Synthesis and Biological Evaluation of 7,8,9,10-Tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimdin-5(6H)-ones as Functionally Selective Ligands of the Benzodiazepine Receptor Site on the $GABA_A$ Receptor

Pamela A. Albaugh,*[,†] Lu Marshall,[‡] James Gregory,[§] Geoff White,[§] Alan Hutchison,[†] Phil C. Ross,[#] Dorothy W. Gallagher,[‡] John F. Tallman,[#] Matt Crago,[||] and James V. Cassella[||]

Neurogen Corporation, 35 Northeast Industrial Road, Branford, Connecticut 06405

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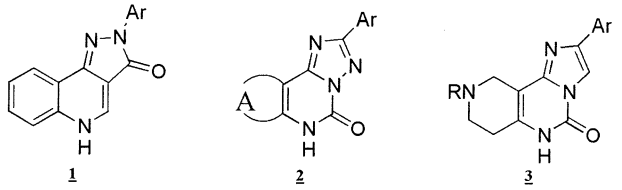
Benzodiazepines are allosteric modulators of the $GABA_A$ receptor. The traditionally prescribed benzodiazepines are nonselective and suffer from numerous side effects. Upon the identification of receptor subtypes, we set out to discover selective agents with the anticipation that these agents would have superior therapeutic potential. Herein, we describe the synthesis and biological evaluation of substituted 7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-ones and disclose that these compounds exhibit functional selectivity at the benzodiazepine receptor of $GABA_A$ receptor subtypes. The α_2/α_3-selective partial agonist **42** exhibited potent in vivo activity.

Introduction

GABA is the major inhibitory neurotransmitter in the central nervous system (CNS). There are three pharmacological classes of GABA receptors: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and the less well-known $GABA_C$ are ligand-gated ion channels, whereas $GABA_B$ is a G-protein-coupled receptor. For $GABA_A$, postsynaptic responses to GABA are mediated by altered chloride conductance, which typically hyperpolarizes the membrane. Benzodiazepines have long been known to bind in an allosteric manner to the $GABA_A$ receptor, and this site has been termed the benzodiazepine receptor (BZR). Binding by ligands at this site modulates the effects of GABA. There is a continuous range of effects, from positive allosteric modulators (agonists) that enhance the GABAergic inhibition to negative allosteric modulators (inverse agonists) that reduce the GABAergic inhibition and lead to excitation of the neuron. Antagonists bind to this site and block the action of both agonists and inverse agonists. Full agonists that act at the benzodiazepine site are known to exhibit anxiolytic, sedative, anticonvulsive, and hypnotic effects, while compounds that act as inverse agonists elicit anxiogenic, cognition enhancing, and proconvulsant effects. Although benzodiazepines have a long history of pharmaceutical use as anxiolytics and hypnotics, they often exhibit a number of unwanted side effects. These may include cognitive impairment, sedation, ataxia, and potentiation of ethanol. Tolerance and withdrawal are problems with repeated use. No inverse agonists are marketed.



1 2 3

Figure 1. Known benzodiazepine receptor ligands **1** and **2** that are reported to exhibit behavioral selectivity. Benzodiazepine receptor ligand **3** is presented here.

At the time our research began, it was thought that partial agonist activity at the GABA receptor would reduce the side effects of the benzodiazepines. In addition, studies[1] with CL218,872, a triazolopyridazine, identified two distinct receptor binding sites that were called BZ-1 and BZ-2. Multiple subunits that comprise the $GABA_A$ receptor were being cloned, and the possibility of multiple receptor subtypes was just emerging as we began our studies. It then became apparent that improvement over existing benzodiazepine agonists could arise from selective and/or partial agonisim at the benzodiazepine receptor binding site. Indeed, as the identity and location of the subtypes became known, interest in designing selective benzodiazepine receptor agonists grew. Now, the Bz-1 type is known to be the α_1 subtype, whereas the Bz-2 type comprises α_2, α_3, and α_5 subtypes. During the time of our work, two agents with higher *affinity* for the Bz-1 receptor have come to the market as hypnotics [Ambien (zolpidem) and Sonata (zaleplon)]. Although these newer hypnotic agents have some advantages over the older class of benzodiazepines, improvement on the side effect profile of these agents has been in debate. This could be due to targeting of the wrong receptor subtype and/or lack of *functional* selectivity (see Discussion below).

Analogues derived from aryl-fused pyrazolo[4,3-*c*]-quinolin-3-ones (**1**, Figure 1) have been claimed[2] to exhibit behavioral selectivity. Various fused pyrazolo-[4,3-*c*]quinolin-3-ones[3,4] have been disclosed, as have

* To whom correspondence should be addressed. Current address: Eli Lilly & Co., Drop Code 0548, Lilly Corporate Center, Indianapolis, IN 46285. Phone: (317) 433-1610. Fax: (317) 277-3652. E-mail: albaugh_pamela@lilly.com.
† Department of Chemistry.
‡ Department of Pharmacology.
§ Department of Electrophysiology.
# Department of Molecular Biology.
|| Department of Behavioral Biology.

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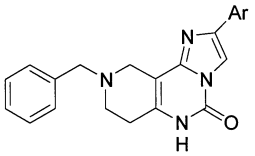
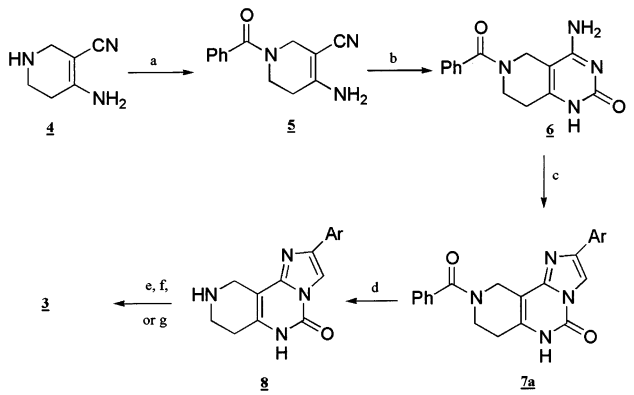
Table 1. Effect of Aryl Modification on Binding Affinity



			α_1		α_2		α_3		α_5	
compd	aryl	K_i [a] (nM)	max[b] (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)
9	H	8.7 ± 0.1	67	17	179	184				
10	2-F	1.3 ± 0.4	56	18	76	20	120	20	31	74
11	3-F	11.3 ± 2.8	92	120	81	154				
12	4-F	21 ± 11	186	136	155	245				
13	3-Cl	71 ± 22								
14	4-Cl	121 ± 27								
15	2-OMe	797 ± 242								
16	3-OMe	2.3 ± 0.3	123	81	115	268				
17	4-OMe	2.6 ± 0.5	122	28	142	143				
18	4-Me	43 ± 8	62	266	94	1179	174	3826	17	650
19	2,4-diF	2.0 ± 0.6	63	92	184	210	95	500	30	323
20	2,5-diF	11.4 ± 0.6	59	36	82	188				
21	3,4-diF	72 ± 16								
22	2-F−4-OMe	0.6 ± 0.1								
23	2-thienyl	3.0 ± 0.2	108	208	194	879				
zolpidem		48	322	198	291	737	700	>3000	<20	>3000
zaleplon		128	236	295	~352	~1626	>280	>1000	>77	>1000
alprazolam		3.3	327	37	333	12	774	69	206	10

[a] Determined by radioligand binding assay as described.[8,9] Values represent the average (±SD). [b] Measured as described by White et al.[12,13]

Scheme 1[a]



[a] Reagents: (a) $(PhCO)_2O$, pyridine; (b) urea, 2-(2-ethoxyethoxy)ethanol; (c) $ArCOCH_2Br$, DMF; (d) aqueous NaOH, EtOH; (e) RX or RCOX, Et_3N, DMF; (f) RCHO, $NaCNBH_3$, HCl/MeOG; (g) (i) RCOX, Et_3N, DMF, (ii) BH_3, CH_2Cl_2.

various fused [1,2,3]triazolo[1,5-*c*]pyrimidin-5(6H)-ones[5,6] (**2**, Figure 1), all of which reportedly gave a range of behavioral activities. Herein, we disclose our efforts around a related template, 7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-ones (**3**, Figure 1). We disclose here functional selectivity of these compounds based on electrophysiology studies.

