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Discovery of 5″-Chloro-*N*-[(5,6-dimethoxypyridin-2-yl)methyl]-2,2′:5′,3″-terpyridine-3′-carboxamide (MK-1064): A Selective Orexin 2 Receptor Antagonist (2-SORA) for the Treatment of Insomnia

Anthony J. Roecker,*[a] Swati P. Mercer,[a] John D. Schreier,[a] Christopher D. Cox,[a] Mark E. Fraley,[a] Justin T. Steen,[a] Wei Lemaire,[b] Joseph G. Bruno,[b] C. Meacham Harrell,[c] Susan L. Garson,[c] Anthony L. Gotter,[c] Steven V. Fox,[d] Joanne Stevens,[d] Pamela L. Tannenbaum,[d] Thomayant Prueksaritanont,[e] Tamara D. Cabalu,[e] Donghui Cui,[e] Joyce Stellabott,[f] George D. Hartman,[a] Steven D. Young,[a] Christopher J. Winrow,[c] John J. Renger,[c] and Paul J. Coleman[a]

The field of small-molecule orexin antagonist research has evolved rapidly in the last 15 years from the discovery of the orexin peptides to clinical proof-of-concept for the treatment of insomnia. Clinical programs have focused on the development of antagonists that reversibly block the action of endogenous peptides at both the orexin 1 and orexin 2 receptors (OX_1R and OX_2R), termed dual orexin receptor antagonists (DORAs), affording late-stage development candidates including Merck's suvorexant (new drug application filed 2012). Full characterization of the pharmacology associated with antagonism of either OX_1R or OX_2R alone has been hampered by the dearth of suitable subtype-selective, orally bioavailable ligands. Herein, we report the development of a selective orexin 2 antagonist (2-SORA) series to afford a potent, orally bioavailable 2-SORA ligand. Several challenging medicinal chemistry issues were identified and overcome during the development of these 2,5-disubstituted nicotinamides, including reversible CYP inhibition, physiochemical properties, P-glycoprotein efflux and bioactivation. This article highlights structural modifications the team utilized to drive compound design, as well as in vivo characterization of our 2-SORA clinical candidate, 5″-chloro-*N*-[(5,6-dimethoxypyridin-2-yl)methyl]-2,2′:5′,3″-terpyridine-3′-carboxamide (MK-1064), in mouse, rat, dog, and rhesus sleep models.

Introduction

Primary insomnia is defined as difficulty initiating/maintaining sleep or finding sleep non-restorative in the absence of psychological or physical ailments, and it affects approximately 50% of the general population at some point in their lives.[1] The current standard of care for insomnia is treatment with non-benzodiazepine GABA modulators such as zolpidem. While this method of treatment is effective for many insomnia patients, significant side effects have been noted including next day residual somnolence, rebound insomnia, amnesia, effects on motor coordination, and parasomnias.[1,2] These side effects have resulted in the issuance of revised labeling and, in some cases, black box warnings.[3] Recently, the US Food and Drug Administration (FDA) also recommended that the dose of zolpidem for women should be decreased by half due to the risk of next-day somnolence.[4] These concerns have encouraged further efforts to discover and develop treatments for insomnia with differentiated mechanisms of action from current therapies.

The orexin peptides, orexin A and orexin B, were originally discovered in 1998 by two independent research groups.[5] These peptides were then associated with activity on two orphan G protein-coupled receptors, orexin 1 (OX_1R) and orexin 2 (OX_2R). Initially thought to be involved in feeding behaviors, the peptides were named after the Greek word "orexis" meaning appetite. Since that time, the effects on appetite have been called into question, but a strong link has been established between the orexin system and effects on

[a] *Dr. A. J. Roecker, S. P. Mercer, J. D. Schreier, Dr. C. D. Cox, Dr. M. E. Fraley, J. T. Steen, Dr. G. D. Hartman, Dr. S. D. Young, Dr. P. J. Coleman*
Department of Medicinal Chemistry
Merck Research Laboratories
P.O. Box 4, Sumneytown Pike, West Point, PA 19486 (USA)
E-mail: anthony_roecker@merck.com

[b] *W. Lemaire, J. G. Bruno*
Department of In Vitro Pharmacology (Merck, West Point)

[c] *C. M. Harrell, S. L. Garson, Dr. A. L. Gotter, Dr. C. J. Winrow, Dr. J. J. Renger*
Department of Neuroscience (Merck, West Point)

[d] *S. V. Fox, J. Stevens, Dr. P. L. Tannenbaum*
Department of In Vivo Pharmacology (Merck, West Point)

[e] *Dr. T. Prueksaritanont, Dr. T. D. Cabalu, Dr. D. Cui*
Department of Drug Metabolism (Merck, West Point)

[f] *J. Stellabott*
Department of Basic Pharmaceutical Sciences (Merck, West Point)

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the sleep/wake cycle from studies in orexin knockout mice,[6] narcoleptic canines with OX_2R receptor mutations,[7] and narcoleptic humans owning low cerebrospinal fluid (CSF) levels of orexin peptides and a loss of hypothalamic orexin neurons.[8] These studies and the pharmacology associated with orexin receptor antagonists have been the topic of several recent reviews.[9] Additionally, intracerebroventricular injection of orexin peptides has been shown to stimulate wakefulness and decreases slow wave sleep in rats.[10] These findings strongly suggest that the orexin peptides are wake-promoting agents, and, by extension, antagonism of these peptides might offer an alternative treatment for insomnia. This strategy is therefore differentiated from that of GABA modulators, which initiate sleep through potentiation of the effects of a ubiquitous inhibitory neurotransmitter. Recently, we have invested further efforts in preclinical differentiation demonstrating that orexin antagonists have improved therapeutic margins versus cognitive endpoints in rats and rhesus monkeys compared with GABA modulators.[11] This differentiated mechanism of action has produced high levels of interest across the scientific and medical communities.

Several companies have disclosed medicinal chemistry programs targeting the discovery and development of dual orexin receptor antagonists (DORAs).[12] Medicinal chemistry efforts from our laboratories describing the discovery of two DORAs, MK-4305 (suvorexant, **1**)[13] and MK-6096 (**2**),[14] have been published (Figure 1). Suvorexant has achieved clinical proof-of-concept for the treatment of primary insomnia, and a new drug application (NDA) for suvorexant was filed with the FDA in 2012.[15] The clinical success of antagonists of both OX_1R and OX_2R has clearly energized the field of orexin research.[16] However, questions still exist surrounding subtype-selective antagonism of the individual receptors.

Genetic and pharmacological evidence indicates a primary role of OX_2R in orexin-mediated arousal. Targeted mutation of OX_2R in mice and genetic loss of the receptor in canines is associated with a narcoleptic phenotype including hypersomnia.[6b,7] In mice, this phenotype is nearly identical, but not quite as pervasive as that displayed by knockouts lacking the gene encoding the orexin ligand,[6b] while OX_1R knockouts have a reportedly mild phenotype with no changes in sleep-stage time and minor sleep fragmentation, suggesting a relatively minor role for OX_1R in sleep regulation.[17] OX_1R and OX_2R have partially overlapping (lateral hypothalamus, locus coeruleus, dorsal raphe, peduncular pontine nucleus) and distinct (tuberomamillary nucleus [TMN] for OX_2R; prefrontal cortex for OX_1R) localization throughout the brain. Selective expression of OX_2R in histaminergic neurons of the TMN supports a primary role of this receptor in driving arousal through stimulation of histamine release.[9a] In fact, DORA-induced effects on sleep time are nearly eliminated in mice lacking OX_2R, indicating that selective OX_2R blockade might be sufficient for sleep-inducing effects of orexin receptor antagonism.[18]

The implications of additional OX_1R antagonism provided by DORAs relative to selective orexin 2 antagonists (2-SORAs) are currently unclear, and previous tool compounds used to delineate these issues have off-target activities[9b] and hydrolytic stability issues potentially contributing to mixed results.[19] In one study, co-administration of the 1-SORA ligand, SB-408124, with the 2-SORA ligand, JNJ-10397049, measurably diminished the sleep-promoting effect of the 2-SORA ligand in rats suggesting improved sleep efficacy for 2-SORA versus DORA compounds.[20] A different group found improved efficacy for the DORA, almorexant, relative to the highly selective 2-SORA, EMPA, at similar OX_2R occupancies.[21] Clearly, a need exists for improved tools to study the underlying pharmacology for reversible and selective blockade of OX_1R and OX_2R. Herein, we describe our efforts toward the discovery of a series of improved 2-SORA ligands culminating in the discovery of clinical candidate, 5″-chloro-*N*-[(5,6-dimethoxypyridin-2-yl)methyl]-2,2′:5′,3″-terpyridine-3′-carboxamide (MK-1064, **3**, Figure 1).[22]

