3-Heteroaryl-2-pyridones: Benzodiazepine Site Ligands with Functional Selectivity for α2/α3-Subtypes of Human $GABA_A$ Receptor-Ion Channels

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A novel series of 3-heteroaryl-5,6-bis(aryl)-1-methyl-2-pyridones were developed with high affinity for the benzodiazepine (BZ) binding site of human γ-aminobutyric acid ($GABA_A$) receptor ion channels, low binding selectivity for α2- and/or α3- over α1-containing $GABA_A$ receptor subtypes and high binding selectivity over α5 subtypes. High affinity appeared to be associated with a coplanar conformation of the pyridone and sulfur-containing 3-heteroaryl rings resulting from an attractive S...O intramolecular interaction. Functional selectivity (i.e., selective efficacy) for α2 and/or α3 $GABA_A$ receptor subtypes over α1 was observed in several of these compounds in electrophysiological assays. Furthermore, an α3 subtype selective inverse agonist was proconvulsant and anxiogenic in rodents while an α2/α3 subtype selective partial agonist was anticonvulsant and anxiolytic, supporting the hypothesis that subtype selective BZ site agonists may provide new anxiolytic therapies.

Introduction

Neurotransmission by γ-aminobutyric acid (GABA) is a major inhibitory mechanism in the human central nervous system (CNS). Given the ubiquity of GABAergic pathways in the CNS, it is unsurprising that pharmacological intervention in this system can elicit diverse responses, ranging from changes in motor activity, muscle tone, and seizure behavior, through sedation and hypnotic effects, to modulation of cognition and mood, particularly anxiety states.[1] Of the three pharmacological classes of GABA receptors, $GABA_A$[2] and $GABA_C$[3] are ligand gated chloride ion channels, whereas $GABA_B$ is a G-protein linked receptor. Postsynaptic $GABA_A$ ion channels open in response to the binding of GABA, and the ensuing chloride flux hyperpolarizes the membrane of the postsynaptic neurone inhibiting further neuronal activity. Recently, subtypes of the $GABA_A$ receptors have been identified, as discussed in detail below. In addition to the GABA binding site, allosteric modulatory sites for numerous ligands have been identified on $GABA_A$ receptors (benzodiazepines (BZs), barbiturates, ethanol, steroids, avermectins, picrotoxin, zinc cations, and loreclezole), of which the BZ site has historically been of the most pharmacological interest.[4]

Ligands at the BZ binding site of $GABA_A$ receptors fall into functional classes categorized by their effect on the ion current elicited by the endogenous neurotransmitter GABA: Agonists (positive allosteric modulators) give an increased ion flux, resulting in a greater inhibitory effect on the postsynaptic neurone, while inverse agonists (negative allosteric modulators) cause a decrease in the ion flux in response to GABA. A continuum of ligand activities is possible, including antagonists (neutral allosteric modulators), which have no effect on the ion channel response to GABA but will competitively displace other BZ site ligands from the receptor. These different efficacies are reflected in the behavioral effects of BZ site ligands. For example, agonists show anxiolytic effects whereas inverse agonists are anxiogenic, and antagonists have no effect on anxiety behavior. Classical BZ drugs for the treatment of anxiety, such as diazepam, are full agonists at the BZ site of the $GABA_A$ receptor with no subtype selectivity. Although clinically useful, such compounds often exhibit undesirable effects,[5] particularly sedation, ataxia, and potentiation with alcohol. There is also a risk of tolerance and dependence developing with chronic use. The need for improved anxiolytic therapies is therefore clear, and potentially fruitful research has grown from an increased understanding of the molecular biology of $GABA_A$ receptors.[6,7]

$GABA_A$ receptors are oligomeric assemblies of a large range of subunits (α1−6, β1−3, γ1−3, δ, ϵ, π, and θ). In vitro, the pharmacology of the natural receptors can be replicated with pentameric combinations of cloned receptor subtypes, provided at least one of each of the α, β, and γ subunits is present, and it is currently thought that the dominant stoichiometry in vivo is $(\alpha)_2(\beta)_2(\gamma)$.[7,8] The subtypes α1βnγ2 correspond pharmacologically to the $GABA_A$ receptors previously classified as BZ-I (or ω_1), while α2βnγ2, α3βnγ2, and α5βnγ2 have been identified as comprising the BZ-II (or ω_2) class. Subtypes containing the α4 and α6 subunits are insensitive to BZs. The γ2 subunit is the predominant γ subunit in the brain. The nature of the β subunits in the receptor complex does not affect the BZ pharmacology. Although characterization of native $GABA_A$ receptor subtypes is far from complete, through in situ mRNA hybridization, subunit specific immunoprecipitation,

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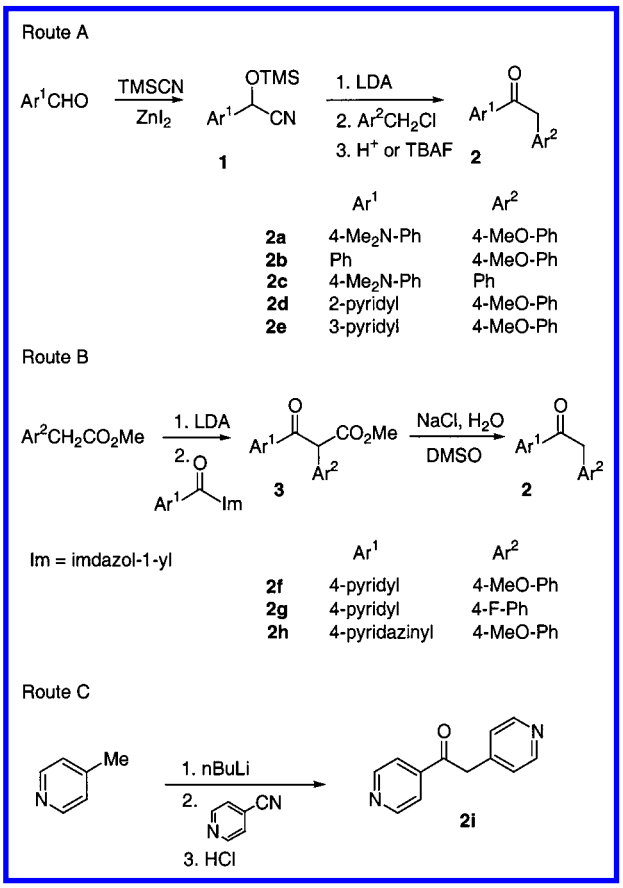
and immunoaffinity chromatography, significant progress has been made in determining the distribution of the individual subunits in the brain, and from these data, the distribution of the $GABA_A$ subtypes has been inferred:[7,8] While the dominant $\alpha1\beta2\gamma2$ subtypes are present in both cerebellum and cortex, the $\alpha2\beta n\gamma2$ and $\alpha3\beta n\gamma2/3$ assemblies are found mainly in the cortex and hippocampus, and the $\alpha5\beta3\gamma2$ and $\alpha5\beta3\gamma3$ are largely confined to the hippocampus. The differential localization of subtypes within the brain suggests that different subtypes may be associated with different physiological processes, and this has been observed in transgenic mice where the α1 subunit was rendered BZ insensitive.[9] In these mice, the sedative and amnesic properties of BZ full agonists were abolished; yet, the anxiolytic, myorelaxant, and partial anticonvulsant effects were retained, clearly identifying selective mediation of the sedative response through α1 subunits.[10]

In light of this, subtype selective ligands should discriminate between the many behaviors mediated by GABA-ergic transmission, and this is supported by data obtained on the limited number of selective compounds known. For example, while unselective full agonist BZs such as diazepam are anxiolytics with sedative side effects apparent at higher doses, the BZ site full agonist zolpidem that has some binding selectivity for α1-containing receptors over other $GABA_A$ subtypes is a clinical hypnotic, again implicating α1-containing subtypes in the sedative response. Other compounds with moderate binding selectivity for α1 subtypes have been described recently, including pyrrolo[2,3-c]pyridines,[11] indoleglyoxamides,[12] and β-carbolines,[13] but there are fewer reports of α2/α3 selective ligands.[13,14] A class of agonist imidazo[1,5-a]quinoxalines[15] have been reported, some of which showed functional selectivity for α1 subtypes over α3. The discovery of functionally selective α2/α3 partial agonist triazolo[4,3-b]pyridazines[16] in our laboratory was recently communicated,[17] along with evidence that such compounds are anxiolytic but not sedating or ataxic in animal models, supporting the hypothesis that the sedative effects of BZ site ligands are mediated through α1-containing receptor subtypes.[10,18] In this paper, we describe a new class of 2-pyridone $GABA_A$ BZ site ligands based on the screening lead **5a** and their adaptation to functionally selective compounds for α2/α3 subtypes.[19]

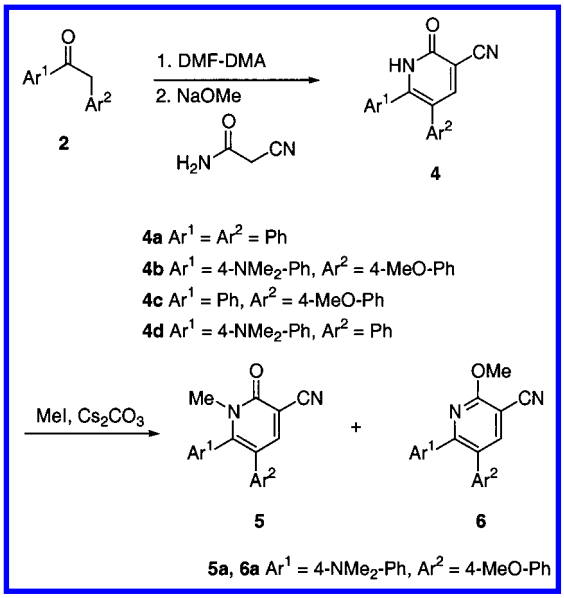
Chemistry

The well-precedented regioselective condensation of 2-cyanoacetamide with 3-(dimethylamino)-2-propenones under basic conditions was used for the construction of the trisubstituted 2-pyridones,[20] requiring the initial preparation of various 1,2-diarylethanones **2** (Scheme 1). The carbanions formed by deprotonation of aryl and heteroaryl *O*-trimethylsilylcyanohydrins **1** were alkylated with benzylic halides to give the ketones **2a**−**e** after acidic hydrolysis (50−72%, route A). An alternative procedure began with a Claisen condensation of 2-aryl acetate esters and heteroaroyl imidazolides to give the β-ketoesters **3**. Decarboxylation under Krapcho's conditions[21] afforded the ketones **2f**−**h** (2−36%, route B). In the case of 4-picoline, deprotonation of the 4-methyl group[20d] and addition to 4-cyanopyridine produced the ketone **2i** directly, albeit in low yield (3%) (route C).

Scheme 1

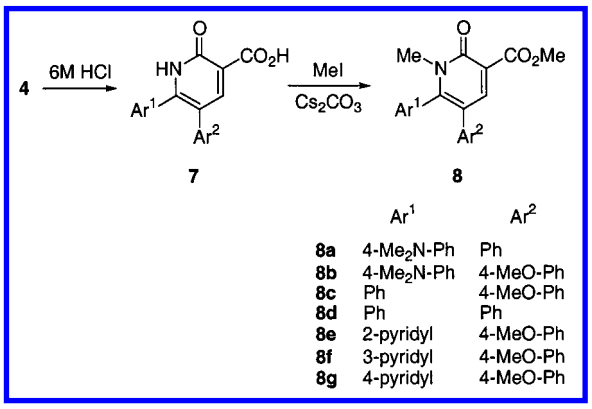


Scheme 2

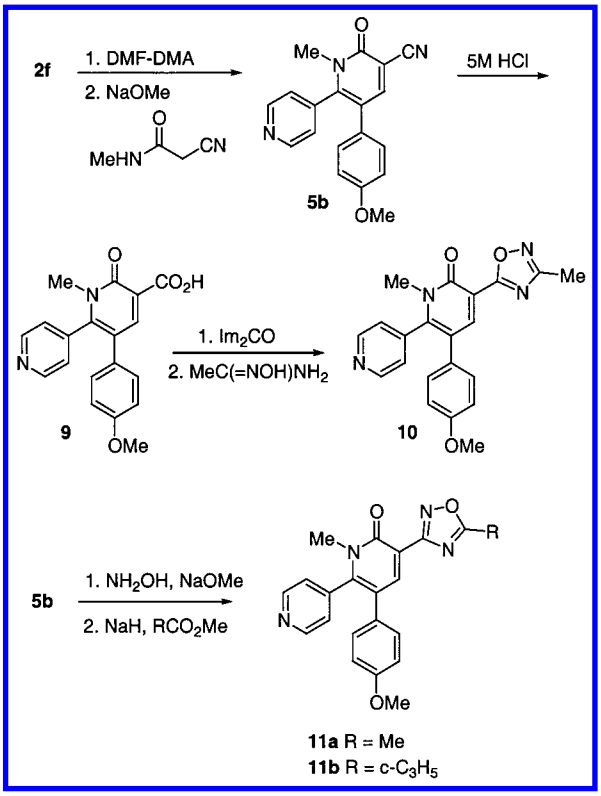


Treatment of the ketones **2** with dimethylformamide−dimethylacetal (DMF−DMA) gave the corresponding 3-dimethylaminopropen-2-ones, and generally without purification, these were condensed with 2-cyanoacetamide to give the 3-cyano-2-pyridones **4** in moderate to good yields (47−80%) (Scheme 2). Alkylation of the pyridone **4b** with methyl iodide and cesium carbonate gave a readily separable mixture of the *N*-methylated lead pyridone **5a** and the isomeric 2-methoxypyridine **6a**.