Chemistry

The known enaminonitrile **4**[7] was protected as the benzoyl amide **5** and then condensed with urea to give aminopyrimidone **6**. Various bromoacetophenones were reacted with **6** to give in one step imidazopyrimidinones **7**. Deprotection of **7** followed by alkylation, acylation, or reductive amination afforded the desired final products **3** (Scheme 1).

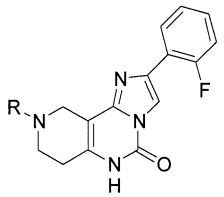
Results

Affinity of test compounds for the benzodiazepine receptor was determined in vitro by their ability to displace ^{3}H-Ro 15-1788 in rat cortical tissue as described by Thomas and Tallman.[8,9] The results are shown in Tables 1−5.

Currently there are at least 6α, 3β, 3γ, 1δ, and 2ρ subunits identified. Since the $GABA_A$ receptor is a pentameric complex, numerous combinations are possible. However, it is generally accepted that the predominant native receptors comprise 2α, 2β, and 1γ subunits. Various evidence[10,11] suggests that the major naturally occurring combinations are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$. Selected compounds were screened for functional efficacy and selectivity using electrophysiological recordings carried out on *Xenopus* oocytes expressing the appropriate constructs, as described by White et al.[12,13] After addition of GABA to the oocyte (benzodiazepine receptor ligands are active only in the presence of GABA), the test compound was added. Any potentiation of the current is recorded over a dose range of the test compound. The fitted curve yields the maximum percent potentiation along with the EC_{50}. The results are shown in Tables 1−5.

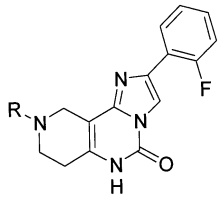
For the initial studies, the *N*-benzyl moiety was used as the common structural feature in order to investigate the impact of the aryl group (see Table 1). The unsubstituted phenyl (**9**) has a K_i of 8.7 nM, but affinity is enhanced 7-fold by an ortho fluoro substituent (**10**). Affinity drops for the meta fluoro group (**11**) and even more so for the para fluoro (**12**). However, the presence of a 4-fluoro is well tolerated in the 2,4-difluoro analogue (**19**). The affinity of the 3,4-difluoro analogue **20** is even worse than either the 3- or 4-fluoro substituent alone, whereas the affinity of the 2,5-difluoro analogue **21** is the same as the 3-fluoro analogue. Both the 3-chloro (**13**) and 4-chloro (**14**) analogues have 6-fold lower affinity than the analogous fluoro analogues. In contrast to fluorine, an ortho methoxy group (**15**) significantly reduces affinity, but affinity improves in the meta (**16**)

Table 2. Effect of Various N-Substitution on Binding Affinity



			α_1		α_2		α_3		α_5	
comd	N−R	K_i (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)
24	H	NA								
25	Me	202 ± 90	0		0					
26	Et	56 ± 7	0		0		14	935	0	
27	allyl	26 ± 0.5	5	170	18	284	20	344	0	
28	*i*-Pr	51 ± 6								
29	*n*-Bu	7.3 ± 3.6	70	258	86	247	72	394	4	291
30	*c*-PrCH_2	30 ± 2	31	135	36	1162	28	424	7	94
31	*c*-Hex-CH_2	0.9 ± 0.3	114	127	71	202	115	213	101	231
32	PhCH_2CH_2	83 ± 20								
33	Ph$CH_2CH_2CH_2$	147 ± 40								
34	pyrimidy-2-yl	133 ± 78	0		44	84	35	117	0	

Table 3. Effect of *N*-Arylmethyl Substituents on Binding Affinity



			α_1		α_2		α_3		α_5	
compd	N−R	K_i (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)
35	2-F−Bz	0.2 ± 0.1	66	93	53	256	39	242	21	346
36	3-F−Bz	0.5 ± 0.1	130	69	82	70	59	65	67	38
37	4-F−Bz	1.7 ± 1	31	41	38	55				
38	3,4-diF−Bz	3.2 ± 0.8	94	133	59	238	42	148	74	491
39	2-Me−Bz	1.5 ± 0.2	156	544	90	134	87	119	47	111
40	4-Me−Bz	13.6 ± 4	28	303	62	327	33	265	11	90
41	4-OMe−Bz	6.6 ± 0.7	30	2200	38	383	43	375	19	112
42	(Pyrid-3-yl)CH_2	1.4 ± 0.2	29	56	78	101	81	23	0	
43	(Pyrid-4-yl)CH_2	0.9 ± 0.2	17	53	42	99	58	33	0	
44	4/5-imidazyl-CH_2	10.1 ± 2.1	40	118	58	459	49	425	44	439
45	2-thienyl-CH_2	0.5 ± 0.2	50	107	54	67	96	367	49	375
46	Ph−(±)-(Me)CH	2.9 ± 0.9	47	60	26	75				
47	Ph−(*S*)-(−)-(Me)CH	6.5 ± 2.7								
48	2-F−Ph−(±)-(Me)CH	1.7 ± 0.1								
49	3-F−Ph−(±)-(Me)CH	8.3 ± 5.4								
50	4-F−Ph−(±)-(Me)CH	14.9 ± 5.7								

and para (**17**) positions. The impact on affinity by an ortho fluoro is again seen with the 2-fluoro-4-methoxy analogue **22**, which shows a 4-fold increase in affinity over the 4-methoxy (**17**) alone. A para methyl group (**18**) leads to a 5-fold drop in affinity. A thienyl group (**23**) in lieu of phenyl leads to a 3-fold enhancement in affinity.

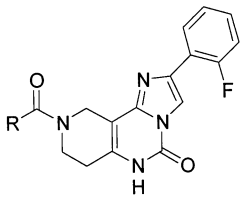
The aryl was then held constant as the ortho fluorophenyl while exploring the impact of the tetrahydropyridine substituent (Tables 2−4). An unsubstitued NH, compound (**24**, Table 2) is inactive. Small alkyl groups (**25**−**28**, **30**) reduce affinity by 10- to 30-fold compared to benzyl. Larger lipophilic alkyl groups (**29**, **31**) significantly improve affinity, comparable to that of *N*-benzyl (**10**). Extension of the carbon chain from benzyl to phenethyl (**32**) or phenpropyl (**33**) results in a dramatic loss in affinity. Pyrimidyl substitution (**34**) also results in significant loss in affinity.

Substitution on the aryl ring of the *N*-benzyl moiety (see Table 3) with halo (**35**−**38**), alkyl (**39**−**40**), or alkoxy (**41**) has only modest impact on affinity. Heteroaryl replacement (**42**−**45**) is well tolerated. Branching on the benzylic carbon is tolerated as demonstrated by analogues (**46**−**50**). Stereochemical preference at this center is not dramatic as shown by only a 2-fold difference between the racemate **46** and the (*S*) isomer **47**.

Acylation (**51**−**56**) and carbamoylation (**57**−**62**) of the tetrahydropyridine affords mostly weak or inactive compounds (see Table 4).

The lead compound **9** exhibits 2.5-fold selectivity for α_2 vs α_1 in maximum potentiation (efficacy) in electrophysiology studies, although the EC_{50} (potency) is shifted to the right (Table 1). All the fluoro analogues (**10**−**12**) have lost this selectivity except for the 2,4-difluoro analogue **19**, of which is comparable. The fluorine substituents also have dramatic differences on

Table 4. Effect of *N*-Acyl Substituents on Binding Affinity



			α_1		α_2		α_3		α_5	
compd	N−R	K_i (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)	max (%)	EC_{50} (nM)
51	Me	41 ± 9	0		0		11	71	0	
52	Et	216 ± 29	12	95	22	110	9	116	0	
53	*n*-Pr	261 ± 41								
54	*n*-pentyl	NA								
55	Ph	83 ± 5								
56	Bz	388 ± 155								
57	2-pyridyl	73 ± 1								
58	3-pyridyl	92 ± 0.2								
59	4-pyridyl	123 ± 47								
60	OEt	64 ± 5								
61	O−*n*-Bu	230 ± 76								
62	OBz	39 ± 8	5	<100	8	<100	0		~3	~1000

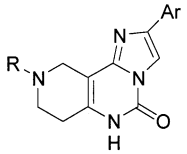
the maximum potentiation of both α_1 and α_2, increasing as the fluorine is moved from the ortho to the meta and then to the para position, albeit all with EC_{50} shifts to the right. The ortho fluoro analogue **10** is more efficacious on α_3 and maintains potency. The para methyl analogue **18** also has α_3 selective efficacy but with reduced potency. The meta (**16**) and para (**17**) methoxy analogues have lost selectivity because of increased α_1 efficacy, as has the thienyl analogue **23**.