Results and Discussion

A recent publication from our group described the discovery of **4**, a novel 2,5-disubstituted nicotinamide 2-SORA ligand identified by hit-to-lead efforts following high-throughput screening of the Merck sample collection (Figure 2).[23] Compound **4** demonstrates low-picomolar affinity for the human OX_2R as measured by a radioligand-displacement binding assay (expressed as K_i values) and high selectivity over OX_1R (>1000-fold). Compound **4** has excellent OX_2R potency and moderate OX_1R selectivity in a fluorometric imaging plate

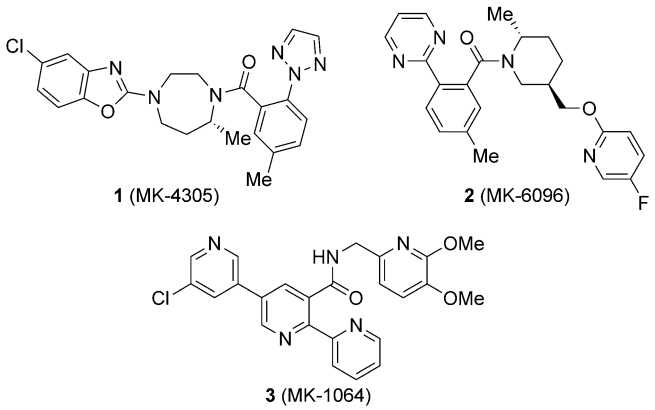
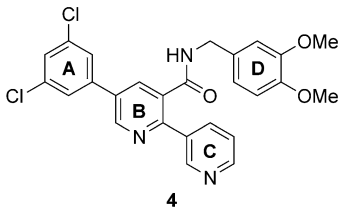


Figure 1. Merck DORAs, MK-4305 and MK-6096, and 2-SORA MK-1064.



OX_2R: K_i = 0.07 nM; IC_{50} = 12 nM
OX_1R: K_i = 94 nM; IC_{50} = 292 nM

Selectivity (K_i / FLIPR): 1343 / 24-fold

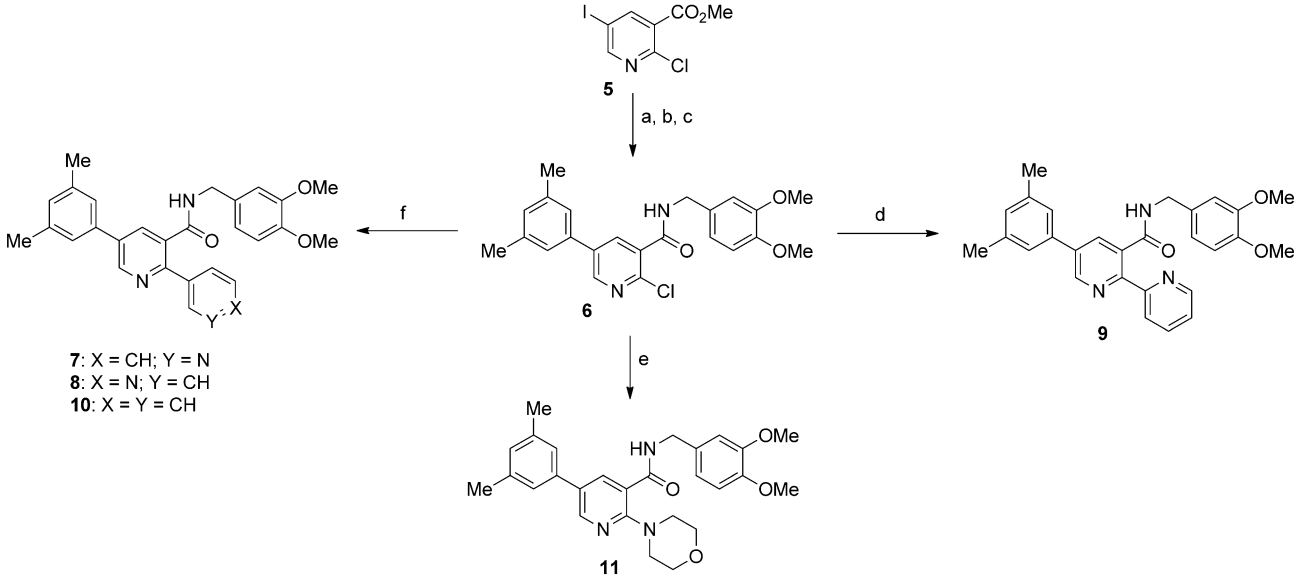
Figure 2. Previously reported 2,5-disubstituted nicotinamide 2-SORA (**4**).

reader (FLIPR) assay that provides a functional readout of orexin receptor antagonism in CHO cells engineered to overexpress the human receptors (expressed as IC_{50} values).[13a] This novel 2-SORA ligand demonstrated sleep efficacy similar to DORA molecules (decreased active wake, increased delta and REM sleep) when dosed orally to rats during their active phase.

Although 2-SORA **4** demonstrated sleep efficacy in a rat electroencephalographic (EEG) model through oral dosing, several key issues precluded advanced characterization. First, the level of functional selectivity for OX_2R might not be high enough to be confident that at plasma concentrations for sleep efficacy compound **4** would not inhibit OX_1R to some extent. Therefore, one focus of the optimization effort was to maximize the selectivity over OX_1R within this series. We targeted 100-fold selectivity over OX_1R in the FLIPR assay as an initial goal. Second, compound **4** is a potent reversible inhibitor of CYP3A4 (IC_{50} = 300 nM).[24] Third, although highly permeable (Papp = 32×10^{-6} cm s^{-1}), compound **4** is a P-glycoprotein (Pgp) substrate with an efflux ratio of 6.4 (human monolayer preparations; substrate ratio $\geq$3).[25] This might limit central nervous system (CNS) penetration, thus requiring significantly higher doses and plasma concentrations for sleep efficacy. Finally, compound **4** has bioactivation risk derived from the dimethoxyphenyl motif.[26] This theoretical liability was confirmed through the identification of high levels of glutathione adducts in human and rat liver microsomal incubations (see below). The aromatic rings of the nicotinamide scaffold are labeled A through D to facilitate the discussion of the profile optimization effort targeting the issues outlined above.

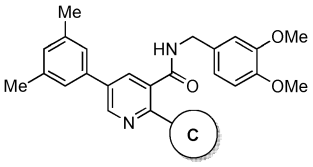
Our previous disclosure around the nicotinamide series of 2-SORA compounds focused on the structure–activity relationships (SARs) of the A- and D-rings of the series leaving the C-ring intact. In order to explore this SAR, the synthesis was modified slightly from previous efforts to place the diversity incorporating step at the end of the route (Scheme 1). Commercially available methyl-2-chloro-5-iodonicotinate (**5**) was transformed into **6** via selective Suzuki coupling, hydrolysis, and amide formation in acceptable yield. This common intermediate was utilized to produce final compounds through additional Suzuki couplings (**7**, **8**, and **10**), Stille couplings (**9**), or nucleophilic substitution reactions (**11**). The 3,5-dimethylphenyl A-ring in compound **7** was used for SAR purposes targeting lower molecular weight and decreased Pgp susceptibility (hPgp ratio: 2; Papp: 31×10^{-6} cm s^{-1}) compared with the 3,5-dichloro A-ring in compound **4**. As shown in Table 1, the position of the nitrogen of the C-ring has very little impact on binding and functional potency on OX_2R with compounds **7**, **8**, and **9**. Selectivity over OX_1R was also in a similar range; however, the reversible inhibition of CYP3A4 was vastly different for these three compounds. The 3- and 4-pyridyl motifs were potent reversible inhibitors of CYP3A4, while the 2-pyridyl substituent significantly decreased this liability (IC_{50} = 38 μM). Interestingly, replacing the pyridyl substituents with phenyl (**10**) or morpholine (**11**) motifs also decreased the reversible CYP3A4 potency, although the former possessed less functional selectivity than the lead compound **4**, and the latter demonstrated weaker binding and functional potency. Hence, the 2-pyridyl motif was selected for additional SAR studies.

While the A- and D-rings were explored previously, it became apparent with leading compounds such as **9** that elevated log*D* (3.2) and high human plasma protein binding (PPB = 99.5%) were nonoptimal. A target for human PPB was not specified in this effort, however, measurable free fraction (>1%) is generally thought to be a desirable profile element in CNS programs.[27] Notably, compound **9** maintained the desirable Pgp profile of earlier lead compound **7** (Table 2). This



Scheme 1. Synthesis of C-ring analogues. *Reagents and conditions*: a) 3,5-dimethylphenylboronic acid, $PdCl_2$(dppf), Cs_2CO_3, DMF/water (19:1), 25 °C, 18 h (83%); b) $KOSiMe_3$, THF, 25 °C, 24 h (100%); c) EDC, HOAt, Et_3N, 3,4-dimethoxybenzylamine, DMF, 45 °C, 3 h (62%); d) 2-(tri-*n*-butylstannyl)pyridine, $Pd(PPh_3)_4$, CsF, CuI, DMF, 160 °C, 20 min, μW (67%); e) morpholine, DMF, 140 °C, 15 min, μW (58%); f) $PdCl_2$(dppf), Cs_2CO_3, DMF/water, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 160 °C, 20 min, μW (62% for **7**), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (20% for **8**), phenylboronic acid (22% for **10**); Abbreviations: dppf = 1,1′-(diphenylphosphino)ferrocene; EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOAt = 1-hydroxy-7-azabenzotriazole.