Scheme 3



Scheme 4

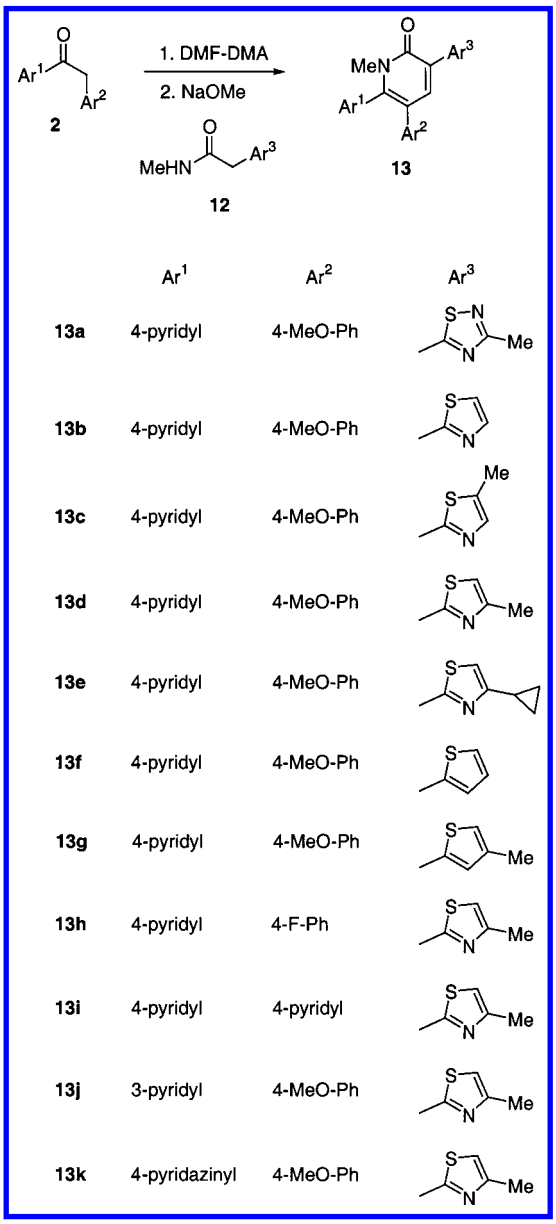


The intermediate 3-cyano-2-pyridones **4** were hydrolyzed upon refluxing in strong aqueous acid to give the carboxylic acids **7**. These intermediates were not generally purified but were methylated to give the 1-methyl-3-methoxylcarbonyl-2-pyridones **8**, again accompanied by the isomeric 2-methoxypyridines (Scheme 3).

To obviate the need for separation of these alkylation products, the condensation of the eneaminoketone derived from ketone **2f** was carried out with *N*-methyl 2-cyanoacetamide to give the 1-methyl-3-cyano-2-pyridone **5b** directly in good yield (50−60%, Scheme 4). Hydrolysis to the acid **9** allowed formation of the 3-methyl-1,2,4-oxadiazole **10**.[45] The isomeric 5-methyl-1,2,4-oxadiazole **11a** and its cyclopropyl analogue **11b** were prepared from the nitrile **5b** by standard chemistry.

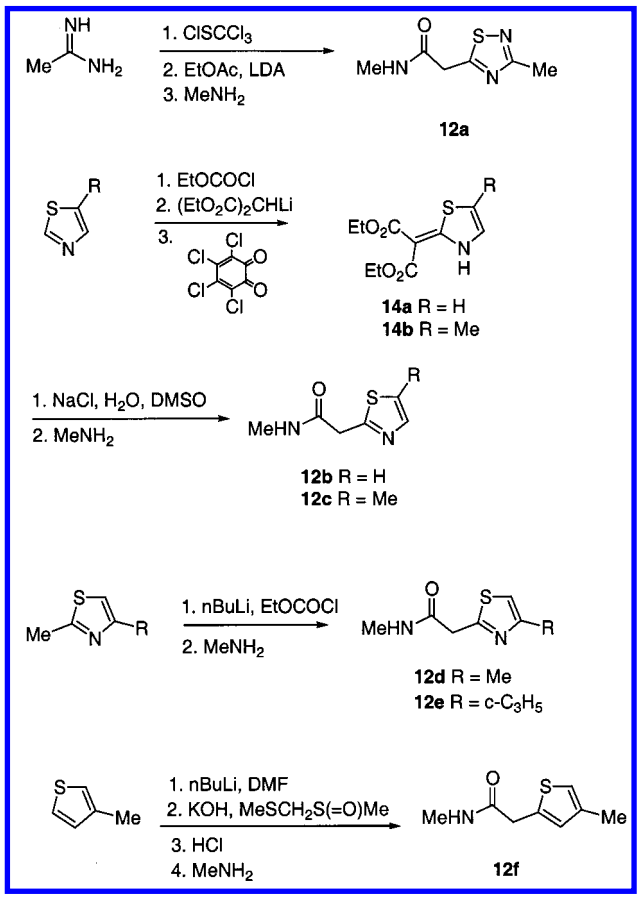
For detailed investigation of heterocyclic groups at the 3-position of the pyridone, a more convenient synthesis was sought, and fortunately, a variety of *N*-methyl heteroarylacetamides **12** were found to undergo the condensation and cyclization reaction with the enaminoketones derived from **2** to give the fully functionalized pyridones **13** (Scheme 5). This direct approach to 3-heteroaryl-2-pyridones, which was particularly efficient with sulfur-containing heterocycles, does not appear to have been exploited before.[20a,b]

Scheme 5



The amides **12** were readily prepared from the corresponding ethyl esters upon treatment with methylamine, and several methods were used to reach these precursors (Scheme 6). The 3-methyl-1,2,4-thiadiazol-5-yl acetamide **12a** was built up from acetamidine by condensation with trichloromethanesulfenyl chloride to give 5-chloro-3-methyl-1,2,4-thiadiazole, followed by S_NAr displacement with 2-lithio ethyl acetate.[22] For the unsubstituted thiazol-2-yl acetamide **12b** and its 5-methyl analogue **12c**, the diesters **14** were synthesized from the thiazoles according to Dondoni's procedure.[23] Krapcho decarboxylation then afforded the monoesters. Selective lateral lithiation[24] of 2-methyl-4-methylthiazole and quenching with ethyl chloroformate provided a fast route to the desired ester precursor for **12d**, but monoacylation was difficult to control and was conse-

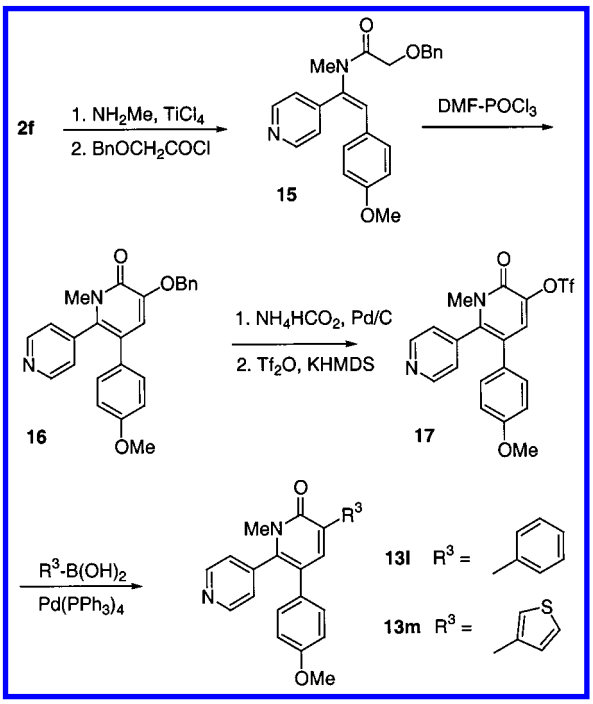
Scheme 6



quently low-yielding.[25] Lithiation of 2-methyl-4-cyclopropylthiazole gave predominantly metalation at C-5 of the thiazole ring, as expected from electronic considerations,[24] leading to ethyl 2-methyl-4-cyclopropylthiazole-5-carboxylate (49%). However, some of the required ethyl 2-(4-cyclopropylthiazol-2-yl)acetate (ca. 6%) was isolated in a crude mixture with unreacted starting material and was successfully purified after conversion to the amide **12e**. In contrast, lithiation of 3-methylthiophene[26] provided a 4:1 mixture of 4-methylthiophene-2-carboxaldehyde and 3-methylthiophene-2-carboxaldehyde in high yield (93%) on quenching with DMF. The mixture was carried through the subsequent one carbon chain extension using methyl (methylthio)-methyl sulfoxide[27] and separated after formation of the amide **12f**.

The direct condensation−cyclization route failed in some cases, notably with substituted phenyl acetamides, and an alternative synthetic route was developed to allow introduction of the 3-substituent on the pyridone in a rapid analogue fashion as the final step of the synthesis (Scheme 7).[28] Thus, the ketone **2f** was converted to the *N*-methyl imine using titanium tetrachloride as a dehydrating agent.[29] Acylation of the crude imine with 2-benzyloxyacetyl chloride, in the absence of any additional base,[30] gave the *N*-acyl enamine **15** (58% over two steps). Vilsmeier formylation and intramolecular cyclization of **15** according to the procedure developed by Meth−Cohn[31] gave the 3-benzyloxy-2-pyridone **16** in moderate yield (28−48%). Hydrogenolytic deprotection was followed by formation of the triflate **17**. Various palladium-catalyzed coupling reactions to **17** were successful;[28] for example, Suzuki couplings[32]

Scheme 7



gave the 3-phenyl-2-pyridone **13l** and the 3-(3-thienyl)-2-pyridone **13m**.