Small *N*-alkyl groups on the tetrahydropyridine (**25**−**27**, **30**) tend to exhibit antagonist or low partial agonist characteristics in electrophysiology studies (Table 2). The larger alkyl groups (**29**, **31**) give much larger partial agonist character. Despite differences in the maximum potentiation between these *N*-alkyl analogues, none exhibit any selectivity. The 2- (**35**) and 4-fluorobenzyl (**37**) analogues (Table 3) exhibit no selectivity and are partial agonists. In contrast, the 3-fluorobenzyl analogue **36** and to some degree the 3,4-difluorobenzyl analogue **38** are more α_1-selective. The 2-methyl analogue **39** also has enhanced α_1 selectivity, whereas the 4-methyl (**40**) and 4-methoxy (**41**) analogues exhibit much lower agonism with modest α_2 selectivity. The heteroarylmethyl analogues **42**−**44** are all partial agonists. The 3- (**42**) and 4- (**43**) pyridylmethyl analogues have α_2/α_3 selectivity. The thienylmethyl analogue (**45**) and the racemic α-methyl analogue (**46**) exhibit significantly less α_2 activity than the corresponding benzyl analogue **9**. The acyl (**51**−**52**) and carbamoyl (**62**) derivatives are essentially antagonists (Table 4).

Discussion

The effect of the aryl substituent has only modest impact on affinity except in the case of ortho fluoro substitution. The ortho fluoro can enhance affinity, especially when combined with another substituent. For example, compare **12** (21 nM) to **19** (2 nM) and compare **66** (240 nM) to **67**(45 nM) (see Tables 1 and 5). Note that for the tetrahydropyridine *N*-benzoyl analogues (Table 5), essentially only the ortho fluoro analogue (**55**) maintains potency. Only small substituents in the ortho position of the aryl are tolerated (**10** vs **15**). Electron-withdrawing groups in the para position are disfavored (**12**, **14**), especially compared to the corresponding meta (**11**, **13**) and ortho (**10**) analogues. There is no strong correlation of the aryl substituent effect on functional activity in electrophysiology studies. Both electron-deficient and electron-rich aryl rings can be small partial agonists or fuller agonists. Neither does size seem to play a role on the functional activity in electrophysiology.

Table 5. Effect of Substituents on Binding Affinity



compd	N−R	aryl	K_i [a] (nM)
63	COPh	Ph	301
9	COPh	2-F−Ph	1.3
64	COPh	3-Cl−Ph	NA[b]
65	COPh	4-OMe−Ph	NA
66	Me	4-OMe−Ph	240
67	Me	2-F−4-OMe−Ph	45
52	COEt	2-F−Ph	216
68	COEt	4-OMe−Ph	NA

[a] Analogues **63**−**68** were run only once as a set of triplicates. [b] NA = not achieved for IC_{50} at the highest dose tested.

In contrast, the substituent on the tetrahydropyridine plays a more significant role. Small alkyl as well as the acyl and carbamoyl substituents all possess reduced affinity. Groups occupying about the same space as benzyl are optimal for affinity. Less lipophilic substituents [small alkyl (**25**−**28**, **30**) or those containing a heteroatom (**34**, **41**−**47**, **51**, **52**, **62**)] tend to exhibit lower, partial agonist characteristics in electrophysiology studies. Both of the pyridylmethyl analogues (**42**, **43**) exhibit α_2/α_3 selectivity. More lipophilic substituents (**31**, **36**, **38**, **39**) tend to have increased efficacy, especially on α_1, but a few have selectivity for the others (e.g., **45** for α_3). Both the 4-Me (**40**) and the 4-OMe (**41**) substituted benzyl analogues have reduced potency such that combined with the low efficacy, they would be considered bordering on antagonism.

Table 6. Rat Behavioral Spontaneous Locomotor Activity Studies

compd	OMNI med[a] (mg/kg)	compd	OMNI med[a] (mg/kg)
11	2	**43**	NS[b]
12	1	zolpidem	0.25
17	0.06	zaleplon	0.25
42	0.5	alprazolam	0.125

[a] Compared with that administered in 50% aqueous PEG-400, iv, used as dosing and control vehicle. [b] NS = not significant.

For the most part, the affinity SAR for the closely related triazolopyrimidones reported previously[6] is similar to the imidazopyridiones reported here. However, the same SAR is not observed with respect to efficacy. No electrophysiology data had been reported for the triazolopyrimidone templates, only GABA shifts. Historically it was thought that the shift in affinity of a ligand in the absence of GABA vs in the presence of GABA reflected the amount of agonist character of the ligand. The amount of shift was reported as the ratio of the IC_{50} values. Thus, a ratio of 1 was deemed an antagonist, those with a ratio less than 1 an inverse agonist, and those with a ratio greater than or equal to 2 an agonist. The corresponding triazolopyrimidone analogues[6] of **9** and **42** reportedly have the same GABA shift (1.4), yet the efficacy of **9** is twice that of **42**. Similarly, the corresponding triazolo analogues[6] of **11** and **12** reportedly have comparable GABA shifts (1.6 and 1.7 respectively), yet **12** has twice the efficacy of **11**. Thus, either there are significant differences in efficacies between these two templates or the use of GABA shifts is not accurate. The latter seems most likely because GABA shifts were typically run on rat brain and thus cannot distinguish between receptor subtypes.

Several compounds were selected to run in rat behavioral locomotor studies. Reduction of spontaneous locomotor activity is often used as a measure of sedation. The results of these studies are shown in Table 6. The observed minimum efficacious doses (med) correlate with the potency (EC_{50}) in electrophysiology. The degree of GABA potentiation in electrophysiology also correlates with efficacy in locomotor behavior. In electrophysiology, **12** is about 2 times more efficacious than **11** and is twice as potent in vivo. In electrophysiology studies, **17** has efficacy equivalent to that of **12**, but **17** is 7-fold more potent. This is reflected in the significant increase in potency of **17** in locomotor activity studies.

There are two compounds (zolpidem and zaleplon) that have higher affinity for the α_1 receptor and are now marketed as hypnotics. However, they can still exhibit the classical side effects such as memory impairment and rebound insomnia.[14] We felt that a true hypnotic agent with a cleaner side effect profile would have minimal activity on α_1 and α_5 subtypes.[15] The α_1 subtype is found predominantly in the cortex, thalamus, and brainstem, while α_5 is the major subtype in the hippocampus, a site known to be involved with memory. In fact, recent studies[16] on α_1 mutant mice, in which GABA still binds but benzodiazepine receptor ligands do not, demonstrate that the *sedative* component of diazepam is due to α_1 receptors but not to the *hypnotic* activity, the latter being a measure of latency to fall asleep. Furthermore, in these same α_1 mutant mice studies, some amnestic abilities were attributed to efficacy on the α_1 subytpe. This would explain the memory impairment sometimes reported[14] for these two marketed hypnotics that are α_1-preferring, despite lacking activity on the hippocampal α_5 subtype.

