

3-Heteroaryl-2-pyridones: Benzodiazepine Site Ligands with Functional Selectivity for $\alpha 2/\alpha 3$ -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 $\alpha 2$ - and/or $\alpha 3$ - over $\alpha 1$ -containing GABA_A receptor subtypes and high binding selectivity over $\alpha 5$ 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 $\alpha 2$ and/or $\alpha 3$ GABA_A receptor subtypes over $\alpha 1$ was observed in several of these compounds in electrophysiological assays. Furthermore, an $\alpha 3$ subtype selective inverse agonist was proconvulsant and anxiogenic in rodents while an $\alpha 2/\alpha 3$ 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_A² and GABA_C³ 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 ($\alpha 1$ –6, $\beta 1$ –3, $\gamma 1$ –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 (α)₂(β)₂(γ).^{7,8} The subtypes $\alpha 1\beta\gamma 2$ correspond pharmacologically to the GABA_A receptors previously classified as BZ-I (or ω_1), while $\alpha 2\beta\gamma 2$, $\alpha 3\beta\gamma 2$, and $\alpha 5\beta\gamma 2$ have been identified as comprising the BZ-II (or ω_2) class. Subtypes containing the $\alpha 4$ and $\alpha 6$ subunits are insensitive to BZs. The $\gamma 2$ 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 $\alpha 1\beta 2\gamma 2$ subtypes are present in both cerebellum and cortex, the $\alpha 2\beta 1\gamma 2$ and $\alpha 3\beta 1\gamma 2/3$ assemblies are found mainly in the cortex and hippocampus, and the $\alpha 5\beta 3\gamma 2$ and $\alpha 5\beta 3\gamma 3$ 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 $\alpha 1$ 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 $\alpha 1$ subunits.¹⁰

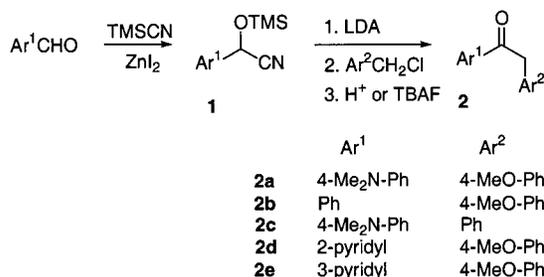
In light of this, subtype selective ligands should discriminate between the many behaviors mediated by GABA-ergic transmission, and this is supported by data obtained on the limited number of selective compounds known. For example, while unselective full agonist BZs such as diazepam are anxiolytics with sedative side effects apparent at higher doses, the BZ site full agonist zolpidem that has some binding selectivity for $\alpha 1$ -containing receptors over other GABA_A subtypes is a clinical hypnotic, again implicating $\alpha 1$ -containing subtypes in the sedative response. Other compounds with moderate binding selectivity for $\alpha 1$ subtypes have been described recently, including pyrrolo[2,3-*c*]pyridines,¹¹ indoleglyoxamides,¹² and β -carbolines,¹³ but there are fewer reports of $\alpha 2/\alpha 3$ selective ligands.^{13,14} A class of agonist imidazo[1,5-*a*]quinoxalines¹⁵ have been reported, some of which showed functional selectivity for $\alpha 1$ subtypes over $\alpha 3$. The discovery of functionally selective $\alpha 2/\alpha 3$ partial agonist triazolo[4,3-*b*]pyridazines¹⁶ 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 $\alpha 1$ -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 $\alpha 2/\alpha 3$ subtypes.¹⁹

Chemistry

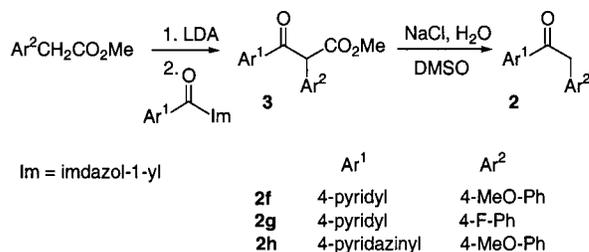
The well-precedented regioselective condensation of 2-cyanoacetamide with 3-(dimethylamino)-2-propenones under basic conditions was used for the construction of the trisubstituted 2-pyridones,²⁰ requiring the initial preparation of various 1,2-diarylethanones **2** (Scheme 1). The carbanions formed by 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 heteroaryl imidazolides to give the β -ketoesters **3**. Decarboxylation under Krapcho's conditions²¹ 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