Biological Methods

The affinities of test compounds for cloned human $\alpha1\beta3\gamma2$, $\alpha2\beta3\gamma2$, $\alpha3\beta3\gamma2$, and $\alpha5\beta3\gamma2$ $GABA_A$ receptors, stably expressed in L(tk$^-$) cells, were determined by displacement of [^{3}H]Ro15-1788.[33] The efficacies of selected compounds were determined at cloned human $\alpha1\beta3\gamma2$, $\alpha2\beta3\gamma2$, and $\alpha3\beta3\gamma2$ $GABA_A$ receptors transiently expressed in *Xenopus* oocytes by measurement of the modulatory effect on the GABA EC_{20} ion current using two electrode voltage-clamp electrophysiology.[34] In all cases, the γ_{2S} splice-variant of the γ subunit was used. The nonselective full agonist chlordiazepoxide and the nonselective full inverse agonist methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) were included as standards in the determination of binding affinities and efficacies. The pharmacokinetic parameters of selected compounds following intravenous and oral dosing in rats were investigated, and occupancy at the $GABA_A$ receptors in rodent brain was determined by inhibition of in vivo [^{3}H]Ro15-1788 binding.[35] Anticonvulsant and anxiolytic properties were investigated in a mouse model of epilepsy[36] and the rat elevated plus maze,[37] respectively. In brief, pro- or anticonvulsant activity was measured in mice (n = 8/group) dosed with test compound or vehicle (i.p. in 0.5% methylcellulose) followed immediately after by various doses of pentylenetetrazole (PTZ; s.c. in 0.9% saline vehicle). Animals were then observed for 30 min, and the number of mice exhibiting tonic convulsions was scored; from these data, the dose corresponding to that required for 50% of animals to demonstrate tonic convulsions (ED_{50}) was calculated. In this assay, a drug with proconvulsant activity will reduce the PTZ ED_{50} whereas an anticonvulsant drug will increase the ED_{50}. In the elevated plus maze, rats (n = 18/group) received either vehicle (i.p. 0.5% aqueous methylcellulose; pretreatment time = 5

Table 1. Binding Affinities and Efficacies of 3-Cyano- and 3-Carbomethoxy-2-pyridones at Cloned Human $GABA_A$ Receptor Subtypes

	K_i (nM)[a]				modulation of GABA EC_{20} current (%)[b]					
no.[c]	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$	$\alpha_1\beta_3\gamma_2$		$\alpha_2\beta_3\gamma_2$		$\alpha_3\beta_3\gamma_2$	
5a	7000 (±1200)	1800 (±320)	860 (±180)	>667[d]	+7 (±3)	30	−16 (±3)	30	+8 (±2)	30
4b	>30 000[e]	>30 000	>30 000	>667	*f*					
6a	>30 000	>30 000	>30 000	>667						
8a	630 (±120)	470[g]	270 (±70)	>667[g]						
8b	>3000[h]	600 (±340)	250 (±97)	>667	+181 (±15)	30	+81 (±13)	30	+132 (±27)	30
8c	625[i] (460, 850)	340 (±31)	210 (±27)	393[g]						
8d	520 (510, 540)		270 (210, 350)							
8e	>3000	>667	510 (470, 570)	>667						
8f	680 (670, 700)	76 (60, 100)	73 (±11)	>667[g]						
8g	1020 (±97)	320 (±19)	79 (±11)	390 (280, 540)	+3 (±7)	10	+8 (±5)	10	−25 (±4)	1
CDZ[j]	560 (410, 780)	460 (380, 560)	275 (250, 310)	320 (290, 350)	+173 (±10)	10	+101 (±8)	10	+165 (±6)	10
DMCM	5.7	8.3	4.0	1.0	−34 (±4)	0.3	−36 (±4)	0.3	−35 (±4)	0.3

[a] Displacement of [^{3}H]Ro15-1788 from $hGABA_A$ receptor subtypes stably expressed in L(tk$^-$) cells, mean (±SEM) for $n = 3-5$, expressed to two significant figures. Six to eight concentrations of each test compound incremented in half-log units were used in the determinations. [b] Modulatory effects of compounds on coapplication with GABA at the GABA EC_{20} (concentration eliciting 20% of maximum GABA current, range 4−30 μM) determined in *Xenopus* oocytes transiently expressing $hGABA_A$ receptors; mean (±SEM) for $n = 3-7$, concentration of test compound (μM). [c] For structures, see Schemes 2 and 3. [d] Denotes <50% inhibition at 2 μM, $n = 2$. [e] Denotes <50% inhibition at 100 μM, $n = 2$. [f] Value not determined. [g] $n = 1$. [h] Denotes <50% inhibition at 10 μM, $n = 2$. [i] $n = 2$, individual determinations in parentheses. [j] CDZ = chlordiazepoxide.

min), 10, 30, or 60 mg/kg test compound (i.p. or p.o. as indicated in text; pretreatment time = 5 min). Animals were then placed on the elevated plus maze, and the time spent in the closed or open arms during a 5 min trial period was recorded. Increased time spent in the closed arms was used as an index of anxiogenesis, and increased time spent on the open arms was used as an index of anxiolysis.[37] In the case of anxiogenic compounds, the nonselective partial inverse agonist FG 7142 (30 mg/kg i.p.; pretreatment time = 30 min) was used as positive control, and for anxiolytic compounds, the positive control was the nonselective full agonist diazepam (5 mg/kg i.p.; pretreatment time = 30 min). Comparisons between groups were made using an analysis of variance with a post hoc Dunnett's *t*-test to test for significant differences between individual groups and control (vehicle-treated) animals.

Results and Discussion

The lead 1-methyl-3-cyano-2-pyridone **5a** (Table 1) emerged from screening of the corporate sample collection as a low-affinity ligand with weak binding selectivity (3−8-fold) for α2 and α3 $GABA_A$ subtypes over α1. Further profiling of **5a** showed it to be an antagonist at α1 and α3 subtypes, with some partial inverse agonist activity at α2 subtypes. In view of the hypotheses described in the Introduction, our initial aim was to improve the affinity and binding selectivity of the lead for α2 and/or α3 subtypes over α1 and to achieve agonist efficacy in this series of compounds.

Simple changes to the lead structure rapidly established that the N-1 methyl group was essential for affinity at human $GABA_A$ receptors, shown by the lack of affinity of the *N*-unsubstituted compound **4b**, and that the isomeric 2-methoxypyridine **6a** would not serve as a replacement for the 2-pyridone (Table 1). Removal of either of the pendant aryl groups and replacement with a methyl group also led to complete loss of affinity (K_i > 30 μM at α1 and α3 subtypes; compounds not shown). However, modification of the 3-cyano group of **5a** to a methyl ester gave **8b**, which had higher affinities than the lead at α1, α2, and α3 subtypes. On measuring the efficacy of **8b**, the change from nitrile to ester was observed to have converted the antagonist/partial inverse agonist character of **5a** to a strong agonist across all three subtypes.

In an attempt to improve affinity and selectivity at α2/α3-containing receptors, the 3-methyl ester was retained, and variations of the pendant aryl substituents at C-5 and C-6 of the 2-pyridone were examined. Because deletion of these units in **5a** had earlier proved fruitless, simple changes to the aromatic substitution patterns were pursued. In the event, the presence or absence of the 4-methoxy and 4-dimethylamino substituents was irrelevant for affinity at the $GABA_A$ receptor subtypes and compounds **8a**, **8c**, and **8d** had affinities similar to the prototype ester **8b**.

To increase the basicity of the molecules and potentially improve aqueous solubility, the introduction of pyridine rings to the C-6 position of the 3-carbomethoxy-2-pyridone was investigated. Although the 2-pyridyl isomer **8e** was of generally lower affinity at the $GABA_A$ receptors, the 3- and 4-pyridyl compounds **8f** and **8g** showed significant improvements in affinity at the α3 subtype over the lead ester **8b** while retaining ca. 10-fold selectivity over α1. Additionally, the 4-pyridyl isomer **8g** showed some weak discrimination (ca. 4-fold) for α3 vs α2 and α5. The effect of the 4-pyridyl isomer **8g** on the GABA EC_{20} ion current was measured, revealing an intriguing functional selectivity for this compound. Whereas **8g** was an antagonist at α1 and α2 receptors, inverse agonist efficacy was indicated at the α3 subtype (−25% as compared to −35% for the standard full inverse agonist DMCM in this assay).

The functional selectivity of compound **8g** as an inverse agonist at α3 receptors and an antagonist at α1 and α2 receptors provided the opportunity to look for the effects of selectively modulating GABA neurotransmission through α3 receptors in vivo (Table 3). The pharmacokinetic behavior of **8g** in rats was poor, with rapid metabolism observed, but CNS penetration of the compound was nonetheless encouraging: On oral dosing as a suspension in aqueous 0.5% methylcellulose at 10 mg/kg, the levels of **8g** in the rat brain reached 170 (±59) ng/g at 30 min postdose, sufficient to progress to testing for pro- or anticonvulsant activity in a mouse model of epilepsy.[36] In this assay, **8g** (30 mg/kg i.p., suspension in aqueous 0.5% methylcellulose) was found

Table 2. Binding Affinities and Efficacies of 3-Heteroaryl- and 3-Aryl-2-pyridones at Cloned Human $GABA_A$ Receptor Subtypes

	K_i (nM)[a]				modulation of GABA EC_{20} current (%)[b]					
no.[c]	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$	$\alpha_1\beta_3\gamma_2$		$\alpha_2\beta_3\gamma_2$		$\alpha_3\beta_3\gamma_2$	
10	>1000[d]	>667[e]	>1000	>667	*f*					
11a	260 (±110)	1100[g] (910, 1300)	320 (±50)	1300[h]	+111 (±28)	30			+81 (±10)	10
11b	310 (±34)	240 (±50)	60 (±15)		+120 (±17)	30	+142 (±33)	30	+150 (±31)	10
13a	90 (±7)	42 (±8)	25 (±4)	>667	+117 (±20)	10	+97 (±24)	10	+138 (±22)	3
13b	45 (±3)	37 (±4)	6.2 (±1.6)	>1000	+56 (±3)	3	+67 (±7)	3	+32 (±3)	1
13c	330 (290, 360)	380 (±47)	250 (±57)	>1000						
13d	17 (±1)	8.6 (±1.8)	3.4 (±1.3)	320 (±38)	+7 (±2)	1	+80 (±13)	1	+43 (±3)	1
13e	31 (±23)	24 (±6)	12 (±3)	>1000	+29 (±8)	1			+35 (±6)	1
13f	30 (±9)	23 (±1)	15 (±3)	350 (310, 390)	+9 (±4)	1	+15 (±6)	1	+36 (±3)	1
13g	41 (±1)	38 (±7)	23 (±2)	340 (270, 410)						
13h	13 (±4)	8.0 (±1.3)	3.5 (±1.0)	380 (±18)	+57 (±10)	3			+41 (±10)	1
13i	24 (24, 25)	20 (18, 23)	6.7 (5.7, 7.8)	270 (260, 280)	−23 (±1)	3			−4 (±3)	1
13j	12.8 (±0.3)	5.0 (±0.4)	3.8 (±0.1)	>667	+78 (±10)	1			+77 (±14)	3
13k	17 (±2)	6.6 (±2.2)	4.1 (2.5, 6.6)	330 (±110)	+7 (±5)	3	+33 (±6)	10	+34 (±7)	1
13l	83 (±18)	130 (±37)	24 (±6)	>1000	+45 (±8)	3			+63 (±5)	3
13m	39 (39, 40)	51 (50, 52)	12 (12, 12)	450 (440, 450)					+18 (±2)	1

[a] Displacement of [^{3}H]Ro15-1788 from $hGABA_A$ receptor subtypes stably expressed in L(tk$^-$) cells, mean (±SEM) for $n = 3-5$, expressed to two significant figures. Six to eight concentrations of each test compound incremented in half-log units were used in the determinations. [b] Modulatory effects of compounds on coapplication with GABA at the GABA EC_{20} (concentration eliciting 20% of maximum GABA current, range 4−30 μM) determined in *Xenopus* oocytes transiently expressing $hGABA_A$ receptors; mean (±SEM) for $n = 3-7$, concentration of test compound (μM). [c] For structures, see Schemes 4−7. [d] Denotes <50% inhibition at 3 μM, $n = 2$. [e] Denotes <50% inhibition at 2 μM, $n = 2$. [f] Value not determined. [g] $n = 2$, individual determinations in parentheses. [h] $n = 1$.

Table 3. Qualitative Summary of Biological Data for Compounds **8g**, **13d**, and **13k**

		effects in vivo	
compd	efficacy profile in vitro	mouse PTZ assay	rat elevated plus maze
8g	α_3 selective inverse agonist	proconvulsant	anxiogenic
13d	α_2/α_3 selective partial agonist	anticonvulsant	
13k	α_2/α_3 selective partial agonist	anticonvulsant	anxiolytic

to be proconvulsant, potentiating the action of PTZ in inducing tonic seizures and reducing the PTZ ED_{50} from 102 (88−116 mg/kg; 95% confidence limits) to 63 mg/kg (55−74 mg/kg; 95% confidence limits). The effects of the compound in the rat elevated plus maze model[37] for anxiety were also examined, and **8g** (30 mg/kg i.p., suspension in aqueous 0.5% methylcellulose) was found to have a statistically significant anxiogenic effect relative to vehicle-dosed control animals.

These experiments provided evidence for a functional role for the α3 subtype in vivo, with the effects observed in agreement with those expected from a BZ inverse agonist and indicating that the α3 subtype is at least partly involved in mediating anxiety behavior. A caveat to this interpretation would be possible interspecies differences in the $GABA_A$ subtype selectivity; however, where we have been able to test other BZ ligands for affinities or efficacies at mouse and rat $GABA_A$ subtypes, we have not observed significant deviations from the profiles observed in vitro with human $GABA_A$ receptors. This is consistent with the high sequence homology (>90%) of $GABA_A$ subunit subtypes between human and rodent.[2a]

A few simple ester analogues of **8g** were prepared (not shown in tables) and demonstrated that groups larger than methyl (e.g., allyl, *tert*-butyl) were tolerated in terms of affinity and provided a general increase in the level of efficacy at α1, α2, and α3 subtypes. Capitalizing on this, we sought to replace the metabolically labile methyl ester of **8g** with aromatic heterocycles (Table 2). 1,2,4-Oxadiazoles have become generally established as bioisosteres for esters, and this equivalence has been investigated in other series of BZ site ligands.[38] While the 3-methyl-1,2,4-oxadiazol-5-yl isomer **10** showed negligible affinity for $GABA_A$ subtypes, the 5-methyl-1,2,4-oxadiazol-3-yl derivative **11a** retained some affinity, although the 10-fold binding selectivity for α3 against α1 of **8g** was lost. By increasing the bulk of the heterocyclic substituent to the cyclopropyl oxadiazole **11b**, affinity was regained. Both **11a** and **11b** were full agonists at all $GABA_A$ subtypes, a sweeping change from the antagonist/inverse agonist profile of **8g** and paralleling earlier observations with simple homologated esters at C-3 of the pyridone.