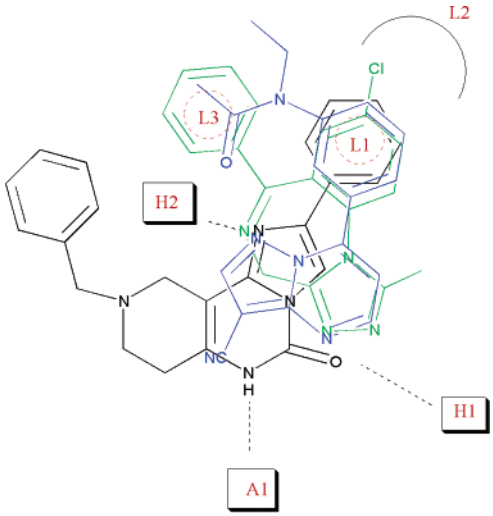


Figure 2. Overlay of **9** (black) with alprazolam (green) and zaleplon (blue). H1 and H2 denote hydrogen donor sites on the receptor. A1 denotes a hydrogen acceptor site on the receptor. L1, L2, and L3 denote lipophilic pockets on the receptor.

Here, we note that sedation is still observed with a lower intrinsic partial agonist bearing α_2/α_3 selectivity (**42**). It is notable that even though **42** is significantly less efficacious in electrophysiology studies[17] than either the marketed hypnotics zolpidem or zaleplon (see Table 1), or even the marketed anxiolytic Xanax (alprazolam; see Table 1), the minimum efficacious doses in locomotor activity are not all that different. Because **42** has minimal functional activity in electrophysiology studies on α_1 and α_5, memory side effects would not be anticipated for this analogue. Also noteworthy is that although analogue **17** is about half as efficacious as the marketed anxiolytic alprazolam in electrophysiology studies (see Table 1), analogue **17** is over twice as potent in vivo (see Table 6). Because no exposure studies were conducted with the analogues reported here, differences in the in vivo efficacy could also possibly be due to differences in plasma and/or brain levels.

In summary, we have shown here the achievement of functional selectivity in ligands that bind to the benzodiazepine receptor. These selective agents such as **42** would be expected to have reduced propensity in a clinical setting for negative side effects such as memory impairment as the classical benzodiazepines. Unfortunately, many of the analogues were too insoluble to run either in electrophysiology studies or in behavioral studies. Furthermore, modeling of our template in the emerging pharmacophore model (see Figure 2) indicated that we were approaching the full agonist pocket of benzodiazepines ("L3" in Cook[18] nomenclature). This pocket is considered to be lipophilic, and we believe it to be predominantly an α_1 pocket. The lower intrinsic activity of the basic heteroarylmethyl analogues (**42**–**44**) adheres to this hypothesis. Efforts were shifted to other templates that we had been investigating that seemed to possess better biopharmaceutical properties. Indeed, these other templates ultimately led to further

refinement of our understanding the importance of the $GABA_A$ subtypes in many CNS disorders, and multiple clinical candidates. Data on the other series and findings will be reported in the future.

Experimental Section

Chemistry. Reagents and solvents were used from commercial sources without purification. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 300 or a Varian Unity 400 MHz spectrometer. Electron ionization mass spectra (MS) were recorded on a Hewlett-Packard 5890 mass spectrometer. Elemental analyses were performed at Robertson Microlabs, Madison, NJ, and are within 0.4% of theoretical value. For those that did not give satisfactory results from elemental analyses, the purity was established via HPLC as provided in the Supporting Information.

9-Benzoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (55). To a stirred suspension of 4-amino-3-cyano-1,2,5,6-tetrahydropyridine[7] (95.51 g, 775 mmol) in pyridine (500 mL), benzoic anhydride (274 g, 1.20 mol) was added in portions over 1−2 h. After the mixture was stirred an additional 0.5 h, the precipitate was collected, washed with toluene and then ether, and dried to give 1-benzoyl-4-amino-3-cyano-1,2,5,6,-tetrahydropyridine as a white solid, mp 178−181 °C.

A slurry of 1-benzoyl-4-amino-3-cyano-1,2,5,6-tetrahydropyridine (35.23 g, 155 mmol) and urea (46.55 g, 775 mmol) in 2-(2-ethoxyethoxy)ethanol (75 mL) was gradually heated to 205 °C and maintained for 1.5 h. Heating was ceased and hot water was *carefully* added while shaking the mixture. The mixture was vacuum-filtered to collect the precipitate while hot. The precipitate was washed with hot water until the filtrate was colorless. The precipitate was then washed with ethanol until the filtrate was colorless and then finally washed with EtOAc and allowed to dry to afford 6-benzoyl-4-amino-6,7,8,9-tetrahydropyrido[3.4-*e*]pyrimidin-2-one as a light-yellow solid.

A mixture of 6-benzoyl-4-amino-6,7,8,9-tetrahydropyrido-[3.4-*e*]pyrimidin-2-one (1 g, 3.7 mmol) and 1-bromo-2′-fluoroacetophenone (0.74 g, 3.7 mmol) in DMF (8 mL) was heated at 150 °C. The reaction mixture was poured into ice/water and the precipitate was collected to give **55**. Later, a second crop was isolated as a cream solid. ^{1}H NMR (DMSO-d_6): δ 7.88−8.18 (m, 2H), 7.24−7.53 (m, 8H), 4.41−4.71 (m, 2H), 3.59−3.94 (m, 2H), 2.68 (s, 2H). LCMS, *m*/*z*: MH^+ 389.2, MH^- 387. Mp 269−271 °C. HPLC purity in Supporting Information.

2-(2-Fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]-pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (24). To a solution of **55** (435 mg, 1.1 mmol) in ethanol (5 mL) was added 5 mL of 50% aqueous sodium hyroxide. The mixture was refluxed for 1 h, poured into saturated aqueous ammonium chloride, and extracted 2× with 10% methanol/EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and triturated with methanol/ether to give **24**, mp >310 °C. ^{1}H NMR (DMSO-d_6): δ 8.21 (t, J = 7.13 Hz, 1H), 8.01 (d, J = 4.02 Hz, 1H), 7.34−7.46 (m, 2H), 4.17 (s, 2H), 2.75−2.77 (m, 2H), 2.54−2.59 (m, 2H). LCMS, *m*/*z*: MH^- 283.3. HPLC purity in Supporting Information.

9-(2-Fluorobenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (35). 2-Fluorobenzyl bromide (54 μL, 0.45 mmol) was added to a solution of **24** (128 mg, 0.45 mmol) and triethylamine (76 μL, 0.54 mmol) in DMF (1 mL) at room temperature. The reaction mixture was stirred and then concentrated. Aqueous sodium bicarbonate was added, the aqueous layer was extracted 2× with 10% methanol/EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and triturated with methanol/ether to give **35** as an off-white solid, mp 270−273 °C. The HCl salt was prepared in ethanol. ^{1}H NMR (DMSO-d_6): δ 8.10 (t, J = 8.1 Hz, 1H), 7.97 (d, J = 3.84 Hz, 1H), 7.83 (t, J = 7.28 Hz, 1H), 7.55−7.58 (m, 1H), 7.31−7.41 (m, 5H), 4.56−4.62 (m, 2H), 4.24−4.41 (m, 2H), 3.53−3.65 (m, 1H), 3.35−3.47 (m, 1H), 3.0−3.12 (m, 1H), 2.76−2.88 (m, 1H). LCMS, *m*/*z*: MH^+ 393.3, MH^- 391.2. Anal. ($C_{22}H_{18}F_2N_4O$·HCL·H_2O) C, H, N.

The following compounds were prepared in a fashion similar to that of **35**, starting with the appropriate 1-bromoacetophenone.

9-Benzyl-2-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*c*]-pyrido[3,4-*e*]pyrimidin-5(6*H*)-one Hydrochloride (9). ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1H), 7.93 (d, J = 8.52 Hz, 2H), 7.65−7.76 (m, 2H), 7.47−7.59 (m, 3H), 7.40 (t, J = 7.42 Hz, 2H), 7.31 (d, J = 7.35 Hz, 1H), 4.54 (s, 2H), 4.18−4.29. HPLC purity in Supporting Information.

9-(2-Benzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (10). ^{1}H NMR (DMSO-d_6): δ 8.12 (t, J = 7.76 Hz, 1H), 7.94 (d, J = 4.23 Hz, 1H), 7.29−7.47 (m, 8H), 3.78 (s, 2H), 3.56 (s, 2H), 2.81−2.84 (m, 2H), 2.66 (s, 2H). LCMS, *m*/*z*: MH^+ 375.3, MH^- 373.3. Anal. ($C_{22}H_{19}FN_4O$·2HCl·0.5H_2O) C, H, N.