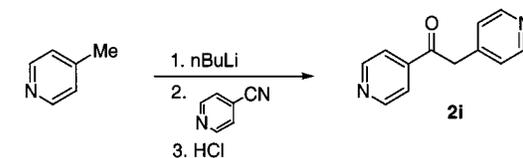
Route A



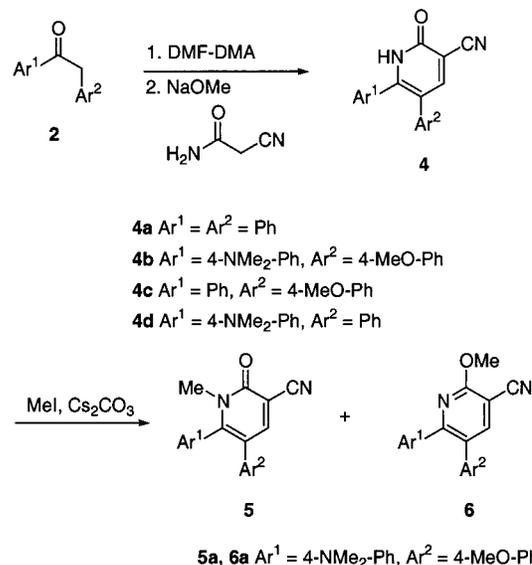
Route B



Route C

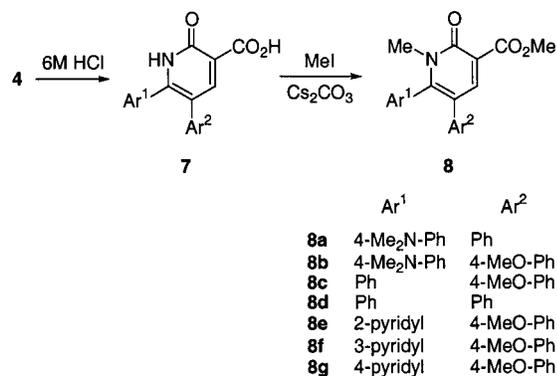


Scheme 2

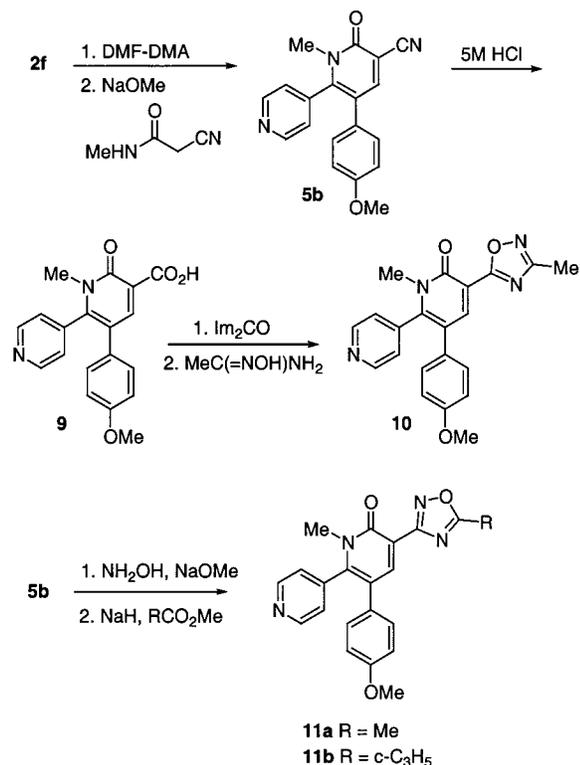


Treatment of the ketones **2** with dimethylformamide–dimethylacetal (DMF–DMA) gave the corresponding 3-dimethylaminopropen-2-ones, and generally without purification, these were condensed with 2-cyanoacetamide to give the 3-cyano-2-pyridones **4** in moderate to good yields (47–80%) (Scheme 2). Alkylation 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