Although the 3-methyl-1,2,4-oxadiazole **10** had shown negligible BZ site affinity, the corresponding 1,2,4-thiadiazole **13a** showed excellent binding and was a full agonist at all subtypes. Further improvements in affinity were seen on deletion of nitrogen in the thiadiazole to generate a group of 3-(2-thiazolyl)-2-pyridones **13b**−**e**. Thus, the unsubstituted thiazole **13b** proved a very high affinity, partial agonist at α3 subtypes, with ca. 6−7-fold binding selectivity over the α1 and α2 subtypes, and inactive at α5 subtypes. The thiazoles were sensitive to substitution pattern: whereas introduction of a 5-methyl group to give **13c** reduced affinity severely, the isomeric 4-methylthiazole **13d** marginally improved affinity at all subtypes, while maintaining a low level of binding selectivity for α3 subtypes over α1 and α2. Most importantly, **13d** had functional selectivity against α1-containing receptors, being an antagonist at this subtype while a partial agonist at α2 and α3 receptors. Increasing the size of the thiazole 4-substituent to cyclopropyl, as in **13e**, somewhat reduced affinity at all subtypes and brought back α1 efficacy.

The apparent preference for sulfur-containing heterocycles was further demonstrated with the thiophen-2-yl derivatives **13f** and **13g**, although with some loss of

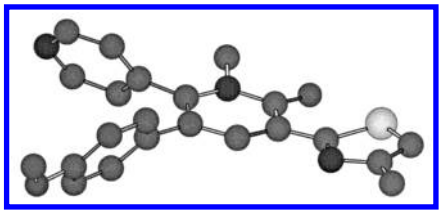


Figure 1. X-ray crystal structure of **13d** (hydrogens omitted for clarity).

affinity. The unsubstituted thiophene **13f** showed functional selectivity for α3 over α1, albeit with reduced efficacy for α2 as compared to **13d**. The thiophene sulfur atom could be translated to the 3-position in **13m** without further loss of affinity. Congruent with this, replacement of the heterocycle with a phenyl ring in **13l** was tolerated, but this compound was an unselective partial agonist at α1 and α3 subtypes.

Examination of the crystal structure of **13d** threw some light on the structure−activity of the C-3 heterocycles (Figure 1). Adjacent pendant aromatic groups might be generally expected to twist out-of-plane relative to the core pyridone to reduce steric repulsions, and this was seen in the crystal structure of **13d** for the C-5 and C-6 aromatic rings (interplanar torsions ca. 58 and 63°, respectively). This conformation in itself may be important for effectively filling the out-of-plane lipophilic pockets postulated in many BZ agonist pharmacophore models.[39] For the sterically less-demanding five-membered C-3 heterocycles, flanked only by a proton and a carbonyl, electronic considerations are important. In **13d**, the thiazole was clearly coplanar with the pyridone ring (interplanar torsion ca. 3°), with a close intramolecular contact of the sulfur and the carbonyl oxygen (S...O = 2.76 Å; van der Waals radii[40] S = 1.80 Å, O = 1.52 Å). This type of attractive intramolecular interaction between a thiazole or thiazolidine S and an adjacent carbonyl O at four bonds distance has been observed before[41] and can be viewed simplistically as a Coulombic attraction between the positively charged S and the negatively charged O.[41b] Similar C═O...S stabilizing interactions have been proposed from the crystal structures of analogous 1,3,4-thiadiazoles[41b] and 2-thiophenes.[42]

As has been remarked elsewhere,[4b] these 2-pyridones are unusual among the many known BZ site ligands in having a monocyclic rather than a fused bi- or tricyclic core, but the presence of a potential conformational lock in **13d**, and by extension the other 2-thiazoles, 2-thiophenes, and 1,3,4-thiadiazoles examined here, arguably renders these compounds pseudotricyclic and may account in part for their higher affinity relative to other five-membered heterocycles. The difference in affinities between compounds **13c** and **13d** thus reflects the positioning of the methyl substituent with respect to the GABA receptor and implies a size-limited binding pocket of defined position relative to the pyridone core. Other five-membered C-3 heterocycles should be able to reach the coplanar orientation but without the benefit of a positive stabilizing interaction. The only slightly reduced affinities of the 3-phenyl-2-pyridone **13l**, which cannot reach coplanarity, and the 3-thienyl analogue **13m**, which does not have the conformational lock, indicate that conformation is not the only factor associated with the C-3 substituent that drives BZ site binding affinity.

Table 4. Pharmacokinetics in Rat of Pyridones **13d** and **13k**

no.	LogD	dose (mg/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	Clp (ng mL/h)	V_{dss} (L/kg)	F_{oral} (%)
13d	3.6	2	1.7	83	0.3	44	3.3	25
13k	2.7	1.5	1.1	170	0.5	35	2.5	65

The models of ligand binding to the BZ site derived so far do not take account of the subtype selective efficacy that can be achieved with these 2-pyridones. However, many BZ site agonist pharmacophore models, although derived from data on mixed populations of $GABA_A$ receptors, contain common elements including interactions between the ligands and two hydrogen bond donors in the receptor.[4a,39] This general arrangement has been maintained in models derived for single subtypes of the $GABA_A$ receptor.[14,43] Assuming that the pyridone carbonyl participates in one such interaction, compounds such as **13f**, **13g**, **13l**, and **13m** may lack a second H bond acceptor site. In the thiazoles, 1,3,4-thiadiazole, and 1,2,4-oxadiazoles, additional heteroatoms in the C-3 substituent may contribute to binding by fulfilling this role. Binding to distinct lipophilic pockets in the receptor appears to be a major determinant of BZ site binding and efficacy.[39] The C-3 substituent of the 2-pyridones may occupy one such region, the gross electronic and steric properties of the heterocycle determining the strength of the binding interaction and the efficacy elicited.

The 2-pyridones described here showed limited binding selectivity between α1, α2, and α3 subtypes, typically 10-fold at greatest, although better discrimination against α5 subtypes could be achieved, a pattern encountered in other BZ site ligands such as zolpidem and a series of indoleglyoxamides.[12] Studies using site-directed mutagenesis or photoaffinity labeling of amino acid residues on both α and γ subunits have located the BZ binding site at the interface of the α and γ subunits in the $GABA_A$ receptor assembly.[44] The lack of binding selectivity might suggest that the 2-pyridones interact with amino acid residues that are conserved or minimally changed between the different α subunits. It is also possible that binding to the γ2 subunit, which is invariant in the constructs examined here, dominates the affinity and could account for the limited α subunit binding selectivity. However, it is clear that interactions with the α subunits are important for determining the efficacy of BZ site ligands and can lead to in vitro functional selectivity that correlates with useful in vivo pharmacology.

The α2/3 selective partial agonist **13d** was investigated in vivo for the anticonvulsant activity expected of a compound with this efficacy profile (Table 3). Indeed, **13d** gave 50% protection against PTZ-induced tonic seizures in mice after i.p. administration at 30 mg/kg as a suspension in aqueous 0.5% methylcellulose, a result complementing the α3-mediated proconvulsant activity of **8g**. However, attempts to look for anxiolytic activity of **13d** in the rat elevated plus maze model (60 mg/kg p.o. dosing) were unsuccessful. This failure was attributed to the poor pharmacokinetic and pharmacodynamic properties of **13d** (Table 4). Determination of the in vivo occupancy[35] of rat $GABA_A$ receptors demonstrated the low levels of compound reaching the phar-

macological target: Administration of **13d** in aqueous 70% PEG300 at a dose of 50 mg/kg p.o. gave only 16 (±8)% occupancy.

To improve the pharmacokinetic properties of **13d**, conservative variations of the pendant aryl groups were made, hoping to retain high affinity by keeping the 4-methylthiazol-2-yl group at C-3 of the pyridone for the reasons discussed above. This proved fruitful, as shown by the four examples **13h**−**k**, where similar affinities to **13d** were observed at all $GABA_A$ subtypes. These examples also served to show that even small changes to the C-5 and C-6 substituents were found to significantly alter the efficacy profile. Thus, modification of the 4-methoxy group in the C-5 phenyl ring to fluorine gave **13h**, an unselective partial agonist at α1 and α3 subtypes, and replacement of this aryl group by 4-pyridyl produced the α1 inverse agonist **13i**. The substitution of 3-pyridyl for 4-pyridyl at the C-6 position of the pyridone, a change that had been shown to maintain affinity at α3 in the series of C-3 esters (**8f** vs **8g**), also modified the efficacy to give the unselective agonist **13j**. However, combining the 3- and 4-pyridyl motif to give the 4-pyridazinyl-substituted compound **13k** restored the functional selectivity, providing an antagonist at the α1 subtype with equal partial agonist activity at α2 and α3 subtypes. Moreover, the oral bioavailability of **13k** was improved over the original α2/3 selective agonist **13d** (Table 4).

The moderately improved bioavailability of **13k** was reflected in its in vivo profile (Table 3). Compound **13k** (i.p. dosing as a suspension in 0.5% aqueous methylcellulose) was anticonvulsant in the mouse model of epilepsy, with an ED_{50} of 3.3 mg/kg for protection against PTZ-induced tonic seizures, significantly more potent than **13d** (50% protection after 30 mk/kg i.p.). Furthermore, as anticipated from the selective partial agonist profile and improved pharmacokinetic parameters relative to **13d**, compound **13k** (30 mg/kg p.o., suspension in 0.5% aqueous methylcellulose) showed a statistically significant anxiolytic effect in the rat elevated plus maze.

The present study, together with the identification of an α2/α3 subtype selective agonist triazolo[4,3-b]pyridazine in our laboratories,[16] demonstrates that functional selectivity between $GABA_A$ receptor subtypes can be achieved in distinct chemical series. While these data suggest that α3 subunit-containing $GABA_A$ receptors play a role in mediating the anxiolytic properties of nonselective BZs, it is not possible to estimate the relative contribution of this receptor subtype as compared to other subtypes. Indeed, experiments with transgenic mice have implicated receptors containing an α2 rather than α3 subunit.[46] The reason for the discrepancy between the pharmacological approach in which α3-containing receptors are involved in anxiolysis and the molecular genetic approach in which anxiolysis appears to be mediated via α2- rather than α3-containing receptors is unclear but may, in part, be methodological.[47,48] Attributing the anxiolytic properties of BZs to particular $GABA_A$ receptor subtypes would be further clarified by additional subtype selective compounds. Nevertheless, the present study clearly demonstrates that it is possible to develop compounds that discriminate, on the basis of efficacy, between $GABA_A$ receptor subtypes. Moreover, the ultimate validation of the hypothesis that a particular subtype mediates anxiolysis, or any other aspect of the clinical diversity of nonselective BZ actions, will necessitate the evaluation of such compounds in the clinic.

Conclusions

A novel series of 3-heteroaryl-5,6-bis(aryl)-2-pyridones were developed with high affinity for the BZ binding site of human $GABA_A$ receptor ion channels and low binding selectivity for α2- and/or α3- over α1-containing $GABA_A$ receptor subtypes. Good binding selectivity was observed over α5-containing subtypes. High affinity in this series appeared to be associated with an attractive intramolecular S...O interaction between the pyridone carbonyl and adjacent thiacycles, evident in the crystal structure of the thiazole **13d**, which favored a coplanar conformation of these two rings. Functional selectivity at $GABA_A$ receptor subtypes was observed in several of these compounds, giving in particular cases no efficacy at the α1 subtype and varying degrees of efficacy at α2 and α3 subtypes. The selective α3 inverse agonist ester **8g** was proconvulsant and anxiogenic in rodents, suggesting that modulation of GABA-ergic transmission through the α3 subtype alone is capable of mediating anxiety behavior. The α2/α3 selective partial agonist thiazoles **13d** and **13k** were anticonvulsant, and the more bioavailable compound **13k** was also anxiolytic on oral dosing. These results are encouraging for the hypothesis that subtype selective BZ site agonists will provide new anxiolytic therapies.

