hz, 2H), 4.19 (s, 3H), 6.59 (d, J = 2.9 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.78 (s, 1H), 7.88 (d, J = 1.7 Hz, 1H), 8.21 (d, J = 7.2 Hz, 1H). LC−MS: m/z 389 $[M + H]^+$.

7-(7-Chloro-1-cyclopropylmethyl-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (27l). To a mixture of **6b** (0.15 g, 0.32 mmol) and **13i** (0.13 g, 0.38 mmol) in a saturated aqueous solution of $NaHCO_3$ (0.5 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 30/70) to give **27l** as a pale yellow solid (0.058 g, 42%). Mp 175.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.36−0.47 (m, 2H), 0.56−0.69 (m, 2H), 1.35−1.45 (m, 1H), 3.80 (q, J = 9.8 Hz, 2H), 4.44 (d, J = 6.9 Hz, 2H), 6.63 (d, J = 3.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.78 (s, 1H), 7.91 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 7.2 Hz, 1H). LC−MS: m/z 429 $[M + H]^+$.

4-{5-[8-Chloro-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridin-7-yl]indol-1-yl}cyclohexanol (27m). To a mixture of **6c** (0.35 g, 0.68 mmol) and **13l** (0.25 g, 0.75 mmol) in a saturated aqueous solution of $NaHCO_3$ (1.5 mL) and 1,4-dioxane (3 mL) was added $Pd(PPh_3)_4$ (0.039 g, 0.034 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, MeOH−NH_3 in CH_2Cl_2, 0/100 to 10/90) to give **27m** as a white solid (0.14 g, 46%). Mp 129.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54−1.67 (m, 3H), 1.82−1.95 (m, 2H), 2.16−2.27 (m, 4H), 3.71−3.88 (m, 1H), 3.77 (q, J = 9.9 Hz, 2H), 4.31 (tt, J = 12.0, 3.4 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 7.25−7.28 (m, 1H), 7.40 (dd, J = 8.6, 1.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.72 (s, 1H), 7.80 (d, J = 1.4 Hz, 1H), 7.99 (d, J = 6.9 Hz, 1H). LC−MS: m/z 448 $[M + H]^+$.

4-[2-Chloro-4-(8-chloro-3-ethylimidazo[1,2-*a*]pyridin-7-yl)-phenylamino]cyclohexanol (27n). To a stirred suspension of **13c** (0.39 g, 1.12 mmol) and **6c** (0.48 g, 0.93 mmol) in a saturated aqueous solution of $NaHCO_3$ (1 mL) and 1,4-dioxane (2 mL) was added $Pd(PPh_3)_4$ (0.054 g, 0.047 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 30/70) to give **27n** as a white solid (0.24 g, 56%). Mp 183.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30−1.41 (m, 2H), 1.42−1.53 (m, 3H), 2.03−2.12 (m, 2H), 2.16−2.26 (m, 2H), 3.33−3.43 (m, 1H), 3.70−3.80 (m, 1H), 3.75 (q, J = 10.0 Hz, 2H), 4.37 (d, J = 7.8 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 6.9 Hz, 1H), 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.70 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H).

8-Chloro-7-(7-chloro-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridine (27o). To a mixture of **6c** (0.21 g, 0.58 mmol) and **13k** (0.18 g, 0.64 mmol) in a saturated aqueous solution of $NaHCO_3$ (1.5 mL) and 1,4-dioxane (3.5 mL) was added $Pd(PPh_3)_4$ (0.034 g, 0.029 mmol). The mixture was heated at 150 °C for 10 min under microwave irradiation. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 30/70) to give **27o** as a pale white solid (0.09 g, 69%). Mp 182.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (q, J = 9.9 Hz, 2H), 6.68 (dd, J = 3.1, 2.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 7.35 (broad t, J = 2.8 Hz, 1H), 7.39 (d, J = 1.4 Hz, 1H), 7.72 (broad d, J = 0.7 Hz, 1H), 7.74 (s, 1H), 8.00 (d, J = 6.9 Hz, 1H), 8.57 (broad s, 1H). LC−MS: m/z 384 $[M + H]^+$.