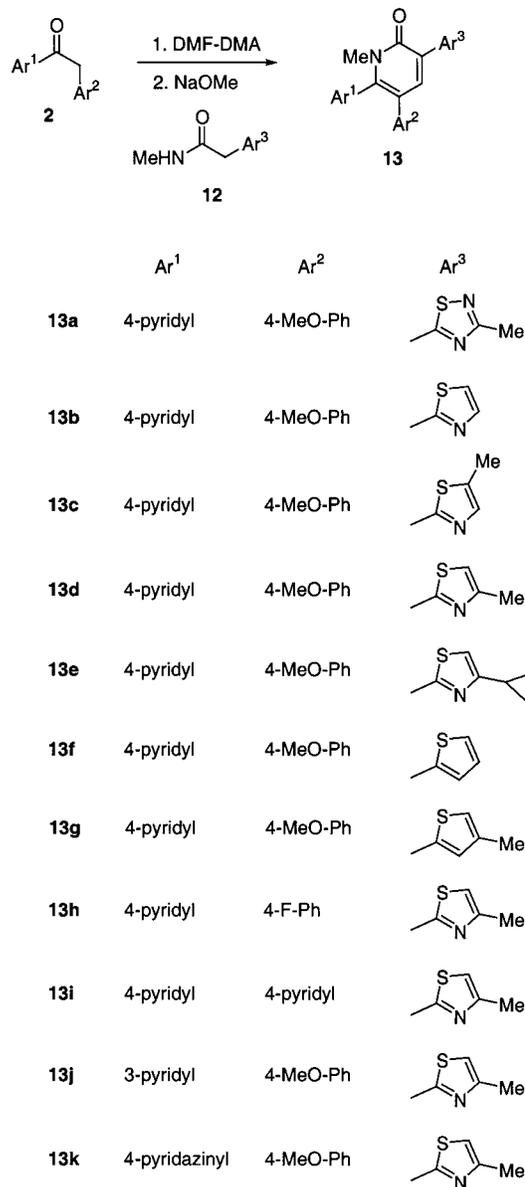


The intermediate 3-cyano-2-pyridones **4** were hydrolyzed upon refluxing in strong aqueous acid to give the carboxylic acids **7**. These intermediates were not generally purified but were methylated to give the 1-methyl-3-methoxycarbonyl-2-pyridones **8**, again accompanied by the isomeric 2-methoxypyridines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

To obviate the need for separation of these alkylation products, the condensation of the enaminoketone 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 enamino-