Table 1. Structure–activity relationships and reversible CYP3A4 inhibition data for C-ring analogues.



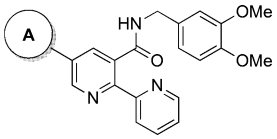
Compd		OX_2R[a] K_i [nM]	OX_2R[a] IC_{50} [nM]	OX_1R[a] K_i [nM]	OX_1R[a] IC_{50} [nM]	SI[b] (K_i/IC_{50})	CYP3A4[c] IC_{50} [μM]
	(**7**)	0.7	17	462	705	660/41	0.1
	(**8**)	1.5	17	523	748	349/44	1
	(**9**)	0.3	8	140	182	467/23	38
	(**10**)	0.2	14	220	245	1100/18	13
	(**11**)	8.3	56	3467	3400	412/61	> 50

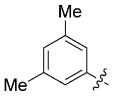
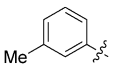
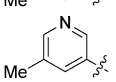
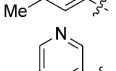
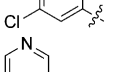
[a] K_i values were determined using a radioligand-displacement binding assay and IC_{50} values were determined using a fluorometric imaging plate reader (FLIPR) assay; each value is the mean of at least two or more independent determinations; for assay details, see Ref. [13a]; [b] Selectivity index (SI) for OX_1R over OX_2R as calculated from the K_i and IC_{50} values; [c] Reversible CYP3A4 inhibition; see the Supporting Information for assay details.

parameter was closely monitored as greater polarity was introduced into analogues. Efforts were then focused on further exploration of A-ring SAR as shown in Table 2 with the aim of improving physical properties. Deletion of a methyl group in compound **12** diminished functional potency on OX_2R by twofold, while increasing selectivity over OX_1R. This modification lowered log *D* by 0.4 units and decreased PPB. In an attempt to further improve physical properties, pyridyl analogues such as **13**, **14**, and **15** were synthesized. Compound **13** maintained the intrinsic and functional potency of compound **12** and similar levels of selectivity over OX_1R while decreased log *D* by 1.3 units and human PPB to 62%. Unfortunately, the incorporation of a basic pyridine in compound **13** resulted in increased Pgp susceptibility. In order to modulate Pgp activity, the methyl group in compound **13** was replaced with a chlorine atom to decrease the basicity of the A-ring pyridine motif. Gratifyingly, compound **14** demonstrated acceptable on target potency, improved selectivity over OX_1R, adequate PPB, and decreased Pgp susceptibility. Compound **15** demonstrated the need for an additional substituent on the pyridine A-ring due to significant decrease in OX_2R potency. Despite significant improvements in reversible CYP3A4 inhibition, selectivity over OX_1R, and physical properties, bioactivation concerns still remained for compounds such as **14**. These challenges were addressed in the D-ring efforts described below.

Indeed, incubation of compound **14** in human liver microsomes in the presence of glutathione (GSH) resulted in the trapping of significant levels of adducts consistent with experiments on compound **4**. Similar bioactivation issues were encountered during the DORA program,[13a] hence, an in vitro glutathione trapping assay was available in house and utilized to select compounds that decreased this metabolic liability. Precedent suggested that oxidation of the dimethoxyphenyl moiety could unveil quinone

Table 2. Structure–activity relationships, and P-glycoprotein (Pgp), Log *D*, and protein binding data for A-ring analogues.

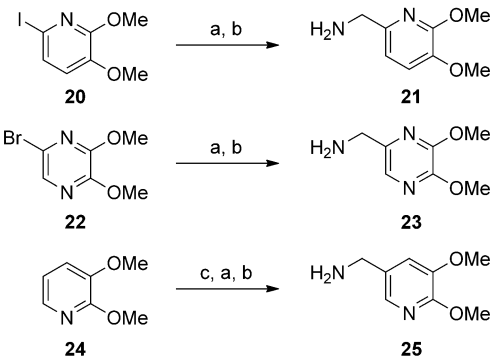


Compd		OX_2R[a] K_i [nM]	OX_2R[a] IC_{50} [nM]	OX_1R[a] K_i [nM]	OX_1R[a] IC_{50} [nM]	SI[b] (K_i/IC_{50})	hPgp[c] (BA/AB)	Papp[c] [10^{-6} cm s^{-1}]	Log *D* (HPLC)	hPPB[d] [%]
	(**9**)	0.3	8	140	182	467/23	1.1	26	3.2	99.5
	(**12**)	1.4	19	2550	985	1821/52	0.7	29	2.8	98.5
	(**13**)	0.6	28	763	1092	1272/39	4.4	28	1.5	62
	(**14**)	0.7	20	2113	1308	3019/65	1.7	29	1.9	94
	(**15**)	5.7	68	13500	> 10000	2328/147	3.4	30	1.3	39

[a] K_i values were determined using a radioligand-displacement binding assay and IC_{50} values were determined using a fluorometric imaging plate reader (FLIPR) assay; each value is the mean of at least two or more independent determinations; for assay details, see Ref. [13a]; [b] Selectivity index (SI) for OX_1R over OX_2R as calculated from the K_i and IC_{50} values; [c] Human P-glycoprotein (hPgp) susceptibility in human preparations and passive permeability (Papp); for assay details, see Ref. [25]; [d] Human plasma protein binding (hPPB); data is the % bound, and values were determined by standard methods; see the Supporting Information for details.

intermediates that can be readily conjugated by organic nucleophiles.[28] Initially, analogues were synthesized that either removed or replaced the methoxy groups in compound **14**, however, these generally increased log*D* and decreased either potency for OX_2R or selectivity over OX_1R (data not shown). Armed with the knowledge that the 3,4-dimethoxy motif was important to the overall profile, several nitrogen-containing heterocycles such as compounds **16**, **17**, and **3** were designed and synthesized. The synthetic strategy to afford these analogues was similar to Scheme 1, and the slight modifications are shown in Schemes 2 and 3. Incorporation of a nitrogen into the D-ring in compound **16** had the desired effect in decreasing GSH adducts in vitro (85% reduction), although intrinsic and functional potency on OX_2R decreased significantly, while Pgp susceptibility increased (Table 3). Dimethoxypyrazine analogue **17** demonstrated similar potency to **14** with improved selectivity[29] and limited impact on Pgp efflux; however, in vitro bioactivation was not decreased as much as in compound **16**. Finally, the pyridine isomer found in compound **3** provided the most balanced overall profile possessing excellent potency on OX_2R, high levels of selectivity over OX_1R, acceptable Pgp susceptibility in human preparations, high levels of passive permeability, and low bioactivation potential in vitro. On the strength of these data, compound **3** was selected for additional profiling.

The pharmacokinetic parameters of compound **3** are shown in Table 4. This compound has moderate clearance in all three species with half-life values in an appropriate range for once-nightly dosing for the treatment of insomnia. Gratifyingly, compound **3** possessed moderate oral bioavailability (%*F*) similar to its predecessor compound **4** demonstrating 54%, 48%, and 16% bioavailability in rat, dog, and rhesus monkey, respectively. Additional in vitro metabolic studies performed in rat, dog, and human liver microsomes (HLM) demonstrated that the major route of metabolism was O-dealkylation of the 5-methoxy group to afford the phenolic product, which was further converted to its sulfate and glucuronide in hepatocytes. CYP3A was determined to be the primary enzyme responsible for this transformation through immuno-inhibition studies in HLM. All metabolites found in human in vitro studies were also seen in rat and dog. Bile duct-cannulated rat studies were also performed utilizing radiolabeled compound **3**, and these experiments suggested excellent oral absorption with nearly 100% of the dose being recovered in urine (~20%) and bile (~79%) after 48 h. Qualitatively, the metabolites observed in rat in vitro (hepatocytes) and in vivo studies were very similar.