8-Chloro-7-(7-chloro-1-cyclopropylmethyl-1*H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-*a*]pyridine (27p). To a mixture of **6c** (0.15 g, 0.15 mmol) and **13i** (0.15 g, 0.45 mmol) in EtOH (3 mL) was added *trans*-diacetylpalladium(II) bis(dicyclohexylamine) (DAPCy) (0.012 g, 0.021 mmol) and K_3PO_4 (0.26 g, 1.23 mmol). The mixture was stirred at room temperature overnight. The mixture was filtered through a Celite pad and the filtrate evaporated to dryness in vacuo. The residue thus obtained was purified by flash column chromatography (silica gel, EtOAc in CH_2Cl_2, 0/100 to 4/94) to give **27p** as a white solid (0.058 g, 42%). Mp 151.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.36−0.47 (m, 2H), 0.57−0.68 (m, 2H), 1.36−1.46 (m, 1H), 3.78 (q, J = 9.8 Hz, 2H), 4.44 (d, J = 6.9 Hz, 2H), 6.59 (d, J = 3.2 Hz, 1H), 7.01 (d, J = 6.9 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.73 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H). LC−MS: m/z 438 $[M + H]^+$.

Biology. Membrane Preparation. CHO cells were cultured to preconfluence and stimulated with 5 mM butyrate for 24 h, prior to washing in PBS, and then collected by scraping in homogenization buffer (50 mM Tris-HCl buffer, pH 7.4, 4 °C). Cell lysates were homogenized briefly (15 s) using an ULTRA-TURRAX homogenizer. The homogenate was centrifuged at 23500*g* for 10 min and the supernatant discarded. The pellet was resuspended in 5 mM Tris-HCl, pH 7.4, and centrifuged again (30000*g*, 20 min, 4 °C). The final pellet was resuspended in 50 mM HEPES, pH 7.4, and stored at −80 °C in appropriate aliquots before use. Protein concentration was determined by the Bradford method (Bio-Rad, U.S.) with bovine serum albumin as standard.

[^{35}S]GTPγS Binding Assay. Measurement of mGluR2 positive allosteric modulatory activity of test compounds in membranes containing human mGluR2 was performed using frozen membranes that were thawed and briefly homogenized prior to preincubation in 96-well microplates (15 mg/assay well, 30 min, 30 °C) in assay buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 3 mM $MgCl_2$, 50 μM GDP, 10 mg mL^{-1} saponin) with increasing concentrations of positive allosteric modulator (from 0.3 nM to 50 μM) and either a minimal predetermined concentration of glutamate (PAM assay) or no added glutamate. For the PAM assay, membranes were preincubated with glutamate at EC_{25} concentration, i.e., a concentration that gives 25% of the maximal response glutamate. After addition of [^{35}S]GTPγS (0.1 nM, fc) to achieve a total reaction volume of 200 μL, microplates were shaken briefly and further incubated to allow [^{35}S]GTPγS incorporation on activation (30 min, 30 °C). The mixture was stopped by rapid vacuum filtration over glass-fiber filter plates (Unifilter 96-well GF/B filter plates, Perkin-Elmer, Downers Grove, IL, U.S.) microplate using a 96-well plate cell harvester (Filtermate, Perkin-Elmer, U.S.) and then by washing three times with 300 μL of ice-cold wash buffer ($Na_2PO_4{\cdot}2H_2O$, 10 mM, $NaH_2PO_4{\cdot}H_2O$, 10 mM, pH 7.4). Filters were then air-dried, and 40 mL of liquid scintillation cocktail (Microscint-O) was added to each well. Membrane-bound [^{35}S]GTPγS was measured in a 96-well scintillation plate reader (Top-Count, Perkin-Elmer, U.S.). Nonspecific [^{35}S]GTPγS binding is

determined in the presence of cold 10 mM GTP. Each curve was performed at least three times using duplicate samples per data point and at 11 concentrations.