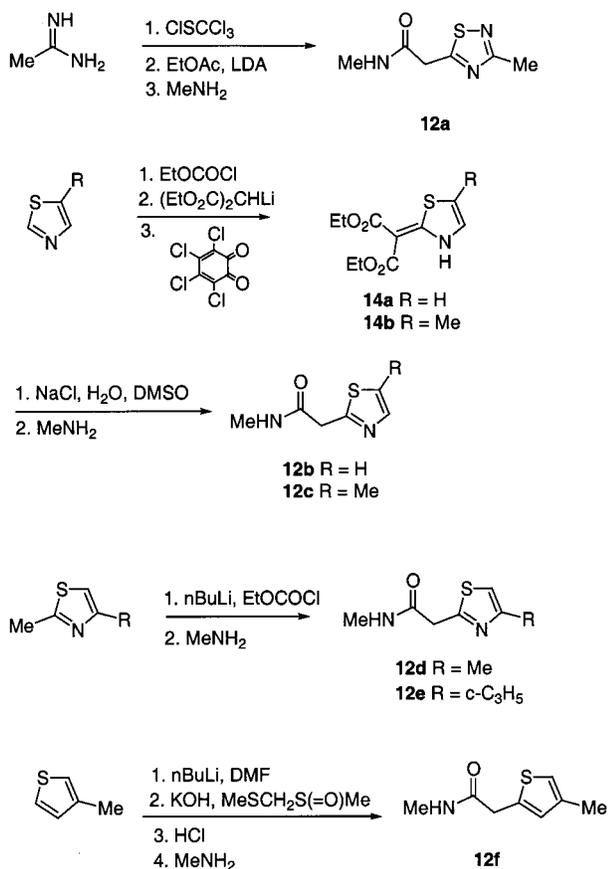
Scheme 5



ketones 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}

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 trichloromethanesulfonyl chloride to give 5-chloro-3-methyl-1,2,4-thiadiazole, followed by S_N-Ar 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 lithiation²⁴ 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-

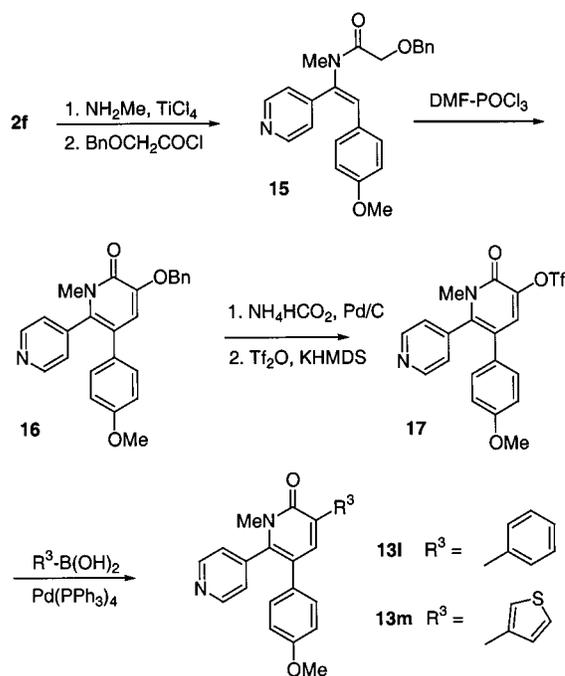
Scheme 6



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-methylthiophene²⁶ 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 sulfoxide²⁷ 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-Cohn³¹ 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 couplings³²

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 $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 2$, and $\alpha 5\beta 3\gamma 2$ GABA_A receptors, stably expressed in L(tk⁻) cells, were determined by displacement of [³H]Ro15-1788.³³ The efficacies of selected compounds were determined at cloned human $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, and $\alpha 3\beta 3\gamma 2$ GABA_A receptors transiently expressed in *Xenopus* oocytes by measurement of the modulatory effect on the GABA EC₂₀ 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 [³H]Ro15-1788 binding.³⁵ Anti-convulsant and anxiolytic properties were investigated in a mouse model of epilepsy³⁶ and the rat elevated plus maze,³⁷ respectively. In brief, pro- or anticonvulsant activity was measured in mice ($n = 8/\text{group}$) dosed with test compound or vehicle (i.p. in 0.5% methylcellulose) followed immediately after by various doses of pentyl-enetetrazole (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 (ED₅₀) was calculated. In this assay, a drug with proconvulsant activity will reduce the PTZ ED₅₀ whereas an anticonvulsant drug will increase the ED₅₀. In the elevated plus maze, rats ($n = 18/\text{group}$) 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

no. ^c	<i>K_i</i> (nM) ^a				modulation of GABA EC ₂₀ current (%) ^b					
	α ₁ β ₃ γ ₂	α ₂ β ₃ γ ₂	α ₃ β ₃ γ ₂	α ₅ β ₃ γ ₂	α ₁ β ₃ γ ₂	α ₂ β ₃ γ ₂	α ₃ β ₃ γ 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	<i>f</i>					
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/	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 [³H]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 EC₂₀ (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 in-

verse 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 EC₂₀ 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