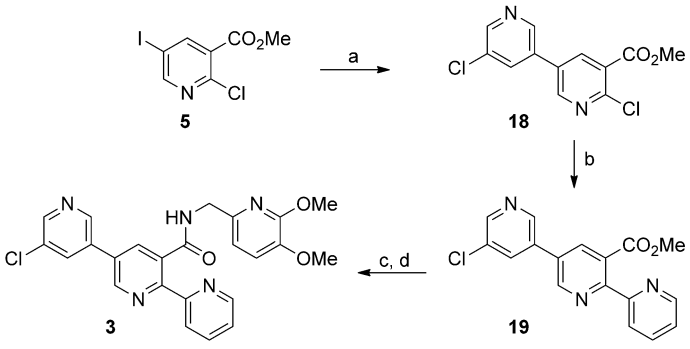


Scheme 3. Synthesis of heterocyclic benzylamines. *Reagents and conditions*: a) CuCN, DMF, 150–185 °C, 15–40 min, μW (79% for **21**; 58% for **23**; 66% for **25**); b) $Pd(OH)_2$, H_2, HCl (concd), MeOH, 25 °C, 1.5–2 h (94% for **21**; 92% for **23**; 49% for **25**); c) bromine, saturated aq $NaHCO_3$/DCM, 0 °C, 2 h (49%).

As described previously, the drug development team utilized an ex vivo humanized transgenic rat occupancy assay to assist in the determination of target engagement.[13a] Due to the low levels of endogenous orexin expressed centrally, it was necessary to produce a colony of rats that overexpressed human OX_2R to reliably measure receptor occupancy. Compound **3** demonstrated 90% occupancy of OX_2R at 695 nM, 203 nM, and 52 nM in the plasma, brain, and CSF, respectively, utilizing a rising intravenous (IV) dosing paradigm (Figure 3).[30] The CSF-to-plasma ratio (0.07) for this experiment was somewhat lower than the free fraction in rat (0.19) consistent with low to moderate Pgp efflux activity. Rat, monkey, and mouse Pgp experiments showed higher ratios than in human with BA/AB ratios of 6.1, 5.5, and 8.4 compared with 2.4 in Table 3. From these data, the impact of Pgp efflux on central penetration in human subjects was predicted to have less of an impact on efficacy than in preclinical species.

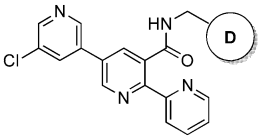
Additional drug metabolism studies revealed that compound **3** is not a potent reversible inhibitor of CYP3A4 (IC_{50} = 28 μM), CYP2C9 (IC_{50} > 100 μM), or CYP2D6 (IC_{50} > 100 μM). Compound **3** does not activate human PXR (EC_{50} > 30 μM; 7% activation compared with rifampicin control). Compound **3** does have moderate time-dependent inhibition (TDI) of CYP3A4 with a K_i value of 9.5 μM and a K_{inact} value of 0.11 min^{-1};[31] however, if target human exposures are low, the potential risk for human drug–drug interactions from this mechanism could be minimal. In order to assess this possibility, compound **3** was advanced into in vivo testing in preclinical models of sleep efficacy.

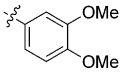
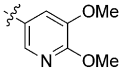
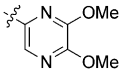
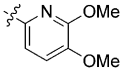
The preclinical sleep facility at Merck has a range of species for the assessment of in vivo efficacy of novel compounds measuring electrocorticogram



Scheme 2. Representative synthesis of A- and D-ring analogues. *Reagents and conditions*: a) 5-(chloropyridin-3-yl)boronic acid, $PdCl_2(dppf)$, Cs_2CO_3, DMF/water (22:1), 25 °C, 18 h (99%); b) 2-(tri-*n*-butylstannyl)pyridine, $Pd(PPh_3)_4$, CsF, CuI, DMF, 80 °C, 2 h (52%); c) NaOH (10 M), THF/MeOH (5:1), 135 °C, 15 min, μW; d) **21**, EDC, HOAt, iPr_2NEt, DMF, 60 °C, 2 h (79% over 2 steps).

Table 3. Structure–activity relationships, and P-glycoprotein (Pgp), glutathione (GSH) trapping/bioactivation data for D-ring analogues.



Compd		OX_2R[a] K_i [nM]	OX_2R[a] IC_{50} [nM]	OX_1R[a] K_i [nM]	OX_1R[a] IC_{50} [nM]	SI[b] (K_i/IC_{50})	hPgp[c] (BA/AB)	Papp[c] [10^{-6} cm s^{-1}]	GSH/IS ratio[d]
	(**14**)	0.7	20	2113	1308	3019/65	1.7	29	0.93
	(**16**)	6.8	70	13620	5200	2003/74	3.1	30	0.14
	(**17**)	2.1	31	7640	4100	3638/132	1.8	34	0.27
	(**3**)	0.5	18	1584	1789	3168/99	2.4	34	0.14

[a] K_i values were determined using a radioligand-displacement binding assay and IC_{50} values were determined using a fluorometric imaging plate reader (FLIPR) assay; each value is the mean of at least two or more independent determinations; for assay details, see Ref. [13a]; [b] Selectivity index (SI) for OX_1R over OX_2R as calculated from the K_i and IC_{50} values; [c] Human P-glycoprotein (hPgp) susceptibility in human preparations and passive permeability (Papp); for assay details, see Ref. [25]; [d] GSH/internal standard (IS) ratio (human); for assay details, see Ref. [13a].

Table 4. Pharmacokinetics of compound **3** in rat, dog, and rhesus monkey after intravenous and oral administration.

Species	Intravenous (IV) administration[a] Dose [mg kg^{-1}]	Cl [mL min^{-1} kg^{-1}]	Vd_{ss} [L kg^{-1}]	$t_{1/2}$ [h]	Oral (PO) administration[b] Dose [mg kg^{-1}]	AUC [μM·h]	C_{max} [μM]	F [%]
Rat	2	39	0.8	0.3	5	2.5	1.5	54
Dog	1	16	1.4	1.0	3	3.4	1.0	48
Rhesus	2	12	0.8	0.8	5	2.2	0.9	16

[a] Vehicle = 1:1:1 *N,N*-dimethylacetamide (DMA)/PEG 200/H_2O for dog ($n = 3$) and rhesus ($n = 3$); DMSO for rat ($n = 2$); [b] Dosed as the free base in 20% D-α-tocopherol polyethylene glycol 1000 succinate (vitamin E–TPGS); $n = 3$ for all species.

(ECoG) and electromyogram (EMG) activities for polysomnographic analysis. Figure 4 illustrates the time course of responses to compound **3** in radiotelemetry-implanted mice, rats, dogs, and rhesus monkeys following oral administration during their wake period. Sleep promotion was observed in all species with similar changes in vigilance state following treatment; attenuated active wake is accompanied by significant increases in both slow-wave sleep (SWS) and REM sleep following treatment. Generally, these sleep-promoting responses to compound **3** are similar to that observed for DORAs suvorexant and MK-6096 in that decreases in active wake are accompanied by significant increases in slow wave and REM sleep.[13b,14b]

Table 5 displays the exposure data from the sleep studies described above as well as binding potencies from each of the species tested. At 100 mg kg^{-1}, MK-1064 showed robust efficacy in mouse models with an AUC value of 33.5 μM·h, a C_{max} value of 10.2 μM, and a value $C_{max,u}$ of 2.0 μM with a short T_{max} value. High levels of efficacy in rat (20 mg kg^{-1}, p.o.) were achieved at similar total and unbound exposures. In order to assure that there were no potency deviations within species, membranes were prepared expressing the species-specific receptors.[32] Notably, the OX_2R potency and selectivity over OX_1R remained consistent for mouse and human, as well as the other species tested. From this consistent level of potency across species and the rat occupancy data (Occ_{90} plasma = 695 nM; CSF = 52 nM; see above), it was concluded that high levels (> 90%) of OX_2R occupancy were achieved in the mouse and rat sleep experiments. It should also be noted that these doses in rodent were not the minimally efficacious doses tested, but representative of the efficacy observed.[33]

In dog, efficacy was achieved at a decresed AUC (0.5 μM·h) and C_{max} (0.3 μM) compared with rodent, and the $C_{max,u}$ value

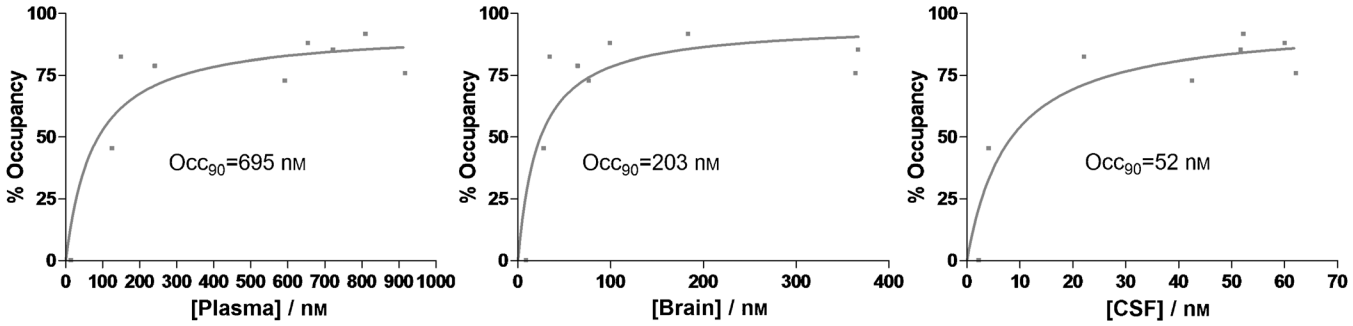


Figure 3. Plots of occupancy versus plasma, brain, and cerebrospinal fluid (CSF) in transgenic rats for compound **3**.