Data Analysis. The concentration−response curves in the presence of added EC_{25} of mGluR2 agonist glutamate to determine positive allosteric modulation (PAM) were generated using the Prism GraphPad software (Graph Pad Inc., San Diego, CA, U.S.). The curves were fitted to a four-parameter logistic equation (Y = bottom + (top − bottom)/(1 + $10^{(\log EC_{50}-X)(\text{Hill slope})}$) allowing determination of EC_{50} values. The EC_{50} is the concentration of a compound that causes a half-maximal potentiation of the glutamate response. This is calculated by subtracting the maximal responses of glutamate in the presence of a fully saturating concentration of a positive allosteric modulator from the response of glutamate in absence of a positive allosteric modulator. The concentration producing the half-maximal effect is then calculated as EC_{50}. The pEC_{50} values below are calculated as the $-\log EC_{50}$ (wherein EC_{50} is expressed in mol L^{-1}).

Sleep−Wake EEG. Animals, Drug Treatment, and Experimental Procedure. All in vivo experimental procedures were performed according to the applicable European Communities Council Directive of November 24, 1986 (86/609/EEC) and approved by the Animal Care and Use Committee of Janssen Pharmaceutical Companies of Johnson & Johnson and by the local ethical committee.

Male Sprague−Dawley rats (Charles River, France) weighing 250−300 g were used. Animals were chronically implanted with electrodes for recording the cortical electroencephalogram (EEG), electrical neck muscle activity (EMG), and ocular movements (EOG). All animals were housed in individually ventilated cages under environmentally controlled conditions (ambient temperature, 22 °C; humidity, 60%) on a 12 h light and 12 h dark cycle (lights on from 12:00 a.m. to 12:00 p.m., illumination intensity of ∼100 lx). The animals had free access to food and tap water.

The effects of the tested molecule and vehicle on sleep−wake distribution during the lights-on period were investigated in 16 rats (n = 8 each group). Two EEG recording sessions were performed: the first recording session started at 13:30 h and lasted 20 h following oral administration of saline. The second recording session was performed during the same consecutive circadian time and for the same duration following administration of either vehicle (20% CD + 2H2T) or tested compound.

Sleep polysomnographic variables were determined offline as described elsewhere using a sleep stages analyzer, scoring each 2 s epoch before averaging stages over 30 min periods. Sleep−wake state classifications were assigned based on a combination of dynamics of five EEG frequency domains, integrated EMG, EOG, and body activity level: active wake (AW); passive wake (PW); intermediate stage (pre-REM transients); rapid eye movement sleep (REM); light non-REM sleep (lSWS) and deep non-REM sleep (dSWS). Different sleep−wake parameters were investigated over 20 h postadministration: amount of time spent in each vigilance state, sleep parameters, latencies for first REM sleep period, and the number of transitions between states.

Statistical Analysis. Time spent in each vigilance state (AW, PW, lSWS, dSWS, IS, and REMS) was expressed as a percentage of the recording period. A statistical analysis of the obtained data was carried out by a nonparametric analysis of variance of each 30 min period, followed by a Wilcoxon−Mann−Whitney rank sum test of comparisons with the control group.

■ ASSOCIATED CONTENT

Supporting Information

Correlation between human and rat mGlu2 receptor GTPγS activity; Sw-EEG tables listing effect of **27o** on total time spent in different vigilance states. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank collaborators from Addex Pharmaceuticals and the members of the Purification and Analysis Group.

■ ABBREVIATIONS USED

ADMET, absorption, distribution, metabolism, excretion, and toxicity; BBB, blood−brain barrier; CNS, central nervous system; DMS-IV, diagnostic statistical manual of mental disorders volume IV; GPCRs, G-protein-coupled receptors; iv, intravenous; mGlu2, metabotropic glutamate 2; ND, not determined; nm, not measurable; PAM, positive allosteric modulator; PK, pharmacokinetics; SAR, structure−activity relationship; SEM, standard error of the mean; po, oral; sc, subcutaneous; SD, standard deviation; sw-EEG, sleep−wake electroencephalogram

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