no. ^c	<i>K_i</i> (nM) ^a				modulation of GABA EC ₂₀ current (%) ^b				
	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_4\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$
10	>1000 ^d	>667 ^e	>1000	>667	<i>f</i>				
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)
13a	90 (±7)	42 (±8)	25 (±4)	>667	+117 (±20)	10	+97 (±24)	10	+138 (±22)
13b	45 (±3)	37 (±4)	6.2 (±1.6)	>1000	+56 (±3)	3	+67 (±7)	3	+32 (±3)
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)
13e	31 (±23)	24 (±6)	12 (±3)	>1000	+29 (±8)	1			+35 (±6)
13f	30 (±9)	23 (±1)	15 (±3)	350 (310, 390)	+9 (±4)	1	+15 (±6)	1	+36 (±3)
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)
13i	24 (24, 25)	20 (18, 23)	6.7 (5.7, 7.8)	270 (260, 280)	-23 (±1)	3			-4 (±3)
13j	12.8 (±0.3)	5.0 (±0.4)	3.8 (±0.1)	>667	+78 (±10)	1			+77 (±14)
13k	17 (±2)	6.6 (±2.2)	4.1 (2.5, 6.6)	330 (±110)	+7 (±5)	3	+33 (±6)	10	+34 (±7)
13l	83 (±18)	130 (±37)	24 (±6)	>1000	+45 (±8)	3			+63 (±5)
13m	39 (39, 40)	51 (50, 52)	12 (12, 12)	450 (440, 450)					+18 (±2)

^a Displacement of [³H]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 EC₂₀ (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**

compd	efficacy profile in vitro	effects in vivo	
		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 ED₅₀ 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 model³⁷ 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 α_3 subtype in vivo, with the effects observed in agreement with those expected from a BZ inverse agonist and indicating that the α_3 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 α_1 , α_2 , and α_3 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 α_3 against α_1 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 thiazole 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 α_3 subtypes, with ca. 6–7-fold binding selectivity over the α_1 and α_2 subtypes, and inactive at α_5 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 α_3 subtypes over α_1 and α_2 . Most importantly, **13d** had functional selectivity against α_1 -containing receptors, being an antagonist at this subtype while a partial agonist at α_2 and α_3 receptors. Increasing the size of the thiazole 4-substituent to cyclopropyl, as in **13e**, somewhat reduced affinity at all subtypes and brought back α_1 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

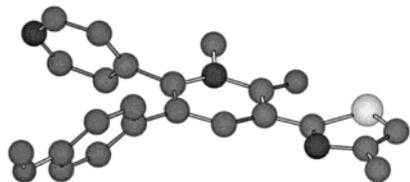


Figure 1. X-ray crystal structure of **13d** (hydrogens omitted for clarity).

affinity. The unsubstituted thiophene **13f** showed functional selectivity for $\alpha 3$ over $\alpha 1$, albeit with reduced efficacy for $\alpha 2$ 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 $\alpha 1$ and $\alpha 3$ 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 radii⁴⁰ 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 before⁴¹ 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 associ-

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_{diss} (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

ated with the C-3 substituent that drives BZ site binding affinity.