9-Benzyl-2-(3-fluorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (11). ^{1}H NMR (DMSO-d_6): δ 8.37 (d, J = 2.88 Hz, 1H), 7.79 (d, J = 7.71 Hz, 1H), 7.73 (d, J = 10.86 Hz, 1H), 7.30−7.46 (m, 5H), 7.29 (d, J = 4.07 Hz, 1H), 7.14 (t, J = 8.48 Hz, 1H), 3.75 (s, 2H), 3.52 (s, 2H), 2.79 (s, 2H), 2.63 (s, 2H). LCMS, *m*/*z*: MH^+ 375.3, MH^- 373.3. Anal. ($C_{20}H_{19}FN_4O$·2HCl·0.25H_2O) C, H, N.

9-Benzyl-2-(4-fluorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one Dihydrochloride (12). ^{1}H NMR (DMSO-d_6): δ 8.35 (s, 1H), 7.97(dd, J = 4.04, 8.79 Hz, 2H), 7.71−7.74 (m, 2H), 7.47−7.49 (m, 3H), 7.23 (t, J = 8.79 Hz, 2H), 4.54 (s, 2H), 4.23 (s, 2H), 3.59−3.71 (m, 1H), 3.29−3.41 (m, 1H), 3.06−3.18 (m, 1H), 2.76−2.88 (m, 1H). LCMS, *m*/*z*: MH^+ 375.3, MH^- 373.3. Anal. ($C_{18}H_{17}FN_4O_2$·H_2O·2HCl) C, H, F, N.

9-Benzyl-2-(3-chlorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one Mesylate (13). ^{1}H NMR (DMSO-d_6): δ 8.47−8.53 (m, 1H), 7.88−7.94 (m, 1H), 7.76−7.82 (m, 1H), 7.65−7.71 (m, 2H), 7.41−7.65 (m, 5H), 4.6−4.71 (m, 2H), 4.41−4.53 (m, 2H), 3.65−3.68 (m, 2H), 3.18−3.24 (m, 2H), 2.68 (s, 6H). LCMS, *m*/*z*: MH^+ 391.2, MH^- 389.2. HPLC purity in Supporting Information.

9-Benzyl-2-(4-chlorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (14). ^{1}H NMR (DMSO-d_6): δ 8.06 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.34−7.44 (m, 6H), 3.81 (s, 2H), 3.68 (s, 2H), 2.87−2.99 (m, 2H), 2.70−2.73 (m, 2H). LCMS, *m*/*z*: MH^+ 391.2, MH^- 389.2. HPLC purity in Supporting Information.

9-Benzyl 2-(2-Methoxyphenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*] pyrimidin-5(6*H*)-one (15). ^{1}H NMR (DMSO-d_6): δ 8.12 (d, J = 7.7 Hz, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.25−7.46 (m, 6H), 7.12 (d, J = 7.7 Hz, 1H), 7.0 (t, J = 11 Hz, 1H), 3.96 (s, 3H), 3.75 (s, 2H), 3.5 (s, 2H), 2.73−2.8 (m, 2H), 2.54−2.62 (m, 2H). LCMS, *m*/*z*: MH^+ 387.3, MH^- 385.3.

9-Benzyl-2-(3-methoxy)phenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (16). ^{1}H NMR (DMSO-d_6): δ 8.25 (s, 1H), 7.25−7.44 (m, 6H), 6.92 (d, J = 8.79 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 2H), 3.48 (s, 2H), 2.74 (s, 2H), 2.59 (s, 2H). LCMS, *m*/*z*: MH^+ 387.3, MH^- 385.3. Anal. ($C_{23}H_{18}N_4O_2$·0.25H_2O) C, H, N.

9-Benzyl-2-(4-methoxyphenyl)-7,8,9,10-tetrahydroimidazo[1,2-c]pyrido[3,4-e]pyrimidin-5(6*H*)-one (17). ^{1}H NMR (DMSO-d_6): δ 8.11−8.16 (m, 1H), 7.82−7.89 (m, 2H), 7.33−7.34 (m, 5H), 6.95−7.0 (m, 2h), 3.74−3.82 (m, 5H), 3.51 (s, 2H), 2.78−2.85 (m, 2H), 2.59−2.65 (m, 2H). LCMS, *m*/*z*: MH^+ 387.2, MH^- 385.3. Anal. ($C_{23}H_{22}N_4O_2$) C, H, N.

9-Benzyl-2-(4-methylphenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (18). ^{1}H NMR (DMSO-d_6): δ 8.12−8.24 (m, 1H), 7.80 (d, J = 7.69 Hz, 2H), 7.35−7.59 (m, 5H), 7.19 (d, J = 7.96 Hz, 2H), 4.1−4.6 (m, 2H), 3.4−3.9 (m, 2H), 2.6−2.9 (m, 2H), 2.35 (s, 3H). LCMS, *m*/*z*: MH^+ 371.3, MH^- 369.3. HPLC purity in Supporting Information.

9-Benzyl-2-(2,4-difluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (19). ^{1}H NMR (DMSO-d_6): δ 8.04−8.09 (m, 1H), 7.86 (d, J = 4.2 Hz, 1H), 7.27−7.38 (m, 5H), 7.14 (t, J = 8.52 Hz, 2H), 3.72 (s, 2H), 3.49 (s, 2H), 2.77 (s, 2H), 2.60 (s, 2H). LCMS, *m*/*z*: MH^+ 393.3, MH^- 391.2. Anal. ($C_{22}H_{18}F_2N_4O$) C, H, F, N.

9-Benzyl-2-(2,5-difluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one Dimeyslate (20). ^{1}H NMR (DMSO-d_6): δ 8.03 (d, J = 3.3 Hz, 1H), 7.75−7.78 (m, 1H), 7.51−7.60 (m, 5H), 7.37−7.45 (m, 1H), 7.25−7.28 (m, 1H), 4.42−4.78 (m, 3H), 4.27−4.32 (m, 1H), 3.76−3.8 (m, 1H), 3.40−3.43 (m, 1H), 2.91 (m, 2H), 2.31 (s, 6H). LCMS, *m*/*z*: MH^+ 393.3, MH^- 391.2. Anal. ($C_{22}H_{18}F_2N_4O{\cdot}MSOH{\cdot}H_2O$) C, H, N, S.

9-Benzyl-2-(3,4-difluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-e]pyrimidin-5(6*H*)-one (21). ^{1}H NMR (DMSO-d_6): δ 8.29−8.41 (m, 1H), 7.94 (t, J = 9.75 Hz, 1 H), 7.71−7.82 (m, 1H), 7.35−7.53 (m, 6H), 4.1−4.7 (m, 2H), 3.6−3.8 (m, 2H), 2.5−2.9 (m, 2H). LCMS, *m*/*z*: MH^+ 393.4, MH^- 391.2. Anal. ($C_{22}H_{187}F_2N_4O{\cdot}2HCL{\cdot}H_2O$) C, H, N.

9-Benzyl-2-(2-fluoro-4-methoxyphenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (22). ^{1}H NMR (DMSO-d_6): δ 7.95 (t, J = 8.93 Hz, 1H), 7.76 (d, J = 4.4 Hz, 1H), 7.28−7.36 (m, 5H), 6.92 (d, J = 13.5 Hz, 1H), 6.82−6.86 (m, 1H), 3.78 (s, 3H), 3.72 (s, 2H), 3.49 (s, 2H), 2.74−2.76 (m, 2H), 2.59 (s, 2H). LCMS, *m*/*z*: MH^+ 405.4, MH^- 403.4. HPLC purity in Supporting Information.

9-Benzyl-2-(2-thienyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (23). ^{1}H NMR (DMSO-d_6): δ 7.89 (s, 1H), 7.29−7.50 (m, 7H), 7.06−7.09 (m, 1H), 3.80 (s, 2H), 3.67 (s, 2H), 2.84−2.88 (m, 2H), 2.68−2.70 (m, 2H). LCMS, *m*/*z*: MH^+ 363.2, MH^- 361.2. HPLC purity in Supporting Information.