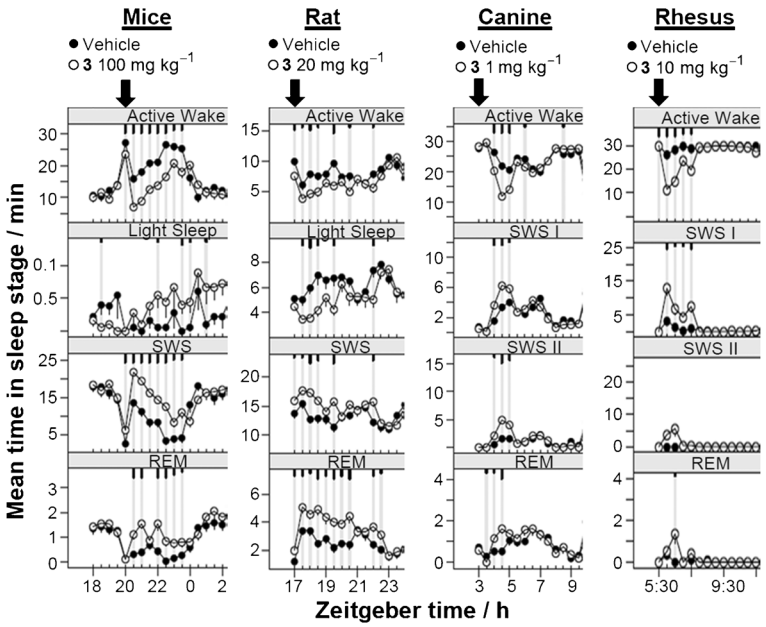


Figure 4. Effects of compound **3** on sleep parameters across mouse, rat, canine, and non-human primate.[a] Sleep-promoting responses to compound **3** in mice ($n=14$), rats ($n=5$), dogs ($n=6$), and rhesus monkeys ($n=6$) following active-phase treatment with the indicated dosages. Mean time spent in each sleep stage during 30 min intervals is plotted for both vehicle (●) and compound **3** (○) dosed orally in either 20% vitamin E–TPGS (mouse, rat, rhesus monkeys) or 10 mM sodium citrate (canine) relative to Zeitgeber time (ZT), where ZT 0:00 refers to lights on for all species. Dose times are indicated by a bold arrow. Treatments were administered in a crossover design such that each subject received drug and vehicle (5 days consecutive treatment for mouse and canine; 7 days for rat; 1 day for monkeys). Mean time in vigilance state in 30 min analysis intervals during vehicle and compound treated conditions were averaged over all days of treatment are compared using a linear mixed effects model for repeated measures t test, where significant responses are indicated by grey lines where tick marks indicate significance level (short, medium, long, $p<0.05$, 0.01, 0.001).

was also decreased at 0.09 μM. Sleep effects in rhesus monkey were observed at similar total concentrations compared with dog and the $C_{max,u}$ value of 0.13 μM. These results could be due to diminished Pgp susceptibility compared with rodent (see above), or a delayed T_{max} (in rhesus) giving rise to more coverage over the course of the experiment. It should be noted that hPPB (97.4%), binding potency ($K_i=0.5$ nM), and Pgp susceptibility (human BA/AB = 2.4; rhesus BA/AB = 5.5 at 0.5 μM) most closely align with the rhesus data. Therefore, human efficacy might most closely align with the rhesus data. In all of these experiments, high levels of OX_2R occupancy are expected with very low-to-moderate antagonism of OX_1R based on functional FLIPR potencies and $C_{max,u}$ values within the experiments. From our previous DORA efforts, suvorexant demonstrated sleep efficacy in dog at a 3 mg kg^{-1} oral dose with an AUC value of 4.0 μM·h, a C_{max} value of 0.82 μM, and a $C_{max,u}$ value of approximately 8 nM.[13b] Rhesus monkey efficacy was achieved with suvorexant at a 10 mg kg^{-1} oral dose with an AUC value of 8.8 μM·h, a C_{max} value of 1.44 μM, and a $C_{max,u}$ value of approximately 14 nM. These data suggest that in higher order species (dog and rhesus), sleep efficacy similar to DORAs can be achieved from selective antagonism of OX_2R.

Based on the in vitro and in vivo efficacy data described above and the assumption that oxidative metabolism is the dominant excretion mode, compound **3** was predicted to be a low-clearance compound (1–4 mL min^{-1} kg^{-1}) in humans with an appropriate half-life (2–16 h) to support insomnia treatment. Compound **3** was highly selective over a range of targets in a Panlabs screen (165 assays) with only two activities of note: guinea pig adenosine receptor activity ($K_i=2.5$ μM) and human histamine 1 activity ($K_i=2.7$ μM). These data represent a greater than 5000-fold margin over the OX_2R human binding activity for compound **3**. Compound **3** is a non-hygroscopic, modestly water soluble (0.015 mg mL^{-1} at neutral pH), moderate molecular weight (462 g mol^{-1}), crystalline material that is well tolerated in preclinical safety studies in a five-day rat toxicology study, achieving an AUC value of 973 μM·h and a C_{max} value of 71 μM (750 mg kg^{-1} dose). No treatment-related changes in organ weight, serum biochemistry or histomorphology were noted in this study. Cardiovascular studies in conscious dogs (170 mg kg^{-1}, p.o.) revealed no conduction changes (PR, QRS, QT/QTc) and no effects on heart rate and blood pressure. Compound **3** was also not genotoxic in preclinical studies. Based on the data presented above, compound **3** was approved for further development and designated MK-1064. Additional preclinical and clinical studies concerning this compound will be reported in due course.

Table 5. Exposure data and binding potencies from sleep studies across species.

Species	Dose[a] [mg kg^{-1}]	AUC [μM·h]	T_{max} [h]	C_{max} [μM]	PPB[b] [%]	$C_{max,u}$ [μM]	K_i [nM][c] OX_2R	K_i [nM][c] OX_1R
Mouse	100	33.5	2.0	10.1	80.3	2.0	1.0	1559
Rat	20	38	4.7	7.2	81.1	1.3	0.8	1069
Dog	1	0.5	0.7	0.3	71.4	0.09	0.8	1300
Rhesus	10	8.6	3.6	2.0	93.6	0.13	0.6	815

[a] For vehicle details, see the footnotes of Table 4; [b] Species-specific plasma protein binding (PPB); data is the % bound, and values were determined by standard methods; see the Supporting Information for details; [c] K_i values were determined using a radioligand-displacement binding assay; each value is the mean of at least two or more independent determinations; for assay details, see Ref. [13a].

Conclusions

We have described the development of 5″-chloro-*N*-[(5,6-dimethoxypyridin-2-yl)methyl]-2,2′:5′,3″-terpyri-

dine-3′-carboxamide (MK-1064), one of the most potent and selective 2-SORA compounds reported to date. This effort required the resolution of numerous issues, including reversible CYP3A4 inhibition, challenging physiochemical properties, central nervous system (CNS) penetration, and bioactivation potential relative to the initial lead. MK-1064 demonstrated efficacy in preclinical sleep models across species and was well tolerated in preclinical safety studies. MK-1064 represents a novel 2-SORA ligand with a desirable profile for the treatment of clinical sleep disorders.

Experimental Section

Biology

Ethical statement: All animal studies were performed according to the US National Research Council's Guide for the Care and Use of Laboratory Animals (http://www.nap.edu/catalog.php?record_id=12910), and experimental protocols were reviewed by the Merck Animal Care and Use Committee. All efforts were made to minimize animal use and suffering.

Radioligand binding assay: This assay was performed in an identical manner as described in Ref. [13a]. For non-human species assays, membranes that express the mouse, rat, dog, or rhesus monkey orexin 2 receptor (OX_2R) and the Ile408-Val variant of the orexin 1 receptor (hOX_1R) were prepared in CHO cells according to the method described by Kunapuli et al.[34]

FLIPR, bioactivation, and rat occupancy assays: These assays were performed in an identical manner as described in Ref. [13a].