Experimental Section

^1H nuclear magnetic resonance (NMR) spectra were recorded on Brucker AM360 or AC250 spectrometers. Chemical shifts (δ), from Me_4Si as internal standard, are given in parts per million and coupling constants (J) in Hertz. Mass spectra were obtained with a VG Quattro spectrometer operating in electrospray positive ion mode. Anhydrous solvents were purchased from the Aldrich Chemical Co. Organic solutions were dried over Na_2SO_4 or $MgSO_4$. Flash chromatography was performed on silica gel Fluka Art. No. 60738. Thin-layer chromatography (TLC) was carried out on Merck 5 cm × 10 cm plates with silica gel 60 F_{254} as sorbant. Preparative TLC was carried out using 20 cm × 20 cm silica gel GF tapered plates supplied by Analtech Inc., Newark. Microanalyses were determined by Butterworth Laboratories, 54−56 Waldegrave Road, Teddington, U.K. Commercially available starting materials were used as supplied.

2-(4-Methoxyphenyl)-1-(4-dimethylaminophenyl)ethan-1-one 2a. Solid ZnI_2 (0.5 g, 1.6 mmol) was added to a stirred solution of 4-dimethylaminobenzaldehyde (53.7 g, 360 mmol) and TMSCN (45 mL, 360 mmol) in CH_2Cl_2 (500 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 6 h and then concentrated. The residue was redissolved in Et_2O and filtered through activated charcoal. The filtrate was dried and concentrated to give the crude cyanohydrin **1a** (86 g, quantitative). A portion of the cyanohydrin (65 g, 280 mmol) was dissolved in dry tetrahydrofuran (THF; 150 mL) and added via cannula to a stirred solution of LDA (280 mmol) in dry THF (500 mL) at −78 °C under N_2. The mixture was stirred for 0.5 h followed by addition of 4-methoxybenzyl chloride (38 mL, 280 mmol). The cooling bath was removed, and the mixture was stirred at room temperature for 18 h, then poured into H_2O (1 L), and extracted with EtOAc (3 × 350 mL). The extracts were washed with H_2O and brine, dried, and concentrated. The residue was dissolved in MeOH (300 mL), and 1 M H_2SO_4 (400 mL) was added. After it had stirred at room temperature for 18 h, the mixture was basified to pH

10 with 4 M NaOH and extracted with EtOAc (3 × 300 mL). The extracts were washed with H_2O and brine, dried, and concentrated. The residue was triturated with Et_2O to give **2a** (50 g, 186 mmol, 67%) as a yellow solid. δ_H (250 MHz, $CDCl_3$): 3.05 (6H, s), 3.77 (3H, s), 4.13 (2H, s), 6.63 (2H, d, *J* 9), 6.84 (2H, d, *J* 9), 7.19 (2H, d, *J* 9), 7.92 (2H, d, *J* 9).

2-(4-Methoxyphenyl)-1-phenylethan-1-one 2b. Yield 64%. δ_H (360 MHz, $CDCl_3$): 3.79 (3H, s), 4.23 (2H, s), 6.87 (2H, d, *J* 9), 7.18 (2H, d, *J* 9), 7.45 (2H, dd, *J* 8, 8), 7.55 (1H, t, *J* 8), 8.00 (2H, d, *J* 8).

1-(4-Dimethylaminophenyl)-2-phenylethan-1-one 2c. Yield 72%. δ_H (250 MHz, dimethyl sulfoxide (DMSO)-d_6): 3.00 (6H, s), 4.19 (2H, s), 6.71 (2H, d, *J* 9), 7.16−7.33 (5H, m), 7.88 (2H, d, *J* 9).

2-(4-Methoxyphenyl)-1-(2-pyridyl)ethan-1-one 2d. Yield 64%. δ_H (360 MHz, $CDCl_3$): 3.78 (3H, s), 4.49 (2H, s), 6.85 (2H, d, *J* 9), 7.24 (2H, *J* 9), 7.44−7.48 (1H, m), 7.78−7.84 (1H, m), 8.01−8.05 (1H, m), 8.73 (1H, d, *J* 8); *m*/*z* (ES^+) 228 ($M + H^+$).

2-(4-Methoxyphenyl)-1-(3-pyridyl)ethan-1-one 2e. Yield 50%. δ_H (250 MHz, $CDCl_3$): 3.78 (3H, s), 4.23 (2H, s), 6.87 (2H, d, *J* 9), 7.18 (2H, *J* 9), 7.40 (1H, dd, *J* 8, 5), 8.25 (1H, ddd, *J* 8, 2, 2), 8.76 (1H, dd, *J* 5, 2), 9.22 (1H, d, *J* 2); *m*/*z* (ES^+) 455 ($M_2 + H^+$).

2-(4-Methoxyphenyl)-1-(4-pyridyl)ethan-1-one 2f. *N*,*N*-Carbonyldiimidazole (20.3 g, 125 mmol) was added portionwise to a stirred suspension of isonicotinic acid (15.4 g, 125 mmol) in dry THF (200 mL). The gently effervescent mixture was stirred at room temperature for 1.5 h forming an orange solution. Meanwhile, a solution of methyl 2-(4-methoxyphenyl)-acetate (45 g, 250 mmol) in dry THF (50 mL) was added dropwise at −78 °C to a stirred solution of LDA (250 mmol) in dry THF (250 mL). The yellow enolate solution was stirred at −78 °C for 20 min, followed by addition of the imidazolide solution dropwise via cannula. After it had stirred at −78 °C for 45 min, the bright yellow suspension was warmed to room temperature, poured into 1.3 M HCl (700 mL), and washed with hexane (200 mL). The aqueous solution was brought to pH 3 with 4 M NaOH and then to pH 7 with saturated $NaHCO_3$. The neutralized solution was extracted with CH_2Cl_2 (2 × 400 mL). The organic extracts were washed with brine (300 mL), dried, and concentrated to give a brown oil that crystallized on standing. The material was triturated with EtOAc−Et_2O (50 mL) and filtered to give 2-(4-methoxyphenyl)-3-oxo-3-(pyridin-4-yl)propionic acid methyl ester **3** as an off-white solid (14.7 g, 52 mmol, 42%). δ_H (250 MHz, $CDCl_3$): 3.77 (3H, s), 3.79 (3H, s), 5.48 (1H, s), 6.90 (2H, d, *J* 9), 7.28 (2H, d, *J* 9), 7.70 (2H, d, *J* 6), 8.77 (2H, d, *J* 6). A mixture of the ester (14.7 g, 53 mmol), NaCl (6.0 g, 103 mmol), and H_2O (1.9 mL, 105 mmol) in DMSO (200 mL) was stirred at 150 °C for 2 h. The solution was cooled to room temperature, poured into H_2O (600 mL), and extracted with EtOAc-Et_2O (1:1; 2 × 400 mL). The extracts were dried and concentrated to give **2f** as a brown solid (10.2 g, 45 mmol, 87%). δ_H (250 MHz, $CDCl_3$): 3.79 (3H, s), 4.44 (2H, s), 6.88 (2H, d, *J* 9), 7.16 (2H, d, *J* 9), 7.77 (2H, d, *J* 6), 8.80 (2H, d, *J* 6); *m*/*z* (ES^+) 228 ($M + H^+$).

2-(4-Fluorophenyl)-1-(4-pyridyl)ethan-1-one 2g. Yield 21%. δ_H (360 MHz, $CDCl_3$): 4.26 (2H, s), 7.00−7.06 (2H, m), 7.18−7.23 (2H, m), 7.75 (2H, d, *J* 6), 8.81 (2H, d, *J* 6); *m*/*z* (ES^+) 216 ($M + H^+$).

2-(4-Methoxyphenyl)-1-(4-pyridazinyl)ethan-1-one 2h. Yield 2%. δ_H (360 MHz, $CDCl_3$): 3.79 (3H, s), 4.24 (2H, s), 6.88 (2H, d, *J* 9), 7.16 (2H, d, *J* 9), 7.84 (1H, dd, *J* 5, 2), 9.42 (1H, d, *J* 5), 9.60 (1H, d, *J* 2).

1,2-Bis(4-pyridyl)ethan-1-one 2i. *n*-BuLi (2.5 M, 52 mL) was added at −78 °C to a stirred solution of picoline (12 g, 129 mmol) in dry THF (300 mL) under N_2. After the mixture had stirred for 1 h, a solution of 4-cyanopyridine (9 g, 86 mmol) in dry THF (100 mL) was added over 10 min. The red suspension was warmed to room temperature and stirred for 1 h, followed by addition of 1 M HCl (150 mL) and further stirring for 1 h. The mixture was neutralized with saturated $NaHCO_3$(aq) and separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried and concentrated. Flash column chromatography, eluting with 97:7 CH_2Cl_2−MeOH, gave a yellow oil (5.4 g). EtOAc (10 mL) was added, and the solution stood at room temperature for 18 h. The solid was collected and washed with EtOAc to give **2i** (0.80 g, 4 mmol, 3%) as a light yellow powder. δ_H (250 MHz, $CDCl_3$): 4.30 (2H, s), 7.20 (2H, d, *J* 6), 7.77 (2H, d, *J* 6), 8.60 (2H, d, *J* 6), 8.85 (2H, d, *J* 6).

5,6-Diphenyl-3-cyano-1*H*-pyridin-2-one 4a. A solution of deoxybenzoin (10 g, 51 mmol) and DMF−DMA (27 mL, 204 mmol) in dry DMF (200 mL) was stirred at 85 °C for 18 h. Solvent and excess reagent were removed by evaporation to give a yellow oil. A solution of the oil in dry DMF (100 mL) with cyanoacetamide (4.75 g, 57 mmol) and MeOH (4.54 mL, 112 mmol) was added via cannula to a stirred suspension of NaH (60%; 4.5 g, 112 mmol) in dry DMF (100 mL) at room temperature under N_2. After it had stirred at room temperature for 15 min, the mixture was stirred at 95 °C for 18 h. The mixture was cooled, and solvents were removed by evaporation. Saturated NH_4Cl(aq) was added to the residues, and the resulting solids were collected, washed with H_2O and Et_2O, and dried under vacuum to give **4a** (7.5 g, 28 mmol, 54%). δ_H (360 MHz, DMSO-d_6): 7.03−7.06 (2H, m), 7.17−7.25 (5H, m), 7.29−7.33 (2H, m), 7.36−7.41 (1H, m), 8.23 (1H, s), 12.79 (1H, br s).

6-(4-Dimethylaminophenyl)-5-(4-methoxyphenyl)-3-cyano-1*H*-pyridin-2-one 4b. Yield 95%. δ_H (360 MHz, $CDCl_3$): 3.00 (6H, s), 3.81 (3H, s), 6.57 (2H, d, *J* 9), 6.83 (2H, d, *J* 9), 7.03 (2H, d, *J* 9), 7.11 (2H, d, *J* 9), 7.85 (1H, s), 10.50 (1H, br s).

5-(4-Methoxyphenyl)-6-phenyl-3-cyano-1*H*-pyridin-2-one 4c. Yield 47%. δ_H (360 MHz, $CDCl_3$): 3.80 (3H, s), 6.81 (2H, d, *J* 9), 6.95 (2H, d, *J* 9), 7.25−7.27 (3H, m), 7.35 (2H, d, *J* 9), 7.96 (1H, s), 11.90 (1H, br s).

6-(4-Dimethylaminophenyl)-5-phenyl-3-cyano-1*H*-pyridin-2-one 4d. Yield 80%. δ_H (250 MHz, DMSO-d_6): 3.00 (6H, s), 7.03−7.06 (2H, m), 7.17−7.25 (4H, m), 7.29−7.33 (2H, m), 7.36−7.41 (1H, m), 8.23 (1H, s), 12.79 (1H, br s).