The following were prepared in a fashion similar to that for **55** starting from **24**.

9-(2-Pyrimidyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one Dihydrochloride (34). ^{1}H NMR (DMSO-d_6): δ 8.46 (d, J = 4.66 Hz, 2H), 8.18−8.23 (m, 1H), 7.99 (d, J = 4.12 Hz, 1H), 7.30−7.43 (m, 3H), 6.74 (d, J = 4.67 Hz, 1H), 4.85 (s, 2h), 4.11 (t, J = 5.77 Hz, 2H), 2.65−2.71 (m, 2H). LCMS, *m*/*z*: MH^+ 363.2, MH^- 361.2. HPLC purity in Supporting Information.

9-(3-Fluorobenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (36). ^{1}H NMR (DMSO-d_6): δ 8.08 (t, J = 7.69 Hz, 1H), 7.89 (d, J = 4.1 Hz, 1H), 7.07−7.43 (m, 7H), 3.75 (s, 2H), 3.53 (s, 2H), 2.77 (s, 2H), 2.61 (s, 2H). LCMS, *m*/*z*: MH^+ 393.2, MH^- 391.2. HPLC purity in Supporting Information.

9-(4-Fluorobenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (37). ^{1}H NMR (DMSO-d_6): δ 8.11 (t, J = 7.75 Hz, 1H), 7.92 (d, J = 4.2 Hz, 1H), 7.26−7.46 (m, 5h), 7.19 (t, J = 8.89 Hz, 2H), 3.79 (s, 2H), 3.53 (s, 2H), 2.73−2.78 (m, 2H), 2.58−2.69 (m, 2H). LCMS, *m*/*z*: MH^+ 393.3, MH^- 391.2. Anal. ($C_{22}H_{18}F_2N_4O_2{\cdot}2HCl{\cdot}H_2O$) C, H, F, N.

9-(3,4-Difluorobenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (38). ^{1}H NMR (DMSO-d_6): δ 8.08 (t, J = 7.83 Hz, 1H), 7.89−7.90 (m, 1H), 7.24−7.45 (m, 6H), 3.72 (s, 2H), 3.53 (s, 2H), 2.76 (s, 2H), 2.60 (s, 2H). LCMS, *m*/*z*: MH^+ 411.3, MH^- 409.3. Anal. ($C_{22}H_{17}F_3N_4O$) C, H, F, N.

9-(2-Methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (39). ^{1}H NMR (DMSO-d_6): δ 8.08 (t, J = 7.1 Hz, 1H), 7.89 (d, J = 4.1 Hz, 1H), 7.17−7.37 (m, 7H), 3.69 (s, 2H), 3.53 (s, 2H), 2.74−2.79 (m, 2H), 2.59 (s, 2H), 2.33 (s, 3H). LCMS, *m*/*z*: MH^+ 389.2, MH^- 387.2. Anal. ($C_{23}H_{21}FN_4O$) C, H, F, N.

9-(4-Methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (40). ^{1}H NMR (DMSO-d_6): δ 8.03−8.12 (m, 1h), 7.88−7.94 (m, 1H), 7.12−7.35 (m, 7H), 3.59−3.76 (m, 2H), 3.41−3.76 (m, 2H), 2.71−2.82 (m, 2H), 2.53−2.71 (m, 2H), 2.29 (s, 3H). LCMS, *m*/*z*: MH^+ 389.4, MH^- 387.2. HPLC purity in Supporting Information.

9-(4-Methoxybenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (41). ^{1}H NMR (DMSO-d_6): δ 8.11 (t, J = 3.85 Hz, 1H), 7.41 (d, J = 4.1 Hz, 1H), 7.27−7.43 (m, 5H), 6.92 (d, J = 8.55 Hz, 2H), 3.75 (s, 3H), 3.68 (s, 2H), 3.5 (s, 2H), 2.77 (s, 2h), 2.62 (s, 2H). LCMS, *m*/*z*: MH^+ 405.3. HPLC purity in Supporting Information.[19]

9-(2-Thienylmethyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (45). ^{1}H NMR (DMSO-d_6): δ 8.09 (t, J = 7.97 Hz, 1H), 7.89 (d, J = 4.12 Hz, 1H), 7.45 (d, J = 5.22 Hz, 1H), 7.24−7.37 (m, 3H), 7.05 (s, 1H), 6.99 (d, J = 4.12 Hz, 2H), 3.95 (s, 2H), 3.57 (s, 2H), 2.75−2.80 (m, 2H), 2.60 (s, 2H). LCMS, *m*/*z*: MH^+ 381.2, MH^- 379.3. Anal. ($C_{20}H_{17}FN_4OS$) C, H, F, N, S.

(+)-9-(α-Methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (46). ^{1}H NMR (DMSO-d_6): δ 8.08−8.14 (m, 1H), 7.91 (d, J = 4.21 Hz, 1H), 7.28−7.42 (m, 8H), 3.97−4.05 (2H), 3.66 (d, J = 14.6 Hz, 1H), 3.5 (d, J = 14.8 Hz, 1H), 2.56−2.76 (m, 3H), 1.41 (d, J = 6.7 Hz, 3H). LCMS, *m*/*z*: MH^+ 389.3, MH^- 387.3. Anal. ($C_{23}H_{21}FN_4O{\cdot}2HCl{\cdot}H_2O$) C, H, F, N.

(*S*)-(+)-9-(α-Methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (47). ^{1}H NMR (DMSO-d_6): δ 8.09 (t, J = 7.42 Hz, 1H), 7.89 (d, J = 2.47 Hz, 1H), 7.25−7.37 (m, 8H), 3.72 (d, J = 5.77 Hz, 1H), 3.63 (d, J = 15.38 Hz, 1H), 3.48 (d, J = 14.28 Hz, 1H), 2.68−2.79 (m, 2H), 2.53−2.62 (m, 2H), 1.4 (d, J = 6.1 Hz, 3H). LCMS, *m*/*z*: MH^+ 389.2, MH^- 387.3. HPLC purity in Supporting Information.

(+) 9-(2-Fluoro-α-methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (48). ^{1}H NMR (DMSO-d_6): δ 8.07−8.14 (m, 1H), 7.89 (d, J = 4 Hz, 1H), 7.22−7.46 (m, 5H), 7.11−7.21 (m, 2H), 3.70−3.79 (m, 1H), 3.61 (d, J = 7.1 Hz, 1H), 3.49 (d, J = 7.1 Hz, 1H), 2.61−2.71 (m, 2H), 1.43 (t, J = 4 Hz, 3H). Anal. ($C_{23}H_{20}F_2N_4O{\cdot}2HCl$) C, H, F, N.

(+) 9-(3-Fluoro-α-methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (49). ^{1}H NMR (DMSO-d_6): δ 8.12−8.24 (m, 1H), 7.94−8.0 (m, 2H), 7.69 (d, J = 9.1 Hz, 1H), 7.57 (s, 2H), 7.26−7.38 (m, 3H), 4.71−4.82 (m, 1H), 4.47−4.65 (m, 1H), 4.03 (s, 1H), 3.47−3.59 (m, 1H), 2.71−3.47 (m, 4H), 1.80 (d, J = 4.9 Hz, 3H). LCMS, *m*/*z*: MH^+ 407.3, MH^- 405.3. HPLC purity in Supporting Information.

(+) 9-(4-Fluoro-α-methylbenzyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (50). ^{1}H NMR (DMSO-d_6): δ 8.10 (t, J = 7 Hz, 1H), 7.89 (d, J = 4 Hz, 1H), 7.25−7.46 (m, 5H), 7.11−7.21 (m, 2H), 3.70−3.79 (m, 1H), 3.61 (d, J = 7.1 Hz, 1H), 3.49 (d, J = 7.1 Hz, 1H), 2.61−2.71 (m, 2H), 1.43 (t, J = 4 Hz, 3H). LCMS, *m*/*z*: MH^+ 407.4, MH^- 405.3. Anal. ($C_{23}H_{20}F_2N_4O{\cdot}2HCl$) C, H, F, N.