Sleep assays in mice, rats, canines and nonhuman primates: Sleep was quantitated by polysomnography in mice and rats subcutaneously implanted with radio-telemetric physiologic monitors (Data Sciences International, Arden Hills, MN, USA) to simultaneously record continuous electrocorticogram (ECoG) and electromyogram (EMG) activities as previously described (Ref. [13b] and Ref. [14b]). In telemetry-implanted dogs and rhesus monkeys, polysomnography was performed via ECoG, EMG and electrooculoram (EOG) as described in Ref. [13b] and Ref. [11], respectively. Sleep scoring and the difference relative to vehicle in time spent in active wake, REM sleep, and slow wave sleep (SWS) (mice, rats) or SWS I and SWS II (dogs, rhesus) during the 2 h following compound treatment has been detailed elsewhere (Ref. [13b] and Ref. [35]). All species were acclimated to 12:12 light/dark cycles prior to the initiation of studies.

In adult male C57/BL6 wild-type mice (~30 grams; Taconic Farms, Germantown, NY, USA), the current studies evaluated compound **3** (free base form) at 100 mg kg^{-1} in a dose volume of 6.67 mL kg^{-1} (p.o.) formulated in 20% D-α-tocopherol polyethylene glycol 1000 succinate (vitamin E–TPGS). Compound and vehicle were administered during the active (dark) phase 4 h prior to lights on (Zeitgeber time [ZT] 20:00, where ZT 00:00 is lights on), for 5 days in a balanced crossover design (5 days of vehicle or compound; 2 day washout; 5 days of compound or vehicle, where groups were reversed relative to the first arm of the crossover). Compound and vehicle conditions for each animal were combined and averaged over a 24 h time scale before determination of compound-induced effects relative to vehicle during the 2 h immediately following treatment.

In adult male Sprague–Dawley rats (~600 g; Taconic Farms, Germantown, NY, USA), compound **3** (free base form) was formulated in 20% vitamin E–TPGS and dosed at 20 mg kg^{-1} in a dose volume of 1.67 mL kg^{-1} (p.o.). Rats were treated for 7 days of consecutive vehicle and compound treatments during the active (dark) phase 7 h prior to lights off (ZT 17:00) in a balanced crossover design (2 days of baseline (all); 2 days vehicle run in (all); 7 days vehicle or compound treatment arm; 7 days compound or vehicle treatment arm).

In adult male beagles (~12 kg; Marshall BioResources, North Rose, NY, USA), compound **3** was combined with excipient, hydroxypropyl methylcellulose acetate succinate (HPMCAS-HG) and spray-dried before resuspension in 10 mM sodium citrate (pH 5.5) vehicle and dosed (p.o.) at 1 mg kg^{-1} (dose volume: 5 mL kg^{-1}). Sleep responses to compound **3** relative to vehicle were averaged from five consecutive days of treatment during the active phase 9 h prior to lights off (ZT 03:00) in a block-repeated measures design: all subjects received vehicle for 5 days followed by a 2 day vehicle treatment washout followed by five consecutive days of compound treatment.

In adult male rhesus monkeys (~11 kg; *Macaca mulatta*), responses to 10 mg kg^{-1} doses of compound **3** were measured following treatment with either vehicle (20% vitamin E TPGS) or compound in a dose volume of 10 mL kg^{-1} (p.o.). Monkeys were dosed during their active (light) phase 6.5 h prior to lights off (ZT 05:30) in a one-day block crossover design: one day vehicle (all); one day compound (all). Compound and control conditions were separately averaged, and the mean difference in sleep stages relative to vehicle was determined for the 2 h following treatment.

Chemistry

General comments: All solvents used were commercially available anhydrous grade, and reagents were utilized without purification unless otherwise noted. Nonaqueous reactions were carried out in oven- or heat-gun-dried glassware under a nitrogen atmosphere. Magnetic stirring was used to agitate the reactions, which were monitored for completion by either thin-layer chromatography (TLC) using silica gel 60 plates (Merck KGaA) or LC/MS. A Smith-Creator microwave from Personal Chemistry was used for microwave heating, and a CombiFlash system utilizing RediSep cartridges by Teledyne Isco was utilized for silica gel column chromatography with fraction collection at 254 nm. Reverse-phase HPLC purification was carried out on a Waters HPLC (XBridge Prep C18 5 μM 19×150 mm column) utilizing a gradient of 0.1% trifluoroacetic acid (TFA) in water/CH_3CN with sample collection triggered by photodiode array detection. The reported yields are for isolated compounds of ≥95% purity, unless otherwise noted; reactions were not extensively optimized. Purity analysis was carried out by HPLC with a Waters 2690 separations module equipped with a YMC Pro 50×3 mm I.D. C-18 column interfaced with a Waters Micromass ZMD spectrometer utilizing a gradient of 0.05% TFA in water/CH_3CN with UV detection at 215 and/or 254 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA 400, 500 or 600 MHz spectrometer, and all chemical shifts (δ) are referenced to an internal standard of tetramethylsilane and the $CDCl_3$ residual solvent peak, respectively, unless otherwise noted. High-resolving power accurate mass measurement electrospray (ES) and atmospheric pressure chemical ionization (APCI) mass spectral data were acquired by use of a Bruker Daltonics 7T Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR MS).

2-Chloro-*N*-(3,4-dimethoxybenzyl)-5-(3,5-dimethylphenyl)pyridine-3-carboxamide (6): To a solution of methyl 2-chloro-5-iodopyridine-3-carboxylate (**5**, 3.00 g, 10.1 mmol) in DMF (34 mL)/water

(1.8 mL) was added 3,5-dimethylphenylboronic acid (1.97 g, 13.1 mmol), $PdCl_2$(dppf) (1.11 g, 1.51 mmol), and Cs_2CO_3 (8.21 g, 25.2 mmol), and the reaction was stirred at 25 °C for 18 h. The reaction mixture was partitioned between EtOAc (150 mL) and water (150 mL). The organic phase was washed with water (2×100 mL) and brine (2×100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (0→25% EtOAc/hexane) to afford methyl 2-chloro-5-(3,5-dimethylphenyl)pyridine-3-carboxylate as a white solid (2.32 g, 83%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 7.18 (s, 2H), 7.09 (s, 1H), 3.99 (s, 3H), 2.40 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 150.1, 148.6, 139.2, 138.7, 136.0, 135.5, 130.7, 126.6, 125.1, 53.1, 21.5 ppm; MS (ESI+): m/z = 276.0 $[M+H]^+$.

To a solution of 2-chloro-5-(3,5-dimethylphenyl)pyridine-3-carboxylate (1.80 g, 6.53 mmol) in THF (33 mL) at 25 °C was added $KOSiMe_3$ (1.26 g, 9.79 mmol). The reaction was stirred at RT until completion was reached after 24 h and Et_2O (25 mL) was added to fully precipitate the product. The reaction was filtered to afford potassium 2-chloro-5-(3,5-dimethylphenyl)pyridine-3-carboxylate as an off-white solid (1.96 g, 100%), which was used in subsequent reactions without further purification.

To a suspension of potassium 2-chloro-5-(3,5-dimethylphenyl)pyridine-3-carboxylate (500 mg, 1.67 mmol) in DMF (8.3 mL) was added 3,4-dimethoxybenzylamine (363 mg, 2.17 mmol), EDC (480 mg, 2.50 mmol), HOAt (341 mg, 2.50 mmol), and Et_3N (506 mg, 5.0 mmol), and the reaction was heated to 45 °C for 3 h. The reaction mixture was cooled and partitioned between EtOAc (50 mL) and saturated aq $NaHCO_3$ (50 mL). The organic phase was washed with saturated aq $NaHCO_3$ (2×50 mL), water (2×50 mL), and brine (2×50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (0→80% EtOAc/hexane) to afford **6** as a white solid (422 mg, 62%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, J = 2.5 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.19 (s, 2H), 7.08 (s, 1H), 6.96–6.92 (m, 2H), 6.86 (d, J = 9.0 Hz, 1H), 4.64 (d, J = 5.5 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.39 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 149.5, 149.2, 148.9, 145.5, 139.2, 138.3, 136.7, 135.5, 130.8, 130.7, 130.0, 125.1, 120.4, 111.5, 111.4, 56.2, 56.1, 44.5, 21.5 ppm; MS (ESI+): m/z = 411.0 $[M+H]^+$.