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 $\alpha 1$, $\alpha 2$, and $\alpha 3$ subtypes, typically 10-fold at greatest, although better discrimination against $\alpha 5$ 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 $\gamma 2$ 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 $\alpha 2/3$ 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 $\alpha 3$ -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 occupancy³⁵ 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 $\alpha 1$ and $\alpha 3$ subtypes, and replacement of this aryl group by 4-pyridyl produced the $\alpha 1$ 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 $\alpha 3$ 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 $\alpha 1$ subtype with equal partial agonist activity at $\alpha 2$ and $\alpha 3$ subtypes. Moreover, the oral bioavailability of **13k** was improved over the original $\alpha 2/3$ 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 ED₅₀ of 3.3 mg/kg for protection against PTZ-induced tonic seizures, significantly more potent than **13d** (50% protection after 30 mg/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 $\alpha 2/\alpha 3$ 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 $\alpha 3$ 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 $\alpha 2$ rather than $\alpha 3$ subunit.⁴⁶ The reason for the discrepancy between the pharmacological approach in which $\alpha 3$ -containing receptors are involved in anxiolysis and the molecular genetic approach in which anxiolysis appears to be mediated via $\alpha 2$ - rather than $\alpha 3$ -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 $\alpha 2$ - and/or $\alpha 3$ - over $\alpha 1$ -containing GABA_A receptor subtypes. Good binding selectivity was observed over $\alpha 5$ -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 $\alpha 1$ subtype and varying degrees of efficacy at $\alpha 2$ and $\alpha 3$ subtypes. The selective $\alpha 3$ inverse agonist ester **8g** was proconvulsant and anxiogenic in rodents, suggesting that modulation of GABA-ergic transmission through the $\alpha 3$ subtype alone is capable of mediating anxiety behavior. The $\alpha 2/\alpha 3$ 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 Bruker AM360 or AC250 spectrometers. Chemical shifts (δ), from Me₄Si 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 Na₂SO₄ or MgSO₄. Flash chromatography was performed on silica gel Fluka Art. No. 60738. Thin-layer chromatography (TLC) was carried out on Merck 5 cm \times 10 cm plates with silica gel 60 F₂₅₄ as sorbent. Preparative TLC was carried out using 20 cm \times 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 ZnI₂ (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 CH₂Cl₂ (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 Et₂O 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 N₂. 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 H₂O (1 L), and extracted with EtOAc (3 \times 350 mL). The extracts were washed with H₂O and brine, dried, and concentrated. The residue was dissolved in MeOH (300 mL), and 1 M H₂SO₄ (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 H₂O and brine, dried, and concentrated. The residue was triturated with Et₂O to give **2a** (50 g, 186 mmol, 67%) as a yellow solid. δ_{H} (250 MHz, CDCl₃): 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, CDCl₃): 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, CDCl₃): 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, CDCl₃): 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 (M₂ + 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 imidazole 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 NaHCO₃. The neutralized solution was extracted with CH₂-Cl₂ (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–Et₂O (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, CDCl₃): 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 H₂O (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 H₂O (600 mL), and extracted with EtOAc–Et₂O (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, CDCl₃): 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, CDCl₃): 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, CDCl₃): 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 N₂. 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 NaHCO₃(aq) and separated. The aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were dried and concentrated. Flash column chromatography, eluting with 97:7

CH₂Cl₂–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, CDCl₃): 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-1H-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 N₂. 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 NH₄Cl(aq) was added to the residues, and the resulting solids were collected, washed with H₂O and Et₂O, 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-1H-pyridin-2-one 4b. Yield 95%. δ_{H} (360 MHz, CDCl₃): 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-1H-pyridin-2-one 4c. Yield 47%. δ_{H} (360 MHz, CDCl₃): 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-1H-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-1H-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 Cs₂CO₃ (1.04 g, 3.2 mmol) in dry DMF (20 mL) at room temperature under N₂. After 1 h, the mixture was partitioned between H₂O and EtOAc (× 3). The organic solution was washed with H₂O and brine, dried, and concentrated. The residual solid was boiled in Et₂O (25 mL) and cooled, and the solid was collected. The material was recrystallized from CHCl₃–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 CH₂Cl₂–MeOH, to give first **6a** (0.304 g, 0.84 mmol, 29%) as a yellow foam that gave light yellow needles on recrystallization from CHCl₃–hexane. Continued elution gave further **5a** (0.10 g, 0.3 mmol, 10%). **5a:** δ_{H} (360 MHz, CDCl₃): 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. (C₂₃H₂₁N₃O₂) C, H, N: **6a:** δ_{H} (360 MHz, CDCl₃): 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. (C₂₃H₂₁N₃O₂) C, N, H: calcd, 5.89; found, 5.35.