9-Propionyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (52). Propionyl chloride (39 μL, 0.4 mmol) was added to a solution of **24** (124 mg, 0.4 mmol) and triethylamine (74 μL, 0.5 mmoL) in DMF (2 mL) at room temperature. The reaction mixture was stirred for 1 h and then was poured into ice/water. The precipitate was collected, washed with water and then with 95% ethanol and dried to yield **52** as a white solid, mp >310 °C. ^{1}H NMR (DMSO-d_6): δ 8.19−8.21 (m, 1H), 7.94 (d, J = 3.9 Hz, 1H), 7.31−7.41 (m, 3H), 4.59 (s, 2H), 3.74−3.79 (m, 2H), 2.65−2.7 (m, 2H), 2.55−2.6 (m, 2H), 1.03 (t, J = 7.33 Hz, 3H). LCMS, *m*/*z*: MH^+ 341.2, MH^- 339.2. Anal. ($C_{18}H_{17}FN_4O_2$) C, H, F, N.

The following compounds were prepared according to a method similar to that of **52**.

9-Acetyl 2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (51). ^{1}H NMR (DMSO-d_6): δ 8.17−8.19 (m, 1H), 7.93−7.95 (m, 1H), 7.29−7.39 (m, 3H), 4.56−4.59 (m, 2H), 3.73−3.78 (m, 2H), 2.66−2.68 (m, 2H), 2.11−2.14 (m, 3H). LCMS, *m*/*z*: MH^+ 327.2, MH^- 325.2. Anal. ($C_{17}H_{15}FN_4O_2$) C, H, F, N.

9-Butanoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (53). ^{1}H NMR (DMSO-d_6): δ 8.20 (t, J = 7.57 Hz, 1H), 7.95 (d, J = 4.12 Hz, 1H), 7.31−7.39 (m, 3H), 3.76−3.78 (m, 2H), 2.67 (s, 2H), 2.56 (s, 2H), 2.37−2.46 (m, 2H), 1.53−1.58 (m, 2H), 0.92 (t, J = 7.33 Hz, 3H). LCMS, *m/z*: MH^+ 355.2, MH^- 353.3. HPLC purity in Supporting Information.

9-Hexanoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (54). ^{1}H NMR (DMSO-d_6): δ 8.15−8.24 (m, 1H), 7.40 (s, 1H), 7.24−7.41 (m, 3H), 4.58 (s, 2H), 3.71−3.82 (m, 2H), 2.65 (s, 2H), 2.43−2.69 (m, 2H), 1.53−1.65 (m, 2H), 1.29−1.41 (m, 4H), 0.76−0.88 (m, 3H). LCMS, *m/z*: MH^+ 383.3, MH^- 381.3. Anal. ($C_{21}H_{23}FN_4O_2$) C, H, F, N.

9-Phenylacetyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (56). ^{1}H NMR (DMSO-d_6): δ 8.23−8.27 (m, 1H), 7.94 (d, J = 3.42 Hz, 1H), 7.23−7.40 (m, 8H), 4.63 (s, 2H), 3.82−3.9 (m 4H), 2.5 (m, 2H). LCMS, *m/z*: MH^+ 403.4, MH^- 401.3. HPLC purity in Supporting Information.

9-Picolinoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (57). ^{1}H NMR (DMSO-d_6): δ 8.63 (d, J = 5.49 Hz, 1H), 7.66 (t, J = 7.01 Hz, 1H), 7.88−7.96 (m, 2H), 7.66 (d, J = 7.69 Hz, 1H), 7.52 (t, J = 6.32 Hz, 1H), 7.27−7.38 (m, 3H), 4.77 (s, 1H), 4.63 (s, 1H), 3.94−4.0 (m, 1H), 2.69 (s, 2H). LCMS, *m/z*: MH^+ 390.2, MH^- 388.2. HPLC purity in Supporting Information.

9-Nicotinoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (58). ^{1}H NMR (DMSO-d_6): δ 8.71−8.73 (m, 2H), 8.24−8.26 (m, 1h), 7.87−8.0 (m, 2h), 7.52−7.57 (m, 1H), 7.25−7.35 (m, 3H), 4.76−4.79 (m, 1h), 4.54−4.59 (m, 1H), 3.95−4.0 (m, 1H), 3.60−3.65 (m, 1h), 2.65−2.70 (m, 2H). LCMS, *m/z*: MH^+ 390.2, MH^- 388.2. HPLC purity in Supporting Information.

9-Isonicotinoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6H)-one Dimesylate (59). ^{1}H NMR (DMSO-d_6): δ 8.96 (s, 2h), 8.21−8.29 (m, 1H), 7.91−8.12 (m, 3H), 7.24−7.47 (m, 3h), 4.46 (s, 1H), 3.98 (s, 1H), 3.57 (s, 1H), 2.62−2.71 (m, 2H), 2.34 (s, 6H). LCMS, *m/z*: MH^+ 390.2, MH^- 388.2. HPLC purity in Supporting Information.

9-Carbobenzyloxy-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (62). Benzyl chloroformate (57 μL, 0.4 mmol) was added to a solution of **24** (124 mg, 0.4 mmol) and triethylamine (74 μL, 0.5 mmol) in DMF (1 mL) at room temperature. The reaction mixture was stirred for 1 h and then was poured into ice/water. The precipitate was collected, washed with 95% ethanol and then ether, dried, and recrystallized from aqueous ethanol to afford **62** as an off-white solid, mp 250 °C (dec). ^{1}H NMR (DMSO-d_6): δ 8.12−8.21 (m, 1H), 7.93 (d, J = 3.84 Hz, 1H), 7.29−7.39 (m, 8H), 5.14 (s, 2H), 4.55 (s, 2H), 3.71−3.76 (m, 2H), 2.53−2.65 (m 2H). LCMS, *m/z*: MH^+ 419.3, MH^- 417.2. HPLC purity in Supporting Information.

The following compounds were prepared in a fashion similar to that for **62**.

9-Carboethoxy-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (60). ^{1}H NMR (DMSO-d_6): δ 8.20 (t, J = 7.38 Hz, 1H), 7.95 (d, J = 4.02 Hz, 1H), 7.31−7.42 (m, 3H), 4.54 (s, 2H), 4.13 (q, J = 7.05 Hz, 2H), 3.72 (s, 2H), 2.62 (s, 2H), 1.24 (t, J = 7.08 Hz, 3H). LCMS, *m/z*: MH^+ 357.2, MH^- 355.2. HPLC purity in Supporting Information.

9-Carbobutoxy-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (61). ^{1}H NMR (DMSO-d_6): δ 8.18 (t, J = 2.99 Hz), 7.94 (d, J = 3.95 Hz), 7.31−7.39 (m, 3H), 4.52 (s, 2H), 4.06−4.08 (m, 2H), 3.71 (s, 2H), 2.61 (s, 2H), 1.58−1.6 (m, 2H), 1.34−1.39 (m, 2h), 0.89−0.93 (m, 3H). LCMS, *m/z*: MH^+ 385.2, MH^- 383.3. Anal. ($C_{20}H_{21}FN_4O_3$) C, H, N.

9-*n*-Butyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (29). To **24** (171 mg, 0.6 mmol) in pH 4−5 HCl/methanol (6 mL) at room temperature was added *n*-butyraldehyde (53 μL, 0.6 mmol) and sodium cyanoborohydride (38 mg, 0.6 mmol). The reaction mixture was stirred for 6 h, and then concentrated HCl was added until the mixture became homogeneous. The solution was diluted with water (5 mL) and extracted 2× with ether. The aqueous layer was made alkaline with aqueous ammonium hydroxide, saturated with sodium chloride, and extracted 2× with 10% methanol/EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the resulting solid was recrystallized from aqueous ethanol to give **29** as a white fluffy solid, mp 251−253 °C. ^{1}H NMR (DMSO-d_6): δ 8.18 (t, J = 7.76 Hz, 1H), 7.93 (d, J = 4.12 Hz, 1H), 7.30−7.40 (m, 3H), 3.53 (s, 2H), 2.71−2.74 (m, 2H), 2.59 (s, 2H), 1.51−1.55 (m, 2H), 1.35 (q, J = 7.52 Hz, 2H), 0.93 (t, J = 7.33 Hz, 3H). LCMS, *m/z*: MH^+ 341.2, MH^- 339.2. Anal. ($C_{19}H_{21}FN_4O$) C, H, N.