***N*-(3,4-Dimethoxybenzyl)-5-(3,5-dimethylphenyl)-2,2′-bipyridine-3-carboxamide (9)**: A solution of **6** (50 mg, 0.12 mmol), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), CsF (55 mg, 0.36 mmol), CuI (4.6 mg, 0.024 mmol), and 2-(tri-*n*-butylstannyl)pyridine (100 mg, 0.24 mmol) was made in DMF (600 μL), and the reaction was heated to 160 °C in a microwave reactor for 20 min. The reaction was partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The reaction was purified by column chromatography (65→100% EtOAc/hexane) to afford **9** as a white solid (37 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, J = 2.0 Hz, 1H), 8.36 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.80 (dt, J = 7.6, 1.6 Hz, 1H), 7.63–7.58 (m, 1H), 7.28–7.23 (m, 3H), 7.08 (s, 1H), 6.86–6.78 (m, 3H), 4.51 (d, J = 5.6 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 2.40 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 157.1, 152.6, 149.3, 148.7, 148.5, 148.1, 139.1, 137.2, 136.6, 136.4, 136.3, 132.2, 130.6, 130.5, 125.2, 124.4, 123.7, 120.6, 111.7, 111.4, 56.2, 56.1, 44.5, 21.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{28}H_{27}N_3O_3$: 454.2125, found: 454.2133.

***N*-(3,4-Dimethoxybenzyl)-5-(3,5-dimethylphenyl)-2-(morpholin-4-yl)pyridine-3-carboxamide (11)**: A solution of **6** (40 mg, 0.097 mmol) and morpholine (85 mg, 0.97 mmol) in DMF (490 μL) was heated to 140 °C in a microwave reactor for 15 min. The reaction was partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The reaction was purified by column chromatography (5→75% EtOAc/hexane) to afford **11** as a white solid (26 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06–8.98 (m, 1H), 8.58 (dd, J = 9.6, 2.4 Hz, 2H), 7.22 (s, 2H), 7.03 (s, 1H), 6.98–6.92 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.62–3.54 (m, 4H), 3.20–3.12 (m, 4H), 2.38 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 159.1, 149.6, 149.0, 148.0, 138.9, 138.8, 136.8, 133.0, 130.9, 129.8, 124.9, 121.2, 120.8, 111.8, 111.5, 66.8, 56.2, 51.8, 43.9, 21.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{27}H_{31}N_3O_4$: 462.2387, found: 462.2374.

***N*-(3,4-Dimethoxybenzyl)-5-(3,5-dimethylphenyl)-2,3′-bipyridine-3-carboxamide (7)**: A solution of **6** (50 mg, 0.12 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)pyridine (37 mg, 0.18 mmol), Cs_2CO_3 (99 mg, 0.30 mmol), and $PdCl_2$(dppf) (13 mg, 0.018 mmol) in DMF (600 μL)/water (20 μL) was heated to 160 °C in a microwave reactor for 20 min. The reaction was partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The reaction was purified by column chromatography (0→20% MeOH/EtOAc) to afford **7** as a white solid (34 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, J = 2.4 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.53 (dd, J = 5.2, 1.6 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.94 (dt, J = 8.0, 2.0 Hz, 1H), 7.26–7.20 (m, 3H), 7.09 (s, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.68–6.60 (m, 2H), 6.15 (t, J = 5.2 Hz, 1H), 4.39 (d, J = 5.6 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.41 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 151.3, 149.9, 149.4, 148.9, 139.1, 136.4, 136.3, 136.0, 135.2, 134.6, 131.9, 130.6, 129.7, 125.1, 123.3, 120.7, 111.7, 111.4, 56.2, 56.1, 44.5, 21.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{28}H_{27}N_3O_3$: 454.2125, found: 454.2138.

***N*-(3,4-Dimethoxybenzyl)-5-(3,5-dimethylphenyl)-2,4′-bipyridine-3-carboxamide (8)**: A solution of **6** (50 mg, 0.12 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)pyridine (37 mg, 0.18 mmol), Cs_2CO_3 (99 mg, 0.30 mmol), and $PdCl_2$(dppf) (13 mg, 0.018 mmol) in DMF (600 μL)/water (20 μL) was heated to 160 °C in a microwave reactor for 20 min. The reaction was partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The reaction was purified by column chromatography (0→20% MeOH/EtOAc) to afford **8** as a white solid (11 mg, 20%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.96 (d, J = 2.0 Hz, 1H), 8.64 (d, J = 6.0 Hz, 2H), 8.14 (d, J = 2.5 Hz, 1H), 7.61 (d, J = 4.5 Hz, 2H), 7.25 (s, 2H), 7.10 (s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 8.5, 2.5 Hz, 1H), 5.78 (m, 1H), 4.39 (d, J = 5.5 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.41 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 151.6, 150.3, 149.5, 149.4, 149.0, 146.3, 139.2, 136.7, 136.2, 135.3, 132.0, 130.8, 129.4, 125.2, 123.5, 120.6, 111.6, 111.5, 56.2, 56.1, 44.7, 21.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{28}H_{27}N_3O_3$: 454.2125, found: 454.2120.

***N*-(3,4-Dimethoxybenzyl)-5-(3,5-dimethylphenyl)-2-phenylpyridine-3-carboxamide (10)**: A solution of **6** (50 mg, 0.12 mmol), phenylboronic acid (44 mg, 0.36 mmol), Cs_2CO_3 (119 mg, 0.37 mmol), and $PdCl_2$(dppf) (13 mg, 0.018 mmol) in DMF (600 μL)/water (20 μL) was heated to 160 °C in a microwave reactor for 20 min. The reaction was partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The reaction was purified by column chromatography (0→75% EtOAc/hexane) to afford **10** as a white solid (12 mg, 22%): ^{1}H NMR (400 MHz, $CDCl_3$): δ =

8.92 (d, J=2.0 Hz, 1H), 8.22 (d, J=2.0 Hz, 1H), 7.68–7.64 (m, 2H), 7.42–7.36 (m, 3H), 7.08 (s, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.55 (d, J=2.0 Hz, 1H), 6.53 (dd, J=8.0, 2.0 Hz, 1H), 5.63 (t, J=5.6 Hz, 1H), 4.32 (d, J=5.6 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.41 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4, 154.5, 149.3, 149.2, 148.8, 139.1, 138.9, 136.7, 135.7, 135.5, 131.1, 130.4, 129.7, 129.2, 129.1, 128.9, 125.2, 120.6, 111.5, 111.3, 56.2, 56.1, 44.6, 21.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{29}H_{29}N_2O_3$: 452.2173, found: 453.2174.

Methyl 5′,6-dichloro-3,3′-bipyridine-5-carboxylate (18): To a solution of **5** (30.0 g, 101 mmol) in DMF (403 mL)/water (18 mL) was added (5-chloropyridin-3-yl)boronic acid (16.2 g, 103 mmol), $PdCl_2$-(dppf) (7.38 g, 10.1 mmol), and Cs_2CO_3 (99.0 g, 303 mmol), and the reaction was stirred at 25 °C for 18 h. The reaction mixture was partitioned between EtOAc (1 L) and water (1 L). The organic phase was washed with water (2×500 mL) and brine (2×500 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by trituration with MeOH (~200 mL) followed by EtOAc/Et_2O (1:1, 500 mL) to afford **18** as a beige solid (28.4 g, 99%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.78–8.70 (m, 2H), 8.67 (d, J=2.5 Hz, 1H), 8.35 (d, J=2.5 Hz, 1H), 7.89 (t, J=2.5 Hz, 1H), 4.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.5, 150.4, 149.7, 149.0, 145.7, 138.7, 134.1, 132.7, 132.5, 131.1, 127.0, 53.2 ppm; MS (ESI+): m/z=282.9 $[M+H]^+$.

Methyl 5″-chloro-2,2′:5′,3″-terpyridine-3′-carboxylate (19): To a solution of **18** (7.6 g, 26.8 mmol) in DMF (107 mL) was added 2-tri-*n*-butylstannylpyridine (13.8 g, 37.6 mmol), CsF (12.2 g, 81.0 mmol), CuI (1.0 g, 5.4 mmol, 0.2 equiv), and $Pd(PPh_3)_4$ (3.1 g, 2.7 mmol), and the system was heated to 80 °C for 2 h. The reaction mixture was cooled, diluted with EtOAc (300 mL), and filtered through a pad of Celite. The reaction mixture was washed with water (3×100 mL) and brine (1×100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (10→100% EtOAc/hexane), followed by normal phase chiral chromatography (Chiracel OD, 10 cm column; hexane/*i*PrOH [1:1], flow rate=150 mL min^{-1}) to afford **19** as a white solid (4.5 g, 52%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.95 (d, J=2.0 Hz, 1H), 8.80 (d, J=2.0 Hz, 1H), 8.66 (d, J=3.0 Hz, 1H), 8.65–8.61 (m, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.13 (d, J=2.0 Hz, 1H), 7.95 (t, J=2.5 Hz, 1H), 7.87 (td, J=7.6, 1.6 Hz, 1H), 7.34 (ddd, J=7.6, 4.8, 1.2 Hz, 1H), 3.85 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 155.3, 155.2, 148.7, 148.6, 148.3, 145.8, 136.9, 135.3, 134.1, 133.5, 132.7, 131.2, 128.9, 124.0, 122.8, 52.6 ppm; MS (ESI+): m/z=326.0 $[M+H]^+$.