6-(4-Dimethylaminophenyl)-5-phenyl-3-carbomethoxy-1-methyl-1H-pyridin-2-one 8a. A solution of **4d** (1.5 g, 4.76 mmol) in 6 M HCl (50 mL) was refluxed under N₂ for 72 h. The mixture was cooled to yield a precipitate that was collected, washed with Et₂O, 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), Cs₂CO₃ (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 N₂ for 18 h. The mixture was partitioned between H₂O and EtOAc (× 3), and the organic extracts were washed with H₂O and brine, then dried, and concentrated. Flash column chromatography, eluting with 98:2

and then 96:4 CH₂Cl₂-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. (C₂₂H₂₂N₂O₃) 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, CDCl₃): 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. (C₂₃H₂₄N₂O₄·0.25(H₂O)) C, H, N.

5-(4-Methoxyphenyl)-6-phenyl-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one 8c. Yield 41%. δ_{H} (360 MHz, CDCl₃): 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. (C₂₁H₁₉NO₄) 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. (C₁₉H₁₇NO₃) 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, CDCl₃): 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. (C₂₀H₁₈N₂O₄) 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, CDCl₃): 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, 8), 8.22 (1H, s), 8.42 (1H, d, *J* 2) 8.60 (1H, dd, *J* 5, 2); *m/z* (ES⁺) 351 (M + H⁺). Anal. (C₂₀H₁₈N₂O₄) 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, CDCl₃): 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. (C₂₀H₁₈N₂O₄) 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 N₂. 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, CDCl₃): 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*-methylcycanoacetamide (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 N₂. 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 CH₂Cl₂-MeOH-NH₃ (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, CDCl₃): 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 NH₃ (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, CDCl₃): 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 N₂ for 48 h. The mixture was cooled and partitioned between H₂O 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 N₂. 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 H₂O. 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, CDCl₃): 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. NH₂OH·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 N₂ for 2 h. Further NaOMe (0.16 g, 3.0 mmol) was prepared and added to the cooled solution, followed by further NH₂OH·HCl (0.10 g, 1.5 mmol). The mixture was refluxed for a further 2 h, then cooled, and diluted with saturated NH₄Cl(aq) (100 mL). The mixture was extracted with CH₂Cl₂ (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, CDCl₃): 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 N₂ 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 H₂O (50 mL) and extracted with CH₂Cl₂-MeOH (90:10) (3 × 30 mL). The extracts were dried and concentrated. Preparative TLC, eluting with CH₂Cl₂-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, CDCl₃): 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. (C₂₃H₂₀N₄O₃) C, H, N.

***N*-Methyl-2-(3-methyl-1,2,4-thiadiazol-5-yl)acetamide 12a.** NaOH (60 g, 1.5 mol) in H₂O (100 mL) was added dropwise at -5 °C over 2 h to a stirred mixture of acetamidine hydrochloride (30 g, 320 mmol) and Cl₃CSCl (59 g, 320 mmol) in CH₂Cl₂ (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 CH₂Cl₂. 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, CDCl₃): 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 N₂. The mixture was warmed to room temperature and stirred for 2.5 h and then partitioned between EtOAc and H₂O. 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-NH₃ (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 N₂. 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 Et₂O (100 mL) and washed with saturated NH₄Cl(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 NaHCO₃ (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 H₂O (2.2 mL, 120 mmol) in DMSO (250 mL) was stirred at 180 °C for 30 min, then cooled, diluted with H₂O (500 mL), and extracted with Et₂O-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 Me₂NH 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-NH₃ (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 N₂. 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 NH₄Cl(aq) (100 mL) and H₂O (100 mL) and extracted with CH_2Cl_2 (100 mL). The extract was dried and concentrated. Flash column chromatography, eluting with 97:3 and then 95:5 CH_2Cl_2 -MeOH, gave a mixture of acylation products and starting material (monoacylation: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 Et₂O 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-methylthiophene²⁶ by homologation²⁷ 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. (C₂₁H₁₈N₄O₂S) 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 Et₂O-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 N₂. 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. (C₂₁H₁₇N₃O₂S) 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. (C₂₂H₁₉N₃O₂S·0.5(C₄H₈O₂)·0.5(H₂O)) 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. (C₂₂H₁₉N₃O₂S) 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. (C₂₄H₂₁N₃O₂S·0.6(H₂O)) 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. (C₂₂H₁₈N₂O₂S) 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, CDCl₃): 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. (C₂₃H₂₀N₂O₂S) C, H, N.