6-(4-Dimethylaminophenyl)-5-(4-methoxyphenyl)-3-cyano-1-methyl-1*H*-pyridin-2-one 5a and 6-(4-Dimethylaminophenyl)-5-(4-methoxyphenyl)-3-cyano-2-methoxypyridine 6a. MeI (0.203 mL, 3.2 mmol) was added to a stirred suspension of **4b** (1.0 g, 2.9 mmol) and Cs_2CO_3 (1.04 g, 3.2 mmol) in dry DMF (20 mL) at room temperature under N_2. After 1 h, the mixture was partitioned between H_2O and EtOAc (× 3). The organic solution was washed with H_2O and brine, dried, and concentrated. The residual solid was boiled in Et_2O (25 mL) and cooled, and the solid was collected. The material was recrystallized from $CHCl_3$−hexane to give **5a** (0.609 g, 1.7 mmol, 59%) as yellow cubes. The mother liquors were concentrated and purified by flash column chromatography, eluting with 99:1 and then 95:5 CH_2Cl_2−MeOH, to give first **6a** (0.304 g, 0.84 mmol, 29%) as a yellow foam that gave light yellow needles on recrystallization from $CHCl_3$−hexane. Continued elution gave further **5a** (0.10 g, 0.3 mmol, 10%). **5a**: δ_H (360 MHz, $CDCl_3$): 2.97 (6H, s), 3.42 (3H, s), 3.75 (3H, s), 6.60 (2H, d, *J* 9), 6.70 (2H, d, *J* 9), 6.83 (2H, d, *J* 9), 6.89 (2H, d, *J* 9), 7.84 (1H, s); *m*/*z* (ES^+) 360 ($M + H^+$). Anal. ($C_{23}H_{21}N_3O_2$) C, H, N. **6a**: δ_H (360 MHz, $CDCl_3$): 2.97 (6H, s), 3.83 (3H, s), 4.13 (3H, s), 6.57 (2H, d, *J* 9), 6.86 (2H, d, *J* 9), 7.11 (2H, d, *J* 9), 7.38 (2H, d, *J* 9), 7.75 (1H, s); *m*/*z* (ES^+) 360 ($M + H^+$). Anal. ($C_{23}H_{21}N_3O_2$) C, N; H: calcd, 5.89; found, 5.35.

6-(4-Dimethylaminophenyl)-5-phenyl-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8a. A solution of **4d** (1.5 g, 4.76 mmol) in 6 M HCl (50 mL) was refluxed under N_2 for 72 h. The mixture was cooled to yield a precipitate that was collected, washed with Et_2O, and dried under vacuum to give the carboxylic acid **7a** (1.36 g, 4.07 mmol, 86%). δ_H (250 MHz, DMSO-d_6): 2.93 (6H, s), 6.64 (2H, d, *J* 9), 7.09−7.16 (4H, m), 7.24−7.34 (3H, m), 8.20 (1H, s), 13.23 (1H, br s). A suspension of the acid (1.0 g, 3.0 mmol), Cs_2CO_3 (2.14 g, 6.6 mmol), and MeI (0.41 mL, 6.6 mmol) in dry DMF (20 mL) was stirred at room temperature under N_2 for 18 h. The mixture was partitioned between H_2O and EtOAc (× 3), and the organic extracts were washed with H_2O and brine, then dried, and concentrated. Flash column chromatography, eluting with 98:2

and then 96:4 CH_2Cl_2−MeOH, followed by recrystallization from EtOAc, gave **8a** (0.34 g, 0.94 mmol, 31%). δ_H (360 MHz, DMSO-d_6): 2.89 (6H, s), 3.25 (3H, s), 3.77 (3H, s), 6.63 (2H, d, *J* 9), 7.00−7.05 (4H, m), 7.10−7.20 (3H, m), 7.99 (1H, s); *m*/*z* (ES^+) 363 ($M + H^+$). Anal. ($C_{22}H_{22}N_2O_3$) C, H, N.

6-(4-Dimethylaminophenyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8b. Yield 44%. δ_H (360 MHz, $CDCl_3$): 2.97 (6H, s), 3.41 (3H, s), 3.75 (3H, s), 3.93 (3H, s), 6.61 (2H, d, *J* 9), 6.69 (2H, d, *J* 9), 6.88 (2H, d, *J* 9), 6.92 (2H, d, *J* 9), 8.22 (1H, s); *m*/*z* (ES^+) 393 ($M + H^+$). Anal. ($C_{23}H_{24}N_2O_4 \cdot 0.25(H_2O)$) C, H, N.

5-(4-Methoxyphenyl)-6-phenyl-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8c. Yield 41%. δ_H (360 MHz, $CDCl_3$): 3.37 (3H, s), 3.72 (3H, s), 3.94 (3H, s), 6.66 (2H, d, *J* 9), 6.85 (2H, d, *J* 9), 7.10−7.12 (2H, m), 7.34−7.36 (3H, m), 8.23 (1H, s); *m*/*z* (ES^+) 350 ($M + H^+$). Anal. ($C_{21}H_{19}NO_4$) C, N; H: calcd, 5.48; found, 4.95.

5,6-Diphenyl-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8d. Yield 7%. δ_H (360 MHz, DMSO-d_6): 3.21 (3H, s), 3.78 (3H, s), 7.00−7.02 (2H, m), 7.11−7.17 (3H, m), 7.29−7.33 (2H, m), 7.35−7.39 (3H, m), 8.01 (1H, s); *m*/*z* (ES^+) 320 ($M + H^+$). Anal. ($C_{19}H_{17}NO_3$) C, H, N.

6-(2-Pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8e. Yield 15%. δ_H (360 MHz, $CDCl_3$): 3.37 (3H, s), 3.73 (3H, s), 3.94 (3H, s), 6.67 (2H, d, *J* 9), 6.87 (2H, d, *J* 9), 6.96−7.00 (1H, m), 7.26−7.30 (1H, m), 7.56−7.62 (1H, m), 8.26 (1H, s), 8.74 (1H, d, *J* 8); *m*/*z* (ES^+) 351 ($M + H^+$). Anal. ($C_{20}H_{18}N_2O_4$) C, H, N.

6-(3-Pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8f. Yield 3%. δ_H (360 MHz, $CDCl_3$): 3.38 (3H, s), 3.73 (3H, s), 3.94 (3H, s), 6.68 (2H, d, *J* 9), 6.84 (2H, d, *J* 9), 7.30 (1H, dd, *J* 8, 5), 7.46 (1H, ddd, *J* 8, 2, 2), 8.22 (1H, s), 8.42 (1H, d, *J* 2) 8.60 (1H, dd, *J* 5, 2); *m*/*z* (ES^+) 351 ($M + H^+$). Anal.($C_{20}H_{18}N_2O_4$) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8g. Yield 4%. δ_H (360 MHz, $CDCl_3$): 3.36 (3H, s), 3.73 (3H, s), 3.94 (3H, s), 6.68 (2H, d, *J* 9), 6.85 (2H, d, *J* 9), 7.09 (2H, d, *J* 6), 8.20 (1H, s), 8.64 (2H, d, *J* 6); *m*/*z* (ES^+) 351 ($M + H^+$). Anal. ($C_{20}H_{18}N_2O_4$) H, N. C: calcd, 68.56; found, 68.99. High-performance liquid chromatography (HPLC) > 99.5%.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-methyl-1*H*-pyridin-2-one 10. A solution of **2f** (10.0 g, 44 mmol) and DMF−DMA (25 mL, 188 mmol) in dry DMF (100 mL) was stirred for 16 h at 80 °C under N_2. Solvent was removed by evaporation, and the brown solid was recrystallized from EtOAc to give 3-(dimethylamino)-2-(4-methoxyphenyl)-1-(pyridin-4-yl)propen-1-one (10.3 g, 36.5 mmol, 83%) as a light orange solid. δ_H (250 MHz, $CDCl_3$): 2.75 (6H, br s), 3.77 (3H, s), 6.81 (2H, d, *J* 9), 7.04 (2H, d, *J* 9), 7.22 (2H, d, *J* 6), 7.38 (1H, s), 8.54 (2H, d, *J* 6); *m*/*z* (ES^+) 283 ($M + H^+$). A portion of this material (5.0 g, 17.7 mmol) and *N*-methylcyanoacetamide (1.75 g, 17.8 mmol) in dry MeOH (40 mL) was added via cannula at 0 °C to a stirred solution of freshly prepared NaOMe (1.94 g, 36 mmol) in dry MeOH (25 mL) under N_2. The suspension was warmed to room temperature and stirred for 18 h and then refluxed for 4.5 h. The mixture was cooled, and solvent was removed by evaporation. The residue was dissolved in CH_2Cl_2−MeOH−NH_3 (90:9:1) and filtered through a silica plug. The filtrate was concentrated to give a brown tar, which was triturated and washed with EtOAc to give **5b** (2.65 g, 8.36 mmol, 47%) as a yellow solid. δ_H (360 MHz, $CDCl_3$): 3.37 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.82 (2H, d, *J* 9), 7.07 (2H, d, *J* 5), 7.88 (1H, s), 8.64 (2H, d, *J* 5); *m*/*z* (ES^+) 318 ($M + H^+$). A solution of **5b** (1.63 g, 5.14 mmol) in 8 M HCl (20 mL) was refluxed for 24 h. The cooled solution was basified with concentrated aqueous NH_3 (100 mL), and solvent and excess ammonia were removed by evaporation to give a gray solid. The solid was extracted with hot EtOAc, and the filtered extract was concentrated to give the acid **9** (0.78 g, 2.33 mmol, 46%) as a pale yellow solid. δ_H (250 MHz, $CDCl_3$): 3.48 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.86 (2H, d, *J* 9), 7.12 (2H, d, *J* 6), 8.60 (1H, s), 8.68 (2H, d, *J* 6), 14.36 (1H, br s); *m*/*z* (ES^+) 336 ($M + H^+$). A mixture of **9** (0.30 g, 0.89 mmol) and 1,1′-carbonyldiimidazole (0.29 g, 1.78 mmol) in dry THF (20 mL) was refluxed under N_2 for 48 h. The mixture was cooled and partitioned between H_2O and EtOAc. The organic layer was dried and concentrated to give an orange foam that was redissolved in dry DMF (5 mL). NaH (55%, 0.04 g, 0.92 mmol) was added to a stirred suspension of acetamide oxime (0.073 g, 0.99 mmol) and freshly activated 4 Å molecular sieves in dry DMF (20 mL) at room temperature under N_2. After it had stirred for 30 min, the solution of the imidazolide was added and the mixture was stirred at 80 °C for 2 h. The mixture was cooled and partitioned between EtOAc and H_2O. The organic extracts were washed with brine, dried, and concentrated to give a yellow solid. Recrystallization from EtOAc gave **10** (0.10 g, 0.267 mmol, 30%) as a pale yellow solid. δ_H (360 MHz, $CDCl_3$): 2.50 (3H, s), 3.44 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.88 (2H, d, *J* 9), 7.13 (2H, d, *J* 6), 8.39 (1H, s), 8.64 (2H, d, *J* 6); *m*/*z* (ES^+) 375 ($M + H^+$). HPLC 99.5%.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1-methyl-1*H*-pyridin-2-one 11a. $NH_2OH \cdot HCl$ (0.24 g, 3.5 mmol) and **5b** (1.0 g, 3.15 mmol) were added to a stirred solution of freshly prepared NaOMe (0.40 g, 7.4 mmol) in dry MeOH (10 mL), and the yellow suspension was refluxed under N_2 for 2 h. Further NaOMe (0.16 g, 3.0 mmol) was prepared and added to the cooled solution, followed by further $NH_2OH \cdot HCl$ (0.10 g, 1.5 mmol). The mixture was refluxed for a further 2 h, then cooled, and diluted with saturated NH_4Cl(aq) (100 mL). The mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the extracts were washed with brine (50 mL), dried, and concentrated to give the amide oxime (1.01 g, 2.87 mmol, 91%) as a yellow solid. δ_H (360 MHz, $CDCl_3$): 3.37 (3H, s), 3.73 (3H, s), 6.36 (2H, br s), 6.67 (2H, d, *J* 9), 6.84 (2H, d, *J* 9), 7.08 (2H, d, *J* 6), 8.14 (1H, s), 8.62 (2H, d, *J* 6). A solution of the amide oxime (0.36 g, 1.03 mmol) in dry DMF (7 mL) was stirred at room temperature under N_2 with freshly activated 4 Å molecular sieves. NaH (55%; 0.05 g, 1.2 mmol) was added, and the mixture was stirred for 30 min, followed by the addition of EtOAc (1 mL, 10.2 mmol). The mixture was stirred at 80 °C for 2 h and then poured into H_2O (50 mL) and extracted with CH_2Cl_2−MeOH (90:10) (3 × 30 mL). The extracts were dried and concentrated. Preparative TLC, eluting with CH_2Cl_2−MeOH (90:10), followed by recrystallization from EtOAC−EtOH (90:10), gave **11a** (0.157 g, 0.42 mmol, 41%). δ_H (360 MHz, DMSO-d_6): 2.65 (3H, s), 3.27 (3H, s), 3.69 (3H, s), 6.76 (2H, d, *J* 9), 6.99 (2H, d, *J* 9), 7.43 (2H, d, *J* 6), 8.13 (1H, s), 8.64 (2H, d, *J* 6); *m*/*z* (ES^+) 375 ($M + H^+$). HPLC 99.1%.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-1-methyl-1*H*-pyridin-2-one 11b. Yield 63%. δ_H (360 MHz, $CDCl_3$): 1.21−1.30 (4H, m), 2.20−2.30 (1H, m), 3.41 (3H, s), 3.74 (3H, s), 6.69 (2H, d, *J* 9), 6.89 (2H, d, *J* 9), 7.11 (2H, d, *J* 6), 8.25 (1H, s), 8.64 (2H, d, *J* 6); *m*/*z* (ES^+) 401 ($M + H^+$). Anal. ($C_{23}H_{20}N_4O_3$) C, H, N.