5″-Chloro-*N*-[(5,6-dimethoxypyridin-2-yl)methyl]-2,2′:5′,3″-terpyridine-3′-carboxamide (3): To a solution of **19** (3.05 g, 9.36 mmol) in THF/MeOH (22 mL/4.5 mL) was added 10 N aq NaOH (1.12 mL, 11.2 mmol), and the system was heated to 135 °C for 15 min in a microwave reactor. The reaction mixture was cooled, concentrated, and azeotroped with EtOAc (2×100 mL) and toluene (3×100 mL) to afford sodium 5″-chloro-2,2′:5′,3″-terpyridine-3′-carboxylate as a white solid (3.12 g, quant.): MS (ESI+): m/z=311.9 $[M+H]^+$.

To a suspension of sodium 5″-chloro-2,2′:5′,3″-terpyridine-3′-carboxylate (3.12 g, 9.35 mmol) in DMF (47 mL) was added 1-(5,6-dimethoxy-pyridin-2-yl)methanamine (**21**, 1.65 g, 9.82 mmol), EDC (3.58 g, 18.7 mmol), HOAt (2.55 g, 18.7 mmol), and DIPEA (4.83 g, 37.4 mmol), and the system was heated to 60 °C for 2 h. The reaction mixture was cooled and diluted with EtOAc (300 mL). The reaction mixture was washed with saturated aq $NaHCO_3$ (2×100 mL), water (2×100 mL) and brine (1×100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (10→100% EtOAc/hexane then 0→23% MeOH/EtOAc) to afford the **3** as a white solid (3.4 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.95 (d, J=2.5 Hz, 1H), 8.80 (s, 1H), 8.66 (d, J=2.0 Hz, 1H), 8.38 (d, J=5.0 Hz, 1H), 8.26 (d, J=2.5 Hz, 1H), 8.04 (d, J=8.0 Hz, 1H), 7.96 (bs, 1H), 7.78 (t, J=3.0 Hz, 1H), 7.47 (bs, 1H), 7.23 (dd, J=7.5, 5.5 Hz, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.85 (d, J=7.5 Hz, 1H), 4.55 (d, J=5.5 Hz, 2H), 3.88 (s, 3H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.0, 155.9, 154.1, 153.8, 148.6, 148.4, 148.0, 145.8, 143.6, 143.2 136.9, 136.2, 134.1, 133.6, 132.7, 132.6, 131.5, 123.9, 123.8, 117.7, 114.7, 55.9, 53.5, 44.6 ppm; HRMS-ESI: m/z $[M+H]$ calcd for $C_{24}H_{20}ClN_5O_3$: 462.1327, found: 462.1331.

2,3-Dimethoxy-6-aminomethylpyridine (21): To a solution of commercially available 6-iodo-2,3-dimethoxypyridine (**20**, 24.0 g, 91 mmol) in DMF (181 mL) was added CuCN (9.73 g, 109 mmol), and the reaction was heated to 150 °C for 20 min in a microwave reactor. The mixture was partitioned between water (400 mL) and EtOAc (400 mL). The organic phase was washed with brine (3×200 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography (0→40% EtOAc/hexane) to yield the 5,6-dimethoxypyridine-2-carbonitrile as an off-white crystalline powder (11.7 g, 79%): MS (ESI+): m/z=165.0 $[M+H]^+$.

To a solution of 2,3-dimethoxy-6-cyanopyridine (5.1 g, 31.1 mmol) in MeOH (260 mL) was added Pearlman's catalyst (2.18 g, 3.11 mmol, 20%/*w*) and 12 M HCl (20.0 mL, 249 mmol). The system was then stirred under an atmosphere of hydrogen for 1.5 h at RT. The reaction mixture was filtered through a pad of Celite, and MeOH was removed in vacuo. The crude mixture was basified using saturated aq Na_2CO_3 (100 mL) and then extracted with $CHCl_3$/EtOH (4:1, 4×200 mL). The organic phase was washed with brine (2×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to yield the **21** as a bone-colored semisolid (4.8 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.00 (d, J=8.0 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 4.04 (s, 3H), 3.87 (s, 3H), 3.81 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.1, 14.8, 142.8, 117.8, 113.5, 56.0, 53.7, 47.0 ppm; MS (ESI−): m/z=152.1 $[M-NH_2]^-$.

2,3-Dimethoxy-5-aminomethylpyrazine (23): To commercially available 5-bromo-2,3-dimethoxypyrazine (**22**, 1.66 g, 12.1 mmol) in DMF (25 mL) was added CuCN (1.20 g, 13.4 mmol), and the mixture was heated to 185 °C for 20 min in the microwave reactor. The mixture was cooled, and partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was washed with brine (2×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography (0→65% EtOAc/hexane) to afford 5,6-dimethoxypyrazine-2-carbonitrile (1.17 g, 58%).

To 5,6-dimethoxypyrazine-2-carbonitrile (1.17 g, 7.1 mmol) in MeOH (59 mL) was added Pearlman's catalyst (0.50 g, 0.71 mmol, 20%/*w*) and 12 M HCl (4.65 mL, 57 mmol). The system was then stirred under an atmosphere of hydrogen for 1.5 h at RT. The reaction contents were filtered through a pad of Celite, followed by removal of MeOH in vacuo. The crude mixture was then dissolved in CH_2Cl_2 (100 mL), basified using saturated aq Na_2CO_3 (50 mL), and then extracted several times with CH_2Cl_2 (4×100 mL). The organic phase was washed with brine (2×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to yield **23** as a bone-colored solid (1.1 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.56 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.81 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.2, 149.6, 144.9, 128.7, 54.1, 53.9, 44.6 ppm; MS (ESI−): m/z=152.8 $[M-NH_2]^-$.

1-(5,6-Dimethoxypyridin-3-yl)methanamine (25): To a solution of commercially available 2,3-dimthoxypyridine (**24**, 2.5 g, 18.0 mmol) in CH_2Cl_2/saturated aq $NaHCO_3$ (80 mL/40 mL) at 0 °C was added Br_2 (0.93 mL, 18.0 mmol), and the reaction mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with solid Na_2SO_3 (~10 g), and the aqueous phase was extracted with CH_2Cl_2 (3× 100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (0→20% EtOAc/hexane) to afford 5-bromo-2,3-dimethoxypyridine as an oil after concentration (2.1 g, 49%): MS (ESI+): $m/z = 218.0$ $[M+H]^+$.

To a solution of 5-bromo-2,3-dimethoxypyridine (100 mg, 0.46 mmol) in DMF (1.5 mL) was added CuCN (82 mg, 0.92 mmol), and the reaction mixture was heated for 40 min at 180 °C in a microwave reactor. The reaction mixture was cooled and partitioned between EtOAc (30 mL) and water (30 mL). The organic phase was washed with water (2×30 mL) and brine (1×30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (0→40% EtOAc/hexane) to afford 5,6-dimethoxypyridine-3-carbonitrile as white solid (50 mg, 66%): MS (ESI+): $m/z = 165.1$ $[M+H]^+$.

To a solution of 5,6-dimethoxypyridine-3-carbonitrile (50 mg, 0.31 mmol) in MeOH (20 mL) under a nitrogen atmosphere was added Pearlman's catalyst (21 mg,0.03 mmol, 0.08 equiv, 20%/*w*) and concd HCl (0.2 mL), and the reaction was placed under an atmosphere of hydrogen. After 2 h, the reaction was placed under an atmosphere of nitrogen and filtered through Celite to remove the catalyst. The reaction was concentrated in vacuo, and the acid was neutralized with saturated aq $NaHCO_3$ (~10 mL). The aqueous phase was extracted with $CHCl_3$/EtOH (4:1; 4×20 mL), dried over $MgSO_4$, filtered and concentrated to afford **25** as an oily solid (25 mg, 49%): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$ (s, 1H), 7.11 (s, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.84 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.9$, 144.3, 135.2, 131.9, 117.0, 55.8, 53.9, 43.7 ppm; MS (ESI+): $m/z = 169.1$ $[M+H]^+$.

Abbreviations: *N*,*N*-Diisopropylethylamine (DIPEA); *N*,*N*-dimethylformamide (DMF); 1,1′-(diphenylphosphino)ferrocene (dppf); 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC); 1-hydroxy-7-azabenzotriazole (HOAt); tetrahydrofuran (THF).

Supporting Information

Experimental procedures for the synthesis of compounds **12**–**17**, as well as reproductions of the ^{1}H and ^{13}C NMR spectra for key compounds can be found in the Supporting Information available on the WWW under http://dx.doi.org/10.1002/cmdc.201300447.

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