6-(4-Pyridyl)-5-(4-fluorophenyl)-3-(4-methylthiazol-2-yl)-1-methyl-1H-pyridin-2-one 13h. Yield 21%. δ_{H} (360 MHz, CDCl₃): 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. (C₂₁H₁₆N₃OSF) C, H, N.

5,6-Bis(4-pyridyl)-3-(4-methylthiazol-2-yl)-1-methyl-1H-pyridin-2-one 13i. Yield 14%. δ_{H} (360 MHz, CDCl₃): 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. (C₂₀H₁₆N₄OS·0.4(H₂O)) C, H, N; H: calcd, 4.61; found, 4.19. HPLC 99.5%.

6-(3-Pyridyl)-5-(4-methoxyphenyl)-3-(4-methylthiazol-2-yl)-1-methyl-1H-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-1H-pyridin-2-one 13k. Yield 6%. δ_{H} (360 MHz, CDCl₃): 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. (C₂₁H₁₈N₄O₂S) C, H, N.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-phenyl-1-methyl-1H-pyridin-2-one 13l. A stirred solution of **2f** (17.5 g, 77 mmol) in CHCl₃ (200 mL) was saturated with MeNH₂ gas at 0 °C. A solution of TiCl₄ in CH₂Cl₂ (1 M, 40 mL, 40 mmol) was added via syringe at 0 °C under N₂. After the solution had stirred at room temperature for 18 h, anhydrous Na₂SO₄ (5 g) was added and the yellow suspension was filtered through Celite, washing with CH₂Cl₂. Evaporation of the filtrate gave the crude imine (16.7 g, 70 mmol, 90%) as an orange oil. δ_{H} (250 MHz, CDCl₃): 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 BrOCH₂COCl (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 N₂. After complete addition, the purple solution was warmed to 0 °C and stirred for 1.5 h. The brown suspension was poured into ice/NaHCO₃(aq) (500 mL) and extracted with EtOAc (2 × 250 mL). The extracts were washed with brine (100 mL), dried, and concentrated. Flash column chromatography on silica, eluting with CH₂Cl₂–MeOH (95:5), gave **15** (17.1 g, 44 mmol, 64%) as a brown gum. δ_{H} (250 MHz, CDCl₃): 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 CH₂Cl₂ (10 mL) was added slowly at room temperature to stirred POCl₃ (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 CH₂Cl₂ (3 × 100 mL). The extracts were washed with H₂O (100 mL) and brine (100 mL), dried, and concentrated. Flash column chromatography on silica, eluting with CH₂Cl₂–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, CDCl₃): 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), HCO₂NH₄ (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 NaHCO₃ and extracted with CH₂Cl₂ (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, CDCl₃): 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⁺). (CF₃SO₂)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 CH₂Cl₂ (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 NaHCO₃(aq) (50 mL), and extracted with CH₂Cl₂ (2 × 30 mL). The extracts were washed with H₂O (50 mL) and brine (30 mL), dried, and evaporated to give a brown oil. Trituration with Et₂O gave **17** (0.78 g, 1.77 mmol, 90%) as a brown solid. δ_{H} (360 MHz, CDCl₃): 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 Na₂CO₃(aq) (2 M, 2 mL, 4 mmol) in (MeOCH₂)₂ (5 mL) was degassed and purged with N₂ at room temperature. Pd(PPh₃)₄ (0.1 g, 0.087 mmol) was added, and the mixture was refluxed under N₂ for 2 h. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The extracts were dried and concentrated. Preparative TLC, eluting with CH₂Cl₂–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, CDCl₃): 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. (C₂₄H₂₀N₂O₂·0.25(H₂O)) C, H, N; calcd, 7.51; found, 6.99. HPLC 98.0%.

6-(4-Pyridyl)-5-(4-methoxyphenyl)-3-(thiophene-3-yl)-1-methyl-1H-pyridin-2-one 13m. Yield 67%. δ_{H} (360 MHz, CDCl₃): 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 (1H, 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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