***N*-Methyl-2-(3-methyl-1,2,4-thiadiazol-5-yl)acetamide 12a.** NaOH (60 g, 1.5 mol) in H_2O (100 mL) was added dropwise at −5 °C over 2 h to a stirred mixture of acetamidine hydrochloride (30 g, 320 mmol) and Cl_3CSCl (59 g, 320 mmol) in CH_2Cl_2 (300 mL). The mixture was stirred at 0 °C for 0.5 h, then warmed to room temperature, and filtered. The biphasic filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried, and solvent was removed by distillation at atmospheric pressure. The residual oil was distilled in vacuo (20 mm Hg, 53−55 °C) to give 5-chloro-3-methyl-1,2,4-thiadiazole (14.5 g, 112 mmol, 35%) as a yellow liquid. δ_H (250 MHz, $CDCl_3$): 2.65 (s). A portion of this material (5 g, 37 mmol) in dry THF (15 mL) was added at −78 °C to a stirred solution of lithio ethyl acetate (2.91 g, 31 mmol) (prepared from LDA and EtOAc at −78 °C) in dry THF (70 mL) under N_2. The mixture was warmed to room temperature and stirred for 2.5 h and then partitioned between EtOAc and H_2O. The organic extract was washed with brine, dried, and concentrated. Flash column chromatography, eluting with hexanes−EtOAc (80:20), gave ethyl 2-(3-methyl-1,2,4-thiadiazol-5-yl)acetate (0.60 g,

3.23 mmol, 9%). δ_H (360 MHz, $CDCl_3$): 1.34 (3H, t, *J* 7), 2.66 (3H, s), 4.16 (2H, s), 4.29 (2H, q, *J* 7). The ester (0.60 g, 3.23 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (8 M, 40 mL, 320 mmol) and briefly warmed to reflux. After it stood at room temperature for 2 h, solvent was removed by evaporation. Flash column chromatography, eluting with CH_2Cl_2−MeOH−NH_3 (92:7:1), gave **12a** (0.29 g, 1.71 mmol, 53%) as a brown solid. δ_H (250 MHz, $CDCl_3$): 2.67 (3H, s), 2.90 (3H, d, *J* 5), 4.04 (2H, s), 6.38−6.58 (1H, br m).

***N*-Methyl-2-(2-thiazolyl)acetamide 12b.** EtOCOCl (11.5 mL, 120 mmol) was added dropwise to a stirred solution of thiazole (7.4 mL, 104 mmol) in dry THF (200 mL) at 0 °C under N_2. After 1 h, a freshly prepared solution of lithio diethylmalonate (19.9 g, 120 mmol) in dry THF (150 mL) was added via cannula and the mixture was stirred at room temperature for 18 h. The mixture was diluted with Et_2O (100 mL) and washed with saturated NH_4Cl(aq) (250 mL) and brine (200 mL), dried, and concentrated. Flash column chromatography, eluting with hexanes−EtOAc (8:2), gave a mixture of the thiazoline and diethylmalonate (28.9 g, 4:1 by NMR) as a colorless oil. A portion of this material (22 g) was stirred at 0 °C in dry CH_2Cl_2 (200 mL), and *o*-chloranil (15.5 g, 63 mmol) was titrated portionwise into the mixture. After complete addition, the mixture was stirred for 1 h and then washed with aqueous $NaHCO_3$ (400 mL) and brine (200 mL), dried, and concentrated. Flash column chromatography, eluting with 6:4 hexanes−EtOAc, gave **14a** (14.7 g, 60 mmol, 58%) as a beige solid. δ_H (360 MHz, DMSO-d_6): 1.25 (6H, t, *J* 7), 4.14 (4H, q, *J* 7), 7.07 (1H, d, *J* 4), 7.81 (1H, d, *J* 4), 12.92 (1H, br s). A solution of **14a** (14.7 g, 60 mmol), NaCl (7 g, 120 mmol), and H_2O (2.2 mL, 120 mmol) in DMSO (250 mL) was stirred at 180 °C for 30 min, then cooled, diluted with H_2O (500 mL), and extracted with Et_2O−EtOAc (1:1, 400 mL). The extract was dried and concentrated. Flash column chromatography, eluting with 7:3 and then 6:4 hexanes−EtOAc, gave ethyl 2-(thiazol-2-yl)acetate (5.0 g, 27 mmol, 48%) as a brown oil. δ_H (360 MHz, $CDCl_3$): 1.29 (3H, t, *J* 7), 4.10 (2H, s), 4.24 (2H, q, *J* 7), 7.33 (1H, d, *J* 3), 7.76 (1H, d, *J* 3). A solution of Me_2-NH in EtOH (8 M, 40 mL, 320 mmol) was added to a stirred solution of ethyl 2-(thiazol-2-yl)acetate (5.0 g, 29 mmol) in EtOH (20 mL) at room temperature After 5 h, solvents and excess amine were removed by evaporation. Flash column chromatography, eluting with EtOAc and then CH_2Cl_2−MeOH−NH_3 (90:9:1), gave partly purified product that was redissolved in EtOAc (50 mL) and filtered, and the filtrate was concentrated to yield **12b** (2.95 g, 18.9 mmol, 65%) as a brown oil. δ_H (250 MHz, $CDCl_3$): 2.85 (3H, d, *J* 5), 3.98 (2H, s), 7.05−7.25 (1H, br m), 7.31 (1H, d, *J* 3), 7.76 (1H, d, *J* 3).

***N*-Methyl-2-(5-methyl-2-thiazolyl)acetamide 12c.** Prepared as above from 5-methylthiazole to give **14b**. Yield 57%. δ_H (250 MHz, DMSO-d_6): 1.23 (6H, t, *J* 7), 2.25 (3H, d, *J* 1), 4.12 (4H, q, *J* 7), 7.15 (1H, q, *J* 1), 12.61 (1H, br s); *m*/*z* (ES+) 258 (M + H^+). **12c**: Yield 83%. δ_H (360 MHz, $CDCl_3$): 2.45 (3H, s), 2.83 (3H, d, *J* 5), 3.87 (2H, s), 7.10−7.25 (1H, br m), 7.37 (1H, s); *m*/*z* (ES+) 171 (M + H^+).

***N*-Methyl-2-(4-methyl-2-thiazolyl)acetamide 12d.** A solution of *n*-BuLi (2.5M, 19 mL) in hexanes was added dropwise to a stirred solution of 2,4-dimethylthiazole (5 mL, 47 mmol) in dry THF (100 mL) at −78 °C under N_2. The bright yellow suspension was stirred for 45 min followed by addition of EtOCOCl (4.8 mL, 50 mmol). After the mixture had stirred at −78 °C for 1 h, the reaction was quenched with saturated NH_4-Cl(aq) (100 mL) and H_2O (100 mL) and extracted with CH_2-Cl_2 (100 mL). The extract was dried and concentrated. Flash column chromatography, eluting with 97:3 and then 95:5 CH_2-Cl_2−MeOH, gave a mixture of acylation products and starting material (monoacylation:diacylation:starting material 4:2:1 by NMR) as an orange oil (2.9 g). The oil was added to a solution of $MeNH_2$ (8M, 20 mL, 160 mmol) in EtOH and stood for 18 h at room temperature. Solvent and excess amine were removed by evaporation. Flash column chromatography, eluting successively with CH_2Cl_2−MeOH (97:3, 96:4, 90:10), gave partly purified product, which was triturated with Et_2O and filtered to remove the white solid. The filtrate was concentrated to give **12d** (1.47 g, 8.65 mmol, 18%) as an orange oil. δ_H (360 MHz, $CDCl_3$): 2.45 (3H, d, *J* 1), 2.84 (3H, d, *J* 5), 3.91 (2H, s), 6.82 (1H, q, *J* 1), 7.00−7.20 (1H, br m); *m*/*z* (ES+) 171 (M + H^+).

***N*-Methyl-2-(4-cyclopropyl-2-thiazolyl)acetamide 12e.** Compound **12e** was prepared as above from 4-cyclopropylthiazole. Yield 4%. δ_H (250 MHz, $CDCl_3$): 0.82−0.89 (2H, m), 0.91−1.01 (2H, m), 2.00−2.11 (1H, m), 2.83 (3H, d, *J* 5), 3.88 (2H, s), 6.77 (1H, s), 7.00−7.20 (1H, br m); *m*/*z* (ES+) 197 (M + H^+).

***N*-Methyl-2-(4-methyl-2-thienyl)acetamide 12f.** Compound **12f** was prepared from 2-formyl-3-methylthiophene[26] by homologation[27] to the methyl ester and treatment with 8 M $MeNH_2$ in EtOH to give **12f** (26%) as a brown oil. Purity 90% by NMR, remainder of material consisted of regioisomeric *N*-methyl-2-(3-methyl-2-thienyl)acetamide. Data for **12f**: δ_H (250 MHz, $CDCl_3$): 2.24 (3H, s), 2.78 (3H, d, *J* 5), 3.72 (2H, s), 5.50−5.80 (1H, br m), 6.74 (1H, s), 6.81 (1H, s); *m*/*z* (ES+) 170 (M + H^+).

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(3-methyl-1,2,4-thiadiazol-5-yl)-1-methyl-1*H*-pyridin-2-one 13a. See preparation of **13b**. Yield 25%. δ_H (360 MHz, $CDCl_3$): 2.70 (3H, s), 3.53 (3H, s), 3.75 (3H, s), 6.71 (2H, d, *J* 9), 6.92 (2H, d, *J* 9), 7.13 (2H, d, *J* 6), 8.63−8.66 (3H, m); *m*/*z* (ES+) 391 (M + H^+). Anal. ($C_{21}H_{18}N_4O_2S$) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(thiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13b. A solution of **2f** (10.2 g, 45 mmol) and DMF−DMA (20 mL, 150 mmol) in dry DMF (50 mL) was stirred at 80 °C for 4 h. The mixture was cooled, poured into water (500 mL), and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with brine (100 mL), dried, and concentrated to give a yellow solid. The material was washed well with Et_2O−hexane (1:9; 2 × 100 mL) and dried in vacuo to give 3-(dimethylamino)-2-(4-methoxyphenyl)-1-(pyridin-4-yl)propen-1-one as a beige solid (7.7 g, 27 mmol, 60%). δ_H (250 MHz, $CDCl_3$): 2.78 (6H, br s), 3.79 (3H, s), 6.79 (2H, d, *J* 9), 7.04 (2H, d, *J* 9), 7.24 (2H, d, *J* 6) 7.40 (1H, s), 8.51 (2H, d, *J* 6). A portion of this material (2.53 g, 8.97 mmol), **12b** (1.70 g, 10.9 mmol), and MeOH (0.73 mL, 18 mmol) was dissolved in dry DMF (20 mL) and added via cannula at room temperature to a stirred suspension of NaH (55%, 0.80 g, 18 mmol) in dry DMF (10 mL) under N_2. The mixture was stirred at 40 °C for 18 h and then poured into water (200 mL). The yellow precipitate was collected and recrystallized from EtOAc to give **13b** (2.18 g, 5.81 mmol, 65%) as a yellow powder. δ_H (360 MHz, $CDCl_3$): 3.50 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.93 (2H, d, *J* 9), 7.15 (2H, d, *J* 6), 7.50 (1H, d, *J* 3), 7.96 (1H, d, *J* 3), 8.64 (2H, d, *J* 6), 8.72 (1H, s); *m*/*z* (ES+) 376 (M + H^+). Anal. ($C_{21}H_{17}N_3O_2S$) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(5-methylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13c. Yield 16%. δ_H (360 MHz, $CDCl_3$): 2.56 (3H, s), 3.48 (3H, s), 3.74 (3H, s), 6.69 (2H, d, *J* 9), 6.93 (2H, d, *J* 9), 7.14 (2H, d, *J* 6), 7.62 (1H, s), 8.64 (2H, d, *J* 6), 8.72 (1H, br s); *m*/*z* (ES+) 390 (M + H^+). Anal. ($C_{22}H_{19}N_3O_2S$·0.5($C_4H_8O_2$)·0.5(H_2O)) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(4-methylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13d. Yield 42%. δ_H (360 MHz, $CDCl_3$): 2.58 (3H, s), 3.50 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.95 (2H, d, *J* 9), 7.08 (1H, s), 7.15 (2H, d, *J* 6), 8.65 (2H, d, *J* 6), 8.90 (1H, br s); *m*/*z* (ES+) 390 (M + H^+). Anal. ($C_{22}H_{19}N_3O_2S$) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(4-cyclopropylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13e. Yield 43%. δ_H (360 MHz, $CDCl_3$): 0.91−0.99 (4H, m), 2.18−2.26 (1H, m), 3.48 (3H, s), 3.75 (3H, s), 6.72 (2H, d, *J* 9), 6.94 (2H, d, *J* 9), 7.98 (1H, s), 7.16 (2H, d, *J* 6), 8.65 (2H, d, *J* 6), 8.76 (1H, br s); *m*/*z* (ES+) 416 (M + H^+). Anal. ($C_{24}H_{21}N_3O_2S$·0.6(H_2O)) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(thiophen-2-yl)-1-methyl-1*H*-pyridin-2-one 13f. Yield 34%. δ_H (360 MHz, $CDCl_3$): 3.45 (3H, s), 3.75 (3H, s), 6.72 (2H, d, *J* 9), 6.91 (2H, d, *J* 9), 7.12 (1H, dd, *J* 5, 4), 7.16−7.19 (2H, m), 7.43 (1H, dd, *J* 5,1), 7.71 (1H, dd, *J* 4,1), 7.90 (1H, s), 8.58−8.66 (2H, m); *m*/*z* (ES+) 375 (M + H^+). Anal. ($C_{22}H_{18}N_2O_2S$) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(4-methylthiophen-2-yl)-1-methyl-1*H*-pyridin-2-one 13g. Yield 34%. δ_H (360