The following compounds were prepared in a fashion similar to that for **29**.

9-Methyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (25). ^{1}H NMR (DMSO-d_6): δ 8.16 (t, J = 7.97 Hz, 1H), 7.92 (d, J = 2.93 Hz, 1H), 7.29−7.39 (m, 3H), 3.51 (s, 2H), 2.65−2.7 (m, 2H), 2.61 (s, 2H), 2.42 (s, 3H). LCMS, *m/z*: MH^- 297.3. HPLC purity in Supporting Information.

9-Ethyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (26). ^{1}H NMR (DMSO-d_6): δ 8.14−8.17 (m, 1H), 7.90 (d, J = 3.84 Hz, 1H), 7.18−7.41 (m, 3H), 3.52 (s, 2H), 2.71 (s, 2H), 2.50−2.59 (m, 4H), 1.12 (t, J = 5.77 Hz, 3H). LCMS, *m/z*: MH^- 311.2. Anal. ($C_{17}H_{17}FN_4O\cdot 0.5NaCl$) C, H, N.[20]

9-Allyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo-[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (27). ^{1}H NMR (DMSO-d_6): δ 8.12−8.15 (m, 1H), 7.91−7.93 (m, 1H), 7.21−7.37 (m, 3H), 5.82−5.94 (m, 1H), 5.30 (d, J = 6.9 Hz, 1H), 5.21 (d, J = 9.9 Hz, 1H), 3.53 (s, 2H), 2.73 (s, 2H), 2.59 (s, 2H). LCMS, *m/z*: MH^- 323.3. Anal. ($C_{18}H_{17}FN_4O$) C, H, F, N.

9-Isopropyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (28). ^{1}H NMR (DMSO-d_6): δ 8.12−8.24 (m, 1H), 7.92 (d, J = 4.4 Hz, 1H), 7.21−7.45 (m, 3H), 3.61 (s, 2H), 2.82−2.94 (m, 1H), 2.74 (s, 2H), 2.57 (s, 2H), 1.08 (s, 6H). LCMS, *m/z*: MH^- 325.3. Anal. ($C_{18}H_{19}FN_4O\cdot 2HCl\cdot H_2O$) C, H, F, N.

9-Cyclopropylmethyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (30). ^{1}H NMR (DMSO-d_6): δ 8.15 (t, J = 7.69 Hz, 1H), 7.87 (d, J = 4.12 Hz, 1H), 7.26−7.34 (m, 3H), 3.60 (s, 2H), 2.75−2.78 (m, 2H), 2.57 (s, 2H), 2.41 (d, J = 6.6 Hz, 2H), 1.75 (s, 2H), 0.85−0.97 (m, 1H), 0.48−0.52 (m, 2H). LCMS, *m/z*: MH^- 337.2. Anal. ($C_{19}H_{19}FN_4O\cdot 2HCl$)) C, H, F, N.

9-Cyclohexylmethyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (31). ^{1}H NMR (DMSO-d_6): δ 8.15 (t, J = 7.55 Hz, 1H), 7.88−7.90 (m, 1H), 7.24−7.41 (m, 3H), 3.48 (s, 2H), 2.67 (s, 2H), 2.56 (s, 2H), 2.31 (d, J = 6.32 Hz, 2H), 1.5−1.82 (m, 6H), 1.06−1.24 (m, 3H), 0.76−0.86 (m, 2H). LCMS, *m/z*: MH^+ 381.3, MH^- 379.4. HPLC purity in Supporting Information.

9-(3-Pyridylmethyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (42). A mixture of **58** (128 mg, 0.33 mmol), CH_2Cl_2 (3 mL), and 1 M borane in THF (3.3 mL) was stirred at room temperature for 16 h. The reaction mixture was carefully acidifed with 6 N HCl (5 mL) and heated at reflux. The reaction mixture was made alkaline with 10% NaOH, and the aqueous layer was extracted 2× with 10% methanol/ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated, and the resulting solid was recrystallized from ethanol to afford **42** as a pale-yellow solid, mp 290−292 °C. ^{1}H NMR (DMSO-d_6): δ 8.86 (s, 1H), 8.78 (d, J = 5.5 Hz, 1H), 8.09 (t, J = 7.97 Hz, 1H), 7.98 (d, J = 4.1 Hz, 1H), 7.71−7.76 (m, 1H), 7.29−7.41 (m, 3H), 4.18−4.53 (m, 6H), 2.82−2.94 (m, 2H), 2.3 (s, 3H). LCMS, *m/z*: MH^+ 376.4, MH^- 374.3. Anal. ($C_{21}H_{18}FN_5O$) C, H, F, N.

The following was prepared in a fashion similar to that for **42**.

9-(2-Phenylethyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (32). ^{1}H NMR (DMSO-d_6): δ 8.18 (t, J = 7.56 Hz, 1H), 7.93 (d, J = 4.01 Hz, 1H), 7.17−7.42 (m, 8H), 3.64 (s, 2H), 3.32 (s, 2H), 2.78−2.84 (m, 4H), 2.58−2.64 (m, 2H). LCMS, *m*/*z*: MH^+ 389.2, MH^- 387.2. HPLC purity in Supporting Information.

9-(3-Phenylpropyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one (33). ^{1}H NMR (DMSO-d_6): δ 8.18 (t, J = 7.76 Hz, 1H), 7.93 (d, J = 4.07 Hz, 1H), 7.19−7.41 (m, 8H), 3.55 (s, 2h), 2.70−2.75 (m, 2H), 2.54−2.68 (m, 6H,), 1.83−1.87 (m, 3H). LCMS, *m*/*z*: MH^+ 403.5, MH^- 401.4. Anal. ($C_{24}H_{23}FN_4O$) C, H, F, N.

9-(4-Pyridylmethyl)-2-(2-fluorophenyl)-7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-one Dimesylate (43). ^{1}H NMR (DMSO-d_6): δ 8.94 (d, J = 5.77 Hz, 1H), 7.97−8.11 (m, 4H), 7.27−7.38 (m, 3H), 4.63−4.65 (m, 2H), 4.27−4.29 (m, 2H), 3.35−3.52 (m, 2H), 2.82−2.93 (m, 2H), 2.32 (s, 6H). LCMS, *m*/*z*: MH^+ 376.3. HPLC purity in Supporting Information.

Biological Procedures. 1. Radioligand Binding Assay. Binding affinities were determined by displacement of ^{3}H-flumazenil from rat cortex homogenates as described previously,[8,9] with minor modifications. A competitive binding curve is obtained with up to 11 points, potentially spanning the compound concentration range from 10^{-12} to 10^{-5} M. K_i values are calculated according to the Cheng−Prussof equation.

2. Electrophysiology. *Xenopus laevis* oocytes were injected with human cRNA of the appropriate α, β, and γ subunits in order to express the desired receptor subtype. After addition of GABA to the oocyte, at least five concentrations of test drug were then added, recording on at least two oocytes per test drug. Percent potentiation values were averaged and fit to the logistic equation, which gave a maximal potentiation, an EC_{50}, and a Hill number (not shown but typically ranging from 0.8 to 1.2). Details of the procedure have been described.[12,13]

3. Spontaneous Locomotor Activity.[17] Male Sprague−Dawley rats were injected iv with the test drug in a vehicle of 50% aqueous PEG-400. The animals were then placed in an automated activity monitor in which movement time, total distance, and vertical activity were assessed over a 15 min period. The minimum efficacious dose is defined as that needed to give a statistically significant ($P < 0.05$) value from control in at least two of the three measurements.

Supporting Information Available: Purity of compounds established from HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Subsequent HPLC analysis indicated the presence of starting material **24**. Because **24** is inactive up to the concentrations tested here, the presence of it was deemed relatively unimportant with regard to the binding affinity of **41**, since **41** is already potent.

(20) HPLC analysis confirmed the purity of organic material. Thus, subsequent analogues with various fractionals in the elemental analysis were not cross-validated.

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