MHz, $CDCl_3$): 2.30 (3H, s), 3.43 (3H, s), 3.75 (3H, s), 6.71 (2H, d, *J* 9), 6.90 (2H, d, *J* 9), 7.00 (1H, s), 7.11 (2H, d, *J* 6), 7.56 (1H, s), 7.85 (1H, s), 8.62 (2H, d, *J* 6); *m*/*z* (ES+) 389 ($M + H^+$). Anal. ($C_{23}H_{20}N_2O_2S$) C, H, N.

6-(4-Pyridyl)-5-(4-fluorophenyl)-3-(4-methylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13h. Yield 21%. δ_H (360 MHz, $CDCl_3$): 2.51 (3H, s), 3.49 (3H, s), 6.85−6.90 (2H, m), 6.97−7.01 (2H, m), 7.06 (1H, s), 7.11 (2H, d, *J* 6), 8.62−8.66 (3H, m); *m*/*z* (ES+) 378 ($M + H^+$). Anal. ($C_{21}H_{16}N_3OSF$) C, H, N.

5,6-Bis(4-pyridyl)-3-(4-methylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13i. Yield 14%. δ_H (360 MHz, $CDCl_3$): 2.52 (3H, s), 3.50 (3H, s), 6.98 (2H, d, *J* 6), 7.08 (1H, s), 7.15 (2H, d, *J* 6), 8.44 (2H, d. *J* 6), 8.64 (1H, s), 8.70 (2H, d, *J* 6); *m*/*z* (ES+) 361 ($M + H^+$). Anal. ($C_{20}H_{16}N_4OS \cdot 0.4(H_2O)$) C, N; H: calcd, 4.61; found, 4.19. HPLC 99.5%.

6-(3-Pyridyl)-5-(4-methoxyphenyl)-3-(4-methylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13j. Yield 32%. δ_H (250 MHz, DMSO-d_6): 2.42 (3H, s), 3.37 (3H, s), 3.68 (3H, s), 6.77 (2H, d, *J* 9), 6.99 (2H, d, *J* 9), 7.34 (1H, s), 7.45 (1H, dd, *J* 8, 5), 7.88 (1H, ddd, *J* 8, 2, 2), 8.42 (1H, s), 8.49 (1H, d, *J* 2), 8.56 (1H, dd, *J* 5, 2); *m*/*z* (ES+) 390 ($M + H^+$). HPLC 95.5%.

6-(4-Pyridazinyl)-5-(4-methoxyphenyl)-3-(4-methylthiazol-2-yl)-1-methyl-1*H*-pyridin-2-one 13k. Yield 6%. δ_H (360 MHz, $CDCl_3$): 2.51 (3H, s), 3.50 (3H, s), 3.74 (3H, s), 6.71 (2H, d, *J* 9), 6.89 (2H, d, *J* 9), 7.08 (1H, s), 7.27 (1H, dd, *J* 5, 2), 8.66 (1H, s), 9.06 (1H, dd, *J* 2, 1), 9.20 (1H, dd, *J* 5, 1); *m*/*z* (ES+) 391 ($M + H^+$). Anal. ($C_{21}H_{18}N_4O_2S$) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-phenyl-1-methyl-1*H*-pyridin-2-one 13l. A stirred solution of **2f** (17.5 g, 77 mmol) in $CHCl_3$ (200 mL) was saturated with $MeNH_2$ gas at 0 °C. A solution of $TiCl_4$ in CH_2Cl_2 (1 M, 40 mL, 40 mmol) was added via syringe at 0 °C under N_2. After the solution had stirred at room temperature for 18 h, anhydrous Na_2SO_4 (5 g) was added and the yellow suspension was filtered through Celite, washing with CH_2Cl_2. Evaporation of the filtrate gave the crude imine (16.7 g, 70 mmol, 90%) as an orange oil. δ_H (250 MHz, $CDCl_3$): 3.48 (3H, br s), 3.77 (3H, s), 4.04 (2H, br s), 6.76−6.85 (2H, m), 6.96−7.05 (2H, m), 7.26 and 7.58 (2H, 2 × d, *J* 6), 8.09 (2H, m). A solution of $BnOCH_2COCl$ (11.7 g, 68 mmol) in dry THF (50 mL) was added via cannula to a stirred solution of the imine (16.7 g, 70 mmol) in dry THF (150 mL) at −78 °C under N_2. After complete addition, the purple solution was warmed to 0 °C and stirred for 1.5 h. The brown suspension was poured into ice/$NaHCO_3$(aq) (500 mL) and extracted with EtOAc (2 × 250 mL). The extracts were washed with brine (100 mL), dried, and concentrated. Flash column chromatogaphy on silica, eluting with CH_2Cl_2−MeOH (95:5), gave **15** (17.1 g, 44 mmol, 64%) as a brown gum. δ_H (250 MHz, $CDCl_3$): 3.16 and 3.24 (3H, 2 × s), 3.68 and 3.73 (3H, 2 × s), 3.85 (2H, s), 4.36−4.50 (2H, m), 6.88−7.02 (3H, m), 7.10−7.40 (9H, m), 8.44 and 8.62 (2H, 2 × d, *J* 6); *m*/*z* (ES+) 389 ($M + H^+$). A solution of **15** (7.37 g, 19 mmol) in the minimum volume of CH_2Cl_2 (10 mL) was added slowly at room temperature to stirred $POCl_3$ (12 mL, 129 mmol). The brown solution was stirred for 1 h and then cooled to 0 °C, and DMF (3 mL) was added dropwise. The mixture was stirred at room temperature for 1 h and then at 75 °C for 1.5 h. The mixture was cooled to 0 °C, and further DMF (1.5 mL) was added dropwise. The mixture was heated at 75 °C for 3 h and then cooled and poured onto ice (300 mL). NaOH (2M, 150 mL, 300 mmol) was added with vigorous stirring, followed by additional base to adjust the solution to pH 9−10. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The extracts were washed with H_2O (100 mL) and brine (100 mL), dried, and concentrated. Flash column chromatogaphy on silica, eluting with CH_2Cl_2−MeOH (96:4), gave **16** (2.12 g, 5.33 mmol, 28%) as a brown foam. A sample was recrystallized from EtOAc. δ_H (360 MHz, $CDCl_3$): 3.36 (3H, s), 3.72 (3H, s), 5.18 (2H, s), 6.65 (2H, d, *J* 9), 6.76 (1H, s), 6.78 (2H, d, *J* 9), 7.04 (2H, d, *J* 6), 7.30−7.47 (5H, m), 8.56 (2H, d, *J* 6); *m*/*z* (ES+) 399 ($M + H^+$). 10% Pd−C (0.5 g) was added at room temperature to a stirred solution of **16** (1.07 g, 2.69 mmol), HCO_2NH_4 (1.26 g, 20 mmol), and AcOH (10 mL, 175 mmol) in MeOH (20 mL). After 3.5 h, the mixture was filtered and the filter cake was washed with 1 M HCl (150 mL). The filtrate was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 100 mL). The extracts were dried and concentrated to give 3-(4-methoxyphenyl)-6-(4-pyridyl)-3-hydroxy-1-methyl-1H-pyridin-2-one (0.62 g, 2.01 mmol, 75%) as a pale pink solid. A sample was recrystallized from EtOAC. δ_H (360 MHz, $CDCl_3$): 3.40 (3H, s), 3.73 (3H, s), 6.67 (2H, d, *J* 9), 6.86 (2H, d, *J* 9), 6.90 (1H, br s), 6.93 (1H, s), 7.06 (2H, d, *J* 6), 8.59 (2H, d, *J* 6); *m*/*z* (ES+) 309 ($M + H^+$). $(CF_3SO_2)_2O$ (0.60 mL, 0.60 mmol) was added dropwise at −78 °C to a stirred suspension of the alcohol (0.60 g, 1.95 mmol) and pyridine (0.40 mL, 3.57 mmol) in dry CH_2Cl_2 (30 mL). The brown suspension was briefly warmed to dissolve all material and then stirred at −78 °C for 1 h. The mixture was warmed to room temperature, poured into saturated $NaHCO_3$(aq) (50 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The extracts were washed with H_2O (50 mL) and brine (30 mL), dried, and evaporated to give a brown oil. Trituration with Et_2O gave **17** (0.78 g, 1.77 mmol, 90%) as a brown solid. δ_H (360 MHz, $CDCl_3$): 3.39 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.84 (2H, d, *J* 9), 7.09 (2H, d, *J* 7), 7.46 (1H, s), 8.64 (2H, d, *J* 7); *m*/*z* (ES+) 441 ($M + H^+$). A mixture of **17** (0.055 g, 0.125 mmol), $PhB(OH)_2$ (0.25 g, 2.05 mmol), and Na_2CO_3(aq) (2 M, 2 mL, 4 mmol) in $(MeOCH_2)_2$ (5 mL) was degassed and purged with N_2 at room temperature. $Pd(PPh_3)_4$ (0.1 g, 0.087 mmol) was added, and the mixture was refluxed under N_2 for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The extracts were dried and concentrated. Preparative TLC, eluting with CH_2Cl_2−MeOH (95:5), gave **13l** (0.028 g, 0.076 mmol, 61%) as a pale pink foam; this was recrystallized from EtOAc−hexane to give a beige powder. δ_H (360 MHz, $CDCl_3$): 3.39 (3H, s), 3.73 (3H, s), 6.69 (2H, d, *J* 9), 6.90 (2H, d, *J* 9), 7.13 (2H, d, *J* 6), 7.35−7.44 (3H, m), 7.59 (1H, s), 7.77 (2H, d, *J* 8), 8.60 (2H, d, *J* 6); *m*/*z* (ES+) 369 ($M + H^+$). Anal. ($C_{24}H_{20}N_2O_2 \cdot 0.25(H_2O)$) C, H. N; calcd, 7.51; found, 6.99. HPLC 98.0%.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(thiophene-3-yl)-1-methyl-1*H*-pyridin-2-one 13m. Yield 67%. δ_H (360 MHz, $CDCl_3$): 3.42 (3H, s), 3.74 (3H, s), 6.70 (2H, d, *J* 9), 6.90 (2H, d, *J* 9), 7.11 (2H, d, *J* 6), 7.35 (1H, dd, *J* 5, 3), 7.54 (1 H, d, *J* 5), 7.76 (1H, s), 8.36 (1H, d, *J* 3), 8.61 (2H, d, *J* 6); *m*/*z* (ES+) 375 ($M + H^+$). HPLC 97.0%.

Supporting Information Available: Data for the X-ray crystal structure determination of **13d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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